Guidance for Industry

Non-Penicillin Beta-Lactam Drugs: A CGMP Framework for Preventing Cross-Contamination

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

April 2013
Current Good Manufacturing Practices (CGMPs)

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I. INTRODUCTION

This guidance describes the importance of implementing manufacturing controls to prevent cross-contamination of finished pharmaceuticals and active pharmaceutical ingredients (APIs) with non-penicillin beta-lactam drugs. This guidance also provides information regarding the relative health risk of, and the potential for, cross-reactivity in the classes of sensitizing beta-lactams (including both penicillins and non-penicillin beta-lactams). Finally, this guidance clarifies that manufacturers generally should utilize separate facilities for the manufacture of non-penicillin beta-lactams because those compounds pose health risks associated with cross-reactivity.

Drug cross-contamination is the contamination of one drug with one or more different drugs. Penicillin can be a sensitizing agent that triggers a hypersensitive exaggerated allergic immune response in some people. Accordingly, implementing methods for preventing cross-contamination of other drugs with penicillin is a key element of manufacturing penicillin and current good manufacturing practice (CGMP) regulations require the use of such methods. See, e.g., 21 CFR §§ 211.42(d), 211.46(d), and 211.176. Non-penicillin beta-lactam drugs also may be sensitizing agents and cross-contamination with non-penicillin beta-lactam drugs can initiate the same types of drug-induced hypersensitivity reactions that penicillins can trigger, including life-threatening allergic reactions. Therefore, manufacturers of non-penicillin beta-lactam drugs should employ similar control strategies to prevent cross-contamination, thereby reducing the potential for drug-induced, life-threatening allergic reactions.

The information in this guidance is intended for manufacturers of finished pharmaceuticals and APIs, including repackagers. Other establishments that handle drugs, such as pharmacy compounders, may find this information useful.

[1] This guidance was developed by the Office of Compliance, Office of Manufacturing and Product Quality, in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidance documents describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA guidance means that something is suggested or recommended, but not required.

II. BACKGROUND

A. Regulatory Framework

Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 351(a)(2)(B)) requires that, with few exceptions, all drugs be manufactured in compliance with current good manufacturing practices (CGMPs). Drugs that are not in compliance with CGMPs are considered to be adulterated. Furthermore, finished pharmaceuticals are required to comply with the CGMP regulations at 21 CFR parts 210 and 211.

Several CGMP regulations directly address facility and equipment controls and cleaning. For example, § 211.42(c) requires building and facility controls in general to prevent cross-contamination of drug products. Specifically, the regulation states, "[t]here shall be separate or defined areas or such other control systems for the firm's operations as are necessary to prevent contamination or mix-ups" during manufacturing, processing, packaging, storage, and holding.

With respect to penicillin, § 211.42(d) requires that "[o]perations relating to the manufacture, processing, and packing of penicillin shall be performed in facilities separate from those used for other drug products for human use." However, FDA has clarified that separate buildings may not be necessary, provided that the section of the manufacturing facility dedicated to manufacturing penicillin is isolated (i.e., completely and comprehensively separated) from the areas of the facility in which non-penicillin products are manufactured.[2] Under § 211.46(d), manufacturers must completely separate air handling systems for penicillin from those used for other drugs for human use. Additionally, § 211.176 requires manufacturers to test non-penicillin drug products for penicillin where the possibility of exposure to cross-contamination exists, and prohibits manufacturers from marketing such products if detectable levels of penicillin are found.[3]

Although FDA has not issued CGMP regulations specific to APIs, the Agency has provided guidance to API manufacturers in the guidance for industry, ICH[4] Q7, *Good Manufacturing*

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[2] Preamble to the final rule, "Current Good Manufacturing Practice, Processing, Packing, or Holding." 43 FR 45014 at 45038 (September 29, 1978).

[3] See "A Review of Procedures for the Detection of Residual Penicillins in Drugs" (Appendix I, *Procedures for Detecting and Measuring Penicillin Contamination in Drugs*, FDA By-Lines No. 8 (November 1977)), available at http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM095812.pdf. NB: This link works as of 5/18/2012.

[4] International Conference on Harmonization.

Practice Guidance for Active Pharmaceutical Ingredients (ICH Q7 guidance).[5] Because some APIs are sensitizing compounds that may cause anaphylactic shock, preventing cross-contamination in APIs is as important as preventing cross-contamination in finished products. The ICH Q7 guidance recommends using dedicated production areas, which can include facilities, air handling equipment and processing equipment, in the production of highly sensitizing materials, such as penicillins and cephalosporins.[6]

B. Beta-Lactam Antibiotics

Beta-lactam antibiotics, including penicillins and the non-penicillin classes, share a basic chemical structure that includes a three-carbon, one-nitrogen cyclic amine structure known as the beta-lactam ring. The side chain associated with the beta-lactam ring is a variable group attached to the core structure by a peptide bond; the side chain variability contributes to antibacterial activity. As of the date of this publication, FDA has approved over 34 beta-lactam compounds as active ingredients in drugs for human use.[7] Beta-lactam antibiotics include the following five classes[8]:

- penicillins (e.g., ampicillin, oxacillin)
- cephalosporins (e.g., cephalexin, cefaclor)
- penems (e.g., imipenem, meropenem)
- carbacephems (e.g., loracarbef)
- monobactams (e.g., aztreonam)

Allergic reactions associated with penicillins and non-penicillin beta-lactams range from rashes to life-threatening anaphylaxis. Immunoglobulin E (IgE) antibodies mediate the immediate hypersensitivity reactions that are responsible for the symptoms of hay fever, asthma, hives, and anaphylactic shock. IgE-mediated hypersensitivity reactions are of primary concern because they may be associated with significant morbidity and mortality. There is evidence that patients with a history of hypersensitivity to penicillin may also experience IgE-mediated reactions to other beta-lactams, such as cephalosporins and penems.[9]

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[5] We update guidance documents periodically. To make sure you have the most recent version of a guidance, check the Guidance Page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[6] See section IV.D Containment (4.4) of the ICH Q7 guidance.

[7] Approved beta-lactam antibiotics are listed in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations*, generally known as the *Orange Book* (available on the Internet at http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm). The Orange Book is searchable by active ingredient and updated as newer drug products are added.

[8] Yao, JDC, and RC Moellering, Jr., Antibacterial agents, in *Manual of Clinical Microbiology*, 9th edition, edited by PR Murray et al., Washington D.C., ASM Press, 2007.

[9] Saxon, A, DC Adelman, A Patel, R Hajdu, and GB Calandra, 1988, Imipenem cross-reactivity with penicillin in humans, J Allergy Clin Immunol, 82:213-217; Saxon, A, GN Beall, AS Rohr, and DC Adelman, 1987, Immediate hypersensitivity reactions to beta-lactam antibiotics, Ann Intern Med, 107(2):204-215; Prescott, Jr., WA, DD

All non-penicillin beta-lactams also have the potential to sensitize individuals, and subsequent exposure to penicillin may result in severe allergic reactions in some patients. Although the frequency of hypersensitivity reactions due to cross-reactivity between beta-lactam classes can be lower than the risk within a class,[10] the hazard posed is present[11] and potentially life-threatening. The potential health hazard of non-penicillin beta-lactams therefore is similar to that of penicillins. Further similarities between non-penicillin beta-lactams and penicillins are as follows:

- It is difficult to define the minimal dose below which allergic responses are unlikely to occur in humans. [12]
- There is a lack of suitable animal or receptor testing models that are predictive of human sensitivity. [13]
- The threshold dose at which allergenic response could occur is extremely low and difficult to detect with current analytical methods.[14]

While beta-lactam antibiotics are similar to one another in many ways, they may differ in pharmacokinetics, antibacterial activity, and potential to cause serious allergic reactions. Because allergy testing methods have not been well-validated,[15] it is clinically difficult to determine the occurrence and rate of cross-reactivity between beta-lactam antibiotics in humans. Therefore, undiagnosed or underreported cases of cross-reactivity likely exist. Some beta-lactam antibiotics have negligible potential for cross-reactivity with beta-lactams of other classes, whereas other beta-lactam compounds may exhibit sensitizing activity as derivatives before the incorporation of side chains that confer antibacterial activity.

Regardless of the rate of cross-reactivity between beta-lactam drugs or the mechanism of action by which such cross-reactivity may occur, the potential health risk to patients indicates that drug

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DePestel, JJ Ellis, and RE Regal, 2004, Incidence of carbapenem-associated allergic-type reactions among patients with versus patients without a reported penicillin allergy, Clin Infect Dis, 38:1102-1107.

[10] Salkind, AR, PG Cuddy, and JW Foxworth, 2001, Is this patient allergic to penicillin? An evidence-based analysis of the likelihood of penicillin allergy, JAMA, 285:2498-2505.

[11] Khan, D. and R Solensky , 2010, Drug Allergy, J Allergy Clin Immunol. 125(2): S131.

[12] Dayan, AD, 1993, Allergy to antimicrobial residues in food: assessment of the risk to man, Vet Microbiol, 35:213-226; Blanca, M, J Garcia, JM Vega, A Miranda, MJ Carmona et al., 1996, Anaphylaxis to penicillins after non-therapeutic exposure: an immunological investigation, Clin Exp Allergy, 26:335-340.

[13] Olson, H, G Betton, D Robinson, K Thomas, A Monro et al., 2000, Concordance of the toxicity of pharmaceuticals in humans and in animals, Regul Toxicol Pharmacol, 32:56-67.

[14] Perez Pimiento, A, M Gomez Martinez, A Minguez Mena, A Trampal Gonzalez, S de Paz Arranz, and M Rodriguez Mosquera, 1998, Aztreonam and ceftazidime: evidence of in vivo cross-allergenicity, Allergy, 53:624-625; Shepard, GM, 1991, Allergy to B-lactam antibiotics, Immunol Allergy Clin North Am, 11(3):611-633.

[15] Bernstein, IL, JT Li, DI Bernstein, et al., 2008, Allergy diagnostic testing: an updated practice parameter, Ann Allergy Asthma Immunol, 100:S1-S148.

manufacturers should take steps to control for the risk of cross-contamination for all beta-lactam products.[16]

C. Beta-Lactamase Inhibitors

Beta-lactam compounds such as clavulanic acid, tazobactam, and sulbactam have weak antibacterial activity but are irreversible inhibitors of many beta-lactamases. These compounds, which are potential sensitizing agents, are typically used in combination with specific beta-lactam agents to preserve antibacterial activity (e.g., amoxicillin-clavulanate, piperacillin-tazobactam). Because these compounds are almost always used in combination with specific beta-lactam agents, any clinical observations of hypersensitivity reactions likely would be attributed to the beta-lactam antibiotic component rather than the inhibitor. Although there have been no case reports confirming anaphylactic reactions to a beta-lactamase inhibitor that is also a beta-lactam, these compounds are potentially sensitizing agents, and manufacturers should implement controls to reduce the risk of cross-contamination with beta-lactamase inhibitors as with all other beta-lactam products.

D. Beta-Lactam Intermediates and Derivatives

Some beta-lactam intermediate compounds and derivatives also possess similar sensitization and cross–reactivity properties. Beta-lactam intermediate compounds usually are API precursor materials that undergo molecular change or purification before use in the manufacture of beta-lactam antibiotic APIs. As a result of these changes, the intermediate compounds may develop antigenic characteristics that can produce allergic reactions. For example, 6-aminopenicillanic acid (6-APA) serves as the intermediate for the formation of all synthetic penicillins that are formed by attaching various side chains. The structure of 6-APA includes unbroken beta-lactam and thiazolidine rings. The beta-lactam ring is relatively unstable, and it commonly breaks open. In the case of 6-APA, this breakage leads to the formation of a penicilloyl moiety, which is the major antigenic determinant of penicillin. This moiety is thought to be a common cause of penicillin urticarial reaction.[17] Degradation of 6-APA can also result in the formation of minor antigenic determinants, including penicilloic acids, penaldic acid, and penicillamine. Anaphylactic reactions to penicillins usually are due to the presence of IgE antibodies to minor determinants in the body. Although 6-APA is not a true antibiotic, it still carries with it a potential to induce allergenicity.

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[16] Following publication of the draft version of this guidance (76 FR 14024), several commenters suggested that monobactams, specifically aztreonam, have a lower risk profile than other beta-lactam products and therefore should be exempted from the separation and control recommendations set forth in this guidance. We have reviewed relevant scientific and medical literature and determined that the relative risk of cross-reactivity associated with aztreonam, when compared to other beta-lactams, is a matter of scientific uncertainty. Accordingly, at this time, FDA does not recommend manufacturing controls that treat aztreonam differently from other beta-lactam products. As with any non-binding recommendations offered in guidance to industry, manufacturers can use an alternative approach if the alternative approach satisfies the requirements of the applicable statutes and regulations. Manufacturers who wish to discuss an alternative separation and control strategy for a non-penicillin beta-lactam such as aztreonam with FDA are invited to do so through the application submission and review process.

[17] Middleton's Allergy: Principles and Practice,7th ed. (electronic) (2009). Chapter 68: Drug Allergy.

Derivatives are unintended by-products that occur during the manufacturing process (i.e., an impurity or degradant). Like intermediates, beta-lactam derivatives could have sensitizing properties and may develop antigenic properties that can produce allergic reactions. Beta-lactam chemical manufacturing processes including, but not limited to, fermentation and synthesis, may create beta-lactam intermediates or derivatives with unknown health consequences. Although the health risk of sensitization and cross-reaction is difficult to predetermine for beta-lactam intermediates and derivatives and is not always well-defined, manufacturing controls intended to reduce the risk of cross-contamination should be considered for operations that produce beta-lactam intermediates or derivatives.

III. RECOMMENDATIONS

Because of the potential health risks associated with cross-reactivity (cross-sensitivity) of beta-lactams, manufacturers should assess and establish stringent controls (including appropriate facility design provisions assuring separation) to prevent cross-contamination. Just as FDA considers the separation of production facilities for penicillins to be current good manufacturing practice, FDA expects manufacturers to treat sensitizing non-penicillin beta-lactam-based products similarly. Specifically, FDA recommends that manufacturers establish appropriate separation and control systems designed to prevent two types of contamination: (1) the contamination of a non-penicillin beta-lactam by any other non-penicillin beta-lactam, and (2) the contamination of any other type of product by a non-penicillin beta-lactam. Accordingly, FDA recommends that the area in which any class of sensitizing beta-lactam is manufactured be separated from areas in which any other products are manufactured, and have an independent air handling system.

As with penicillin, the section of a facility dedicated to manufacturing a sensitizing non-penicillin beta-lactam should be isolated (i.e., completely and comprehensively separated) from areas in the facility in which other products are manufactured. This control applies to each of the five classes of sensitizing beta-lactams; the area in which any class of sensitizing beta-lactam is manufactured should be separated from areas in which any other products are manufactured, including any other class of sensitizing beta-lactam. Manufacturing that is restricted to a specific class of beta-lactam compound (e.g., the cephalosporin family of products) generally would not mandate separate facilities and air handling systems, and could permit production campaigning and cleaning as sufficient control.

Finally, as discussed above, beta-lactam intermediates and derivatives may induce allergic reactions and therefore pose risks of cross-contamination. Accordingly, firms that manufacture beta-lactam intermediates or receive them for further processing, as well as firms whose manufacturing processes result in beta-lactam derivatives, should evaluate their manufacturing operations for the possibility of cross-contamination and implement appropriate controls to reduce or mitigate the potential for cross-contamination. As with penicillin and non-penicillin beta-lactam drugs, such controls could include, but are not limited to, isolation and separation of intermediate and derivative materials, facilities, equipment, and personnel.

Clinical Pharmacology of Human Insulin

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Nowadays, human insulin is used daily by millions of diabetic patients. The biological effect of human insulin is comparable to that of porcine insulin. However, after subcutaneous injection, pharmacological and clinical studies showed pharmacokinetic and pharmacodynamic differences between human and animal insulins. Human insulin tends to have faster absorption and shorter duration of action compared with animal insulin. These differences are more pronounced and can be of clinical relevance with intermediate- and long-acting insulin preparations. Optimal metabolic control can be achieved with either human or highly purified animal insulin preparations, provided appropriate insulin replacement strategies are used.

The development of manufacturing techniques for human insulin has made it possible to treat IDDM patients with a hormone that has an amino acid sequence identical to endogenous insulin. After characterization of the biological activity of human insulin in vitro and in animal studies, a series of efficacy and safety trials with human insulin in humans was performed (1,2). In the first years, several studies compared the potency of human insulin and animal insulin preparations with regard to their pharmacological properties. Later, such studies were performed to compare human insulin preparations manufactured using different methods (3,4).

It is surprising how much of the literature on human insulin, including proceedings of commercially sponsored symposia as well as papers and reports published in books and supplements to well-known journals, was printed 10 years ago, all non-peer-reviewed, compared with the number of original papers published on human insulin that have passed a peer-review system. This is disturbing, because pharmacological differences between human insulin and animal insulin might have practical implications for the daily therapy of millions of patients.

In this paper, we will review the properties of human insulin preparations available today for clinical practice. Furthermore, we will describe the pharmacological differences between human insulin and highly purified (monocomponent) insulin preparations of animal origin. We attempt to give a balanced overview of the results of all studies, comparing various pharmacological aspects of human insulin and animal insulin. As a result, it was necessary to quote papers that were not peer-reviewed.

A major emphasis of this review is the presentation of the time-action profiles of the most widely used human insulin preparations. A mere discussion of differences between human insulin and animal insulins would be somewhat out of date, because, in many countries, human insulin is already used by most patients.

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IDDM, insulin-dependent diabetes mellitus; NIDDM, non-insulin-dependent diabetes mellitus.

STRUCTURE, PRODUCTION, PURITY, AND POTENCY OF HUMAN INSULIN

Structure

The structure of animal insulin has minor but potentially important differences from human insulin: Porcine insulin differs by one amino acid (alanine instead of threonine at the carboxy-terminal of the B-chain, i.e., position B30), and beef insulin differs by two additional alterations of the sequence of the A-chain (threonine and isoleucine on positions A8 and A10 are alanine and valine). Thus, there is nearly a complete homology between human insulin and porcine insulin in the amino acid sequence.

None of the differences between human insulin and animal insulins is thought to be at sites crucial to the binding or action of insulin. Therefore, it could be expected that the receptor binding and cellular interactions of human insulin would not differ significantly from those of pork or beef insulin (2). The amino acid on position B30 is near one of the parts of the insulin molecule thought to be involved in the self-association of two insulin molecules into dimers. Thus, the self-association tendency could be different between human insulin and porcine insulin (5).

The physicochemical properties of human, pork, and beef insulins differ somewhat because of their different amino acid sequence. Threonine adds

one extra hydroxyl group to the human insulin molecule. This increases its hydrophilic properties and decreases the lipophilic properties, as compared with that of porcine insulin. Thus, the solubility of human insulin in aqueous solutions is higher than that of porcine insulin.

Production

One way to mass produce human insulin was to exchange alanine in position B30 of porcine insulin with threonine, using an enzymatic-chemical method (semi-synthetic technique) (6). During the last decades, biosynthetic production of human insulin was made possible through advances in genetic engineering, especially in recombinant DNA technology (7,8). Methods used to produce human insulin have changed considerably during the last decade. At the end of the 1980s, the semi-synthetic production of human insulin was essentially stopped and replaced by biosynthetic production. In the beginning of the biosynthetic production of human insulin, the A and B chains were produced separately and had to be combined. At present, biosynthetic human insulin is produced with a perfect three-dimensional structure; that is, all foldings and disulfide bridges of the insulin precursor produced by the bacteria or yeast cells are identical to endogenous insulin. The correct spherical structure is important for the insulin-insulin receptor interaction, and hence for the biological action of insulin. Porcine insulin has a slightly different three-dimensional structure when compared with human insulin (9).

Purity

To ascertain a low immunogenicity of human insulin preparations, impurities had to be avoided. The semi-synthetic human insulin production could take advantage of the well-established production and purification methods for porcine insulin, which was used as the original substrate. Possible contaminations with proinsulinlike or glucagonlike substances, pancreatic polypeptide, somatostatin, and vasoactive intestinal peptides were avoided by using monocomponent porcine insulin. Contamination by enzymes or waste products, as a result of the enzymatic-chemical exchange of one amino acid during the secondary production step, also could be avoided (10). In contrast, the insulin production methods that use recombinant DNA technology have a higher propensity for contamination of the insulin product with various bacterial or yeast cell polypeptides. The first biosynthetic human insulin production using bacteria had more obstacles in achieving purity, attributable to the fact that the A- and B-chains had to be extracted separately, and the two chains had to be combined with an intact insulin molecule. Thus, proteins and other substances of bacterial origin, as well as waste products of the insulin recombination, had to be eliminated. Later, purification methods were developed to obtain insulin preparations free of any potentially harmful contamination by *Escherichia coli*-derived peptides (11–13). Antibodies to such peptides could not be detected in 10 patients treated with human insulin for 6 mo (12). Some of the problems of the recombinant DNA technique were circumvented when it became possible to produce homologous proinsulin by *E. coli* (13). Thus, only the C-peptide-like sequence had to be cleaved to achieve human insulin. Human insulin produced biosynthetically from yeast cells with a different insulin precursor (not identical to human proinsulin) was even easier to clear from impurities because the precursor is secreted into the medium, and after cleavage of C-peptide, the intact molecule can be obtained (14,15). Because of the sophisticated purification techniques, it can be assumed that advanced human insulin preparations are pure and free of any significant contamination (16). In regular insulin preparations, insulin molecules self-associate to dimers and large oligomers. In addition, a small amount of covalently aggregated dimers and other insulin-transformation products is formed in commercial insulin. These transformation products prevail in the blood of insulin-treated diabetic patients because they have a slower metabolic clearance relative to insulin monomers (17–19). Human insulin was reported as more susceptible to the production of such products than beef insulin (19). These transformation products are claimed to be highly immunogenic. In addition, degradation of the injected insulin occurs in the subcutaneous depot, resulting in degradation products that also might have immunogenic activity (20).

It has to be emphasized that even with a hormone identical to the human insulin, there are still major differences compared with the naturally occurring hormone. The route of insulin administration is different, and the insulin preparations contain additives like antiseptics, stabilizers, and, with NPH-insulins (Isophane), xenomorphous proteins like protamine.

Potency

In the first study that reports the effects of short-acting human insulin produced by recombinant DNA technology in healthy men, the plasma glucose decrement after subcutaneous injection of human insulin was similar to that of highly purified porcine insulin (21,22). The potency of semi-synthetic human insulin or biosynthetic human insulin also was reported to be similar to that of animal insulin after intravenous insulin infusion at various doses or after subcutaneous injection in diabetic patients (2).

In the rabbit hypoglycemia bioassay, used to estimate insulin strength, porcine and human insulin also had a similar potency (11,23). However, in this model, human insulin showed a more rapid onset and a shorter duration of action, along with a lower potency, compared with bovine insulin (23). Most investigators came to the conclusion that there is no difference in the biological potency of human insulin and animal

insulins (1,2). However, this seems to apply only for the intravenous route and not for subcutaneously injected insulin. Differences in the absorption properties of human insulin and animal insulins, and the results of clinical studies (see below), led to the suggestion that the daily dose of insulin should be reduced by 10 to 25% when switching from animal insulin to human insulin (24). Such a dosage reduction may be needed especially in those patients previously treated with bovine insulin or with mixed animal insulins.

The *British Pharmacopoeia; Codex medicamentarius* and the *Pharmacopeia of the United States* permit deviations from the declared concentration of commercial insulins of ± 5 and ± 10%, respectively. Thus, it cannot be excluded that some of the differences in the reported potencies could be attributable to variations in insulin dose.

HUMAN INSULIN PREPARATIONS

Shortly after its introduction human insulin became available in short-, intermediate-, and long-acting formulations. In principle, these formulations are identical to their porcine or bovine counterparts with respect to the content of auxiliary substances. Because most brands with animal insulins are still available, clinicians and patients are faced with a plethora of different insulin preparations. Even professionals find it difficult to keep track of the insulin preparations available in different countries, because various names may be used for the same insulin with different compositions and concentrations. Some of the insulin preparations marketed are of questionable usefulness, for example, mixtures of short- and intermediate-acting human insulin in 10% steps ranging from 10%:90% to 50%:50%. However, this comment should not be misinterpreted as a suggestion to withdraw animal insulin preparations from the market altogether. Some manufacturers of insulin have tried to withdraw animal insulins from the market (and some have actually done so). This is understandable from a commercial point of view (standardization of production). However, because human insulin has no clear clinical benefit, animal insulins should stay available.

PHARMACOKINETIC AND PHARMACODYNAMIC PROPERTIES OF HUMAN INSULIN PREPARATIONS

Methods used to study the pharmacological properties of insulin preparations

In many studies investigating insulin absorption (pharmacokinetic studies) and/or insulin action (pharmacodynamic studies), inappropriate methods, different doses, and sites of administration have been used. This makes the comparison of the results difficult. In some studies, the diabetic patients investigated had been previously treated with animal insulins. As a result, these patients might have had insulin antibodies, which might have influenced the pharmacological properties of exogenous insulin preparations. In fact, the variable dissociation rates of insulin from circulating antibodies are likely to contribute to the high variability in the bioavailability of any insulin preparation.

In principle, the pharmacokinetic properties of insulin preparations could be studied using the direct method (i.e., measurement of serum insulin concentration) or an indirect method (i.e., injection of radiolabeled insulin and registration of the disappearance from the subcutaneous tissue). The problems and pitfalls that limit the use of the indirect method have been discussed in detail elsewhere (25).

Pharmacodynamic properties can be studied by following the blood glucose-lowering effect of a subcutaneous insulin injection over time. This test of insulin activity results in a stimulation of the counterregulatory response caused by hypoglycemia. The effect of the counterregulatory hormones tends to increase blood glucose, thereby leading to an underestimation of the response to the injected insulin. Thus, relevant pharmacodynamic differences can only be detected if doses or activities of the insulins investigated are substantially different. To avoid hypoglycemic episodes, blood glucose can be kept constant by an intravenous glucose infusion targeted to maintain blood glucose at normoglycemic values (euglycemic glucose clamps). Because the glucose requirement is proportional to the biological activity of insulin, it provides a direct measure of potency, at least with regard to glucose metabolism. Endogenous insulin secretion in healthy volunteer subjects can be suppressed by a low-dose intravenous insulin infusion. In our opinion, the euglycemic glucose clamp technique is the best method currently available to study pharmacodynamic properties of various insulin preparations. Moreover, pharmacokinetic properties can be studied simultaneously (2,26,27)

A recent survey of the literature showed that time-action profiles of many insulin preparations are not well-defined because different methods, patient-selection criteria, insulin doses, methods of insulin administration, insulin concentrations, and injection sites are used (28). This survey also highlights the large differences in the reported pharmacological properties of the same insulin preparations caused by the method used. For example, in the 22 studies analyzed, the onset of action after subcutaneous injection of human regular insulin ranged from 0.08–0.5 h, with peak action from 0.75–4 h, and duration of action from 4–12 h.

The direct comparison of pharmacokinetic and pharmacodynamic results obtained with the same group of volunteer subjects showed a considerable difference between the insulin concentration-time profile and the glucose infusion rate-time profile. Thus, an increase in serum insulin concentration does not result in an instantaneous increase in glucose metabolism (Fig. 1).

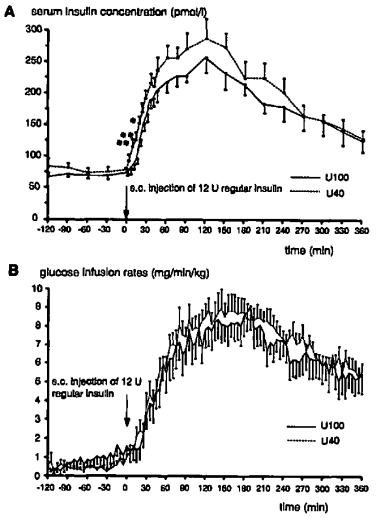

Figure 1—A: *Serum insulin concentrations during an 8-h euglycemic glucose clamp in 8 normal subjects. A subcutaneous injection of 12 U of regular human insulin was given at time 0, with a U40 formulation (mean + SE) on one day and a U100 formulation (mean − SE) on another day. Asterisks mark significantly different serum insulin concentrations.* *, $P < 0.05$; **, $P < 0.02$; *paired Student's t test) (55);* B: *Glucose infusion rates on the U40- (mean + SE) and on the U100- (mean − SE) insulin injection day.*

This phenomenon becomes more clear in view of more recent studies about the importance of the endothelial barrier on insulin transport across the capillary wall (29,30). A long series of events is interposed between the appearance of insulin in blood and changes in glucose metabolism. Thus, the time-dependent characteristics used to describe the pharmacological characteristics of insulin preparations have to be different for its kinetic and dynamic properties.

Short-acting preparations

Pharmacological studies. Pharmacokinetic properties of short-acting human insulin individually assessed by decline of radioactivity of subcutaneously injected ^{125}I-labeled insulin showed a similar insulin absorption process of human and porcine insulin (31,32). However, in another study with the same method, human insulin was more rapidly absorbed than porcine insulin (33). Administration of human or porcine insulin by intravenous bolus in healthy volunteer subjects and IDDM patients showed that both insulins have similar biological activities (34). In studies with intravenous infusion of human or porcine insulin, plasma insulin concentrations and metabolic effects were comparable and strictly dose dependent (35–37). Combining intravenous insulin infusion with the euglycemic clamp technique showed that the pharmacodynamic properties of semi-synthetic human insulin and porcine insulin were indistinguishable in normal individuals as well as in diabetic patients (26,38–40).

The appearance of human insulin in plasma after subcutaneous injection was more rapid than after a similar dose of porcine insulin (32,33,41–43). However, no dose-dependent changes in pharmacokinetic parameters could be demonstrated after a subcutaneous insulin injection measuring blood glucose decline (21,44).

Measurement of the time-action profile of short-acting human insulin after its subcutaneous injection by the glucose clamp technique showed a more rapid onset of action and an earlier peak action than after injection of porcine insulin in healthy volunteer subjects as well as in IDDM patients (42).

In summary, in 11 of 16 studies analyzed, the authors concluded that human insulin was absorbed slightly faster from the subcutaneous injection site, independent of its semi-synthetic or biosynthetic origin (3,22,32,33,41–43,45–48). No difference in insulin absorption kinetics was seen in five studies (31,44,49–51). The mechanism of the faster absorption of human insulin in comparison to pork-regular insulin might be explained by the greater hydrophilicity of the human insulin molecule (9). X-ray studies of the tertiary structures of human and porcine insulin show differences only at the B30 region, where changes in the water attraction are located. Another explanation for the faster absorption of human insulin was the influence that the amino acid in position B30 has on the strength by which the dimers are held together within the hexamer (5). The changed solvent structure in the B28-B30 region and alterations in the intermolecular contacts have a weakening effect on the hexamer stability, resulting in a greater tendency to dissociate with decreasing concentration of insulin (5,9).

Clinical studies. In double-blind crossover studies in type I diabetic patients, treated either conventionally or with subcutaneous insulin infusion, blood glucose control, insulin requirement, and number of hypoglycemic episodes were not substantially different between human insulin and porcine insulin (46,52,53). However, in one double-blind study in 21 diabetic children who were in poor metabolic control, significantly higher HbA_1 values were reported during the treatment period with human insulin, compared with that with porcine insulin (15.7 ± 2.3 vs. 14.2 ± 2.3%; $P < 0.01$) (54).

Time-action profile and influence of insulin concentrations. Studies of short-acting human insulin in different concentrations (U40 vs. U100; Actrapid HM, Novo/Nordisk, Bagsvaerd, Denmark) found the onset of action occurred within 15–30 min, and peak action was observed 150–180 min after subcutaneous injection of 12 U (Fig. 1*B*) (55). No significant differences were observed in the glucose infusion rates needed to keep blood glucose constant after injection of insulin, with either U40 or U100 concentrations. However, serum insulin concentrations showed small but significant differences shortly after injection (Fig. 1*A*): Serum insulin concentrations were significantly higher 10–20 min after injection of the U40 formulation in comparison with the U100 formulation.

However, glucose infusion rates during this time were not significantly different. In this experiment, 6 h after injection of a moderate dose of "short-acting" insulin, still more than 50% of maximal glucose infusion rates were needed to keep blood glucose concentration constant. Therefore, compared with the endogenous insulin response to a meal, onset of action and peak action occurred considerably later. In addition, duration of action was longer, requiring consumption of a snack 2–3 h after insulin injection to prevent hypoglycemia. Moreover, it has to be emphasized that considerable deviations from the described time-action profile can occur depending on the subject's insulin sensitivity (i.e., in diabetic patients, depending on the degree of metabolic control or depending on the insulin doses used).

Clinical implications. Rapid initial delivery of insulin plays a crucial role in the control of meal-related glycemic excursions. Thus, the more rapid onset of action of human insulin might have an advantage over short-acting animal insulins. It was shown in two studies that subcutaneously injected human insulin was superior to porcine insulin in the control of meal-related glycemic excursions in IDDM patients (48,56). In another study with IDDM patients, no differences in postprandial glycemic excursions could be demonstrated (51). The preprandial glucose levels were elevated in this study (>13.5 mM), and, therefore, prandial glycemic increases were small, ranging from 0–4.4 mM. In this context, the slightly faster absorption of human insulin did not result in clinically important differences.

Obviously, the pharmacodynamic characteristics of human short-acting human insulin are far from ideal. In other words, the time-action profile of these preparations differs considerably from the prandial insulin requirements. Development of short-acting insulin analogues with a significantly faster onset of action might help to improve prandial control (5,57,58).

Intermediate-acting preparations (NPH and lente)

Pharmacological studies. Intermediate-acting human insulin preparations injected subcutaneously showed variable results in pharmacological studies when compared with their animal insulin counterparts. No differences in the decline of blood glucose concentrations after injection of biosynthetic human insulin or porcine insulin could be observed in the first pharmacodynamic study with NPH insulins (44). However, NPH insulins with human insulin showed a more rapid onset and shorter duration of action than corresponding animal insulins in a series of later pharmacological studies (4,27,41,59,60). In contrast to these results, the disappearance rates of ^{125}I-labeled human or porcine NPH insulin preparations were not significantly different when given to diabetic patients (32,61).

The differences in the pharmacological properties were attributed to the more hydrophilic properties of human insulin and to differences in the interaction of human insulin and animal insulin with protamine (41). Also, formulation differences, such as the nature and quantity of the protamine in the formulas used were implied.

Direct comparison of semi-synthetic and biosynthetic human NPH insulin after injection in healthy volunteer subjects showed a similar maximal hypoglycemic effect within 3–5 h after administration (4). Thereafter, with semi-synthetic NPH insulin, plasma glucose remained significantly lower than with biosynthetic NPH insulin. These results suggested that the biosynthetic human NPH insulin had a less potent glucose-lowering effect and a relatively shorter duration of action compared with semi-synthetic NPH insulin.

Comparison of human protamine-sodium insulin with human NPH insulin in normal subjects during a euglycemic clamp showed a slightly earlier peak in plasma insulin concentrations with the protamine sodium insulin and a longer duration of action with the NPH insulin (62). In a disappearance study in diabetic patients, human NPH insulin showed a decline of radioactivity similar to the Monotard (Monotard MC, Novo/Nordisk) (61). A semi-synthetic human insulin preparation (Monotard HM, Novo/Nordisk) showed similar disappearance rates compared with a porcine lente preparation in 11 IDDM patients (31). In accordance with this, no significant differences were found in serum insulin concentrations between human and porcine Monotard in short-term studies with healthy volunteer subjects (41,46).

Clinical studies. In the first clinical trial with diabetic patients, significantly higher blood glucose levels were observed with human insulin before the morning and evening injection compared with the levels when treated with animal insulin. This was attributed to a more rapid absorption of the human NPH insulin (63). In a 15-mo double-blind crossover study, Home et al. (64) found a small but significant difference in the metabolic control between human and porcine insulin in 96 insulin-treated diabetic patients. The fasting blood glucose concentration and HbA_1 were significantly higher with human insulin than with porcine insulin (11.1 vs. 9.3 mM and 11.7 vs. 11.1%, respectively). A short-term double-blind crossover study in 8 IDDM patients, comparing human with porcine lente insulin, resulted in no differences in blood glucose control (31).

Thus, the use of human NPH insulin instead of animal NPH insulin could be a disadvantage. This finding was tested by another 6-mo double-blind, crossover study in 22 IDDM patients, which resulted in similar 24-h blood glucose profiles, fasting blood glucose levels, HbA_{1c} levels, number of hypoglycemic events, and insulin-dose requirements when using semi-synthetic human NPH insulin and porcine NPH insulin (65). The authors discuss the possibility that it might be of clinical importance whether semi-synthetic or

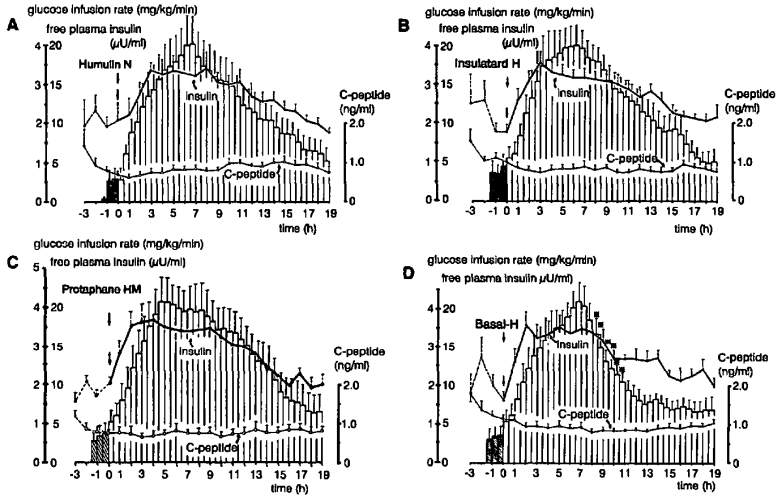

Figure 2—*Glucose infusion rates (▭), plasma free insulin (- - -), and C-peptide (———) concentrations after subcutaneous injection of 12 U of 4 different human NPH insulin formulations (biosynthetic origin: Humulin N [A], Lilly, Indianapolis, IN; semi-synthetic origin: Insulatard H [B] and protaphane HM [C], Novo/Nordisk; Basal H-Insulin [D], Hoechst AG, Frankfurt/Main, Germany; all U40) at time 0 during 19-h euglycemic glucose clamps in 6 normal subjects. (▨), Basal glucose infusion rate, expressed as means + SD. *, Significantly different glucose infusion rates of Basal-H human insulin as compared with the other NPH insulins (P < 0.05; ANOVA and Student's t test [67]).*

biosynthetic human NPH insulin preparations are used.

Time-action profile. Human NPH insulins were absorbed at a faster rate than human zinc insulins (lente insulin) in an euglycemic clamp study over 8 h with healthy volunteer subjects. The result was an increased metabolic effect within the first 4 h after injection (66). Thus, early after injection, the metabolic effects of human NPH and human zinc insulin preparations are different from each other.

The time-action profiles of four widely used human NPH insulin preparations were investigated in healthy subjects using the euglycemic clamp technique (Fig. 2) (67). The overall time-action profiles were interchangeable. The onset of action (defined as half-maximal action) of all NPH insulins tested was within 2.5–3 h, with peak action after 5–7 h, and duration of action (defined as >25% of maximal action) between 13–16 h. This study showed that there are no clinically important differences in the duration of action of human NPH insulins from different insulin manufacturers.

Clinical implications. The more rapid absorption and shorter duration of action of intermediate-acting human insulin preparations have clinical implications. Injecting human NPH insulin before dinner instead of at bedtime might impair metabolic control during the night. Higher fasting blood glucose concentrations in the morning, attributable to a waning of insulin action, have been observed in diabetic patients using human NPH insulins compared with porcine NPH insulins (54,63).

Use of NPH insulin and long-acting insulin preparations. The problem of elevated fasting blood glucose concentrations when human NPH insulin was used as the evening injection led to trials in which the evening injection was moved to bedtime, or long-acting human insulin preparations (Ultratard HM) were used. Fasting blood glucose concentrations were significantly lower when the evening dose of human NPH insulin was given at bedtime instead of at dinner (7.5 ± 1.1 vs. 10.0 ± 1.6 mM; $P < 0.02$) (68). Human ultralente insulin injected at bedtime, with its longer duration of action, resulted in lower fasting blood glucose concentrations compared with human NPH insulin (69,70).

In a crossover, randomized double-blind trial of 82 IDDM patients, the use of human lente (Monotard HM, Novo/Nordisk) or NPH insulin, given twice daily in combination with regular human insulin, resulted in comparable metabolic control (71). With both regimens, the major problem was elevated blood glucose concentrations before breakfast (NPH insulin versus lente insulin: 8.8 ± 0.5 vs. 9.0 ± 0.5 mM, NS). Thus, the use of human lente insulin instead of NPH insulin does not appear to result in better metabolic control during the night.

In the above study (and others quoted), the diabetic patients mixed the regular insulin with the lente insulin immediately before the injection. It is well known that this procedure results in modifications of the time-action profile of regular insulin (see below).

Long-acting human insulin preparations

Ultralente insulin preparations made with bovine or porcine insulin have a different pharmacokinetic profile from those made with human insulin (72,73). It is known that human zinc insulin crystals bind water more avidly than pork insulin crystals. It may be that this causes a faster dissociation of those zinc insulin complexes (2,9). Thus, a better solubility of the crystals of the human insulin ultralente preparations compared with

those of bovine insulin could possibly explain the faster absorption (74).

Pharmacological studies. The ultralente formulation with bovine insulin does not show a peak action. Its long duration of action lasts up to 32 h (72,73,75). In contrast, the human ultralente insulin preparations show a peak of action after 8.5 h (73). In one study, the duration of action of human ultralente was reported to be no shorter than that of bovine ultralente (73).

Hildebrandt et al. (74) reported that human ultralente had a substantially faster absorption than bovine ultralente, when comparing the disappearance rates of ^{125}I-labeled insulin preparations at different doses in IDDM patients. The faster absorption of human ultralente compared with bovine was confirmed in healthy volunteer subjects by measuring blood glucose decline after injection (72).

A comparison between a human insulin zinc suspension (Humulin Zn, Lilly), which was entirely crystalline in its formulation (like ultralente), and the intermediate-acting porcine lente insulin zinc suspension (Monotard MC, Novo/Nordisk; 30% amorphous and 70% crystalline formulation) showed no differences in the duration of hypoglycemic action in a single-dose crossover study in 10 healthy men (76).

Clinical studies. Ultratard HM was studied in a double-blind crossover study in 18 insulin-treated IDDM and NIDDM patients and found to be as effective as bovine ultralente in controlling basal plasma glucose with once-daily morning injections (77). The authors concluded that Ultratard HM is suitable for meeting basal insulin requirements in diabetic patients. In this study, there was no indication that Ultratard HM has a faster absorption from subcutaneous tissue than bovine ultralente.

Time-action profile. The variable results of the pharmacological and clinical studies do not provide a definite answer to the clinically important question of whether the duration of action of human ultralente falls between that of intermediate-acting and long-acting insulin, or whether it is similar to that of long-acting insulin.

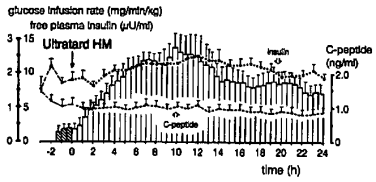

Figure 3—*Glucose infusion rates (□), plasma free insulin (– – –), and C-peptide (———) concentrations after subcutaneous injection of 12 U of a human lente insulin formulation (Ultratard HM) at time 0 during 24-h euglycemic glucose clamps in 7 normal subjects. (▨), Basal glucose infusion rates; means + SD (78).*

A study of the time-action profile of Ultratard HM using the euglycemic clamp technique (injection of 12 U in healthy subjects) revealed that peak action (reached after 10 h) was two-thirds that of a NPH insulin (Fig. 3, in comparison to Fig. 2c) (78). With both insulins, after 20 hours free plasma insulin concentrations had returned to basal values and glucose infusion rates indicated that the metabolic effect had nearly returned to basal values. Thus, the duration of action of human ultralente is not considerably longer than that of NPH insulin.

Clinical implications. Thus, once-daily injections of Ultratard HM in the given dose (12 U) will not provide sufficient basal insulinemia during the whole day. Twice-daily injections of human ultralente insulin are necessary to achieve basal insulin requirements.

Clinical trials showed that such an insulin regimen resulted in lower fasting blood glucose concentrations than twice-daily injections of human lente insulin (79,80). If only once-daily injection of human ultralente was used, injection in the morning resulted in a higher fasting blood glucose concentration than injection at bedtime (81,82). In a study of IDDM patients that used a multiple-injection regimen to compare human isophane insulin with human ultralente at bedtime, blood glucose at 0800 was significantly lower with isophane insulin than with the ultralente preparation (10.2 ± 1.2 vs. 14.3 ± 1.3 mM); although the dose of the bedtime ultralente insulin injection (0.35 U · kg^{-1} · day^{-1}) was significantly higher than the dose of isophane insulin (0.25 U · kg · day^{-1}; $P < 0.005$) (83).

Treatment with a once-daily injection of human ultralente over a period of 6 mo resulted in a significant improvement in metabolic control (a drop in HbA_{1c} from 13.2 to 10.6%) in 22 NIDDM patients with secondary sulfonylurea failure (84). However, there were frequent episodes of hypoglycemia. In the same study, 10 patients who were receiving once-daily injections of a bovine lente insulin preparation showed a similar improvement in metabolic control (from 13.1 to 11.2%), but the frequency of hypoglycemic episodes was significantly lower. In this study, the pharmacodynamic properties of human ultralente in comparison with the more flat action profile of bovine lente insulin are clearly unsuitable as a single-daily injection in NIDDM patients when aiming at improved metabolic control.

In contrast to the comment we made regarding the shorter duration of action of human NPH insulins, no clinical disadvantage could be seen with the shorter duration of action of human ultralente compared with its bovine counterpart. For example, we do not recommend use of bovine ultralente to our patients because of the prolonged duration of action, which potentially could cause an overlapping interaction between the metabolic activity of the insulin of the current injection and that of the previous day. This unpredictable accumulation of insulin action can result in prolonged and severe hypoglycemias. Moreover, the patient cannot adapt the dose to changing insulin needs, for example, when exercise is planned. Thus,

the shorter duration of action of human ultralente appears to be an advantage and not a disadvantage in clinical practice.

Miscibility. One problem of Ultratard (and other human lente insulin preparations) is that it cannot be premixed with short-acting insulins in one syringe without a considerable change in the time-action profile (i.e., a retardation of the onset of action of the short-acting insulin). This effect is pronounced even when the mixed human lente insulin preparations are injected immediately after being drawn into the syringe (25,85–88). This delay is caused by a binding of the added regular insulin to zinc, present in excess in the ultralente (and lente) insulins, which results in an amorphous precipitation of zinc insulin. Mixing of human regular and NPH insulin does not result in blunting of the action of the soluble component, regardless of whether it is readily mixed or premixed (3,89).

Another problem with ultralente insulin preparations is the high variability of its insulin bioavailability after injection, a phenomenon well known to the clinician. However, data showing this variability are only available for bovine ultralente (75,90), and, to our knowledge, no formal investigations of this aspect have been published for Ultratard.

EFFECT OF HUMAN INSULIN ON INTERMEDIARY METABOLITES AND LIPID METABOLISM

In vitro studies with insulin receptors from human lymphocytes, as well as measurements of lipid metabolism in rat adipocytes and hepatocytes, showed that the biological actions of biosynthetic human insulin and porcine insulin were identical (91,92). Injection of 0.075 U/kg of either human insulin or porcine insulin by intravenous bolus were reported to result in differences in intermediate metabolites and counterregulatory hormones (93). However, no statistical analysis was given and the reported differences appear to be small. Effects on intermediary metabolite concentrations (blood lactate, pyruvate, alanine, glycerol, and 3-hydroxybutyrate) were similar after subcutaneous injection of human insulin, porcine, and bovine insulin (49,50), or during euglycemic clamp studies with intravenous infusion of human insulin or porcine insulin (26,38, 39,94).

Although, the initial studies showed differences in hepatic action between human insulin and porcine insulin (21), this was not confirmed in later turnover studies. Suppression of hepatic glucose production and stimulation of peripheral glucose utilization were basically identical with human insulin and porcine regular insulin (94)

CONCLUSIONS

Human insulin preparations of both biosynthetic and semi-synthetic origin have similar, but not identical, pharmacological properties when compared with purified porcine insulin. Pharmacodynamic differences between human insulin and animal insulin preparations in clinical pharmacology are small with short-acting insulin preparations, considerable with NPH insulins, and substantial concerning long-acting insulin preparations. Development and introduction of human insulin has not revolutionized insulin treatment of IDDM patients. Obviously, the change from animal to human insulin per se does not improve metabolic control.

The choice of insulins with appropriate pharmacological characteristics, purity, and origin of the insulin preparations are important prerequisites for optimal therapy. A successful insulin regimen must consider insulin replacement strategies that are appropriate for the patient's lifestyle and individual treatment goals (95–97). And, most important, the patients must receive instruction on the time-action profiles of the insulins they use, and information on how to adapt the doses to achieve good metabolic control while avoiding hypoglycemic episodes.

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FDA Drug Shortages

Current and Resolved Drug Shortages and Discontinuations Reported to FDA

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A drug receives Resolved status when the Drug Shortages Staff (DSS) determines that the market is covered, based on information from all manufacturers. The market is considered covered when supply is available from at least one manufacturer to cover total market demand. However, some manufacturers may not have all presentations available. DSS monitors the supply of products with Resolved status. For the most current supply information, contact the manufacturers.

Generic Name or Active Ingredient	Status
Acetohydroxamic Acid (Lithostat) Tablets	***Currently in***

	Shortage
Ammonium Chloride Injection	***Currently in Shortage***
Anagrelide Hydrochloride Capsules	***Currently in Shortage***
Aprepitant (Emend) Capsules	***Resolved***
Atropine Sulfate Injection	***Currently in Shortage***
Azathioprine Tablet	***Resolved***
Bleomycin Sulfate for Injection	***Currently in Shortage***
Caffeine Anhydrous (125mg/mL); Sodium Benzoate (125mg/mL) Injection	***Currently in Shortage***
Calcium Chloride Injection, USP	***Currently in Shortage***
Calcium Gluconate Injection	***Currently in Shortage***
Cefazolin Injection	***Resolved***
Cefepime Injection	***Currently in Shortage***
Cefotaxime Sodium (Claforan) Injection	***Currently in Shortage***
Cefotetan Disodium Injection	***Currently in Shortage***
Chloramphenicol Sodium Succinate Injection	***Currently in Shortage***
Chloroquine Phosphate Tablets	***Resolved***
Desmopressin Acetate Injection	***Currently in Shortage***
Dexamethasone Sodium Phosphate Injection	***Currently in Shortage***
Dextrose 5% Injection Bags	***Currently in Shortage***
Dextrose Injection USP, 70%	***Currently in Shortage***
Disopyramide Phosphate (Norpace) Capsules	***Currently in Shortage***

Doxorubicin (Adriamycin) Injection	***Resolved***
Doxorubicin Lyophilized Powder for Injection	***Currently in Shortage***
Epinephrine Injection	***Currently in Shortage***
Eptifibatide (Integrilin) Injection	***Resolved***
Ethiodized Oil (Lipiodol) Injection	***Currently in Shortage***
Fentanyl Citrate (Sublimaze) Injection	***Currently in Shortage***
Fomepizole Injection	***Currently in Shortage***
Gemifloxacin Mesylate (Factive) Tablets	***Currently in Shortage***
Haloperidol Lactate Injection	***Resolved***
Imipenem and Cilastatin for Injection, USP	***Currently in Shortage***
Indigotindisulfonate Sodium (Indigo Carmine) Injection	***Currently in Shortage***
Ketorolac Tromethamine Injection	***Resolved***
L-Cysteine Hydrochloride Injection	***Currently in Shortage***
Leucovorin Calcium Lyophilized Powder for Injection	***Currently in Shortage***
Leuprolide Acetate Injection	***Currently in Shortage***
Levetiracetam (Keppra) Injection	***Resolved***
Lidocaine Hydrochloride (Xylocaine) Injection	***Currently in Shortage***
LifeCare PCA™ Sterile Empty Vial and Injector	***Currently in Shortage***
Liotrix (Thyrolar) Tablets	***Currently in Shortage***
Mecasermin [rDNA origin] (Increlex) Injection	***Currently in Shortage***
Memantine Hydrochloride (Namenda) XR	***Resolved***

Capsules	
Meropenem for Injection, USP	***Resolved***
Methyldopate Hydrochloride Injection	***Currently in Shortage***
Methylphenidate Hydrochloride ER Capsules/Tablets	***Resolved***
Methylprednisolone Sodium Succinate for Injection, USP	***Currently in Shortage***
Metoprolol Injection	***Resolved***
Morphine Sulfate Injection, USP, CII, (Preservative-Free)(For PCA Use Only)	***Currently in Shortage***
Multi-Vitamin Infusion (Adult and Pediatric)	***Currently in Shortage***
Mupirocin Calcium Nasal Ointment	***Currently in Shortage***
Nebivolol (BYSTOLIC) Tablets	***Resolved***
Nimodipine (Nymalize) Oral Solution	***Currently in Shortage***
Penicillin G Benzathine (Bicillin L-A) Injection	***Currently in Shortage***
Peritoneal Dialysis Solutions	***Currently in Shortage***
Phentolamine Mesylate Injection	***Resolved***
Piperacillin and Tazobactam (Zosyn) Injection	***Currently in Shortage***
Potassium Acetate Injection, USP	***Resolved***
Potassium Chloride Injection	***Currently in Shortage***
Reserpine Tablets	***Currently in Shortage***
Sacrosidase (Sucraid) Oral Solution	***Currently in Shortage***
Sodium Acetate Injection, USP	***Currently in Shortage***
Sodium Bicarbonate Injection, USP	***Currently in Shortage***

Sodium Chloride 0.9% Injection Bags	***Currently in Shortage***
Sodium Chloride 23.4% Injection	***Currently in Shortage***
Sufentanil Citrate (Sufenta) Injection	***Currently in Shortage***
Sumatriptan (Imitrex) Nasal Spray	***Currently in Shortage***
Technetium Tc99m Succimer Injection (DMSA)	***Currently in Shortage***
Theophylline Extended Release Tablets and Capsules	***Currently in Shortage***
Tigecycline (Tygacil) Injection	***Currently in Shortage***
Tiopronin (Thiola)	***Resolved***
Tobramycin Injection	***Currently in Shortage***
Tretinoin Capsules	***Currently in Shortage***
Triamcinolone Hexacetonide Injectable Suspension (Aristospan)	***Currently in Shortage***
Trimipramine Maleate (SURMONTIL) Capsules	***Currently in Shortage***
Vancomycin Hydrochloride for Injection, USP	***Currently in Shortage***

Note: If you need help accessing information in different file formats, see Instructions for Downloading Viewers and Players.

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Guidance for Industry

Changes to an Approved NDA or ANDA

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
April 2004
CMC

Revision 1

Guidance for Industry

Changes to an Approved NDA or ANDA

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
April 2004
CMC

Revision 1

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*Contains Nonbinding Recommendations**

Guidance for Industry[1]

Changes to an Approved NDA or ANDA

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public.** You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

** Insofar as this guidance adjusts reporting categories pursuant to section 506A of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.70, it does have binding effect. If you have any questions about the effect of any portion of this guidance, contact the Office of Pharmaceutical Science, Center for Drug Evaluation and Research (HFD-003), Food and Drug Association, 5600 Fishers Lane, Rockville, MD 20857.

I. INTRODUCTION AND BACKGROUND

This guidance provides recommendations to holders of new drug applications (NDAs) and abbreviated new drug applications (ANDAs) who intend to make postapproval changes in accordance with section 506A of the Federal Food, Drug, and Cosmetic Act (the Act) and § 314.70 (21 CFR 314.70). The guidance covers recommended reporting categories for postapproval changes for drugs other than specified biotechnology and specified synthetic biological products. It supersedes the guidance of the same title published November 1999. Recommendations are provided for postapproval changes in (1) components and composition, (2) manufacturing sites, (3) manufacturing process, (4) specifications, (5) container closure system, and (6) labeling, as well as (7) miscellaneous changes and (8) multiple related changes.

Recommendations on reporting categories for changes relating to specified biotechnology and specified synthetic biological products regulated by CDER are found in the guidance for industry

[1] This guidance has been prepared under the direction of the Chemistry, Manufacturing and Controls Coordinating Committee in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA).

Paperwork Reduction Act Public Burden Statement: This guidance contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (PRA) (44 U.S.C. 3501-3520). The collection(s) of information in this guidance were approved under OMB Control No. 0910-0538 (until August 31, 2005).

* Insofar as this guidance adjusts reporting categories pursuant to section 506A of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.70, it does have binding effect.

entitled *Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products* (July 1997).[2]

On November 21, 1997, the President signed the Food and Drug Administration Modernization Act of 1997 (the Modernization Act).[3] Section 116 of the Modernization Act amended the the Act by adding section 506A, which provides requirements for making and reporting manufacturing changes to an approved application and for distributing a drug product made with such changes. The FDA has revised its regulations on supplements and other changes to an approved application (21 CFR 314.70) to conform to section 506A of the Act.

This guidance does not provide recommendations on the specific information that should be developed by an applicant to assess the effect of the change on the identity, strength (e.g., assay, content uniformity), quality (e.g., physical, chemical, and biological properties), purity (e.g., impurities and degradation products), or potency (e.g., biological activity, bioavailability, bioequivalence) of a drug product as these factors may relate to the safety or effectiveness of the drug product. An applicant should consider all relevant CDER guidance documents for recommendations on the information that should be submitted to support a given change.[4]

CDER has published guidances, including the SUPAC (scale-up and postapproval changes) guidances, that provide recommendations on reporting categories. To the extent that the recommendations on ***reporting categories*** in this guidance are found to be inconsistent with guidances published before this guidance was finalized, the recommended reporting categories in such previously published guidances are superseded by this guidance. This guidance does not provide extensive recommendations on reporting categories for components and composition changes (see section V). Therefore, recommended reporting categories for components and composition changes provided in previously published guidances, such as the SUPAC guidances, still apply. Section 506A of the Act and § 314.70(c) provide for two types of changes-being-effected supplements (see section II), while previously there was only one type. It is important for applicants to use this guidance to determine which type of changes-being-effected supplement is recommended. CDER intends to update the previously published guidances to make them consistent with this guidance.

If guidance for either recommended reporting categories or information that should be submitted to support a particular change is not available, the appropriate CDER chemistry or microbiology review staff can be consulted for advice.

FDA's guidance documents, in general, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required. Insofar as this guidance adjusts reporting categories pursuant to section 506A of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.70, it does have binding effect. If you

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[2] FDA is currently revising the 1997 guidance and intends to issue it in draft for public comment.

[3] Public Law 105-115.

[4] A list of CDER guidances is available on the Internet at http://www.fda.gov/cder/guidance/index.htm.

* Insofar as this guidance adjusts reporting categories pursuant to section 506A of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.70, it does have binding effect.

have any questions about the effect of any portion of this guidance, contact the Office of Pharmaceutical Science, Center for Drug Evaluation and Research (HFD-003), Food and Drug Association, 5600 Fishers Lane, Rockville, MD 20857.

II. REPORTING CATEGORIES

Section 506A of the Act and § 314.70 provide for four reporting categories that are distinguished in the following paragraphs.

A ***major change*** is a change that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product. A major change requires the submission of a supplement and approval by FDA prior to distribution of the drug product made using the change. This type of supplement is called, and should be clearly labeled, a ***Prior Approval Supplement*** (§ 314.70(b)). An applicant may ask FDA to expedite its review of a prior approval supplement for public health reasons (e.g., drug shortage) or if a delay in making the change described in it would impose an extraordinary hardship on the applicant. This type of supplement is called, and should be clearly labeled, a *Prior Approval Supplement - Expedited Review Requested* (§ 314.70(b)(4)).[5] FDA is most likely to grant requests for expedited review based on extraordinary hardship for manufacturing changes made necessary by catastrophic events (e.g., fire) or by events that could not be reasonably foreseen and for which the applicant could not plan.

A ***moderate change*** is a change that has a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product. There are two types of moderate change. One type of moderate change requires the submission of a supplement to FDA at least 30 days before the distribution of the drug product made using the change. This type of supplement is called, and should be clearly labeled, a ***Supplement - Changes Being Effected in 30 Days*** (§ 314.70(c)(3)). The drug product made using a moderate change cannot be distributed if FDA informs the applicant within 30 days of receipt of the supplement that a prior approval supplement is required (§ 314.70(c)(5)(i)). For each change, the supplement must contain information determined by FDA to be appropriate and must include the information developed by the applicant in assessing the effects of the change (§ 314.70(a)(2) and (c)(4)). If FDA informs the applicant within 30 days of receipt of the supplement that information is missing, distribution must be delayed until the supplement has been amended to provide the missing information (§ 314.70(c)(5)(ii)).

FDA may identify certain moderate changes for which distribution can occur when FDA receives the supplement (§ 314.70(c)(6)). This type of supplement is called, and should be clearly labeled, a ***Supplement - Changes Being Effected***. If, after review, FDA disapproves a changes-being-effected-in-30-days supplement or changes-being-effected supplement, FDA may order the

[5] Internal Agency policies and procedures relating to processing requests for expedited review of supplements to approved ANDAs and NDAs are documented in CDER's Manual of Policies and Procedures (MAPP) at 5240.1 and 5310.3, respectively. MAPPs can be located on the Internet at lttp://www.fda.gov/cder/mapp.htm.

* Insofar as this guidance adjusts reporting categories pursuant to section 506A of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.70, it does have binding effect.

manufacturer to cease distribution of the drug products made using the disapproved change (§ 314.70(c)(7)).

A ***minor change*** is a change that has minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product. The applicant must describe minor changes in its next ***Annual Report*** (§ 314.70(d)).

Under § 314.70(e), an applicant can submit one or more protocols (i.e., comparability protocols) describing tests, studies, and acceptance criteria to be achieved to demonstrate the absence of an adverse effect from specified types of changes. A comparability protocol can be used to reduce the reporting category for specified changes. A proposed comparability protocol that was not approved as part of the original application must be submitted as a prior approval supplement (314.70(e)). On February 25, 2003, FDA issued a draft guidance on comparability protocols entitled *Comparability protocols - Chemistry, Manufacturing, and Controls Information*.

III. GENERAL REQUIREMENTS

Other than for editorial changes in previously submitted information (e.g., correction of spelling or typographical errors, reformatting of batch records), an applicant must notify FDA about each change in each condition established in an approved application beyond the variations already provided for in the application (§ 314.70(a)(1)).

A supplement or annual report must include a list of all changes contained in the supplement or annual report. On the list, FDA recommends that the applicant describe each change in enough detail to allow FDA to quickly determine whether the appropriate reporting category has been used. For supplements, this list must be provided in the cover letter (§ 314.70(a)(6)). In annual reports, the list should be included in the summary section (§ 314.81(b)(2)(i)). The applicant must describe each change fully in the supplement or annual report (§ 314.70(a)(1)).

An applicant making a change to an approved application under section 506A of the Act must also conform to other applicable laws and regulations, including current good manufacturing practice (CGMP) requirements of the Act (21 U.S.C. 351(a)(2)(B)) and applicable regulations in Title 21 of the *Code of Federal Regulations* (e.g., 21 CFR parts 210, 211, 314). For example, manufacturers must comply with relevant CGMP validation and recordkeeping requirements and ensure that relevant records are readily available for examination by authorized FDA personnel during an inspection.

A changes-being-effected supplement providing for labeling changes under § 314.70(c)(6)(iii) must include 12 copies of the final printed labeling (§ 314.70(c)(1)). In accordance with

* Insofar as this guidance adjusts reporting categories pursuant to section 506A of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.70, it does have binding effect.

§ 314.70(a)(4), an applicant also must promptly revise all promotional labeling and drug advertising to make it consistent with any labeling change implemented in accordance with § 314.70(b) or (c).

Except for supplements providing only for a change in labeling, an applicant must include in each supplement and amendment to a supplement a statement certifying that a field copy has been provided in accordance with 21 CFR 314.440(a)(4)[6] (§ 314.70(a)(5)).

IV. ASSESSING THE EFFECT OF MANUFACTURING CHANGES

A. Assessment of the Effects of the Change

The holder of an approved application under section 505 of the Act ***must assess the effects of the change before distributing a drug product made with a manufacturing change*** (§ 314.70(a)(2)).[7] For each change, the supplement or annual report must contain information determined by FDA to be appropriate and must include the information developed by the applicant in assessing the effects of the change (section 506A(b), (c)(1), (d)(2)(A), and (d)(3)(A) of the Act). The type of information that must be included in a supplemental application or an annual report is specified in § 314.70(b)(3), (c)(4), and (d)(3).

1. Conformance to Specifications

An assessment of the effects of a change on the identity, strength, quality, purity, and potency of the drug product should include a determination that the drug substance intermediates, drug substance, in-process materials, and/or drug product affected by the change conform to the approved specifications.[8] A *specification* is a quality standard (i.e., tests, analytical procedures, and acceptance criteria) provided in an approved application to confirm the quality of drug substances, drug products, intermediates, raw materials, reagents, components, in-process materials, container closure systems, and other materials used in the production of a drug substance or drug product. *Acceptance criteria* are numerical limits, ranges, or other criteria for the tests described (§ 314.3(b)). Conformance to a specification means that the

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[6] Mailing information for field copies is provided in 21 CFR 314.440(a)(4). FDA recommends that the *applicant's home FDA district office* referred to in the regulations be the district office where the applicant's headquarters is located.

[7] *Assess the effects of the change* means to evaluate the effects of a manufacturing change on the identity, strength, quality, purity, and potency of a drug product as these factors relate to the safety or effectiveness of the drug product. The terms *assess* or *assessment* as used in this guidance are not the same as validation. Certain validation information, such as for sterilization processes, is considered information that is needed to assess the effect of the change as specified in § 314.70(a)(2) and should be submitted in an NDA or ANDA. Unless otherwise specified by FDA, validation (e.g., process, equipment) data need not be submitted in the application, but should be retained at the facility and be available for review by FDA at the Agency's discretion under CGMPs.

[8] If a specification needs to be revised as a result of the change, this would be considered a multiple change (see sections VIII and XII).

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material, when tested according to the analytical procedures listed in the specification, will meet the listed acceptance criteria.

2. Additional Testing

In addition to confirming that the material affected by manufacturing changes continues to meet its specification, we recommend that the applicant perform additional testing, when appropriate, to assess whether the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product have been or will be affected. The assessment should include, as appropriate, evaluation of any changes in the chemical, physical, microbiological, biological, bioavailability, and/or stability profiles. This additional assessment could involve testing of the postchange drug product itself or, if appropriate, the material directly affected by the change. The type of additional testing that an applicant should perform would depend on the type of manufacturing change, the type of drug substance and/or drug product, and the effect of the change on the quality of the drug product. For example:

- Evaluation of changes in the impurity or degradant profile could first involve profiling using appropriate chromatographic techniques and then, depending on the observed changes in the impurity profile, toxicology tests to qualify a new impurity or degradant or to qualify an impurity that is above a previously qualified level.[9]

- Evaluation of the hardness or friability of a tablet after certain changes.

- Assessment of the effect of a change on bioequivalence when required under 21 CFR part 320 could include, for example, multipoint and/or multimedia dissolution profiling and/or an in vivo bioequivalence study.

- Evaluation of extractables from new packaging components or moisture permeability of a new container closure system.

An applicant should refer to all relevant CDER guidance documents for recommendations on the information that should be submitted to support a given change. If guidance for information that should be submitted to support a particular change is not available, applicants can consult the appropriate CDER chemistry or microbiology review staff for advice.

B. Equivalence

When testing is performed, the applicant should usually assess the extent to which the manufacturing change has affected the identity, strength, quality, purity, and potency of the

[9] Recommendations on identifying, qualifying, and reporting impurities can be found in relevant guidances (e.g., ICH Q3B *Impurities in New Drug Products* (November 1996)).

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drug product. Typically this is accomplished by comparing test results from pre- and postchange material and determining if the test results are equivalent. Simply stated: Is the drug product made after the change equivalent to the drug product made before the change? An exception to this general approach is that when bioequivalence is redocumented for certain ANDA postapproval changes, FDA recommends that the comparator be the reference listed drug. Equivalence comparisons frequently have a criterion for comparison with calculation of confidence intervals relative to a predetermined equivalence interval. For this, as well as for other reasons, *equivalent* does not necessarily mean *identical*. Equivalence may also relate to maintenance of a quality characteristic (e.g., stability) rather than a single performance of a test.

C. Adverse Effect

Some manufacturing changes have an adverse effect on the identity, strength, quality, purity, or potency of the drug product. In many cases, the applicant chooses not to implement these manufacturing changes, but sometimes the applicant wishes to do so. If an assessment indicates that a change has adversely affected the identity, strength, quality, purity, or potency of the drug product, FDA recommends that ***the change be submitted in a prior approval supplement regardless of the recommended reporting category for the change.*** For example, a process change recommended for a changes-being-effected-in-30-days supplement could cause the formation of a new degradant that requires qualification and/or identification.[10] The applicant's degradation qualification procedures may indicate that there are no safety concerns relating to the new degradant. Even so, we recommend that the applicant submit this change in a prior approval supplement with appropriate information to support the continued safety and effectiveness of the drug product. During the review of the prior approval supplement, the FDA will assess the impact of any adverse effect on the drug product as this change may relate to the safety or effectiveness of the drug product.

Applicants are encouraged to consult with the appropriate CDER chemistry or microbiology review staff if there are any questions on whether a change in a characteristic would be viewed by CDER as adversely affecting the identity, strength, quality, purity, or potency of the drug product.

V. COMPONENTS AND COMPOSITION

Changes in the qualitative or quantitative formulation, including inactive ingredients, as provided in the approved application, are considered major changes requiring a prior approval supplement, unless exempted by regulation or guidance (§ 314.70(b)(2)(i)). The deletion or reduction of an ingredient intended to affect only the color of the drug product may be reported in an annual report (§ 314.70(d)(2)(ii)). Guidance on changes in components and composition that may be submitted in a changes-being-effected supplement or annual report is not included in this document because

[10] Recommendations on identifying, qualifying, and reporting impurities can be found in relevant guidances.

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of the complexity of the recommendations, but may be covered in one or more guidance documents describing postapproval changes (e.g., SUPAC documents).

VI. MANUFACTURING SITES[11]

A. General Considerations

CDER must be notified when a manufacturer changes to a manufacturing site that is different from those specified in the approved application (314.70(a)). Sites can include those used by an applicant to (1) manufacture or process drug products,[12] in-process materials, drug substances, or drug substance intermediates, (2) package drug products, (3) label drug products, and (4) test components, drug product containers, closures, packaging materials, in-process materials, or drug products. Sites include those owned by the applicant or contract sites used by an applicant. Testing sites include those performing physical, chemical, biological, and microbiological testing to monitor, accept, or reject materials, as well as those performing stability testing. Sites used to label drug products are considered those that perform labeling of the drug product's primary or secondary packaging components. Sites performing operations that place identifying information on the dosage form itself (e.g., ink imprint on a filled capsule) are considered to be facilities that manufacture or process the drug product. FDA recommends that the supplement or annual report identify whether the proposed manufacturing site is an alternative to or replacement for the site or sites provided for in the approved application.

FDA recommends that a move to a different manufacturing site, when it is a type of site routinely subject to FDA inspection, be submitted as a prior approval supplement if the site does not have a ***satisfactory CGMP inspection***[13] for the ***type of operation***[14] being moved (see sections VI.B.1 and 2).

For labeling, secondary packaging, and testing site changes, the potential for adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product is considered to be independent of the type of drug product dosage form or specific type of operation being performed. Therefore, the recommended reporting category for any one of these manufacturing site changes will be the same for all types of drug products and operations. For manufacturing sites used to (1) manufacture or process drug products, in-process materials, drug substances, or drug substance intermediates or (2) perform primary packaging operations,

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[11] See Attachment A for a discussion of the definition of *same manufacturing site* and *different manufacturing site*.

[12] Manufacturing or processing drug product would also include the preparation (e.g., sterilization, depyrogenation, irradiation, washing) by the applicant or applicant's contractor of container closure systems or packaging components. Changes in the site used to fabricate packaging components (e.g., bottles) or manufacture packaging materials (e.g., resins) need not be reported to CDER if there are no other changes (e.g., dimensions, compositions, processing aids). If other changes occur, the reporting category should be based on the recommended reporting categories for these changes (i.e., the manufacturing site change does not need to be considered when determining the appropriate reporting category).

[13] See Glossary for a definition of *satisfactory CGMP inspection*.

[14] See Attachment B for a discussion of the term *type of operation*.

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the potential for adverse effect depends on factors such as the type of drug substance or drug product and operation being performed. Therefore, recommended reporting categories may differ depending on the type of drug product and operations.

Except for the situations described in sections VI.B.4, VI.C.1.b, and VI.D.5, construction activities at a manufacturing site or moving production operations within a building or between buildings at the same manufacturing site do not have to be reported to CDER.

We recommend that a move to a manufacturing site that involves other changes (e.g., process, equipment) be evaluated as a multiple related change (see section XII) to determine the appropriate reporting category.

B. Major Changes (Prior Approval Supplement)

The following are examples of changes considered to have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product.

1. A move to a different manufacturing site, except one used to manufacture or process a drug substance intermediate, when the new manufacturing site has never been inspected by FDA for the type of operation that is being moved or the move results in a restart at the new manufacturing site of a type of operation that has been discontinued for more than two years.

2. A move to a different manufacturing site, except one used to manufacture or process a drug substance intermediate, when the new manufacturing site does not have a satisfactory CGMP inspection for the type of operation being moved.

3. A move to a different manufacturing site for (1) the manufacture, processing, or primary packaging of drug products when the primary packaging components control the dose delivered to the patient or the formulation modifies the rate or extent of availability of the drug, or (2) the manufacture or processing of in-process materials with modified-release characteristics. Examples of these types of drug products include modified-release solid oral dosage forms,[15] transdermal systems, liposomal drug products, depot drug products, oral and nasal metered-dose inhalers (MDIs), dry powder inhalers (DPIs), and nasal spray pumps.

4. Transfer of the manufacture of an aseptically processed sterile drug substance or aseptically processed sterile drug product to (1) a newly constructed or refurbished aseptic processing facility or area or (2) an existing aseptic processing facility or area that does not manufacture similar (including container types and sizes) approved drug products. An example

[15] Certain operations relating to the manufacture, processing, or primary packaging of modified-release solid oral dosage form drug products need not be reported in a prior approval supplement (see sections VI.C.1.c and VI.D.6).

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would be transferring the manufacture of a lyophilized drug product to an existing aseptic process area where no approved lyophilized drug products are manufactured or where the approved lyophilized drug products being manufactured have different container types and/or sizes than the container of the drug product being transferred. See section VI.C.1.b for recommendations for other manufacturing site changes relating to aseptically processed sterile drug substance or aseptically processed sterile drug product.

5. Transfer of the manufacture of a finished drug product sterilized by terminal processes to a newly constructed facility at a different manufacturing site. Once this change has been approved, subsequent site changes to the facility for similar drug product types and processes may be submitted as a changes-being-effected-in-30-days supplement (see section VI.C.1.a).

C. Moderate Changes (Supplement - Changes Being Effected)

The following are examples of changes considered to have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product. If the new site does not have a satisfactory CGMP inspection for the type of operation being moved (see sections VI.B.1 and 2), then FDA recommends that the changes listed below (excluding changes relating to drug substance intermediate manufacturing sites) be submitted in a prior approval supplement.

1. Supplement - Changes Being Effected in 30 Days

a. A move to a different manufacturing site for the manufacture or processing of any drug product, in-process material, or drug substance that is not otherwise provided for in this guidance.

b. For aseptically processed sterile drug substance or aseptically processed sterile drug product, a move to an aseptic processing facility or area at the same or different manufacturing site except as provided for in section VI.B.4.

c. A move to a different manufacturing site for the primary packaging of (1) any drug product that is not otherwise listed as a major change and (2) modified-release solid oral dosage form drug products.

d. A move to a different manufacturing site for testing if (1) the test procedures approved in the application or procedures that have been implemented via an annual report are used, (2) all postapproval commitments made by the applicant relating to the test procedures have been fulfilled (e.g., providing methods validation

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samples), and (3) the new testing facility has the capability to perform the intended testing.

2. *Supplement - Changes Being Effected*

A move to a different manufacturing site for the manufacture or processing of the final intermediate.

D. Minor Changes (Annual Report)

The following are examples of changes considered to have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product. If the new site does not have a satisfactory CGMP inspection for the type of operation being moved, then FDA recommends that the changes listed below (excluding changes relating to drug substance intermediate manufacturing sites) be submitted in a prior approval supplement (see sections VI.B.1 and 2).

1. A move to a different manufacturing site for secondary packaging.

2. A move to a different manufacturing site for labeling.

3. A move to a different manufacturing site for the manufacture or processing of drug substance intermediates other than the final intermediate.

4. A change in the contract sterilization site for packaging components when the process is not materially different from that provided for in the approved application

5. A transfer of the manufacture of a finished product sterilized by terminal processes to a newly constructed building or existing building at the same manufacturing site.

6. A move to a different manufacturing site for the ink imprinting of solid oral dosage form drug products.

VII. MANUFACTURING PROCESS

A. General Considerations

The potential for adverse effects on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product depends on the type of manufacturing process and the changes being instituted for the drug substance or drug product. In some cases, there may be a substantial potential for adverse effect regardless of direct testing of the drug substance or drug product for conformance with the approved specification. When there is a substantial potential for adverse effects, a change must be submitted in a prior approval supplement (section 506A(c) of the Act).

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B. Major Changes (Prior Approval Supplement)

The following are examples of changes considered to have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product.

1. Changes that may affect the controlled (or modified) release, metering or other characteristics (e.g., particle size) of the dose delivered to the patient, including the addition or deletion of a code imprint by embossing, debossing, or engraving on a modified-release solid oral dosage form.

2. Changes that may affect drug product sterility assurance including, where appropriate, process changes for sterile drug substances and sterile packaging components. These include:

   - Changes in the sterilization method (e.g., gas, dry heat, irradiation). These include changes from sterile filtered or aseptic processing to terminal sterilization, or vice versa.
   - Addition, deletion, or substitution of sterilization steps or procedures for handling sterile materials in an aseptic processing operation.
   - Replacing sterilizers that operate by one set of principles with sterilizers that operate by another principle (e.g., substituting a gravity displacement steam process with a process using superheated water spray).
   - Addition to an aseptic processing line of new equipment made of different materials (e.g., stainless steel versus glass, changes between plastics) that will come in contact with sterilized bulk solution or sterile drug components, or deletion of equipment from an aseptic processing line.
   - Replacing a Class 100 aseptic fill area with a barrier system or isolator for aseptic filling. Once this change has been approved, subsequent process changes for similar product types in the same barrier system or isolator may be submitted as a changes-being-effected-in-30-days supplement.
   - Replacement or addition of lyophilization equipment of a different size that uses different operating parameters or lengthens the overall process time.
   - Changes from bioburden-based terminal sterilization to the use of an overkill process, and vice versa.
   - Changes to aseptic processing methods, including scale, that extend the total processing, including bulk storage time, by more than 50 percent beyond the validated limits in the approved application.
   - Changes in sterilizer load configurations that are outside the range of previously validated loads.

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- Changes in materials or pore size rating of filters used in aseptic processing.

3. The following changes for a natural product:[16]

   - Changes in the virus or adventitious agent removal or inactivation methods. This applies to any material where such procedures are necessary, including drug substance, drug product, reagents, and excipients.
   - For drug substance and drug product, changes in the source material (e.g., microorganism, plant) or cell line.
   - For drug substance and drug product, establishment of a new master cell bank or seed.

4. Any fundamental change in the manufacturing process or technology from that currently used by the applicant. For example:

   a. Drug product

      - Dry to wet granulation or vice versa.
      - Change from one type of drying process to another (e.g., oven tray, fluid bed, microwave).

   b. Drug substance

      - Filtration to centrifugation or vice versa.
      - Change in the route of synthesis of a drug substance.

5. The following changes for drug substance

   - Any process change made after the final intermediate processing step in drug substance manufacture.

   - Changes in the synthesis or manufacture of the drug substance that may affect its impurity profile and/or the physical, chemical, or biological properties.

6. Addition of an ink code imprint or change to or in the ink used for an existing imprint code for a solid oral dosage form drug product when the ink as changed is not currently used on ***CDER-approved drug products***.[17]

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[16] For the purposes of this guidance, *natural product* refers to materials (e.g., drug substance, excipients) that are derived from plants, animals, or microorganisms, and that are subject to approval under section 505 of the Act. The specific recommendations for natural products are not applicable to inorganic compounds (e.g., salts, minerals).

[17] See Attachment C for a discussion of *CDER-approved drug products.*

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7. Establishing a new procedure for reprocessing a batch of drug substance or drug product that fails to meet the approved specification.

C. Moderate Changes (Supplement - Changes Being Effected)

The following are examples of changes considered to have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product.

1. Supplement - Changes Being Effected in 30 Days

a. For drug products, any change in the process, process parameters, and/or equipment except as otherwise provided for in this guidance.

b. For drug substances, any change in process and/or process parameters except as otherwise provided for in this guidance.

c. For natural protein drug substances and natural protein drug products:

- Any change in the process, process parameters, and/or equipment except as otherwise provided for in this guidance (e.g., section VII.B.5, VII.D.7).
- An increase or decrease in production scale during finishing steps that involves different equipment.
- Replacement of equipment with equipment of different design that does not affect the process methodology or process operating parameters.

d. For sterile drug products, drug substances, and components, as appropriate:

- Changes in dry heat depyrogenation processes for glass container systems for drug substances and drug products that are produced by terminal sterilization processes or aseptic processing.
- Changes to filtration parameters for aseptic processing (including flow rate, pressure, time, or volume, but not filter materials or pore size rating) when additional validation studies for the new parameters should be performed.
- Filtration process changes that provide for a change from single to dual sterilizing filters in series, or for repeated filtration of a bulk.

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- Changes from one qualified sterilization chamber to another for in-process or terminal sterilization that result in changes to validated operating parameters (time, temperature, F_0, and others).
- Changes in scale of manufacturing for terminally sterilized drug products that increase the bulk solution storage time by more than 50 percent beyond the validated limits in the approved application when bioburden limits are unchanged.

e. For drug substances, redefinition of an intermediate, excluding the final intermediate, as a starting material.

2. *Supplement - Changes Being Effected*

a. A change in methods or controls that provides increased assurance that the drug substance or drug product will have the characteristics of identity, strength, quality, purity, or potency that it purports or is represented to possess.

b. For sterile drug products, elimination of in-process filtration performed as part of the manufacture of a terminally sterilized drug product.

D. Minor Changes (Annual Report)

The following are examples of changes considered to have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product.

1. For drug products, changes to equipment of the same design and operating principle and/or changes in scale except as otherwise provided for in this guidance (e.g., section VII.C.1.c, VII.D.7).

2. A minor change in an existing code imprint for a dosage form. For example, changing from a numeric to alphanumeric code.

3. Addition of an ink code imprint or a change in the ink used in an existing code imprint for a solid oral dosage form drug product when the ink is currently used on CDER-approved drug products.

4. Addition or deletion of a code imprint by embossing, debossing, or engraving on a solid dosage form drug product other than a modified-release dosage form.

5. A change in the order of addition of ingredients for solution dosage forms or solutions used in unit operations (e.g., granulation solutions).

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6. Changes in scale of manufacturing for terminally sterilized drug products that increase the bulk solution storage time by no more than 50 percent beyond the validated limits in the approved application when bioburden limits are unchanged.

7. For natural protein drug products and natural protein drug substances:

   - An increase or decrease in production scale during finishing steps that does not involve an equipment change.
   - Replacement of equipment with equipment of the same design, operating principle, and capacity with no change in production scale.

VIII. SPECIFICATIONS

A. General Considerations

All changes in specifications from those in the approved application must be submitted in a prior approval supplement unless otherwise exempted by regulation or guidance (§ 314.70(b)(2)(i)). *Specifications* (i.e., tests, analytical procedures, and acceptance criteria) are the quality standards provided in an approved application to confirm the quality of drug substances, drug products, intermediates, raw materials, reagents, components, in-process materials, container closure systems, and other materials used in the production of a drug substance or drug product. For the purpose of defining specifications, *acceptance criteria* are numerical limits, ranges, or other criteria for the tests described. Examples of a test, an analytical procedure, and an acceptance criterion are, respectively, an assay, a specific, fully described high pressure liquid chromatography (HPLC) procedure, and a range of 98.0–102.0 percent. The recommendations in this section also apply to specifications associated with sterility assurance that are included in NDA and ANDA submissions.[18]

A *regulatory* analytical procedure is the procedure in the approved application that is designated for use in evaluating a defined characteristic of the drug substance or drug product. Section 501(b) of the Act recognizes the analytical procedures in the *U.S. Pharmacopeia/National Formulary* (USP/NF) as the regulatory analytical procedures for compendial items. Tests and associated acceptance criteria and regulatory analytical procedures in addition to those specified in the USP/NF may be required for approving compendial items (section 505 of the Act).

The applicant may include in its application *alternatives* to the approved regulatory analytical procedures for testing the drug substance and drug product. However, for purposes of determining compliance with the Act, regulatory analytical procedures are used.

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[18] See FDA guidance for industry on the *Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products* (November 1994).

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In sections B through D below, the use of the term *analytical procedure* without a qualifier such as *regulatory* or *alternative* refers to an analytical procedure used to test materials other than the drug substance or drug product.

B. Major Changes (Prior Approval Supplement)

The following are examples of changes in specifications considered to have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product.

1. Relaxing an acceptance criterion except as otherwise provided for in this guidance (e.g., section VIII.C.1.b, VIII.C.1.e).

2. Deleting any part of a specification except as otherwise provided for in this guidance (e.g., section VIII.D.2).

3. Establishing a new regulatory analytical procedure including designation of an alternative analytical procedure as a regulatory procedure.

4. A change in a regulatory analytical procedure that does not provide the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the regulatory analytical procedure described in the approved application.

5. A change in an analytical procedure used for testing components, packaging components, the final intermediate, in-process materials after the final intermediate, or starting materials introduced after the final intermediate that does not provide the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application except as otherwise noted. For example, a change from an HPLC procedure that distinguishes impurities to (1) an HPLC procedure that does not, (2) another type of analytical procedure (e.g., titrimetric) that does not, or (3) an HPLC procedure that distinguishes impurities but the limit of detection and/or limit of quantitation is higher.

6. Relating to testing of raw materials for viruses or adventitious agents:[19] (1) relaxing an acceptance criterion, (2) deleting a test, or (3) a change in the analytical procedure that does not provide the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application.

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[19] In this context, testing for adventitious agents is not considered to include tests that are found in an official compendium (e.g., USP <61>).

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C. Moderate Changes (Supplement - Changes Being Effected)

The following are examples of changes in specifications considered to have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product.

1. Supplement - Changes Being Effected in 30 Days

a. Any change in a regulatory analytical procedure other than those identified as major changes or editorial changes.

b. Relaxing an acceptance criterion or deleting a test for raw materials used in drug substance manufacturing, in-process materials prior to the final intermediate, starting materials introduced prior to the final drug substance intermediate, or drug substance intermediates (excluding final intermediate) except as provided for in section VIII.B.6.

c. A change in an analytical procedure used for testing raw materials used in drug substance manufacturing, in-process materials prior to the intermediate, starting materials introduced prior to the final drug substance intermediate, or drug substance intermediates (excluding final intermediate) that does not provide the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application except as provided for in section VIII.B.6.

d. Relaxing an in-process acceptance criterion associated with microbiological monitoring of the production environment, materials, and components that are included in NDA and ANDA submissions. For example, increasing the microbiological alert or action limits for critical processing environments in an aseptic fill facility or increasing the acceptance limit for bioburden in bulk solution intended for filtration and aseptic filling.

e. Relaxing an acceptance criterion or deleting a test to comply with an official compendium that is consistent with FDA statutory and regulatory requirements (§ 314.70(c)(2)(iii)).

2. Supplement - Changes Being Effected

a. An addition to a specification that provides increased assurance that the drug substance or drug product will have the characteristics of identity, strength, quality, purity, or potency that it purports or is represented to possess. For example, adding a new test and associated analytical procedure and acceptance criterion.

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b. A change in an analytical procedure used for testing components, packaging components, the final intermediate, in-process materials after the final intermediate, or starting materials introduced after the final intermediate that provides the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application.

D. Minor Changes (Annual Report)

The following are examples of changes in specifications considered to have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product.

1. Any change in a specification made to comply with an official compendium, except the changes described in section VIII.C.1.e, that is consistent with FDA statutory and regulatory requirements (§ 314.70(d)(2)(i)).

2. For drug substance and drug product, the addition or revision of an alternative analytical procedure that provides the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application or deletion of an alternative analytical procedure.

3. Tightening of acceptance criteria.

4. A change in an analytical procedure used for testing raw materials used in drug substance synthesis, starting materials introduced prior to the final drug substance intermediate, in-process materials prior to the final intermediate, or drug substance intermediates (excluding final intermediate) that provides the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application.

IX. CONTAINER CLOSURE SYSTEM

A. General Considerations

The potential for adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product when making a change to or in the container closure system is generally dependent on the route of administration of the drug product, performance of the container closure system, and the likelihood of interaction between the packaging component and the dosage form. In some cases there may be a substantial potential for adverse effect, regardless of direct drug product testing for conformance with the approved specification.

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A change to or in a packaging component will often result in a new or revised specification for the packaging component. This situation does not have to be considered a multiple related change. Only the reporting category for the packaging change needs to be considered.

B. Major Changes (Prior Approval Supplement)

The following are examples of changes considered to have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product.

1. For liquid (e.g., solution, suspension, elixir) and semisolid (e.g., creams, ointments) dosage forms, a change to or in polymeric materials (e.g., plastic, rubber) of primary packaging components, when the composition of the component as changed has never been used in a CDER-approved drug product of the same dosage form and same route of administration. For example, a polymeric material that has been used in a CDER-approved topical ointment would not be considered CDER-approved for an ophthalmic ointment.

2. For liquid (e.g., solution, suspension, elixir) and semisolid (e.g., creams, ointments) dosage forms in permeable or semipermeable container closure systems, a change from an ink and/or adhesive used on the permeable or semipermeable packaging component to an ink or adhesive that has never been used in a CDER-approved drug product of the same dosage form and same route of administration ***and*** with the same type of permeable or semipermeable packaging component (e.g., low density polyethylene, polyvinyl chloride).

3. A change in the primary packaging components for any drug product when the primary packaging components control[20] the dose delivered to the patient (e.g., the valve or actuator of a metered-dose inhaler).

4. For sterile drug products, any change that may affect drug product sterility assurance, such as:[21]

    - A change from a glass ampule to a glass vial with an elastomeric closure.

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[20] A container closure system that is considered to control the dose delivered to the patient is a container closure system where the system itself, rather than a person, regulates the amount of drug product ultimately delivered to a patient. A container closure system where a person controls the amount of drug product administered or that allows verification that the appropriate amount has been administered (e.g., number of tablets, milliliters of liquid) is not considered a container closure system that controls the dose delivered to the patient.

[21] Some of these identified changes, depending on the circumstances, may have to be submitted as original NDAs or ANDAs instead of as supplements. Applicants can consult the appropriate CDER chemistry division/office if there are questions.

* Insofar as this guidance adjusts reporting categories pursuant to section 506A of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.70, it does have binding effect.

- A change to a flexible container system (bag) from another container system.
- A change to a prefilled syringe dosage form from another container system.
- A change from a single unit dose container to a multiple dose container system.
- Changes that add or delete silicone treatments to container closure systems (such as elastomeric closures or syringe barrels).
- Changes in the size and/or shape of a container for a sterile drug product.

5. Deletion of a secondary packaging component intended to provide additional protection to the drug product (e.g., carton to protect from light, overwrap to limit transmission of moisture or gases) or a change in the composition of, or the addition of, a secondary packaging component that may affect the impurity profile of the drug product.

6. A change to a new container closure system if the new container closure system does not provide the same or better protective properties than the approved container closure system.

C. Moderate Changes (Supplement - Changes Being Effected)

The following are examples of changes considered to have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product.

1. Supplement - Changes Being Effected in 30 Days

a. A change to or in a container closure system, except as otherwise provided for in this guidance, that does not affect the quality of the drug product.

b. Changes in the size or shape of a container for a sterile drug substance.

c. A change in the number of units (e.g., tablets, capsules) or labeled amount (e.g., grams, milliliters) of a nonsterile drug product in a unit-of-use container.[22]

2. Supplement - Changes Being Effected

[22] A unit-of-use container is one that contains a specific quantity of a drug product and is intended to be dispensed to the patient without further modification except for the addition of appropriate labeling.

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a. A change in the size and/or shape of a container for a nonsterile drug product, except for solid dosage forms (see section IX.D.2), without a change from one container closure system to another (§ 314.70(c)(6)(ii)).

b. A change in the labeled amount (e.g., grams, milliliters) of drug product for a nonsterile drug product in a multiple-unit container,[23] except for solid dosage forms (see section IX.D.3) .

c. A change in or addition or deletion of a desiccant.

D. Minor Changes (Annual Report)

The following are examples of changes considered to have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product.

1. A change in the container closure system for a nonsterile drug product, based on a showing of equivalency to the approved system under a protocol approved in the application or published in an official compendium (§ 314.70(d)(2)(v)).

2. A change in the size and/or shape of a container for a nonsterile solid dosage form (§ 314.70(d)(2)(iv)).

3. A change in the number of units (e.g., tablets, capsules) or labeled amount (e.g., grams) of nonsterile solid dosage form in a multiple-unit container.

4. The following changes in the container closure system of solid oral dosage form drug products as long as the new package provides the same or better protective properties (e.g., light, moisture) and any new primary packaging component materials have been used in and been in contact with CDER-approved solid oral dosage form drug products:[24]

   - Adding or changing a child-resistant closure, changing from a metal to plastic screw cap, or changing from a plastic to metal screw cap.

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[23] A multiple-unit container is a container that permits withdrawal of successive portions of the contents without changing the strength, quality, or purity of the remaining portion. This type of container is not distributed directly to patients but is used by health care practitioners who dispense the drug product in smaller amounts to a patient in accordance with a physician's instructions.

[24] For sections IX.D.4 to IX.D.7, changes in the container closure system that result in drug product contact with a component material that has never been used in any CDER-approved drug product of the same type should be submitted as a changes-being-effected-in-30-days supplement (section IX.C.1) or prior approval supplement (section IX.B.1).

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- Changing from one plastic container to another of the same type of plastic (e.g., high density polyethylene (HDPE) container to another HDPE container).
- Changes in packaging materials used to control odor (e.g., charcoal packets).
- Changes in bottle filler (e.g., change in weight of cotton or amount used) without changes in the type of filler (e.g., cotton to rayon).
- Increasing the wall thickness of the container.
- A change in or addition of a cap liner.
- A change in or addition of a seal (e.g., heat induction seal).
- A change in an antioxidant, colorant, stabilizer, or mold releasing agent for production of the container and/or closure to one that is used at similar levels in the packaging of CDER-approved solid oral dosage form drug products.
- A change to a new container closure system when the container closure system is already approved in the NDA or ANDA for other strengths of the drug product.

5. The following changes in the container closure system of nonsterile liquid drug products as long as the new package provides the same or better protective properties and any new primary packaging component materials have been used in and been in contact with CDER-approved liquid drug products with the same route of administration (i.e., the material in contact with a liquid topical should already have been used with other CDER-approved liquid topical drug products):

   - Adding or changing a child-resistant closure, changing from a metal to plastic screw cap, or changing from a plastic to metal screw cap.
   - Increasing the wall thickness of the container.
   - A change in or addition of a cap liner.
   - A change in or addition of a seal (e.g., heat induction seal).

6. A change in the container closure system of unit dose packaging (e.g., blister packs) for nonsterile solid dosage form drug products as long as the new package provides the same or better protective properties and any new primary packaging component materials have been used in and been in contact with CDER-approved drug products of the same type (e.g., solid oral dosage form, rectal suppository).

7. The following changes in the container closure system of nonsterile semisolid drug products as long as the new package provides the same or

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better protective properties and any new primary packaging component materials have been used in and been in contact with CDER-approved semisolid drug products:

- Changes in the closure or cap.
- Increasing the wall thickness of the container.
- A change in or addition of a cap liner.
- A change in or addition of a seal.
- A change in the crimp sealant.

8. A change in the flip seal cap color as long as the cap color is consistent with any established color coding system for that class of drug products.

X. LABELING

A. General Considerations

A drug product labeling change includes changes in the package insert, package labeling, or container label. In accordance with § 314.70(a)(4), an applicant must promptly revise all promotional labeling and drug advertising to make it consistent with any labeling change implemented in accordance with paragraphs (b) or (c) of § 314.70. All labeling changes for ANDA drug products must be consistent with section 505(j) of the Act.

B. Major Changes (Prior Approval Supplement)

Any proposed change in the labeling, except changes designated as moderate or minor by regulation or guidance, must be submitted as a prior approval supplement (§ 314.70(b)(2)(v)(A)). If applicable, any change to a Medication Guide required under 21 CFR part 208, except for changes in the information specified in § 208.20(b)(8)(iii) and (b)(8)(iv), must be submitted in a prior approval supplement (§ 314.70(b)(v)(B)). The following list contains some examples of changes currently considered by CDER to fall into this reporting category.

1. Changes based on postmarketing study results, including, but not limited to, labeling changes associated with new indications and usage.

2. Change in, or addition of, pharmacoeconomic claims based on clinical studies.

3. Changes to the clinical pharmacology or the clinical study section reflecting new or modified data.

4. Changes based on data from preclinical studies.

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5. Revision (expansion or contraction) of population based on data.

6. Claims of superiority to another drug product.

7. Change in the labeled storage conditions, unless exempted by regulation or guidance.

C. Moderate Changes (Supplement - Changes Being Effected)

Under § 314.70(c)(6)(iii), a changes-being-effected supplement must be submitted for any labeling change that (1) adds or strengthens a contraindication, warning, precaution, or adverse reaction, (2) adds or strengthens a statement about drug abuse, dependence,

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psychological effect, or overdosage, (3) adds or strengthens an instruction about dosage and administration that is intended to increase the safe use of the drug product, (4) deletes false, misleading, or unsupported indications for use or claims for effectiveness, or (5) normally requires a supplement submission and approval prior to distribution of the drug product that FDA specifically requests be submitted under this provision. A changes-being-effected supplement that provides for a labeling change under §§ 314.70(c)(6)(iii) must include 12 copies of final printed labeling (§ 314.70(c)(1)). The following list includes some examples of changes currently considered by CDER to fall into this reporting category.

1. Addition of an adverse event due to information reported to the applicant or Agency.

2. Addition of a precaution arising out of a postmarketing study.

3. Clarification of the administration statement to ensure proper administration of the drug product.

D. Minor Changes (Annual Report)

Labeling with editorial or similar minor changes or with a change in the information concerning the description of the drug product or information about how the drug is supplied that does not involve a change in the dosage strength or dosage form should be described in an annual report (§ 314.70(d)(2)(ix) and (d)((2)(x)) . The following list includes some examples currently considered by CDER to fall into this reporting category.

1. Changes in the layout of the package or container label that are consistent with FDA regulations (e.g., 21 CFR part 201) without a change in the content of the labeling.

2. Editorial changes, such as adding a distributor's name.

3. Foreign language versions of the labeling if no change is made to the content of the approved labeling and a certified translation is included.

4. Labeling changes made to comply with an official compendium.

XI. MISCELLANEOUS CHANGES

A. Major Changes (Prior Approval Supplement)

The following are examples of changes considered to have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product.

* Insofar as this guidance adjusts reporting categories pursuant to section 506A of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.70, it does have binding effect.

1. Changes requiring completion of studies in accordance with 21 CFR part 320 to demonstrate equivalence of the drug product to the drug product as manufactured without the change or to the reference listed drug (§ 314.70(b)(2)(ii)).

2. Addition of a stability protocol or comparability protocol.

3. Changes to an approved stability protocol or comparability protocol unless otherwise provided for in this guidance (e.g., VIII.C, VIII.D, XI.C.2).

4. An extension of an expiration dating period based on (1) data obtained under a new or revised stability testing protocol that has not been approved in the application or (2) full shelf life data on pilot scale batches using an approved protocol.

5. Changes to a drug product under an application that is subject to a validity assessment because of significant questions regarding the integrity of the data supporting that application (§ 314.70(b)(2)(viii)).

B. Moderate Changes (Supplement - Changes Being Effected)

The following are examples of changes considered to have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product.

1. Supplement - Changes Being Effected in 30 Days

Reduction of an expiration dating period to provide increased assurance of the identity, strength, quality, purity, or potency of the drug product. Extension of an expiration date that has previously been reduced under this provision should be submitted in a changes-being-effected-in-30-days supplement even if the extension is based on data obtained under a protocol approved in the application.

2. Supplement - Changes Being Effected

No changes have been identified.

C. Minor Changes (Annual Report)

The following are examples of changes considered to have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product.

1. An extension of an expiration dating period based on full shelf life data on production batches obtained under a protocol approved in the application (§ 314.70(d)(2)(vi)).

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2. Addition of time points to the stability protocol or deletion of time points beyond the approved expiration dating period.

3. A change from previously approved stability storage conditions to storage conditions recommended in International Conference on Harmonisation (ICH) guidances.

4. Non-USP reference standards:

   - Replacement of an in-house reference standard or reference panel (or panel member) according to procedures in an approved application.
   - Tightening of acceptance criteria for existing reference standards to provide greater assurance of drug product purity and potency.

XII. MULTIPLE RELATED CHANGES

Multiple related changes involve various combinations of individual changes. For example, a site change may also involve equipment and manufacturing process changes or a components and composition change may necessitate a change in a specification. For multiple related changes where the recommended reporting categories for the individual changes differ, CDER recommends that the submission be in accordance with the most restrictive of the categories recommended for the individual changes. When the multiple related changes all have the same recommended reporting category, CDER recommends that the submission be in accordance with the reporting category for the individual changes.

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ATTACHMENT A: MANUFACTURING SITES

All owners or operators of all drug establishments (not exempt by regulation) that engage in the manufacture, preparation, propagation, compounding, or processing of a drug or drugs are required to register with the FDA (21 CFR 207.20). An *establishment* means a place of business under one management at one general physical location (§ 207.3(a)(7)). A *general physical location* is reasonably construed to include separate buildings within the same city ***if*** the activities in the buildings are closely related to the same business enterprise, are under the supervision of the same local management, and are all inspected at the same time (ORA Field Management Directive No. 132).

For the purposes of determining the reporting category for moves between buildings, the terms *same manufacturing site* and *different manufacturing site* mean:

Domestic Establishments

Same manufacturing site:

- The new and old buildings are included under the same drug establishment registration number[25]

and

- The same FDA district office is responsible for inspecting the operations in both the new and old buildings.

Different manufacturing site:

- The new and old buildings have different drug establishment registration numbers

or

- Different FDA district offices are responsible for inspecting operations in the new and old buildings.

For domestic establishments, the terms *same manufacturing site* and *different manufacturing site* supersede the terms *contiguous campus*, *same campus*, and *different campus* as used in the SUPAC guidances.

Foreign Establishments

[25] The registration number is the number assigned to the establishment as part of the registration process (e.g., ORA Field Management Directive No. 92).

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Foreign establishments are not currently required to register with the FDA. On May 14, 1999, FDA published a proposed rule to require registration of foreign establishments (64 FR 26330). Until registration of foreign establishments is required, same and different manufacturing sites mean:

Same manufacturing site:

- A contiguous or unbroken site or a set of buildings in adjacent city blocks.

Different manufacturing site:

- The new and old buildings are not on a contiguous site or not in adjacent city blocks.

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ATTACHMENT B: TYPE OF OPERATION AND CGMP INSPECTIONS

Section VI states that a change to a different manufacturing site should be submitted in a prior approval supplement when (1) the new manufacturing site has never been inspected by FDA for the type of operation being moved, (2) the move results in a restart at the new manufacturing site of a type of operation that has been discontinued for more than two years, or (3) the new manufacturing site does not have a satisfactory current good manufacturing practice (CGMP) inspection for the type of operation being moved.

A *profile class system* is used by FDA to assist in (1) managing the CGMP inspection process, (2) evaluating the findings and the compliance follow-up needed, and (3) communicating the results of inspections. A profile class can relate to the manufacture of a particular dosage form (e.g., large volume parenterals, oral liquids), type of drug substance (e.g., sterile bulk by chemical synthesis), or specific function performed at a site (e.g., control testing laboratory). There are profile class codes for major categories of drug substance processes, dosage forms, and manufacturing functions (see table below). However, the system is not comprehensive for all operations performed in the pharmaceutical industry (see not elsewhere classified (NEC) profile class code).

The term *type of operation* refers to the specialized or even unique conditions and practices that are employed to manufacture a class or category of drug substance or drug product or to perform a limited segment of the manufacturing process. These conditions and practices exist and are performed within the framework of CGMPs, along with general conditions and practices that contribute to the manufacture of all drug products at a given manufacturing site. The conditions and practices, both general and specific, are inspected to evaluate the CGMP acceptability of a manufacturing site. A wide variety of classes or categories of drug substances and drug products may be produced at a manufacturing site, or the manufacturing site may only produce a single class of drug substance and/or drug product or perform a limited segment of a manufacturing process. Each type of operation is represented by a ***profile class code.***

Generally, a satisfactory CGMP status for a profile class code is used to communicate a satisfactory CGMP clearance for all of the products and for all of the operations included within the category that code represents. Thus the profile class code for a particular dosage form or type of drug substance is used to communicate the CGMP status for all aspects of manufacturing, processing, packing, or holding that are performed at the specific manufacturing site relating to that particular dosage form or type of drug substance, including packaging and labeling operations, testing, and quality control. The profile class code for a particular dosage form or type of drug substance is also used to communicate the CGMP status for manufacturing sites that produce in-process material (e.g., controlled-release beads), package drug products, or label drug products, even if these are stand-alone (e.g., contractor) operations.

A few profile class codes that describe certain types of operations (see items in boldface in table) are provided to report the CGMP status for contractor firms whose only function in the manufacturing process is to perform this operation. If one of these operations (e.g., steam sterilization process) is performed at the manufacturing site involved in producing the drug product/drug substance, the CGMP status for that operation is reported as part of the profile class code for the particular dosage form or type of drug substance. For example, a manufacturing site

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producing a terminally sterilized small volume parenteral drug product would be reported with the profile class code for the dosage form (SVT), not by the profile code for the sterilization process (SSP).

Certain inspections may be required by program priorities even if the rating for a profile class code indicates an acceptable CGMP status. The current profile codes/classes for human drugs are:

ADM	Aerosol dispensed medication	NEC	Not elsewhere classified (when using this class, specific drug products are noted)
CBI	Biotechnology crude drug	OIN	Ointment, nonsterile (includes cream, jelly, paste)
CEX	Plant/animal extraction crude drug	POW	Powders (includes oral and topical)
CFS	Sterile bulk by fermentation crude drug	RAD	Radiopharmaceutical
CFN	Nonsterile bulk by fermentation crude drug	**RSP**	**Radiation sterilization process**
CHG	Capsule, prompt release	SNI	Sterile noninjectable
CRU	Crude bulk drugs-nonsynthesized	SOP	Soap
CSG	Capsules, soft gelatin	**SSP**	**Steam sterilization process**
CSN	Nonsterile bulk by chemical synthesis	SUP	Suppositories
CSP	**Chemical sterilization process**	SVL	Small volume parenterals (lyophilized)
CSS	Sterile bulk by chemical synthesis	SVS	Sterile-filled small volume parenterals
CTL	**Control testing laboratories**	SVT	Terminally sterilized small volume parenteral
CTR	Capsules, modified-release	TCM	Tablets, prompt-release
GAS	Medical gas (includes liquid oxygen and other)	TCT	Tablets, delayed-release
GSP	**Gas sterilization process**	TDP	Transdermal patches
HSP	**Dry heat sterilization process**	**TSP**	**Fractional (tyndallization) sterilization process**
LIQ	Liquid (includes solutions, suspension, elixirs, and tinctures)	TTR	Tablets, extended-release
LVP	Large volume parenterals	**WSP**	**Water sterilization process**

CGMP inspectional status, based on the profile class, is available through FDA's Freedom of Information (FOI) Office. (See Glossary under Satisfactory Current Good Manufacturing Practice (CGMP) Inspection for more information regarding FOI requests.)

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Examples of postapproval manufacturing site changes and recommended reporting categories:

- An applicant wants to move the manufacture of an immediate-release tablet (TCM) to a different manufacturing site that currently manufactures, and has satisfactory CGMP status for, capsules (CHG) and powders for oral solution (POW). This manufacturing site change should be submitted in a prior approval supplement because the new manufacturing site does not have a satisfactory CGMP inspection for immediate-release tablets.
- An applicant wants to contract out packaging operations for immediate-release tablets (TCM) and capsules (CHG) and modified-release capsules (CTR). The potential contract packager has a satisfactory CGMP status for immediate-release and modified-release capsules but has never packaged immediate-release tablets. The packaging site change for the immediate-release tablet drug products should be submitted in a prior approval supplement. The packaging site change for the capsule drug products should be submitted as recommended in section VI of this guidance for packaging sites with a satisfactory CGMP inspection.
- An applicant wishes to consolidate product testing to a single analytical laboratory at a manufacturing site. This manufacturing site produces various solid oral dosage form drug products, has an operational analytical laboratory currently at the site, and satisfactory CGMP inspections for the manufacturing occurring at the facility. Some of the drug products that will be tested at the analytical laboratory when the consolidation occurs are not solid oral dosage form products. Unlike most other production operations, testing laboratories (and other operations in boldface in the table) are not inspected on a dosage form/type of drug substance specific basis. The satisfactory CGMP inspection of the analytical laboratory, which was performed as part of the CGMP inspection for manufacture of the solid oral dosage form drug products, is considered to apply to all dosage forms, including those not actually produced at the site. The consolidation can be submitted in a changes-being-effected-in-30-days supplement if the change is consistent with the recommendations in section VI.C.1.d.

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ATTACHMENT C: CDER-APPROVED DRUG PRODUCTS

In several places throughout the guidance, different reporting categories are proposed for changes to or the addition of certain components based on whether the component/material has been used in and has been in contact with CDER-approved drug products. Different reporting categories are recommended once CDER has reviewed certain components/materials in association with a drug product approval because similar subsequent changes then have a reduced potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product. For example, certain changes in the container closure systems of solid oral dosage form drug products may be included in an annual report as long as the new package provides the same or better protective properties and any new primary packaging component materials have been used in and been in contact with CDER-approved solid oral dosage form drug products (see section IX.D.4). If the new primary packaging component material has not been used in or has not been in contact with CDER-approved solid oral dosage form drug products, then submission of the change in an annual report is not recommended.

CDER-approved drug products are considered those drug products subject to an approved NDA or ANDA. Some information on which components/materials are used in CDER-approved products is available from the Agency (e.g., FDA, CDER, *Inactive Ingredient Guide*, 1996, Division of Drug Information Resources). When information is not available, an applicant should use reliable sources of information to determine that the component or material has been used in and has been in contact with a CDER-approved drug product of the same dosage form and route of administration, as appropriate. The applicant should identify in the supplement or annual report the basis for the conclusion that the component or material is used in a CDER-approved drug product.

If an applicant cannot confirm that a component or material has been used in and has been in contact with a CDER-approved drug product of the same dosage form and route of administration, the applicant has the option of submitting the change for a single NDA or ANDA using the higher recommended reporting category and, after approval, submitting similar changes for other NDAs and ANDAs using the lower recommended reporting category.

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GLOSSARY

Acceptance Criteria: Numerical limits, ranges, or other criteria for the tests described (21 CFR 314.3(b)).

Active Ingredient/Drug Substance: Any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of a disease, or to affect the structure or any function of the human body, but does not include intermediates used in the synthesis of such ingredient. The term includes those components that may undergo chemical change in the manufacture of the drug product and are present in the drug product in a modified form intended to furnish the specified activity or effect (21 CFR 210.3(b)(7) and 314.3(b)).

Assess the Effects of the Change: To evaluate the effects of a manufacturing change on the identity, strength, quality, purity, and potency of a drug product as these factors may relate to the safety or effectiveness of the drug product (21 CFR 314.3(b)).

Container Closure System: The sum of packaging components that together contain and protect the dosage form. This includes primary packaging components and secondary packaging components if the latter are intended to provide additional protection to the drug product.

Component: Any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such drug product (21 CFR 210.3(b)(3)).

Drug Product: A finished dosage form, for example, tablet, capsule, or solution, that contains an active ingredient generally, but not necessarily, in association with inactive ingredients (21 CFR 210.3(b)(4)).

Final Intermediate: The last compound synthesized before the reaction that produces the drug substance. The final step forming the drug substance involves covalent bond formation or breakage; ionic bond formation (i.e., making the salt of a compound) does not qualify. Consequently, when the drug substance is a salt, the precursors to the organic acid or base, rather than the acid or base itself, should be considered the final intermediate.

Inactive Ingredient: Any intended component of the drug product other than an active ingredient.

In-process Material: Any material fabricated, compounded, blended, or derived by chemical reaction that is produced for, and used in, the preparation of the drug product (21 CFR 210.3(b)(9)). For drug substance, in-process materials are considered those materials that are undergoing change (e.g., molecular, physical).

Intermediate: A material that is produced during steps of the synthesis of a drug substance and undergoes further molecular change before it becomes a drug substance.

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Package: The container closure system and labeling, associated components (e.g., dosing cups, droppers, spoons), and external packaging (e.g., cartons, shrink wrap).

Packaging Component: Any single part of a container closure system.

Primary Packaging Component: A packaging component that is or may be in direct contact with the dosage form.

Reference Listed Drug: The listed drug identified by FDA as the drug product on which an applicant relies in seeking approval of its abbreviated application (21 CFR 314.3(b)).

Satisfactory Current Good Manufacturing Practice (CGMP) Inspection: A satisfactory CGMP inspection is an FDA inspection during which (1) no objectionable conditions or practices were found (No Action Indicated (NAI)) or (2) objectionable conditions were found, but voluntary corrective action is left to the firm and the objectionable conditions will not be the subject of further administrative or regulatory actions (Voluntary Action Indicated (VAI)).

Information about the CGMP status of a firm may be obtained by requesting a copy of the Quality Assurance Profile (QAP) from the FDA's Freedom of Information (FOI) Office. The QAP contains information on the CGMP compliance status of firms that manufacture, package, assemble, repack, relabel, or test human drugs, devices, biologics, and veterinary drugs. All FOI requests must be in writing (21 CFR 20.40(a)) and should be prepared following the instructions found in the reference entitled *A Handbook for Requesting Information and Records from FDA*. An electronic version of this reference is available on the Internet at http://www.fda.gov/opacom/backgrounders/foiahand.html.

Secondary Packaging Component: A packaging component that is not and will not be in direct contact with the dosage form.

Specification: The quality standard (i.e., tests, analytical procedures, and acceptance criteria) provided in an approved application to confirm the quality of drug substances, drug products, intermediates, raw materials, reagents, components, in-process materials, container closure systems, and other materials used in the production of a drug substance or drug product (21 CFR 314.3(b)).

* Insofar as this guidance adjusts reporting categories pursuant to section 506A of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.70, it does have binding effect.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

----------x
STEADYMED LTD.,

Petitioner,

vs.

UNITED THERAPEUTICS CORPORATION,

Patent Owner.
----------x

VIDEOTAPED DEPOSITION OF

JEFFREY D. WINKLER, Ph.D.

New York, New York

June 14, 2016

9:33 a.m.

Reported by:
Jennifer Ocampo-Guzman, CRR, CLR
JOB NO. 44975

June 14, 2016

9:33 a.m.

Videotaped Deposition of JEFFREY D. WINKLER, Ph.D., held at the offices of DLA Piper LLP (US), 1251 Avenue of the Americas, New York, New York, pursuant to notice, before Jennifer Ocampo-Guzman, a Certified Real-Time Shorthand Reporter and a Notary Public of the State of New York.

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SHAUN SNADER, ESQ. (UNITED THERAPEUTICS)

(Winkler Exhibit 1, Curriculum Vitae of Jeffrey David Winkler, [SteadyMed-Exhibit 1010], marked for identification, this date.)

(Winkler Exhibit 2, Declaration of Jeffrey D. Winkler in Support of Petition for Inter Partes Review of Claims 1-22 of U.S. Patent No. 8,497,393, [SteadyMed-Exhibit 1009], marked for identification, this date.)

(Winkler Exhibit 3, Copy of U.S. Patent No. 8,497,393, [SteadyMed-Exhibit 1001], marked for identification, this date.)

THE VIDEOGRAPHER: This is media unit number 1 in the video deposition of Jeffrey D. Winkler in the matter of SteadyMed Limited, petitioner, versus United Therapeutics Corporation, patent owner.

This deposition is being held at DLA Piper LLP, 1251 Avenue of

the Americas, New York, New York on June 14, 2016, at approximately 9:33 a.m.

My name is Jose Rivera from the firm of David Feldman Worldwide and I am the legal video specialist. The court reporter is Jennifer Ocampo-Guzman in association with David Feldman Worldwide, located at 450 Seventh Avenue, New York, New York.

For the record, will counsels please introduce themselves.

MR. DELAFIELD: Bobby Delafield of Wilson Sonsini Goodrich & Rosati representing patent owner, United Therapeutics Corporation.

MR. MAEBIUS: Stephen Maebius, Foley & Lardner, representing patent owner, United Therapeutics Corporation.

MR. SNADER: Shaun Snader, United Therapeutics, Washington,

DC, for patent owner, United Therapeutics.

MR. POLLACK: Stuart E. Pollack from DLA Piper LLP (US) on behalf of Professor Winkler and on behalf of SteadyMed Limited.

THE VIDEOGRAPHER: Now will the court reporter please swear in the witness.

J E F F R E Y D. W I N K L E R, called as a witness, having been duly sworn, was examined and testified as follows:

EXAMINATION BY

MR. DELAFIELD:

Q. Good morning, Dr. Winkler.

A. Good morning.

Q. Could you please state and spell your full name for the record?

A. Jeffrey David Winkler, J-E-F-F-R-E-Y, D-A-V-I-D, W-I-N-K-L-E-R.

Q. Have you been deposed before?

A. Yes, I have.

Q. About how many times?

Winkler

A. About ten or 12 times.

Q. Okay. Well, you probably know all the ground rules, but I just want to go over a few just to refresh your memory. I'll be asking a series of questions and you need to provide an answer, unless your counsel instructs you not to do so.

Because this is being recorded, the answers need to be in verbal form, and so no head shakes or nods, because it won't be recorded by the stenographer.

You are reminded your testimony is under oath, so your answers need to be truthful and full to the best of your knowledge.

I might ask a confusing question, and if so, feel free to ask me to clarify, if you have any issues with my question.

Also, the stenographer has to record everything we say, so I'm asking if you could not speak over me or vice

Winkler

versa, so that she can record both of what we're saying.

Also, if you need a break at any time, feel free to just tell me, and we can take a break, as long as a question isn't pending.

Is there any reason you can think of why you will not be able to answer my questions today fully and accurately?

A. No.

Q. Are you taking any medication or drugs of any kind that might make it difficult for you to understand and answer my questions?

A. No.

Q. Okay. So you've provided a declaration regarding the '393 patent in this case; is that correct?

A. Yes, it is.

Q. So I want to go ahead and hand you three exhibits.

(Discussion off the record.)

MR. POLLACK: Thank you.

Winkler

Q. So if you turn to Exhibit 1, can you tell me what that exhibit is?

A. Exhibit 1 is my curriculum vitae.

Q. Is that a true and accurate copy of your CV?

A. Yes, it is.

Q. Can you briefly summarize your educational background?

A. So I was an undergraduate at Harvard College. I graduated with honors in 1977, and I then pursued graduate studies at Columbia University, under the direction of the Professor Gilbert Stork, where I received an MA and MPhil and finally a Ph.D. degree in 1981. I stayed at Columbia as an American Cancer Society post-doctoral fellow in the laboratory of Professor Ronald Breslow from 1982 to 1983.

And that was the end of my formal education.

Q. Okay. So looking at page 1 of your CV, it lists your professional

Winkler

experience. Is that a complete listing of your professional experience since getting your Ph.D.?

A. Yes, it is.

Q. So you've never worked as a chemist outside of academia; is that correct?

A. Well, actually I spent a year long sabbatical at Bristol-Myers Squibb in Lawrenceville, New Jersey, in about 2000 or 2001. And I've consulted with a number of pharmaceutical and chemical companies over the course of my career.

Q. Okay. But other than the sabbatical, you've never been employed full time at a chemical company apart from your job as a --

MR. DELAFIELD: Strike that.

Q. Apart from the year long sabbatical, your full-time employment has been with universities; is that correct?

MR. POLLACK: Objection to form.

You can answer.

Winkler

A. Well, as I stated, my -- I've been involved with companies over the course of my career full time, only during that year at BMS.

Q. And what did you do during that year at BMS?

MR. POLLACK: I'm just, don't reveal any confidential information that belongs to BMS, but if it's not confidential, you can reveal that now.

A. So during the year at BMS, I was part of I think two different research teams investigating various aspects of drug development, and then I also taught a course to BMS scientists that was ongoing throughout the course of the year.

Q. Have you ever formulated a drug product?

MR. POLLACK: Objection, objection to form, vague.

A. I'm sorry. What do you mean by "formulated a drug product"?

Q. Have you ever worked in a lab for a pharmaceutical company to make a drug product?

A. Well, I guess I would say that in my time during the sabbatical year, I was working with two teams on the development of drug products.

Q. Have you ever synthesized a drug substance?

A. I'm sorry, I don't understand what you mean by that.

Q. Well, have you ever personally or directed others to actually synthesize a drug substance that was used in a commercially available drug product?

A. Yes, I have.

Q. And what was that?

A. For a while, in the 1990s, my laboratory was involved in the synthesis of Ritalin, of -- of 30, P-H-R-E-O, Phenidate, P-H-E-N-I-D-A-T-E, which is the API in Ritalin, R-I-T-A-L-I-N.

Q. And so was that API actually used in a commercial product?

Winkler

MR. POLLACK: Objection to form.

You can answer.

A. I don't know the answer to that question.

Q. Have you ever submitted a filing to the FDA regarding any drug product or drug substance?

A. No, I have not.

Q. Have you ever corresponded with the FDA at all about any drug?

A. No, I have not.

Q. Have you ever developed a protocol for evaluating the impurity profile of a drug?

A. Well, my laboratory is routinely involved in the purification and the assay of the substances that we create in our laboratory.

Q. Sorry. Maybe you misunderstood my question.

Have you ever developed an impurity profile for a drug product?

MR. POLLACK: Objection to

form.

A. I'm afraid I don't understand your question.

Q. Well, you understand that to have a drug substance or a drug product you must submit an impurity profile to the FDA. Do you understand that?

A. I have never submitted a drug impurity profile to the FDA.

Q. Okay. Have you ever developed the impurity profile for someone else to submit to the FDA?

A. Not that I can think of sitting here now.

Q. Do you have any experience synthesizing prostaglandins?

A. I have certainly studied the synthesis of prostaglandins and taught the synthesis of prostaglandins.

Q. And you have or people working for you ever synthesized prostaglandins?

A. My laboratory has worked on the development of the methodology, synthetic methodology that could be

Winkler

applicable to the synthesis of prostaglandins.

Q. But you or your lab haven't actually synthesized prostaglandins; is that correct?

A. Sitting here I can't think of an example where we have synthesized prostaglandins.

Q. Do you have any experience manufacturing --

A. Excuse me. Although, I should add that my laboratory has synthesized compounds that are certainly related to the prostaglandins.

Q. Okay. Do you have any prior experience synthesizing or analyzing treprostinil or any of its derivatives? Prior to this case?

MR. POLLACK: Objection to form, compound.

A. Prior to this case, I have not had -- I'm sorry, could you repeat the question, please?

Q. Prior to this case, did you

have any experience synthesizing or analyzing treprostinil?

A. Prior to this case, I have not had experience with treprostinil, specifically.

Q. Do you have any experience scaling up drug substances from lab scale to industrial scale?

A. In my role as a consultant in the pharmaceutical industry, I certainly have had experience with the scale up of reactions in the pharmaceutical industry.

Q. When you say you have experience with reactions, what do you mean by that?

A. Excuse me. In saying that I have experience with scale up, that means that as part of my association with pharmaceutical companies, I've had the opportunity to consult on and discuss with pharmaceutical scientists and advise pharmaceutical scientists on large scale reactions.

Q. Have you or your lab performed

Winkler

any large scale reactions?

A. I'm afraid I don't understand exactly what you mean by "large scale reactions."

Q. Well, you just mentioned that you had advised and mentioned the term "large scale reactions," and so I guess to put a number on it, have you or your lab performed any syntheses on a kilogram scale?

A. I would have to go back to the lab notebooks in my research group to know whether we had done reactions on that scale.

So sitting here, I can't really answer that.

Q. But sitting here today, you can't remember anything specific on that scale, or larger; is that correct?

MR. POLLACK: Objection to form.

A. I can't remember having done reactions on kilogram scale, but I certainly can't remember not having done

Winkler

them on kilogram scale.

Q. Are you familiar with the FDA guidelines regarding impurity profiles for a drug?

A. No, I am not.

Q. Do you know what is required in order to change a drug specification with the FDA?

A. No, I do not.

Q. Are you familiar with published guidances from the FDA regarding changes to new drug applications or abbreviated new drug applications?

A. I'm sorry, could you repeat the question?

Q. Are you familiar with published guidances from the FDA regarding changes to new drug applications or abbreviated new drug applications?

A. No, I am not familiar with that.

Q. You had mentioned you had been

Winkler

deposed several times. Do you recall how many patent litigations you've worked on?

A. I don't remember exactly, no.

Q. So let's look at Exhibit 3, which is the '393 patent. Do you recognize this document?

A. Yes, I do.

Q. And this is the '393 patent that is at issue in this case, correct?

A. That's my understanding, yes.

Q. If you could turn to column 2 -- actually, column 3, I'm sorry.

And do you see in column 3 structure Roman numeral (IV)?

A. Yes, I do.

Q. Do you recognize that structure?

A. I do, yes.

Q. And what is that structure?

A. That is the chemical structure of treprostinil.

Q. Would you agree that treprostinil has five chiral centers?

A. Yes, I would, five chiral

Winkler

centers or 5 stereo centers, yes.

Q. So if a molecule has five chiral centers, that means that it has 32 possible stereoisomers; is that right?

A. Two to the five, that's correct.

Q. Is it fair to say that treprostinil is a complex molecule?

MR. POLLACK: Objection to form.

A. I think that's a difficult question for me, because the question would be, complex relative to what?

Q. Well, just your experience as a chemist, would you consider treprostinil to be complex compared to other chemicals that you've since synthesized?

MR. POLLACK: Objection to form.

A. We've synthesized compounds in my laboratory that are much more complex than treprostinil, and we've synthesized some molecules that are less complex than

Winkler

treprostinil.

Q. You've reviewed the synthesis for treprostinil for the '393 patent, correct?

A. Yes, I have.

Q. And you've reviewed some of the prior art that had other syntheses for treprostinil; is that right?

A. Yes, I have.

Q. And the total synthesis is, I believe, roughly 20 steps, depending on which synthesis, but it's a multi-step process; is that correct?

MR. POLLACK: Objection to form.

A. I'm sorry, I don't understand the question.

Q. You would agree that the synthesis for treprostinil is approximately 20 steps?

A. I actually haven't counted the number of steps in the synthesis.

Q. Would you consider the synthesis of treprostinil to be complex?

Winkler

MR. POLLACK: Objection to form.

A. Again, the problem that I would have in answering that question is: Complex to relative to what? There are things that are much more complex than treprostinil, and there are things that are decidedly less complex.

Q. Well, would you expect, let's say, undergraduate students to be synthesizing treprostinil or structures similar to treprostinil in their lab?

A. That's a very difficult question for me to answer, because it would depend on the level and skill of the undergraduate student.

Q. Well, just as a matter of course, within the courses you teach, for example, are you aware of any syntheses that are multiple steps that have --

MR. DELAFIELD: Strike that.

Q. Do you teach organic chemistry?

A. Yes, I do.

Winkler

Q. And in your experience in teaching organic chemistry, do students typically synthesize structures that have five or more chiral centers from commercially available starting materials?

A. I don't know the answer to that.

Q. But sitting here today, you can't think of any?

A. I'm sorry, I don't understand the question.

Q. Sitting here today, you are not aware of any syntheses that your students perform synthesizing molecules with five or more chiral centers?

A. Sitting here today, I can't think of any examples.

Q. Do your undergraduate students typically perform kilogram scale reactions?

A. I'm afraid I don't understand the question.

Q. Well, you teach undergraduate

chemistry, correct?

A. That is correct.

Q. And in those classes and labs, they perform experiments, right?

A. The students in the laboratories, in the teaching laboratories certainly do perform experiments, yes.

Q. And are you aware if those students perform syntheses on a kilogram scale?

A. I am not --

MR. POLLACK: Objection to form.

A. I am not aware.

Q. Do you know if the lab equipment in undergraduate labs is even capable of synthesizing kilogram scale reactions?

A. I do not know.

Q. Would it surprise you if they didn't?

MR. POLLACK: Objection to form.

Winkler

A. I'm sorry, I don't understand your question.

Q. Well, you're aware of the equipment used in undergraduate laboratories, correct?

A. No, I am not.

Q. So you're not aware of what laboratory equipment is used in the undergraduate courses that you teach?

A. Well, the undergraduate courses that I teach are lecture courses, so they don't have laboratory components to them.

Q. So you don't teach the lab courses?

A. I do not.

Q. If you could look at Exhibit 2, which is a copy of your declaration -- well, first, is that a true and correct copy of your declaration?

A. Yes, it is.

Q. Are you aware of any errors in your declaration?

Winkler

A. I am.

Q. And what are those errors?

A. There's a citation to Phares, Exhibit 1005, at the bottom of page 14 that continues on to page 15, and it cites Exhibit 1005, page 24, bottom paragraph, and that number should actually be page 22.

Q. Okay. Are you aware of any other errors?

A. No, I am not.

Oh, excuse me. There is one other error, I guess. There appears to be a duplicate signature page at the end of the report. I'm not sure what the reason is for that.

Q. So if we could take a look at paragraph 14 in your declaration, do you see that?

A. Yes, I do.

Q. And paragraph 14 says, "Given the high education level of the scientists actually working in this field, a person of ordinary skill in the

art ('POSA') of chemistry at the time of the alleged invention would have a master's degree or a Ph.D. in medicinal or organic chemistry, or a closely related field. Alternatively a person of ordinary skill would include a bachelor's degree and at least five years of practical experience in medicinal or organic chemistry." Do you see that?

A. Yes, I do.

Q. And you agree with that definition of person of ordinary skill with regard to the '393 patent?

A. Yes, I do.

Q. So do you recall how you came up with that definition?

A. I came up with that definition as a function in large measure of looking at the inventors of the patent and what their level of expertise and training was.

Q. Did you do anything else to determine what the level of ordinary skill would be?

Winkler

A. I think my opinion was formed based on the background of the inventors and on my own reading of the patent.

Q. So when you say your own reading of the patent, what informed your decision to choose that level of skill based on your reading of the patent?

A. I formed that opinion based on the science, the chemistry that was in the patent.

Q. And so you would agree that to understand the science and chemistry of the patent, you would need this level of skill in the art?

A. Yes, that is my opinion.

Q. Okay. So let's turn back to paragraph 3 in your report.

And the last full sentence says, "The technology of the '393" --

MR. DELAFIELD: Strike that.

Q. -- "The technology of the '393 patent involves nothing more than basic organic chemistry techniques-in my view, 'organic chemistry 101'-all of which were

Winkler

well-known in the art prior to December 17, 2007."

Do you see that?

A. Yes, I do.

Q. So do you disagree with that statement then?

A. No, I do not.

Q. Well, I believe you just said that you agree that to understand the science and chemistry of the '393 patent you would need that level of skill in the art being a Ph.D. or master's with experience in medicinal or organic chemistry, correct?

A. I'm sorry, could you repeat that, please?

Q. I believe you just previously answered that you would need the level of skill in the art that you list in paragraph 14 to understand the chemistry of the '393 patent, correct?

A. I don't think that's really what I said. I think what I said was that a person of ordinary skill in the

art at the time of the invention would have a master's degree or a Ph.D. Alternatively, the person of ordinary skill would include an individual with a bachelor's degree and at least five years of practical experience.

Q. Yes, but I believe your testimony was that to understand the chemistry, you would need the level of ordinary skill in the art described in paragraph 14, whether it's a Ph.D. and master's with less experience or a bachelor's with more experience?

A. I'm sorry, I must have misspoken.

What I meant to say was that my definition of a person of ordinary skill in the art is as listed here in paragraph 14.

I'm afraid I may not have understood the question that you asked me.

Q. So the technology of the '393 patent involves more than just organic

Winkler

chemistry 101, if the ordinary level of skill in the art is a Ph.D. with years of experience in medicinal and organic chemistry, correct?

MR. POLLACK: Objection to form.

A. No, I don't think that's correct at all. I think the statement that I'm making in paragraph 3 is that the technology of the patent involves basic organic chemistry techniques. That is my opinion.

I think that the definition that I gave of a person of ordinary skill in the art is one who would have a master's degree or a Ph.D. in organic chemistry or a person of ordinary skill with at least five years of practical experience.

Q. But if the chemistry involved in the '393 patent involves no more than organic chemistry 101, why would you need a master's degree or Ph.D. in medicinal chemistry or closely related field or a

Winkler

bachelor's degree with at least five years of experience in medicinal and organic chemistry?

MR. POLLACK: Objection to form.

A. Well, my opinion is that a person of ordinary skill would have the qualifications that I listed in paragraph 14 based on the expertise of the patent authors.

But the technology that we're discussing here in my opinion is basic, and as I stated in paragraph 3, it involves nothing more than basic organic chemistry techniques, in my view, as I state here, "organic chemistry 101."

Q. So if a person took organic chemistry 101, would they be a person of ordinary skill in the art with regard to the '393 patent?

MR. POLLACK: Objection to form.

A. If a person took organic chemistry 101, they would certainly have

Winkler

been exposed to the technology of the '393 patent, and I would say, understand the technology of the '393 patent.

Q. So do you want to change your level of ordinary skill in the art?

A. No, I do not.

Q. So I guess I just am not understanding how someone would need a Ph.D., if your opinion is that there is nothing in the '393 patent beyond basic organic chemistry.

So you would agree that a person who had taken organic chemistry 101 would not be a person of ordinary skill in the art with respect to the '393 patent, correct?

A. A person who had taken only the first year of organic chemistry would not qualify as a person of ordinary skill in the art, per the definition that I've offered in paragraph 14, that is correct.

Q. And so your definition does require a lot more than taking one year of organic chemistry to be a person of

Winkler

ordinary skill in the art, correct?

A. To be a person of ordinary skill in the art, according to the definition that I've offered in paragraph 14, would require a master's or Ph.D. degree or bachelor's degree with at least five years of practical experience.

Q. In the courses you teach in chemistry, is organic chemistry a 100 level course?

MR. POLLACK: Objection to form.

A. The number of the undergraduate course that I teach at the University of Pennsylvania in introductory organic chemistry is chemistry 241, it's not a 100 level course. It's a 200 level course.

Q. So there is not actually an organic chemistry 101; is that right?

A. Not precisely. My view of the organic chemistry 101 in paragraph 3 was just to indicate a descriptor of basic organic chemistry, or introductory

organic chemistry.

Q. Earlier we briefly discussed impurity profiles for drug substances, and I believe you testified that you had not prepared an impurity profile for a drug substance; is that correct?

MR. POLLACK: Objection to form.

A. Again, I'm not actually sure what you mean by that question.

Q. Have you prepared any impurity profile for any drug substance?

A. I guess I don't understand what you mean by "impurity profile," and I don't understand what you mean by "drug substance" in the context of this question.

Q. Well, do you know what an impurity profile is?

A. Well, I would interpret an impurity profile as the profile of impurities in a substance.

Q. And do you understand the FDA requires that impurity profiles be

Winkler

submitted with drug substances?

A. I don't think I am aware of that.

Q. Do you know what the purpose of an impurity profile is?

A. I'm afraid I don't understand the question.

Q. What is the purpose of an impurity profile?

A. Well, again, I don't understand in the context to which you're referring.

To me an impurity profile would simply be the profile of the impurities of the substance, what the impurities were.

Q. And why would someone be concerned about what impurities are present in a drug substance, for example?

A. I'm not sure that I understand the question.

Q. I'm just asking why would a person be --

MR. DELAFIELD: Strike that.

Winkler

Q. Can you think of any reason why someone would want to analyze the impurities of a drug substance?

A. I'm sorry, what do you mean by "drug substance"?

Q. Are you not familiar with that term?

A. Not formally, no.

Q. When I say "drug substance," I mean the active pharmaceutical ingredient in a drug product. Does that help your understanding?

A. Yes.

Q. So can you think of any reason why someone would want to analyze the impurities of an active pharmaceutical ingredient in a drug product?

A. Well, I would -- I would think that one would want to know what the impurities were in the API.

Q. Why is that?

A. To know what other compounds are in the API, or what their proportions are.

Winkler

Q. Do you know why they would want to know that?

A. Well, it's possible that the, that the impurities could negatively impact the API material, and so it would be important to know what the amounts were of these compounds or what the purity was of the API.

Q. Have you ever studied the negative impact of impurities on any API?

A. I think that I have, but sitting here, I can't think of concrete examples.

Q. Okay. So sitting here today, you can't think of any specific examples, where you studied the negative impacts of impurities on any API; is that correct?

A. Well, I'm pretty sure that I have, but I can't think of specific examples, sitting here now.

Q. Are you familiar with the use of treprostinil?

MR. POLLACK: Objection to form, vague.

Winkler

A. I'm afraid I don't know what you mean by that.

Q. Do you know what treprostinil is used for?

A. My understanding is that treprostinil is used as a therapy for pulmonary arterial hypertension.

Q. Would you agree that the treprostinil is a very potent drug?

MR. POLLACK: Objection to form.

A. I have -- I was not asked to form an opinion on that and I do not have one.

Q. So you don't know whether it's potent or not, correct?

MR. POLLACK: Objection to form.

A. As I said, I had not formed an opinion on that.

(Winkler Exhibit 4, Excerpt of the prosecution history for the '393 patent, [SteadyMed-Exhibit 1002], marked for identification,

Winkler

this date.)

THE WITNESS: Thank you.

Q. You've been handed what's been marked Exhibit 4, which is a copy of the file history for the '393 patent.

Do you recognize that document?

MR. POLLACK: Just for the record, counsel, this is pages 235 through 405 of Exhibit 1002?

MR. DELAFIELD: I am not sure why that starts there, but I will just call it an excerpt then.

MR. POLLACK: An excerpt from the prosecution?

MR. DELAFIELD: Yes.

Q. Do you recognize this document?

A. Yes, I do.

Q. And did you review this document in forming your opinions in your declaration?

A. Yes, I did.

Q. So if you could turn to --

Winkler

A. I'm sorry, if I could just return to a previous answer that I gave.

I have my declaration still here, and on paragraph 3, when I talk about the technology of the '393 patent, what I'm referring to is the idea of taking a carboxylic acid, making a carboxylic acid amine salt, and regenerating the free acid. Those are the techniques that would have been obvious, or the technology that would not have been anything more than basic organic chemistry. In other words, that's what I was referring to as "organic chemistry 101" in paragraph 3 of my declaration.

Q. So just to go back then, so then is it your opinion that you would need the level of education that you give in paragraph 14 to perform those reactions that you just mentioned?

MR. POLLACK: Objection to form.

A. My opinion is that the

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technology of the '393 patent as it involves the formation of a carboxylate salt and the regeneration of the carboxylic acid, those steps represent nothing more than basic organic chemistry techniques, and that's what I was referring to when I described it as "organic chemistry 101," when I described it figuratively, if you will, as organic chemistry 101.

Q. So do you mean a master's degree or Ph.D. in the medicinal or organic chemistry or in a closely related field to perform those steps?

A. I think to perform a carboxylate salt and to regenerate the carboxylic acid, that's something that I would expect a student in basic organic chemistry to be able to do.

Q. So you don't agree that your definition of a person of ordinary skill in the art should be that high level of education?

MR. POLLACK: Objection to

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form.

A. I'm sorry, I don't understand your question.

Q. Well, in paragraph 14 you say, "Given the high level of" --

MR. DELAFIELD: Strike that.

Q. "Given the high education level of the scientists actually working in this field, a person of ordinary skill in the art of chemistry at the time of the alleged invention would have a master's degree or a Ph.D. in medicinal or organic chemistry or closely related field." And then you say, or a bachelor's with more experience.

Do you see that?

A. I do.

Q. But you're saying that to perform the steps of the '393, you actually don't need that level of ordinary skill; is that correct?

A. I think to perform the steps of the salt formation and regeneration of the carboxylic acid, those are steps that

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are taught in the equivalent of organic chemistry 101. That's the statement that I'm making, or that's the point that I am trying to make in paragraph 3.

Q. And is that your understanding of the entire technology of the '393 patent?

A. No, it is not.

Q. So in paragraph 3 when you say the technology of the '393 patent involves nothing more than organic chemistry techniques, you're only referring to the last few steps and not the entire technology as it's stated there?

A. My particular focus in paragraph 3 when I wrote this sentence was referring to the formation of carboxylate salt and then regeneration of the free acid.

Q. But paragraph 3 doesn't say that, right?

A. It does not say that. Well, I mean it says that in that the technology

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of the '393 involves nothing more than basic organic chemistry techniques, but the technology that I was referring to here was the formation of the carboxylate salt and the regeneration of the free acid.

Q. If you could turn back to Exhibit 4, which an excerpt of the file history of the '393 patent. If you could turn to page 346 in the exhibit.

And this is the first page of the declaration of David Walsh under 37 C.F.R. 1.132. Do you see that?

A. Yes, I do.

Q. And have you reviewed this declaration?

A. Yes, I have.

Q. So if you look at the next page, 347 in paragraph 6, there Walsh states, "In my opinion, each of treprostinil as the free acid and treprostinil diethanolamine prepared according to the process specified in claim 1 or 10 the present application is

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physically different from treprostinil prepared according to the proces of 'Moriarty.'"

Do you see that?

A. Yes, I do.

Q. And he based that analysis on the fact that the impurity profiles were different, correct?

MR. POLLACK: Objection to form.

A. The Walsh report states that each of treprostinil as the free acid and treprostinil diethanolamine prepared according to the process specified in claim 1 or 10 differed from treprostinil prepared according to the process in Moriarty in their respective impurity profiles.

Q. So you agree that Dr. Walsh based his analysis on the fact that the impurity profiles are different, correct?

MR. POLLACK: Objection to form.

A. Could you repeat the question,

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please?

Q. There Walsh concluded that the treprostinil made by the '393 process was different than the treprostinil made by the Moriarty process based on differences in impurity profiles, correct?

A. Well, what Walsh states here is that they differ according -- they differ in their respective impurity profile.

Q. So is that a yes to my question?

A. What was your question? I'm sorry.

Q. Dr. Walsh concluded that the treprostinil made by the '393 patent process is different from the treprostinil made by the Moriarty process because their impurity profiles were different, correct?

A. Walsh states that each of the treprostinil is the free acid and the treprostinil diethanolamine prepared according to claim 1 differ from the

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treprostinil prepared according to the process in Moriarty in their respective impurity profiles. That's what it says here.

Q. I don't believe you answered my question. It's just a yes or no question.

It's just saying that he believes that they're different because they have different impurity profiles. Is that correct?

MR. POLLACK: Objection to form.

A. That they differ in their respective impurity profiles, that's what it says here.

Q. And you understand this was submitted during prosecution of the '393 patent, correct?

A. That is correct.

Q. Now, are you generally familiar with the process of prosecuting a patent with the patent office?

MR. POLLACK: Objection to

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form.

A. I'm sorry, I don't understand exactly what you mean.

Q. Do you understand that Dr. Walsh submitted this declaration to point out differences between the '393 patent and the prior art, correct?

A. I think that's correct.

Q. Sir, if you turn to page 350, Dr. Walsh signed his declaration on June 4, 2013; is that correct?

MR. POLLACK: Objection to form.

A. That's what it says here, yes.

Q. And turn to page 354, do you see at the top of the page it says, "Notice of Allowance and Fees Due"?

A. Yes.

Q. And at the top right it says "date mailed June 12th, 2013." Do you see that?

A. Yes, I do.

Q. So the '393 patent was allowed a week after Dr. Walsh submitted his

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declaration; is that right?

A. Eight days later I would guess.

Q. Yes.

And if you look at the pages in between, nothing was filed from the time Dr. Walsh submitted his declaration until the time the notice of allowance was submitted, correct?

A. Not that I can see here, no.

Q. So the patent office during prosecution considered impurity profiles to be important as to how the claims are interpreted, correct?

MR. POLLACK: Objection to form.

A. I really can't speak to how the patent office interpreted this.

Q. Well, you understand that the patent office allowed it eight days after the submission of the declaration, correct?

A. It appears that there was a notice of allowance from the patent

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office eight days after the submission of the Walsh declaration.

Q. So is it fair to say that the patent was allowed as a result of Dr. Walsh filing his declaration?

MR. POLLACK: Objection to form.

A. Again, I don't think I can really speak to that question.

Q. But you submit that Dr. Walsh submitted his declaration in order to show differences between the '393 patent and the prior art, correct?

A. I think what Dr. Walsh states on page 347 is that each of treprostinil as the free acid and as the salt, prepared according to the process specified in claim 1 or 10, differ from the treprostinil prepared according to Moriarty in their respective impurity profile.

Q. But you don't know if the patent office allowed the patent based on that declaration?

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MR. POLLACK: Objection to form, asked and answered.

A. I do not, no.

Q. Do you think it's possible the patent office allowed it because of the declaration?

MR. POLLACK: Objection to form.

A. I don't know the answer to that question.

Q. Are you aware of any other reason the patent office would have allowed the patent?

A. I don't know.

Q. So looking back at his declaration at page 347, do you see that?

A. Yes, I do.

Q. And there is a chart at the bottom of the page that shows the impurity profile that says, "Treprostinil free acid prepared according to 'Moriarty.'" Do you see that?

A. Yes, I do.

Q. And at the bottom it says,

bottom left says, "Total Related Substances." Do you see that?

A. Yes, I do.

Q. And in the far right it says, "0.6 percent," correct?

A. Yes, it does.

Q. So that is the total amount of impurities in that sample added up; is that correct?

A. Well, all I can read from this is that that's the total of related substances in this sample, of this material that was sampled.

Q. And that's a measure of the purity of the substance, right?

A. I don't know the answer to that question.

Q. So you didn't use the numbers from the Walsh declaration in determining the purity of the '393 patent batches or the Moriarty batches; is that right?

A. Well, actually in my declaration, I actually discuss why the Walsh declaration cannot be used to

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support the question of the purity that the patent owner claims.

Q. So if you keep open the Walsh declaration and then if you also look at your declaration at paragraph 65.

A. Yes.

Q. So paragraph 65, second sentence, you state, "Patent Owner contended based upon Dr. Walsh's measurement that his purification method achieved 99.8 percent purity, while the prior art Moriarty reference achieved 'only' 99.4 percent," and then you cite Exhibit 1002 to page 347. Do you see that?

A. I do.

Q. So if you look at page 347, can you tell me where you got 99.4 percent purity reference from paragraph 65?

A. I obtained that by subtracting .6 percent from 100 percent.

Q. So earlier you said you didn't know if "Total Related Substances" was a

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measure of purity, correct?

MR. POLLACK: Objection to form.

A. My confusion sitting here is that this gives a number for "Total Related Substances" but no number for total unrelated substances, which I've seen in other of the documents, so I made the assumption in my declaration that the purity of the sample was indicated from these data to be only 99.4 percent on that basis.

Q. So you used the "Total Related Substances" number as a measure for purity, correct?

MR. POLLACK: Objection to form.

A. So the patent owner, if I'm not mistaken, claims that Moriarty here was 99.4 percent, pure. Was only 99.4 percent pure, based on the "Total Related Substances" value obtained here of .6 percent.

The point that I was trying to

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make was that the upper limit for this lot would have been 99.4, but could have been lower if there were unrelated substances in the preparation.

I also pointed out in my report, several examples of why these data would be, would be difficult to interpret.

Q. But at least one way to measure the purity is to look at the "Total Related Substances" in a batch, correct?

MR. POLLACK: Objection to form.

A. Well, again, as I mentioned, one way would be to look at "Total Related Substances," but there were other purity profiles that I looked at in the course of my review of the documents that showed related substances as well as unrelated substances.

Q. But looking at "Total Related Substances" is one, possibly many ways, to determine the purity, correct?

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MR. POLLACK: Objection to form.

A. I think without knowing the percent of unrelated substances, it would be less than accurate to describe the purity of this sample as 99.4.

Q. And when you say "unrelated substances," what do you mean by that?

A. I think, as I said, in the course of my review of the documents some of these purity profiles indicated a percent of related substances and then also a percent of unrelated substances. I'm not sure exactly what they would have been referring to.

Q. So looking back at the Walsh declaration at page 347, above the "Total Related Substances" it lists several different impurities. Do you see that?

A. I do.

Q. And then in the far right column there are numbers and the letters ND. Do you know what "ND" stands for?

A. I think that "ND" stands for

not determined, or I'm sorry, not determined or not detected. That's the typical context in which I've seen those numbers.

Q. So you've seen "ND" referred to meaning not detected, correct?

A. Not detected and not determined, yes.

Q. So you see that, for example, the impurity 2A90 was reported as less than 0.05 percent. Do you see that?

A. Yes, I do.

Q. And 97W86 impurity which is Benzidene trial, which was reported as 0.7 percent. Do you see that?

A. Yes, I do.

Q. So the instrument used to analyze these impurities could detect down to at least 0.07 percent, correct?

A. That's what this would, these numbers would suggest, yes. Although there is no indication of what the error is in these measurements.

Q. In the middle column you see

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that it lists specification for each of these impurities. Do you see that?

A. Yes, I do.

Q. And for 2AU90 it says not more than 0.1 percent, correct?

A. That is correct.

Q. So even if this doesn't report the error, is it fair to say that the error would have to be less than 0.1 percent in order for 0.1 percent to be a meaningful number?

MR. POLLACK: Objection to form.

A. I'm sorry, could you repeat that question, please?

Q. So the specification says not more than 0.1 percent, correct?

A. That is correct.

Q. And although this does not report the amount of error associated with that number in order for a 0.1 percent to be relevant, the error would have to be lower, correct?

A. I'm sorry, could you repeat

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the question, please.

MR. DELAFIELD: Could you read back the question.

(A portion of the record was read.)

A. I think for the measurement of the 2AU90, if the error in the measurement was more than .1 percent, it would be difficult to claim not more than .1 percent.

Q. Okay. So you agree that if you're reporting a number not more than a certain percentage, the error associated with that number would necessarily need to be lower than that, right?

A. I would think that it should be, but I'm just not sure that it is in this case.

MR. DELAFIELD: We've been going about an hour and a half, would you like to take a break, Dr. Winkler?

THE WITNESS: That would be fine.

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THE VIDEOGRAPHER: The time is 10:53 a.m., and we're going off the record.

(A brief recess was taken.)

THE VIDEOGRAPHER: This begins media unit number 2. The time is 11:09 a.m. and we're back on record.

Q. Hello, Dr. Winkler. During the break, did you discuss with your attorney any of the substance of your testimony today or anything about the case?

A. No, I did not.

Q. So if you could turn back to Exhibit 4, which is the excerpt of the file history we were talking about, Dr. Walsh's declaration. And on page 347, we were discussing the amounts of impurities for --

MR. DELAFIELD: Strike that.

Q. We were discussing the limitations on the impurities in that chart. Do you recall that?

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A. Yes, I do.

Q. And we were discussing that for the impurity 2AU90 the limit for the impurity was no more than 0.1 percent, correct?

A. That's what it says here, yes.

Q. And I believe you testified that you didn't know what the experimental error associated with that number is, because there is not enough information here to determine that; is that right?

A. That's correct.

Q. But it would be reasonable to think that the error would need to be lower than 0.1 percent in order for the limit to be 0.1 percent; is that fair?

MR. POLLACK: Objection to form.

A. I think that actually depends on whether you're referring to a relative error or the absolute error in measuring the .1 percent.

Q. Well, in either case, in order

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for the limit to be 0.1 percent, the error would likely be less than 0.1 percent, correct?

MR. POLLACK: Objection to form.

A. I would think that the error in the measurement for the 2AU90 would be, should be less than .1 percent.

Q. And generally for all the numbers, the error should be less than the maximum number reported, correct?

A. The error should be less than the maximum number reported, that's correct, for the measurement of the materials that are described here.

Q. Sir, if you turn to page 348, on the next page it shows two similar impurity profiles to the treprostinil diethanolamine prepared according to claims 1 and 10, and the treprostinil as the free acid prepared according to claims 1 or 10.

Do you see that?

A. Yes, I do.

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Q. And the top chart, the bottom row says, "Impurities (HPLC) (Total Related Substances.)" Do you see that?

A. "Total related substances," yes, I see that.

Q. And on the far right it says 0.1 percent, correct?

A. It does say that, yes.

Q. And likewise, on the chart below that, it says "Total Related Substances," and the corresponding number 0.2 percent, correct?

A. That's what it says here, yes.

Q. So like the 2AU90 number we discussed before, the error associated with those numbers would also need to be less than the number reported, correct?

MR. POLLACK: Objection to form.

A. Well, again, the issue would be whether we're dealing with relative or absolute errors, for these numbers.

Q. But whether it's relative or absolute error, in order to report a

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number, the error should be less than the number reported, correct?

MR. POLLACK: Objection to form.

A. The error should be less than the number reported.

Q. So if you could turn back to your declaration, which is Exhibit 2, and if you look at paragraph 68, are you there?

A. I am at paragraph 68.

Q. You say, "Third, a 0.1 percentage difference in purity between Walsh's measurement of Moriarty's purity and Claim 2 and Claim 10's 99.5 purity is well within experimental error for measuring impurities, and would not represent a significant deviation from the processes of the prior art."

Do you see that?

A. Yes, I do.

Q. But you don't know what the experimental error is associated with these measurements, correct?

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MR. POLLACK: Objection to form.

A. I don't know precisely what the errors are, but I know that there clearly must be error in these measurements. For example, I know that the Moriarty purity is reported here as 99.4, but in fact in Moriarty, it's reported as 99.7. So that represents a spread of .3 percent in terms of the purity of the products.

Q. But as we just discussed, the numbers recorded in Walsh's declaration, which you're relying on, the errors should be less than the numbers reported, and therefore, less than .1, correct?

MR. POLLACK: Objection to form.

A. Well, I don't -- I don't think that's what I said. And, for example, if you look at the Moriarty data on page 347, that number is .6, so that would suggest a larger possible range.

For this particular lot that

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was tested, they claim an impurity level of .1 percent. The impurity level for the free acid is claimed as .2 percent.

So, again, these are specific lots, and I'm not sure what I could conclude based on this limited data set.

Q. So based on this information you have no idea what the experimental error would be, correct?

MR. POLLACK: Objection to form.

A. Well, again, I assume that the error, at least in the case of Moriarty, is going to be somewhere on the range of plus or minus .2 percent at a minimum. There is other data that I saw in materials that were supplied after my declaration was produced that suggest that the HPLC purities are off by as much as 1 or 2 percent.

Q. But do you agree the HPLC purities given in the Walsh declaration should have experimental errors below that of .1 percent, correct?

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MR. POLLACK: Objection to form.

A. Well, I think in my reading of the data on page 348, I certainly agree that these measurements for these two particular lots should have errors that are less than .1, .2 respectively, but I don't know that that's the case, and given the other data that I've seen, I am imagining that these sorts of differences would all be within the range of experimental.

Q. But in order to know what the experimental error range is you need to know what HPLC was used and whether the same HPLC was used for one analysis in another analysis, correct?

A. I think there are multiple factors that would be required to determine what the experimental error would be.

Q. And because there are multiple factors that would be required to determine what the experimental error

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would be, you don't actually know what would be within or outside experimental error; it's just an assumption, correct?

MR. POLLACK: Objection to form.

A. Looking at these numbers, I can be certain that there is experimental error, but I can't say exactly how large that error is.

Q. So if you look at paragraph 69 of your report, you say, "even a difference of 0.4 percent as discussed below between the claim processes of '393 patent and prior art such as Moriarty would be attributable to experimental error, and that the claimed degree of purity under the claimed processes of the '393 patent presents no distinction from prior art."

Do you see that?

A. Yes, I do.

Q. So based on the multiple factors, you would need to know what the limit of the experimental error is; you

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don't in fact know that 0.4 percent would be within the experimental error, correct?

MR. POLLACK: Objection to form.

A. Well, actually, I think I do know that the experimental error could be as high as .4 percent, because of the data that's included in the '393 patent.

Q. And what data are you referring to?

A. I'm referring to the data that's described in paragraph 70 of my report, in which I state in the second sentence, that "in the present case we can estimate the precision of the equipment the inventors actually used since the inventors found that Example 4's Batch 1 had an HPLC Assay of 100.4 percent, which is obviously greater than the 100 percent value theoretically achievable," and that would suggest to me there that is a variation of at least a .4 percent in these measurements.

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Q. And so because the number is over 100 percent, that is your basis for saying that at least .4 percent is due to experimental error; is that correct?

A. That's one of the bases for my opinion.

Q. And in paragraph 70, you mention that the HPLC was an assay of 100.4 percent, right?

A. That's correct.

Q. What is an assay?

A. An assay is a test.

Q. What does it mean in this context?

A. What I interpret this to mean is that the HPLC is a determination of the compound.

Q. Now, earlier in the Walsh declaration we were looking at the "Total Related Substances" as a measure of the purity. Do you remember that?

A. Yes, I do.

Q. Is that the same as an assay?

A. Well, my experimentation --

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could I refer back to the '393?

Q. Sure. It's Exhibit 3.

A. So I would interpret this HPLC assay to be the same purity assay that is described at the bottom of column 14 of the patent; in other words, the area under the curve after the treprostinil, or treprostinil diethanolamine salt that was being assayed.

Q. But you don't know if that's the same purity referred to as the "Total Related Substances" in the Walsh declaration, correct?

A. I'm afraid I don't understand your question.

Q. Well, you referred to the bottom of column 14 in the '393 patent, and that is the number you were referring to with regard to purity in paragraph 70 of your declaration, correct?

A. No, I don't think that's true. What I was referring to in 70 is in the table that sits at the bottom of column 13, at the bottom of the column 13 for

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Batch 1, the HPLC assay indicates a purity, I'm assuming that the HPLC assay there refers to the same purity as described at the bottom of 14, and it gives a purity of 100.4 percent.

From that, I conclude that these numbers can't be better than .4 percent, because it obviously would not be possible to have a material that is more than 100 percent pure.

Q. Are you familiar with the term "reference standard"?

A. I'm sorry?

Q. Are you familiar with the term "reference standard"?

A. Yes, I am.

Q. What is your understanding of what a "reference standard" is with regard to a drug substance?

A. Well, a reference standard is typically authentic sample of a substance.

Q. And what are they used for?

A. Well, they can be used for

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many different things.

Q. Do you have any samples of what they might be used for?

A. They could be used, for example, to calibrate retention times on HPLC.

Q. Are you aware of reference standards being used as the standard in which other samples are compared to?

A. Yes, that would certainly be possible as well.

Q. And so a reference standard is usually a very high purity sample, correct?

MR. POLLACK: Objection to form.

A. It can be.

Q. Now, earlier you said you had reviewed some documents that were filed after you submitted your declaration; is that right?

A. That is correct.

Q. Did you review all the exhibits that were attached to United

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Therapeutics' brief?

A. I am pretty sure that I did.

(Winkler Exhibit 5, Letter dated 1/2/09, [UT Exhibit 2006], marked for identification, this date.)

THE WITNESS: Thank you.

Q. I've handed you what's been marked as Exhibit 5, which is a letter to the FDA from United Therapeutics.

MR. DELAFIELD: I would like to also note for the record that parts of the deposition will be confidential.

MR. POLLACK: Do you want to make this section confidential?

MR. DELAFIELD: Yes.

(The following portion has been deemed confidential and bound under separate cover.)

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Q. Do you recognize this document?

A. Yes, I do.

Q. If you turn to page 5, this table shows drug substance specification comparison. Do you see that?

A. Yes, I do.

Q. And it continues on to page 6, if you would turn to the next page. And do you generally understand what this chart shows?

A. I think so, yes.

Q. So on page 6, the second row, it says, "Chromatographic Purity (HPLC)." Do you see that?

A. I do.

Q. And then there are various impurities listed and next to that are the limits for those impurities. Do you see that?

A. Yes, I do.

Q. And again, for example, for [redacted], it says, not more than [redacted] percent, correct?

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A. That is correct.

Q. And then below that row is another row that says "Assay (HPLC)." Do you see that?

A. Yes, I do.

Q. And then the first column it says, not less than [redacted] percent and not more than [redacted] weight per weight on the volatiles freebases. Do you see that?

A. I do.

Q. So right above "Assay," it says "Total Related Substances." Do you see that?

A. I do.

Q. So here this is showing two separate ways that you can assess the purity of this substance, correct?

MR. POLLACK: Objection to form.

A. I'm afraid I don't understand your question.

Q. So earlier we discussed how "Total Related Substances" was a measure of purity, correct?

MR. POLLACK: Objection to form.

A. I'm afraid I still don't understand your question.

Q. Earlier when we discussed Dr. Walsh's declaration, we discussed how the measurement associated with "Total Related Substances" was a way to determine the purity of the substance, correct?

MR. POLLACK: Objection to form.

A. I think that we had used "Total Related Substances" to generate a -- an upper limit for what the purity of a substance could be.

Q. So it's one way to determine the purity, correct?

MR. POLLACK: Objection to form.

A. I think that I just said that it could be used to determine the upper limit of purity.

Q. And you see that "Assay" below

that is a different measurement, correct?

A. Different in what way? I'm afraid I don't understand the question.

Q. So according to this chart, "Assay" is listed separately from "Total Related Substances," correct?

A. That is correct.

Q. And both "Assay" and "Total Related Substances" are different ways that you can estimate the purity of a substance, correct?

A. They could be used to determine the purity of a substance, yes.

Q. And here it's showing that they're not necessarily the same number, correct?

A. I'm afraid I don't understand your question.

Q. Well, because they are listed separately, they're not one and the same thing, correct?

A. I'm afraid I still don't understand your question. There are different numbers given here for "Total

Related Substances" and "Assay" by HPLC.

Q. They are different analyses, right?

A. I'm afraid I don't understand what you mean by that.

Q. You don't understand whether or not the measurement for "Total Related Substances" is different than the measurement for the assay?

A. I understand the "Total Related Substances" as expressed here and the assay are different.

Q. Okay.

THE WITNESS: Excuse me. Excuse me. They're different but clearly related because the [redacted] percent HPLC assay certainly looks like it's correlated to the not more than [redacted] percent of "Total Related Substances," so I would think that these values are in fact related somehow.

Q. But in the last column, it says, not less than [redacted] percent for assay

but not more than [redacted] percent for total related substances, correct?

A. Yes, it does.

Q. So they are different analyses, right?

A. Based on that they would appear to be, yes.

Q. So we were talking about a reference standards and how sometimes they are used to compare samples against to determine a purity relative to the reference standard.

Do you understand that?

A. I think I do.

Q. So here when it talks about assay on a weight-per-weight basis, if assay means the amount of substance in a sample compared to the amount in a reference standard, that would be one way to determine the purity in relation to a reference standard, correct?

A. I could imagine the use of a reference standard to do that, yes.

Q. So if that were the case, if

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the sample were made by an improved process that had a higher purity than the reference standard, you could get over 100 percent and it not be experimental error, correct?

MR. POLLACK: Objection to form.

A. That's not the way I understand the use of a reference standard.

Q. Well, if a reference standard, for example, has 99 percent of a substance and the sample you're comparing it against is 100 percent, then that would be 1 percent more than the reference standard, correct?

A. That is correct.

Q. And both of these --

A. But that would not give a calculated value of, say, of more than 100 percent purity. I don't think there is any logical calculation that would allow you to determine greater than 100 percent purity, at least none that

I've ever seen, before looking at these data.

Q. So in the "Assay" column --

MR. DELAFIELD: Strike that.

Q. In the "Assay" row on this page, you see that the proposed change is actually raising the upper limit from [redacted] percent to [redacted] percent. Do you see that?

A. I do see that.

Q. So then is it your belief that they're proposing more experimental error?

A. Well, if I see a number of [redacted] percent purity, that suggests to me that that value is going to be off by [redacted] percent.

Q. So you're not aware of a purity analysis where a sample is compared to a less pure reference standard ending up with over 100 percent?

A. In my experience of less than 100 percent pure reference standard should never give a value of more than

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100 percent purity in the assayed material. There should be a correction for the lack of purity in the reference standard.

Q. So why --

A. Because it -- I'm sorry -- because it wouldn't make sense to one of skill in the art or myself to have a sample or have a measurement that would indicate that a sample was more than 100 percent pure.

Q. So you understand that this letter was submitted to the FDA to change the specification for treprostinil, correct?

MR. POLLACK: Objection to form.

A. I'm not sure exactly what the purpose was of this letter.

Q. Well, you understand that it was submitted to the FDA at least?

A. I do understand that it was submitted to the FDA, yes.

Q. And looking back at page 6,

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you also understand that the proposed change was to the assay, raising the assay from [redacted] to [redacted] to [redacted] to [redacted] percent. Do you see that?

A. I see -- I see a currently approved specification and then a proposed new specification.

Q. So you don't understand why it would be changed from [redacted] to [redacted] percent; is that correct?

MR. POLLACK: Objection to form.

A. I don't know, no.

Q. And it's your understanding that the experimental error in the first column is at least [redacted] percent because it says, not more than [redacted] percent, and the experimental error in the second column must be [redacted] percent because it says [redacted] percent. Is that fair to say?

MR. POLLACK: Objection to form.

A. I think what the data here indicate to me is that in the first

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column, I would read this as saying that the experimental error could certainly be as high as [redacted] percent.

And that in the second column, the experimental error could be as high as [redacted] percent. Because I don't think it's possible to have a sample that is [redacted] percent pure.

Q. And you don't think it's possible that these numbers represent an analysis of a sample compared to a reference standard that is less pure such that's you would end up with over 100 percent? You don't think that's possible?

A. Well, again, I don't think that comparison of an unknown sample to a less than 100 percent pure reference standard should give a value of more than 100 percent purity in the unknown. I think one should be able to understand what the purity is of reference standard and to use that information to develop a more real picture of what the purity of

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the sample is, so that one doesn't get essentially auspicious result that is a purity of greater than 100 percent.

Q. But again, given all of these numbers, you don't know specifically what the experimental error associated with any measurement for treprostinil, correct?

MR. POLLACK: Objection to form.

A. I think the thing that I am able to conclude from the data that is on page 6 of this, of this letter is that the error in the HPLC assay could be as high as [redacted] percent in the first column and by my analysis could be as high as [redacted] percent in the second column.

THE WITNESS: Excuse me.

Q. Do you know why the assay is reported as not less than a number and not more than a number, as opposed to just not more than that, as the chromatographic purity was listed --

MR. DELAFIELD: Strike that.

Q. Do you know why the chromatographic purity in the second row is reported differently than the assay purity?

A. No, I don't.

Q. Sir, if you could look back at your declaration, at paragraph 68, if you recall, you reference in the first sentence, Moriarty's purity of 99.4 percent. Do you see that?

A. I'm sorry, could you repeat that?

Q. In paragraph 68 you reference Moriarty's purity as 99.4 percent, correct?

A. I actually describe Walsh's measurement of Moriarty's purity.

Q. Yes.

And that purity number came from subtracting from 100, the "Total Related Substances" in Walsh's declaration, correct?

A. That is correct.

Q. And then if you look at

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paragraph 70 --

A. Well, excuse me, that appears to be correct. That's the number that I think comes from the patent owner.

Q. Yes, the ".6 Total Related Substances."

A. Right.

No, the description of Moriarty's purity is 99.4 percent. If I'm not mistaken that number comes from the patent owner.

Q. I'm sorry, do you mean, do you the mean Walsh's declaration?

A. I think that in the documents of the -- for the petition or the response of the patent owner is where the 99.4 percent number comes from.

Q. I think I can help you there. If you look at paragraph 65?

A. Of?

Q. Your last sentence?

A. I'm sorry, 65 of what?

Q. Of your declaration?

A. Okay.

Q. The last line says, "While the prior art Moriarty reference achieved only 99.4 percent," and then you cite page 347.

A. Okay.

Q. And that is the file history which is Exhibit 4.

A. Okay. Oh, I see.

Q. Which reports the .6 total related --

A. Yes.

Q. So your number of 99.4 percent purity comes from subtracting the "Total Related Substances" from 100, correct?

A. Correct.

Q. So going back to --

A. As -- as a -- in this case, as an upper limit to the purity of that sample.

Q. Okay. So then if you could turn to paragraph 70 of your declaration, and in the second sentence you say, "In the present case we can estimate the precision of the equipment the inventors

actually used since the inventors found that Example 4's Batch 1 and HPLC assay of 100.4 percent which is obviously greater than 100 percent value theoretically achievable." Do you see that?

A. Correct, I do.

Q. And you are using here the assay number as a measure of purity, correct?

A. Yes.

Q. But "Assay" and "Total Related Substances" are different analyses, correct?

A. They can be different.

Q. Well, they're reported as different in the UTC's letter to the FDA, right?

A. Well, the -- the letter to the F -- I'm sorry, I'm confused. I was on the Walsh declaration.

In the letter to the FDA the chromatographic purity by measurement of total related substances appears to be

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different from the HPLC assay.

Q. Yes.

So because they are different measurements, you can't say specifically what the experimental error would be, correct?

MR. POLLACK: Objection to form.

A. Well, I think I can say what the experimental error would be, because, as I state in paragraph 70 of my report, given the fact that the assay comes up over 100 percent, comes up to 100.4 in batch 1 of example 4, from that, I can conclude that the error in these measurements or determinations must be at least .4 percent.

And in fact the, in the patent, in the '393, I think there is actually no measurement of impurities, but the purity was determined by this HPLC assay or this so called AUC, the area under the curve.

Q. Right, because the assay in

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"Total Related Substances" are different analyses, you can't say what the experimental error is with regard to the "Total Related Substances," correct?

MR. POLLACK: Objection to form.

A. Well, there is no description of the "Total Related Substances" in the '393 -- I'm afraid I don't understand your question.

Q. Well, the basis for you saying that it has a .4 percent experimental error is based on an assay analysis, not total related substance analysis, right?

A. The basis for my determination of experimental error is, among other things, the HPLC assay of 100.4 percent, the difference between the Walsh determination of the Moriarty purity and the Moriarty purity described by Moriarty, both being HPLC measurements and my understanding of HPLC. And the issues that I discussed in paragraph 70 where the relative standard deviation for

an HPLC instrument in the literature is being described about being about 1 percent.

Q. "Assay" and "Total Related Substances" two different analyses, right?

A. Yes.

Q. And they may have different experimental errors associated with them, correct?

A. Well, I think the point of my analysis is that HPLC carries experimental error, and that there would be experimental error in any HPLC determination, whether we're looking at an impurity profile or whether we are looking at the HPLC assay as described in the '393.

Q. But you don't know exactly what that number would be?

MR. POLLACK: Objection to form.

A. I don't know exactly what the experimental error will be, and but as I

mentioned, based on the data that I've seen here, in my understanding of the HPLC, it looks like the error could be as high as 1 or 2 percent.

(Continued in nonconfidential portion of transcript.)

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THE WITNESS: Excuse me.

(Winkler Exhibit 6, Document entitled, "Getting Started in HPLC," [SteadyMed-Exhibit 1017], marked for identification, this date.)

THE WITNESS: Thank you.

Q. I've handed you what's been marked as Exhibit 6, which is a document entitled, "Getting Started in HPLC."

Do you recognize this document?

A. Yes, I do.

Q. And is this a document you relied upon in your declaration?

A. Yes, I did.

Q. Do you know who the author is of this document?

A. No, I do not.

Q. Did you obtain this from a website?

A. I did.

Q. Do you know if the website is maintained --

Winkler

MR. DELAFIELD: Strike that.

Q. Do you know who maintains the website?

A. I do not know the answer to that question.

Q. Now, you rely on this document for the argument you make that HPLC has 1 percent error; is that right?

A. I think what I -- excuse me -- what I stated here was that HPLC methods are expected to have CV values, and the CV is did he staled at coefficient of variance, which is an equivalent of the RSD of the relative standard deviation, and that that number is on the order of 1 percent for HPLC.

Q. So first, if you look at paragraph 70 in your declaration, you state that relative standard deviation is about 1 percent and you cite this exhibit?

A. Correct.

Q. And then you state that, in the last sentence, "This deviation

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between the experimental and theoretical shows that the instrument can have variations of at least 0.4 percent, which is greater than the difference in purity that the inventors offered to support their contention regarding greater purity over the prior art," correct?

A. Correct.

Q. But you don't know what instruments were used to determine the purity in Moriarty, the Walsh declaration or the '393, correct?

MR. POLLACK: Objection to form.

A. The Moriarty reference may mention the HPLC equipment that was used but I don't remember.

Q. And this reference that you cite for the 1 percent, relative standard deviation, doesn't say that there would be a 1 percent error in all HPLC measurements, correct?

A. I think what the reference states is that for most purposes HPLC

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methods are expected to have CV values or coefficient of variation values on the order of 1 percent.

Q. But you don't know what it would be for any of the testing done for treprostinil, correct?

MR. POLLACK: Objection to form.

A. I'm afraid I don't understand your question.

Q. You don't know what the CV value would be for any of the HPLC tests performed on treprostinil that we discussed today?

MR. POLLACK: Objection to form.

A. I think I only know that the HPLC methods are expected to have CV values on the order of 1 percent.

Q. Is it fair to say that HPLC equipment may have different experimental errors associated with it, depending on the time frame that that the HPLC was used?

Winkler

MR. POLLACK: Objection to form.

A. Could you repeat that, please?

MR. DELAFIELD: Let me rephrase it.

Q. So if took an HPLC In the 1980s and HPLC today, they may very well have different experimental errors associated with it, correct?

A. I think it's possible that they could.

Q. And if you look at Exhibit 6, on page 3, at the bottom left it says, last revised April 6, 2001.

Do you see that?

A. Yes, I do.

Q. And the '393 patent wasn't filed until 2007, correct?

A. I'm sorry, could you repeat that, please?

Q. The '393 patent wasn't filed until -- let me get the -- I believe 2007.

Yes, the first application for

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the '393 patent wasn't filed until April 2007, correct?

A. The priority date I think is 2007.

Q. So HPLC determinations could have changed since 2001, correct?

MR. POLLACK: Objection to form.

A. I wouldn't have expected a large difference in HPLC performance over the six-year period, but I can't be certain.

Q. Now, looking back at your declaration, at paragraph 66, you say "First, the data in the Walsh declaration was derived from limited sample set - indeed, only two specific batches of treprostinil."

Do you see that?

A. Yes, I do.

Q. And you say, "There could be significant batch-to-batch variations in the impurity profile of each batch of treprostinil, which does not provide

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sufficient evidence to support the conclusion that purification method achieves 99.5 percent purity or above for the claimed treprostinil."

Do you see that?

A. Yes, I do.

Q. So if more batches demonstrated the same results then that would be additional evidence that it does achieve 99.5 percent purity, correct?

A. More batches would be -- would further support this idea, yes, that's true. Assuming that the numbers were consistent.

Q. Have you performed any of the synthetic steps identified in the '393 patent?

A. No, I have not.

Excuse me. I certainly prepared the salts of carboxylic acids and regenerated the acid, but I have not performed the precise steps that are described in the patent.

Q. So you have not performed

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those steps with respect to the treprostinil or treprostinil diethanolamine?

A. I have not prepared treprostinil or treprostinil diethanolamine.

Q. Has anyone under your direction prepared any of the steps in the '393 patent?

A. As I mentioned before, certainly people in my laboratory had prepared the salts of carboxylic acids and we generated the carboxylic acid, but we have not prepared in my laboratory treprostinil or treprostinil diethanolamine.

Q. And if you look at the next paragraph in your declaration, it says, "Variations in the processes of making the claimed product could also impact and vary the degree of purity of the product" --

A. I'm sorry, could you tell me where we are?

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Q. I'm sorry. Paragraph 67 of your declaration.

A. Yes, go ahead, please.

Q. So you state, "Second, variations in the processes of making the claimed product could also impact and vary the degree of purity of the product. Do you see that?

A. Yes, I do.

Q. So if variations in the process could have impact the degree of purity, then --

MR. DELAFIELD: Strike that.

Q. Do you know what the variations in the processes were used in the prior art versus the '393 process?

A. I'm afraid I don't understand the question.

Q. I'm just trying to understand the purpose of your paragraph 67 to say that variations in the process could impact the purity.

Basically if you change the process, you would not be able to tell

what the experimental error is by comparing two different methods that have different solvents, processes, et cetera, right?

A. I'm sorry, I don't understand your question at all.

Q. In order to determine the experimental error between two different samples, don't they need to have been performed or made by the same process?

MR. POLLACK: Objection to form.

A. I guess I have no idea what you're talking about. When you ask about the experimental error in the substance, prepared by different processes.

I don't understand what you're saying.

Q. Let's look at prior art, and maybe that will help clear it up.

MR. POLLACK: If you are going to another exhibit, would this be a good time for a break?

MR. DELAFIELD: Sure.

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THE VIDEOGRAPHER: The time is 12:09 p.m. and we're going off the record.

(A brief recess was taken.)

(Winkler Exhibit 7, Excerpt from book entitled, "Organic Chemistry, Second Edition," [SteadyMed-Exhibit 1008], marked for identification, this date.)

THE VIDEOGRAPHER: The time is 12:27 p.m. and we're back on the record.

Q. Hi, Dr. Winkler, you've been handed what's been marked as Exhibit 7, which is an excerpt from a book entitled "Organic Chemistry," whose author is Ege. I'm not sure how to pronounce that. It might be Ege.

Do you recognize this document?

A. I do.

Q. And is this one of the documents that you relied upon in your declaration?

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A. Yes, it is.

Q. So if you could turn to page 8 in the document, I believe you cite this page and the second full paragraph says, "Carboxylate acids that have low solubility in water, such as benzoic acid, are converted to the water-soluble salts by reaction with aqueous base."

Do you see that.

Oh, page 8 of the Ege reference?

A. Oh, I'm sorry. Yes. I'm on page 8.

Q. And in the second sentence of the second paragraph says, "Protonation of the carboxylate anion by a strong acid regenerates the water-insoluble acid. These properties of the carboxylic acids are useful in separating them from reaction mixtures containing neutral and basic compounds."

Do you see that?

A. Yes, I do.

Q. Is this what you were citing,

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from this reference, regarding your opinion on obviousness?

A. Can I take a look at my report?

Q. Sure, sure.

A. Yes, I'm sorry. Could you ask the question again, please?

Q. In your declaration you refer to page 8 of this document, are you citing the second paragraph that I just read from your declaration?

A. I think what I'm -- what I'm citing specifically is that the protonation of the carboxylate anion by a strong acid regenerates the carboxylic acid.

Q. And do you agree with the last sentence in that paragraph that states, "These properties of carboxylic acid are useful in separating them from reaction mixtures containing neutral and basic compounds"?

A. I think that these properties can be used to separate them from a

neutral and basic compounds, but the cite to Ege in my declaration was to the point of that protonation of a carboxylate anion is well-known with strong acid to regenerate the pure carboxylic acid.

Q. So is it your understanding that that process would remove impurities?

A. I think that process can be used to remove impurities, but the cite to Ege is specifically for the protonation of the carboxylate anion to deliver the free acid.

Q. By reacting a carboxylate anion with a strong acid, is it your opinion that that would remove impurities?

A. Again, the protonation of the carboxylate anion specifically with strong acid would simply regenerate the carboxylic acid, and that was the point that I was taking for that data.

Q. Well, I'm not referring to Ege now. I'm just saying in general, is it

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your opinion that reaction of a strong acid with a carboxylate anion would remove impurities?

A. It's my opinion -- I'm sorry, could you repeat the question, please?

Q. Is it your opinion that regenerating the carboxylic acid by reacting a strong acid with the carboxylate anion would remove impurities?

A. No, it is not my opinion that protonation of a carboxylate by itself would eliminate impurities.

Q. So you disagree with this last sentence that states, "These properties of carboxylate acids are useful in separating them from reaction mixtures containing neutral and basic compounds"?

MR. POLLACK: Objection to form.

A. I do not disagree with that statement.

Q. So separating neutral and basic compounds from a reaction mixture,

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is that not considered removing impurities?

MR. POLLACK: Objection to form.

A. I think that in general terms separating compounds, separating impurities is a method of purification.

I'm afraid I don't completely understand your question.

Q. So maybe to clarify, if you could look at paragraph 88 in your declaration, you say, "Accordingly, a person of ordinary skill in the art would want to perform the treprostinil diethanolamine salt purify it and then convert it back to its free form in order to obtain excellent crystallinity and increased purity." Do you see that?

A. Yes, I do.

Q. So converting it back to its free form involves the reaction with a strong acid, correct?

A. That is correct.

Q. And you would do that in order

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to obtain excellent crystallinity and increased purity, right?

MR. POLLACK: Objection to form.

A. I think what I say in paragraph 88, in fact I know what I say, is that accordingly, a person of ordinary skill in the art would want to form the salt, purify it, and then convert it back to its free form, in order to obtain excellent crystallinity and increased purity.

Q. So is it your opinion that converting the salt back to the free form carboxylic acid increases its purity?

A. My opinion is that the protonation after the carboxylate salt in itself does not increase the purity.

Q. But it is your opinion that it would be obvious to do that still, correct?

A. I think what I state in paragraph 88 is that a person of ordinary skill would form a salt, purify it, and

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then convert it back to its free form to obtain excellent crystallinity and purity.

Q. So it's your opinion that the reaction with the strong acid does nothing in terms of purity of the substance; is that correct?

A. I think that the protonation of the carboxylate salt would not be expected to increase the purity of the final product, per se.

Q. So it would be unexpected if the purity did increase as a result of that step?

MR. POLLACK: Objection to form.

A. Well, I think what I say here is that one would form a salt, purify it, and then convert it back to its free acid, to obtain excellent crystallinity and increased purity.

Q. But you're referencing three steps to form the salt, purify it and convert it back, and then saying, you do

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that in order to obtain excellent crystallinity and increased purity.

So which of those steps are performed to obtain excellent crystallinity and increased purity?

MR. POLLACK: Objection to form.

A. Could you repeat the question, please?

Q. Well, in your sentence you reference three steps, correct? The first sentence of paragraph 88?

A. I reference the formation of the salt, its purification, and then its conversion back to the free form, yes.

Q. Yes.

And in that same sentence, you say, you do those three steps to obtain excellent crystallinity and increased purity, right?

A. That is correct.

Q. So which of those three steps are performed to obtain excellent crystallinity and increased purity?

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MR. POLLACK: Objection to form.

A. Well, the total process delivers a material with excellent crystallinity and increased purity.

Q. So you can't say which of those steps contributes to crystallinity or purity?

MR. POLLACK: Objection to form.

A. I think that it would be a combination of the steps that would lead to the excellent crystallinity and increased purity of the final carboxylic acid.

Q. But you can't say for sure that reacting a salt with a strong acid would increase its purity; is that correct?

MR. POLLACK: Objection, form.

A. Sitting here, I'm not certain that the protonation step, the final protonation step in itself would increase purity, but the protonation step would

deliver the crystalline, the final crystalline material.

Q. So with that three-step process of forming a salt, purifying it and converting it back to the free acid, what types of impurities would that remove?

A. This process of forming which is, as I mentioned before is standard practice in organic chemistry, or organic chemistry 101 as I referred to in paragraph 3, of forming the carboxylate salt using an amine, and then purifying that salt, and regenerating the acid could eliminate any of a number of impurities.

Q. But you don't have an opinion as to the type of impurity it would eliminate?

A. I think there are examples in the literature of using exactly this kind of purification process to remove all different kinds of impurities.

Q. Does the pH of the impurity

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matter in terms of this process and whether or not it would be removed?

A. It might or might not.

Q. So if you can look back at the Ege reference on page 8, the last sentence of the second paragraph states that "These properties of carboxylic acids are useful in separating them from the reduction mixtures containing neutral and basic compounds." And you said you agreed with that?

A. "These properties of carboxylic acids are useful in separating them from reaction mixtures containing neutral and basic compounds," I agree with that statement, but I don't agree with the limitation of the statement; that is, I think that the formation of an amine salt of a carboxylic acid, purification of said salt, and then the regeneration of the carboxylic acid could be used to separate a carboxylic acid from any of a number of compounds, not limited to simply and neutral and basic

Winkler

compounds.

Q. So do you have any opinion as to the type of impurities that are removed in this process?

MR. POLLACK: Objection to form.

A. Sitting here I have no opinion about the types of impurities that are removed in the '393 process. I simply know as a function of my experience in organic chemistry that one can remove neutral compounds, one can remove basic compounds, one can in fact remove other acidic compounds using the formation of the amine salts, its purification, and then the regeneration of the carboxylic acid from the salt.

THE WITNESS: Excuse me.

Q. So if you had a mixture of two carboxylic acids --

A. Yes.

Q. -- and you formed a salt by reacting them with a base so that there is two carboxylic salts as a result, and

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then reacted that same mixture with a strong acid, both would be converted back to the free form carboxylic acid, correct?

A. In the hypothetical that we took a mixture of two amine carboxylate salts and treated them with acid, I would expect both of them to revert back to the parent, or the starting carboxylic acid, that's correct.

Q. Okay.

A. But the fact is that there is an extra step here that we're leaving out and that's the purification of the salt. At the step at which the salt is being purified, there is an opportunity to separate undesired compliments of the mixture that may or may not be available at the stage of the free acid. And so that's why the formation of a carboxylate salt, specifically an amine carboxylate salt, and its purification followed by the regeneration of the parent carboxylic acid could affect purification of the

Winkler

carboxylic acid from neutral components, basic compounds, as well as other acidic components.

And in fact there are examples of such in the literature.

THE WITNESS: Excuse me.

Q. So if you could turn back to Exhibit 4 which is the file history of the '393 patent.

MR. POLLACK: Are we done with this one?

MR. DELAFIELD: Yeah, we're done.

MR. POLLACK: You can clean up if you need to.

MR. DELAFIELD: Yeah.

Q. And if you turn to page 348 of the file history excerpt, in paragraph 7?

A. Yes.

Q. So paragraph 7 states that there are eight impurities analyzed for these samples. Do you see that?

A. Yes, I do.

Q. And it states 1AU90, 2AU90 and

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3AU90 each of which is a stereoisomer treprostinil. Do you see that?

A. Yes.

Q. So as a stereoisomer of treprostinil, each of those impurities are the also carboxylic acid, correct?

A. That is correct.

Q. And then --

MR. DELAFIELD: Well, strike that.

Q. So in the purification process you just described, there is no reason that only certain stereoisomers would be removed and others not removed, right?

A. No, that's not true.

Q. So are you able to predict which stereoisomer would not be removed?

A. I'm not sure that I could necessarily predict offhand which one would be removed, but it would be a standard practice for one of skill in the art to prepare the ammonium salts of the carboxylic acids, purify those salts, and then see what the composition of or what

Winkler

the -- what the impurity levels of these different materials would be.

Q. But the fact that this purification process does not remove all stereoisomers is not predictable, correct?

A. Well, I think the point is that it would be straightforward organic chemistry, or organic chemistry 101, to prepare salts, crystallize them, and then see which would be the most effective at removing impurities from the starting treprostinil.

There are certainly multiple examples in the literature of people preparing the amine salts of carboxylic acids that contain mixtures of stereoisomers and crystallizing them to obtain pure materials.

In other words, to separate the undesired stereoisomers.

Q. But there is nothing in the process you just described that would explain only why certain stereoisomers

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are removed and while others are not, correct?

A. Well, again, as I stated, I think this would be a straightforward empirical exercise to determine which salts would be optimal for the removal of which stereoisomers. So this wouldn't be a particularly difficult thing to do.

Q. But sitting here today, you can't explain why this process only removed certain stereoisomers and not others, correct?

MR. POLLACK: Object to form.

A. I think, as I stated, one would simply look at the crystallization of the amine salt or of a series of different amine salts and then look at the purity profile of the resulting crystalline ammonium salt before regenerating the carboxylic acid to determine which would be the most effective.

But it's certainly a standard practice in organic chemistry to do so.

Winkler

Q. So in paragraph 7 it mentions there's three stereoisomer impurities, correct?

A. Yes, it does.

Q. And also two dimers, correct?

A. Yes, it does.

Q. So in the purification steps of reacting the sample with the base to form salts, and then reacting with a strong acid to convert back to the free acid, all of the --

MR. DELAFIELD: Strike that.

Q. Treprostinil and its stereoisomers and dimers could all be theoretically transferred back to the free acids, correct?

A. That is correct, but as I've already stated, at the step of the ammonium salt formation, of the ammonium carboxylate formation, I would expect that that step of purification would be possible to remove undesired, undesired isomers or dimers of the desired carboxylic acid.

Winkler

THE WITNESS: Excuse me.

Q. It's also possible that an impurity that is a stereoisomer to treprostinil could increase as a result of those steps, correct?

A. It's not obvious to me how an impurity would increase during the course of this attempted purification. Because I don't see how there would be interconversion of the stereoisomers possible under the conditions of the salt formation, and then the regeneration of the acid.

Q. Well, what would make the different stereoisomers react differently depending on what salt form is used?

A. Well, it turns out that the literature, the chemical literature is replete with examples of the separation of diastereomer salts and even a separation of enantiomeric salts using this process of forming the ammonium carboxylate salt purifying that salt and then regenerating the acid.

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Q. Sitting here today, there is nothing in the prior art that you know of that would allow you to predict which specific stereoisomers would be removed as a result of the process in the '393 patent, correct?

A. I think my understanding of the scientific literature, of the chemical literature is such that there are sufficient examples of the purification of the carboxylic acids separating them from diastereomers, from enantiomers and from other undesired impurities that I would have a high level of confidence that I could form the ammonium carboxylate, purify that, and then regenerate the acid to obtain a product, as I state here, with -- in paragraph 88 with excellent crystallinity and increased purity.

Q. But none of the prior art you cited discloses separation of stereoisomers in treprostinil, correct?

A. Well, to reach the opinion

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that I -- that I state in paragraph 88, it's not necessarily for me to see an example of the stereoisomers of treprostinil specifically, but simply to show that as a general rule, one of skill would know and be familiar with the formation of the ammonium salt of the carboxylic acid, its purification, and then the regeneration of the free acid to generate a material that, as I state here, could have excellent crystallinity and increased purity.

MR. DELAFIELD: Let's move on to a different topic.

Q. So generally speaking, the substances involved in a chemical reaction are described as reactants in products, correct?

A. You know, we were -- I just had one addition I wanted to make to what I had said previously.

In the FDA letter, they -- before I put this away, they actually describe or admit a [redacted] percent

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variability, United Therapeutics admits a [redacted] percent variability in the assay on page 3 of Exhibit -- I can't read -- of Exhibit 5.

They go on to describe essentially what I talked about, that the purity can't be greater 100 percent, and therefore, they have a [redacted]percent variability in their assay.

I'm sorry, where are we now?

Q. Well, since you brought that up, so what page were you looking at?

A. So I'm on page 3, Winkler Exhibit 5.

Q. Uh-huh.

A. And in the last paragraph it says, "During the initial analytical method validation, the results indicated there is about a [redacted] percent variability. Our spec of [redacted] to [redacted] was centered at [redacted] percent purity for the API." So again with a [redacted]percent variability, when the process for the manufacture was instituted in Silver Spring, the purity

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went up from a statistical standpoint, a variability of [redacted]percent may have result in -- I don't remember what "OOS" is -- on the high side when the upper limit of the spec is [redacted] percent.

So they're even now going, at least in their treatment of this, going over [redacted] percent, API cannot have a purity of greater than 100, so if the API 100 percent pure, there must be a [redacted]percent variability in the assay.

So that would suggest to me that these HPLC assays that they're essentially stating that they have a variability of [redacted]percent.

I just wanted to clear that up based upon what we talked about before.

Q. So if you look on page 4 of that same exhibit --

A. Yes.

Q. -- the first full sentence says, "UT proposes to shift the specification for the HPLC assay of treprostinil from [redacted] to [redacted] centered at

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[redacted] to [redacted] to [redacted] centered at [redacted] due to improved purity of the API produced in the Silver Spring, and an analytical variation of [redacted] percent in the HPLC assay method."

A. Yes.

Q. So the fact that it changed from a [redacted] to [redacted] percent was not because of an increase in the experimental error, it was due to an increase in the purity, correct?

A. Well, I think they're claiming increased purity, but I think the important thing here is that there is a variation of [redacted] percent that they're admitting to in the assay, which means that any number that they're obtaining here is going to necessarily, at least my interpretation, and I think one of skill would interpret this to mean that the number that they obtained is going to be plus or minus [redacted] percent.

They certainly are suggesting greater purity in Silver Spring, but

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they're still acknowledging the [redacted]percent variation, or [redacted]percent variability in the assay.

Q. Now, this is referring to the specification limits, correct?

A. Well, I think it's referring to the HPLC assay numbers which we see from the spec -- I don't know if they provide -- they don't provide any raw data here, but they certainly say that the spec can be as high as [redacted] percent.

And so, therefore, they explain that with a [redacted]percent variability in the assay. At least that's the way I understand this.

Q. So you understand that the specification is a range of allowable samples; is that a fair statement?

A. My understanding is that the specification that they're doing here is going to be either a range or a limit. In the case of the HPLC assay it certainly is a range.

Q. And if you look back at page

6, that we were discussing before, in assay, it changes the specification from not less than [redacted] percent to not more than [redacted] percent to not less than [redacted] percent, to not more than [redacted]. Do you see that?

A. Yes, I do.

Q. So because this is a specification, this is simply indicating what samples are, would pass specification, correct?

A. Yes. I think -- I'm reading this in the context of the sentence on page 3 that says that the results indicated [redacted] percent variability in the assay. That's really the most important sentence in the way I think, in explaining the variability that can be observed in these measurements; and therefore, if you will, the lack of precision in the assay. At least that's my interpretation on this statement. And I think how one of skill would interpret it.

Q. So for any specification

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submitted to the FDA, there must some range associated with the each value, correct?

A. Well, again, I can't speak to FDA submissions or specifications in general. I can only look at the one that is in front of me here. From chromatographic impurity of the impurities, it doesn't really supply a range, per se, but simply an upper limit. For the HPLC assay of the purity of the API, it does apply a range, but the range goes over 100 percent.

Q. So in your declaration, I believe you mention that there could be batch-to-batch variation, correct, in terms of the making treprostinil?

MR. POLLACK: Where are you pointing?

MR. DELAFIELD: Well, strike that.

Q. For the FDA specification, is it possible that these ranges are just an indication of what is acceptable and not

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what is experimental error?

A. Well, again I wasn't asked to opine on FDA specifications, specifically, if you will, but when I see that an assay range is over 100 percent, and I know that it's not physically possible to be over 100 percent, then that's suggests to me that the range that is over 100 percent is defining the error in the measurements that are being. Or at least the possible, as was stated by United Therapeutics in the letter on page 3, the [redacted] percent variability in the assay. And I think that's really the important thing, or that's the important thing that I note here.

Q. Okay. Going back to my question earlier, when you have a chemical reaction, you have both reactants in the products, correct?

A. Chemical reaction classically is consisting of reactants in products, correct.

Q. And usually the species

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written on the left-hand side of a reaction arrow are called reactants, right?

A. The species on the left are typically the reactants, that's correct.

Q. And the species on the right are typically called products, correct?

A. And the species on the right of the arrow are typically called product, that's correct.

I guess, I'm sorry, the only thing that I would add to that is that the products could contain impurities. In other words, there could be desired products as well as undesired products in a chemical reaction of starting material product formation.

And excuse me, there is one other thing I would add, which would be that there could be reagents of some kind, that would be added to the reaction as well.

Q. Okay. But product typically refers to what is produced as a result of

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the chemical reaction, right?

A. The product is typically the result of a chemical reaction, right, and again the crude product could be contain impurities of some kind as well.

(Winkler Exhibit 8, Excerpt from textbook entitled "Chemistry," [UT Exhibit 2011], marked for identification, this date.)

Q. You've been handed what's been marked as Exhibit 8, I believe.

A. Yes.

Q. Which is an excerpt from a "Chemistry" textbook authored by a Steven Zumdahl?

A. Yes.

Q. Do you recognize this document?

A. I'm trying to remember whether I consulted this document in my --

Q. I don't believe you cited it.

A. Okay.

Q. But --

A. I'm familiar with Zumdahl,

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yes.

Q. Sir, if you look on page 4, in the left column, it says --

A. I'm sorry. Could you just give me a minute to look at it?

Q. Sure, sure.

A. Thank you. Okay.

Q. So on the left column it lists the term "Product," do you see that?

A. Yes.

Q. And it says, "a substance resulting from a chemical reaction"?

A. Yes.

Q. Do you agree with that?

A. Well, as I mentioned, a product typically is a substance resulting from a chemical reaction. It's typically shown on the right of the arrow in the equation, but I think when we think about product or products of a reaction that could certainly include multiple products or impurities within the reaction would be part of the product of a reaction.

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Q. So purities would be part of the product of the reaction; is that correct?

A. I would certainly think of anything that is formed in a chemical reaction from a given starting material, to be part of the product of the reaction. It might or might not be the desired product. It might not or might not be the final product. It might or might not be the purified product, but it I would call all of that "product."

Q. And so if two products had different impurities, then they would be different products, correct?

A. Well, if two products contained different purities, the products, the desired material, if you will, is the same material, but the mixtures, the two mixtures would be different presumably prior to their purification.

Q. But because the product encompasses impurities, if impurities are

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different, then the products are different, correct?

A. Well, I think that depends whether we're talking about the crude product reaction before purification or after purification.

Q. So if after purification the impurities are different, then the products would be different, correct?

A. I don't think I would call the products different. I think I would say that the products are the same. The impurities within the products could be different in different chemical reactions.

Q. But if impurities are part of the product, if impurities are different, then wouldn't that necessarily make the product different?

A. Well, I think the product is -- is the product. The product is the molecule. If, for example, it were treprostinil, it's treprostinil. That would be the product regardless of

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whether there were impurities there or not.

And so I'm not sure I completely understand your question.

Q. Well, I think maybe I'm misunderstanding your answer.

You said the product is the molecule regardless of whether there are impurities there or not, but early I believe you testified the impurities are part of the product.

MR. POLLACK: Objection to form.

Q. So which is it?

A. I think the impurities are part of what I call the crude product. In other words, the product mixture, if you will. And then on purification one could isolate a pure or relatively pure product.

Relatively pure, if you will, final product.

So I'm differentiating between the crude mixture, which would be

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containing the product, which would be the initially formed reaction, and the final purified material.

Q. So if the crude product --

MR. DELAFIELD: Strike that.

Q. If one crude product had different impurities from another crude product, would they be different products?

A. They would be different mixtures but they would contain the same desired product.

Q. But the products would be different?

A. The mixtures could be different. But I don't know that they would be different.

THE WITNESS: Excuse me.

Q. So as this definition states, "Product" does refer to the result of a chemical reaction, correct?

A. The Zumdahl definition here states that, or at least the definition in this glossary states that a product is

a substance resulting from a chemical reaction.

Q. And you agree with that definition?

A. Well, again, I agree with it in a sense, but I think it's a little simplistic, because there could be multiple, multiple products formed in a reaction. There can be desired and undesired products. There can be impurities. And all of this could be part of the reaction mixture that results from any chemical reaction.

Q. So not all chemical compositions are products, correct?

A. Not all chemical compositions are products? I'm thinking about that.

I'd have to think about that.

Q. Well, put it another way: Product refers to the result of a chemical reaction and not just the fact that it is a chemical, correct?

A. Well, I think I speak to this in my report.

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Q. Is that part of your report that you wanted to discuss?

A. I thought I -- I must be thinking of something else. I'm sorry.

Q. So going back to product --

A. Yes.

Q. -- the word "product" has a subset definition to chemical composition, right?

A. Well, the definition of product in Zumdahl here is clearly a substance resulting from a chemical reaction.

Q. And you agree with that?

A. I think that this is certainly a definition, but I think that it's rather broad in not making clear whether it's the crude product or the final product, the desired product or the undesired product.

Q. So if the definition of "product" was just a chemical composition, would you agree with that?

A. If the definition of a product

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is simply a chemical composition, I think that certainly is one definition of a "product," but there are other definitions obviously, including the one shown here in Zumdahl.

Q. But a chemical composition can be a lot more than just a product, correct?

MR. POLLACK: I am going to object to form, lack of foundation.

A. I guess hypothetically a chemical -- I'm sorry, I forgot the definition you just gave.

Could you repeat it, please?

Q. Well, let me rephrase.

A reactant can be a chemical composition, correct?

A. A reactant can be a chemical composition, yes.

Q. So chemical composition and product are not synonymous, correct?

A. I think that it's true that a chemical composition is not necessarily the same as a product, but could be the

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same as a product.

Q. Is it fair to say that the term "chemical composition" doesn't indicate whether it's a product or not?

A. I think I've just stated a chemical composition could be a product or might not be a product.

Q. But just the term "chemical composition," from that term alone, you can't determine whether it's referring to a product or a reactant or a reagent, correct?

A. I think a chemical composition could include a product or a starting compound or a reagent, among other things.

MR. DELAFIELD: I think we're almost out of time if we want to break for lunch.

THE WITNESS: I'm in no hurry to break. I could keep going.

MR. DELAFIELD: We've got five minutes left on the tape.

MR. POLLACK: You want to go

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the five minutes and then we will break.

MR. DELAFIELD: Sure.

Actually I need to get other exhibits, so I think now is a good time to break.

MR. POLLACK: All right. Why don't we break.

THE VIDEOGRAPHER: The time is 1:24 p.m. and we're going off the record.

(Lunch recess taken at 1:24 p.m.)

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A F T E R N O O N S E S S I O N

(Time noted: 2:24 p.m.)

THE VIDEOGRAPHER: This begins media unit number 3. The time is 2:24 p.m. and we're back on record.

MR. DELAFIELD: Welcome back, Dr. Winkler, I hope you had a good lunch.

THE WITNESS: Thank you.

(Winkler Exhibit 9, Excerpt from textbook entitled, "Chemistry, The Central Science," [UT Exhibit 2012], marked for identification, this date.)

J E F F R E Y D. W I N K L E R, resumed.

EXAMINATION (Cont'd.)

BY MR. DELAFIELD:

Q. So I've handed you what has been marked as Exhibit 9, which is an excerpt from another chemistry textbook entitled "Chemistry, The Central Science," by Theodore L. Brown and others.

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Have you seen this document?

A. I don't think so.

Q. Okay. Are you familiar with this book?

A. No, I am not.

Q. Are you familiar with Brown and LeMay in terms of being chemistry authors of textbooks?

A. No, I am not.

Q. Well, if you turn to page 4, which is the back, very last page, at the upper left is another definition of "Product." Do you see that?

A. Yes, I do.

Q. And it says, "product is a substance produced in a chemical reaction; it appears to the right of the arrow in a chemical equation." Do you see that?

A. Yes, I do.

Q. And do you agree with that?

A. I certainly agree that that's one definition of a product.

Q. And that's similar to the

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definition from the other textbook we looked at right before lunch, right?

A. I would have to go back and look at that.

Q. Oh, that's okay. We can move on.

(Winkler Exhibit 10, Excerpt from textbook entitled, "Conceptual Chemistry, Understanding Our World of Atoms and Molecules," [UT Exhibit 2014], marked for identification, this date.)

Q. I've handed you what's been marked as Exhibit 10 which is another excerpt from another chemistry textbook entitled "Conceptual Chemistry, Understanding Our World of Atoms and Molecules," authored the by John Suchocki. Do you recognize this document?

A. No, I do not.

Q. If you look at page 3, about the middle of the left column, you see a definition for "Product"?

A. I do.

Q. And it says, "a new material formed in a chemical reaction appearing after the arrow in a chemical equation." Do you agree with that definition?

A. I think that certainly represents a definition of product.

Q. Is it an accurate definition?

A. I don't know what you mean by "accurate."

Q. Is that how you use the term "product"?

A. I think that this would be a possible definition of product, but would not be the only possible definition of product.

Q. But is this how you would use the word "product"?

MR. POLLACK: Objection to form.

A. I don't think I would use this precise definition, no.

Q. Why not?

A. I don't think I would, I don't

think I would use these exact words for my definition of product.

Q. Why not?

A. Because I don't -- I just don't think I would state it this way.

Q. But you don't have a reason to disagree with this definition?

A. Well, again, I think it's limiting, and I think a product could be more than what's described in this definition.

I'm not disagreeing with this as a definition of product, but I wouldn't think that this would be the only or exclusive definition.

Q. Are products ever not formed in a chemical reaction?

A. I think one could say that, yes.

Q. So you've used the term product to mean something other than a substance formed in a chemical reaction?

A. I think one could use product in a different, in a way different from

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that, yes.

Q. Can you think of an example?

A. I think one could think about a manufacturing product, for example, and that might not be the product of a chemical reaction, per se.

Q. Are you referring to the word "product" not referring to the chemistry definition of the word?

A. I'm afraid I don't understand your question.

Q. You said that one example would be a manufacturing product. Did you mean in a nonchemistry manner?

MR. POLLACK: Objection to form.

A. Not in a formal chemistry manner, but simply describing the word "product," a product could have numerous definitions and numerous meanings in different contexts.

Q. If you were teaching one of your chemistry students what a product is, would this be an acceptable

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definition?

A. I don't know that the material formed in the chemical reaction, for example, would have to be a new material to qualify as a product by my definition.

Q. Would a substance formed in a chemical reaction be an acceptable definition if you're teaching the concept of a chemical product to a student?

A. Well, I think I've discussed this question before. "Product" is a very broad descriptor and so the question is, is this initially formed product, is it the final product, is it the crude product? Those are all products, in fact. So the definition is rather a broad one.

The definition that I would use would be rather a broad one, in the absence of limiting descriptors.

Q. Well, if there were no other adjectives and you were just defining the word product, would this --

MR. DELAFIELD: Scratch that.

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Q. Assuming there are no adjectives defining the word "product," would the definition of substance formed in a chemical reaction be an acceptable definition to tell a chemistry student?

A. Well, again, the product of a chemical reaction would be essentially all of the substances that result from the treatment of a particular reactant with a particular set of reagents.

(Winkler Exhibit 11, A paper entitled, "A Pauson-Khand Approach to the synthesis of Ingenol," marked for identification, this date.)

Q. I'm handing you what's been marked as Exhibit 11, which is a paper entitled, "A Pauson-Khand Approach to the synthesis of Ingenol."

MR. DELAFIELD: I'm sorry.

MR. POLLACK: Do you have another copy?

MR. DELAFIELD: Sorry about that.

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Q. Do you recognize this document?

A. Yes, I do.

Q. Are you one of the authors of this document?

A. I am.

Q. So if you look at the abstract, the first sentence you state, "Pauson-Khand cyclization of dioxanone photoadduct 21 leads to the formation of a single product in good yield."

Do you see that?

A. I do see that.

Q. So your use of the word "product" here is in reference to what comes after the arrow in that chemical reaction, correct?

A. That is correct.

Q. And that's the result of the chemical reaction, correct?

A. I'm sorry, I don't understand your question.

Q. When you used the word "product" here, you're referring to the

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result of the chemical reaction, correct?

A. Yes, I am.

Q. So that's how you have used the word "product" in at least this paper, correct?

A. Well, in this paper, what I state is that "cyclization of the dioxanone photoadduct 21 leads to the formation of a single product in good yield." And so that single product in fact is the compound that's shown as 22 in the box above.

Q. Okay. And if you turn to page 1491, in the document, and the first full sentence on the left column underneath scheme 6 says, "The structure of 18, the sulfone derived from 17, was confirmed by x-ray crystallographic analysis" --

MR. DELAFIELD: Actually, strike that.

Q. The next sentence says, "Heating sulfoxide photoadduct 17 to 160 degrees celsius in quinoline led to the formation of the desired methylene

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photoadduct 11, the formal product of [2+2] cycloaddition of 10 (Scheme 4) in good yield."

Do you see that?

A. Heating sulfoxide 17 led to the formation of -- two plus two -- yes, I do see that.

Q. So in that sentence when you use the word "product," you're referring to the substance that forms in the chemical reaction, right?

A. Well, what I'm referring to here is that 11, structure 11 is the formal product that would result from two plus two cycloaddition of ten, the structure which is shown in scheme 4.

Q. And so the product is what results from the cycloaddition, correct?

A. Well, it's not actually true, because 10 does not undergo -- I think in this paper, we explain that at ten does not undergo the cycloaddition, and so instead, I refer compound 11 as the formal product of cycloaddition, and that

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is that is the compound that would have been obtained had chem undergone cycloaddition.

And that's why I refer to it as a "formal product."

So in fact 11 in this particular case never results from compound ten.

So that would be an example of -- of the vagaries, I guess, of the use of the word "product," because in this particular case, from my own, my own research work, you can see that I've characterized the compound as a product, when in fact it does not result from the reaction of the starting compound, because it is in fact, in this case, a formal product.

Q. But here you use the word "product" in the hypothetical sense as the result of the cycloaddition of 10; is that fair to say?

MR. DELAFIELD: Strike that.

Q. You wouldn't say the formal

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reactant of two plus two cycloaddition of 10, correct?

A. Well, I think the formal reactant in the two plus two cycloaddition would be compound 10.

But in fact compound 10 does not undergo -- excuse me -- cycloaddition.

Q. But that would be different than the formal product of two plus two cycloaddition of 10, correct?

A. I'm sorry, could you repeat the question?

Q. You said that the formal reactants of two plus two cycloaddition of ten would be ten, right?

A. That is correct.

Q. That's different than the formal product of two plus two cycloaddition of ten, correct?

A. The formal product of ten, right, is different from ten, that's certainly correct. But it underscores the idea that in this particular context,

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the product does not result from the starting tip.

Q. But the word "product" is just used to indicate had cycloaddition of ten worked, that would have been the result; is that fair to say?

I mean that's why you're using the word "product" as opposed to "reactant" as opposed to "chemical"?

A. Well, I don't know that the cycloaddition of ten would give 11, because it never -- it never transpired. But I describe in this paper 11 as the formal product of cycloaddition of ten, because that was the product that I anticipated would be formed if ten had been able to undergo reaction, which it could not, and in fact, that is really much of what the paper is describing, that, that chemistry.

Q. So let's look back at the '393 patent, which is Exhibit 3. If you look at claim 1, this is on column 17.

A. Column 17, okay.

Winkler

Q. And claim 1 says, "A product comprising a compound of formula I or a pharmaceutically acceptable salts thereof, wherein said product is prepared by a process." Do you see that?

A. Yes.

Q. So when it says, "A product comprising a compound formula I or a pharmaceutically acceptable salt thereof," is it your opinion that product includes any amount of impurities?

A. I think I addressed this question in my report. I guess it's not here. I must have read it somewhere else.

But my understanding is that the term "comprising" when added into the claim indicates that this describes the product comprising of formula compound I means that it includes the compound of formula I but can include other materials as well.

Q. Okay. But you don't offer any opinions regarding how the claim should

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be construed, correct?

A. No. My understanding simply of what comprising means in the context of the claim is that it would include the product of, the compound of formula I, and the possibility of other things being there, such as impurities. That is my opinion.

Q. And similarly you weren't asked to apply certain claim constructions to your opinion, correct?

MR. DELAFIELD: Strike that.

Q. Your declaration does not contain any specific claim constructions with respect to the claim terms, correct?

A. I don't think so, but I would have to check.

Q. Well, when you just checked your declaration, were you checking for claim constructions?

A. I simply looked for a discussion of "comprising," which I know I have seen some of the documents and thought was in my report, but -- I'm

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sorry, in my declaration, but was not.

But my understanding of the common usage of "comprising" here is that we -- include the compound the formula I and other things, or at least it would allow the possibility for other things, including impurities being met.

Q. So then the term product --

MR. DELAFIELD: Strike that.

(Winkler Exhibit 12, Patent application WO 2005/007081, [SteadyMed - Exhibit 1005], marked for identification, this date.)

Q. Sir, you've been handed what has been marked Exhibit 12, which is a patent application WO 2005/007081, which we refer to as the Phares application. Do you recognize this document?

A. Yes.

Q. And this is one of the documents that you rely upon in your declaration, correct?

A. Yes, it is.

Q. So if you keep that open and

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if you could also look at your declaration.

So in your declaration, if you look at paragraph 48 --

A. Yes.

Q. -- you state, "Phares inherently discloses the same synthesis of treprostinil as set forth in the independent claims, Claims 1 and 9, of the '393 patent. "

And then at the bottom of that paragraph you say, "Accordingly, Phares inherently anticipates both independent of Claims 1 & 9."

Do you see that?

A. Yes, I do.

Q. Sir, what do you mean by "inherently anticipates"?

A. So what I mean by "inherently anticipates" in paragraph 48 is that what Phares describes on pages 41 and 42 -- actually starting -- excuse me -- starting at the bottom of 39, Phares teaches that minus treprostinil, which is

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the enantiomer of treprostinil, can be synthesized as follows, and then shows a synthetic re, which is quite similar to that shown in the Moriarty teaching, but this one delivers compound 2, which is the enantiomer of treprostinil, that is treprostinil minus.

And the point is that at the top of, in the middle of 39, it teaches that enantiomers can be synthesized using reagents and synthons of an enantiomeric chirality, which is to say that my opinion is that the scheme on page 40 teaches inherently anticipates the synthesis of the plus treprostinil.

Q. So I'm not clear about what is inherent about the disclosure you just described.

So why is it your opinion this inherently anticipates as opposed to just anticipates?

A. Well, I guess it's a subjective question of whether it anticipates inherently or expressly, but

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the reason I use the word "inherently" here is that the actual synthetic route that is shown on page 40 is for the synthesis of the enantiomer of the desired product, of the API.

But certainly one of skill and myself could look at this and see that one could use this information that's included on page 40 here to prepare either the enantiomer, the minus compound, as shown or could also be used to prepare the plus compound.

It does not show the plus compound, the synthesis of the plus compound explicitly, although it certainly shows compounds derived from the plus compound in the teachings of the patent.

But I say that there is inherent anticipation because one of skill would understand that the synthesis of the plus enantiomer is, if you will, anticipated by the chemistry that is shown on page 40.

Winkler

Q. So the Phares reference doesn't explicitly disclose the synthesis of treprostinil, correct?

A. Well, that's not actually true. The Phares reference explicitly discloses the synthesis of minus treprostinil, and explains that one of skill -- I'm sorry. It explains that enantiomers could be synthesized using reagents and synthons of enantiomeric chirality.

So inherently or implicit in the teaching on page 40 is the synthesis of the plus or, if you will, desired enantiomer of treprostinil.

Q. As written, the exact synthesis of plus treprostinil is not explicitly disclosed in Phares, correct?

MR. POLLACK: Objection to form, and asked and answered.

A. I think I've already answered that, that is that one of skill would look at the route that is provided on page 40 and the information that is given

on page 39 about being able to prepare either an enantiomer and use this teaching as, to inherently, if you will, understand that one could prepare either plus or minus treprostinil using the route that is shown here.

Q. So is it your opinion that it is explicitly disclosed or not?

A. I think what my opinion is on paragraph 48 that is that Phares inherently anticipates the claim because it shows the synthesis of treprostinil, it happens to show the synthesis of the minus compound, but one of skill could use essentially the same route to make the plus compound.

Q. And you used the word "inherently," because the plus compound synthesis is not explicitly disclosed in Phares?

A. I use "inherently anticipates" because it is the synthesis of the minus compound that is explicitly shown on page 40.

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Q. Okay.

A. But again, implicit in the disclosure on page 40 would be the synthesis of the plus compound as well.

Q. So is it your opinion that a person of ordinary skill would need to experiment based on this disclosure to get to treprostinil because it's not explicitly disclosed?

MR. POLLACK: Objection to form.

A. Well, my opinion is that the Phares patent on page 40 teaches the synthesis of the minus treprostinil and teaches by the information on page 39, that the enantiomer of the compound could be synthesized, using, if you will, enantiomeric starting compounds.

THE WITNESS: Excuse me.

Q. There are several different synthetic routes to make treprostinil; is that correct?

A. I have seen more than one synthetic route for the preparation of

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treprostinil, that is correct.

Q. And Phares lists several of those in the document, correct?

MR. POLLACK: Objection to form.

A. I don't remember. I'd have to look.

Q. If you look at page 99?

A. I'm sorry, 99 on Bates or 99 on the document?

Q. On Bates.

A. Okay.

Q. You cite this in your declaration as disclosing treprostinil diethanolamine salt, and that's at paragraph 51, if you want to look at that. Is that accurate?

A. Yes.

Q. But the Phares reference does not disclose the full synthesis of how that's made, correct?

MR. POLLACK: Objection to form.

A. Well, actually I think that it

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does disclose how that compound is made. In fact, it teaches on page 22, page 24 Bates, it teaches that treprostinil diethanolamine UT-15C is prepared by dissolving treprostinil acid acid -- I assume that's mistake. It should be acid once -- "is dissolved in a one-to-one molar ratio mixture of ethanol: Water and the diethanolamine is added and dissolved. The solution is heated and acetone is added as an antisolvent during cooling."

So the synthesis of the compound of claim 1 with the structure shown in 49 is described on page 24, Bates, of the Phares reference.

Q. And on that same page though where it says the treprostinil acid is dissolved, it doesn't indicate the source of that treprostinil acid?

A. It does not give us a cite to where in the patent the treprostinil acid comes from, but as we've already discussed, beginning the fact that the

synthetic route is shown on -- synthetic route is shown on page 42 of the Bates, the presumption that I made, and I think that one of skill would make is that this would be this route or the corresponding route that would lead to the preparation of the pulse treprostinil that would be used to prepare the compound that's discussed on page 24 of the reference.

Q. But as you mentioned earlier, the actual synthesis for plus treprostinil is not explicitly disclosed in Phares, right?

A. I think it's not explicitly shown, but it would certainly be apparent to one of skill and to myself that if one knows how to make the enantiomer, given the teaching on page 39 of the document, page 41 Bates, enantiomers of these compounds can be synthesized using reagents and synthons of enantiomeric chirality of the above reagents, certainly implicit in that statement is that the enantiomers of these compound,

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in other words, the enantiomer of minus treprostinil can be prepared in the same manner.

Q. If you look at page 11 in the Phares document, Bates page 11 --

A. Yes.

Q. -- at the bottom of the second paragraph, it says, "compounds of the present invention can also be provided by modifying the compounds found, U.S. Patent numbers 4,306,075 and 5,153,222 in like manner.

Do you see that?

A. Yes, I do.

Q. Do you recall reviewing either of those patents?

A. I don't remember those numbers offhand.

Q. So if treprostinil was made by a different process, and then subjected to form the diethanolamine salt, it could have a different impurity profile, correct?

A. I think the sort, the

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different synthetic procedures could lead to different impurity profiles, but again, my conclusion from reading Phares is that the material that's described on page 24 was prepared according to the synthetic scheme that is shown on page 42 Bates.

I think that would be the logical conclusion that one of skill would draw, and certainly what I concluded from reading Phares.

Q. But there is nothing in this document that says that is how they prepared treprostinil, correct?

MR. POLLACK: Objection to form.

A. I think the point is that if they go about showing a synthesis of treprostinil and they show subsequent chemistry of treprostinil, the opinion of one of skill, and certainly my opinion is that they would have use the treprostinil, the synthesis of which is described in the patent to make these

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other compounds.

Q. But as you said, the synthesis of the plus treprostinil isn't explicitly disclosed. It's only mentioned as a possibility from enantiomer, correct?

A. Well, I think --

MR. POLLACK: Objection to form. You can answer. Asked and answered. You can answer.

A. I think it would be obvious to one of skill having outlined the synthesis, the explicit synthesis of the enantiomer and acknowledging that one can prepare either of the two enantiomers depending on the chirality of the starting material, it would be obvious to one of skill that one could prepare plus treprostinil from the information that is given in the patent.

Q. Is there a difference between inherent anticipation and obviousness?

MR. POLLACK: Objection to form, lack of foundation.

A. So I think I discussed this in

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my report. I discussed the legal concepts that were explained to me in paragraph 16.

Excuse me.

I state that counsel explained to me that the law recognizes anticipation in which a single prior art reference must disclose each and every element of a claim either expressly or inherently to anticipate the claim and render it invalid. And then I understand on paragraph 18 that obviousness, a patent claim is invalid for obviousness if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious to a person of ordinary skill in the art at the time of invention. For, I understand, I go on to say, I understand that for a single reference or a combination of references to render the claimed inventions obvious a person of ordinary skill in the art must have been

able to arrive at the claims by modifying or combining the applied references.

So that's the difference as I see it.

Q. So then is it your opinion that the treprostinil diethanolamine disclosed in Phares would have been obvious based on the description of how you could make the enantiomer?

A. I think what I said in my -- in my declaration is that Phares inherently anticipates the claim and then I go on to say that under obviousness that the combination of Moriarty with Phares or Kawakami would have made the '393 obvious.

Q. The Phares reference doesn't disclose any specific impurities in treprostinil or treprostinil diethanolamine, correct?

A. The Phares teaching does not disclose the impurities, but it does in fact disclose the purity in the sense that we have the melting point by DSC by

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differential, D-I-F-F-E-R-E-N-T-I-A-L, scanning, S-C-A-N-N-I-N-G, calorimetry C-A-L-O-R-I --

THE WITNESS: You're going to have to do that one yourself.

A. Calorimetry that the melting point of the form B material that was obtained suggests based on the other information that I've seen that the material was quite pure.

Q. But Phares doesn't disclose any specific impurities, correct?

A. Phares does -- I don't think -- I would to check through, but I don't think that Phares discloses impurities, per se.

Q. And in terms of --

A. But does show -- excuse me -- but does this show this sharp melting form B material that suggests something of quite high purity.

Q. In terms of the level of purity, it doesn't disclose a number for that purity other than melting point,

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correct?

A. I don't remember, but I think that's true.

Q. Now, you mentioned the --

A. I would have to check.

Q. If you turn to page 91 of Phares, it says on the first full paragraph, "The thermal data for form B as shown in figure 21, the DSC thermogram shows a single endotherm at 107 degrees celsius that is consistent with a melting event."

Is that the melting point that you referred to?

A. Yes, it is.

Q. So if we turn to figure 1, that's on page 121?

A. Yes.

Q. And it shows the melting point of 107.06; is that correct?

A. That is correct.

Q. And the substance starts to melt when that peak starts to go down and basically stops melting once the peak

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goes back up; is that a fair characterization of what that peak means?

MR. POLLACK: Objection to form.

A. I think that's right but I would have to check.

Q. Are you not sure what this graph represents?

A. Well, I know that this graph represents the DSC thermogram of the sample.

Q. So if you look at that peak in the temperature range at the bottom, it looks as though the peak starts at a little above 100 and stops at the next mark, which I guess is 110 or 115, based on the scale.

Do you see that?

A. It's hard for me to eyeball exactly where it starts and where it stops.

Q. But would you agree that it starts to melt close to 100?

MR. POLLACK: Objection to

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form.

A. I think you can certainly see a change in the thermogram starting at about 100 degrees.

Q. And then the peak ends close to 110?

A. I think that's about right.

Q. So that indicates a melting range of approximately 10 degrees; is that right?

MR. POLLACK: Objection to form.

A. I don't think that's how -- how DSC is typically interpreted, because, for example, if you look at figure 18 and look at the -- the thermogram for the form A, what you see is a similar, relatively similar range in terms of the width at the top of the scan. But in fact you see a very different, sharp minimum at 103 degrees. And so I think that these thermograms are taken to be quite accurate descriptors of melting temperature and you can see in

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fact, even though the wide part of the thermogram is roughly comparable, I would say, in figure 18 and figure 21, we see very sharp minima with very different numbers, and so that's why I'm quite comfortable relying on figure 21 as expressing a melting temperature of 107 degrees.

Q. So you referred to figure 18 as form A -- excuse me -- the treprostinil diethanolamine; is that right?

A. Correct.

Q. And there is little hash marks to the left and right of the peak at 87.81 degrees celsius and 112.09 degrees celsius. Do you see that?

A. Yes. Excuse me.

Q. And so doesn't that indicate the start and stop of the melting range for form A?

MR. POLLACK: Objection to form.

A. I'm not sure exactly what the

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significance is of the 87.81 and the 112.09. I think the thing that I focused on was the rather dramatic difference between 103 sharp peak and the 107 sharp peak in figures 18 and 21 respectively.

Q. But you relied on this information as a proxy for the purity of the treprostinil diethanolamine, right?

A. I did in the context of the 103 number, and 107 number that I see clearly as at the bottom of the sharp peaks that we see for the thermograms for these two substances.

Q. So sitting here today, you can't say whether the beginning of the peak on the left side is when the sample started to melt?

A. I think what I -- what I really mean to say here is that I don't know sitting here -- I can't remember sitting here today whether -- what the significance is of the 87.81 and 112.09 in figure 18 relative to the information that is imparted by the sharpness of the

peak at 103, and it's the difference between the sharpness of the peak at 103 in figure 18, and the sharpness of the peak at 107 in figure 21 that I use to conclude that the purity of the form B that was obtained in Phares was such that a 107-degree melting point was obtained.

Q. But looking at figure 21, the peak at its base is approximately 10 degrees across, right?

A. Well, I don't know what you mean by -- by the "base."

Q. When the peak starts to form and then when the peak stops on the other side.

A. Yes, there appears to be a range there of what could be about 10 degrees.

Q. And sitting here today, you can't say whether or not that indicates when it starts and stops melting?

A. I don't remember.

Q. This is a graph of heat flow versus temperature, right?

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A. That's correct.

Q. And as the temperature rises, it starts to melt and then degrade, or decompose after a certain temperature; is that fair to say?

A. I don't know whether it's decomposing or simply melting.

Q. So at 107 degrees you don't know if that is a melting point or a decomposition point?

A. No. In other words, I said that this is the melting point at 107 degrees. I thought you said that it decomposed, and I'm not sure that it undergoes decomposition at its melting temperature.

Q. Isn't it true that the peak is caused by the fact that melting is endothermic which causes a reduction in heat flow as the temperature rises?

A. That is my understanding, yes.

Q. And so when the melting starts, the endothermic reaction starts which causes the speak to start to form,

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right?

MR. POLLACK: Objection to form.

A. I'm afraid I don't understand your question.

Q. So I guess I just want to clarify, sitting here today, you don't know whether the base of that peak at the top of the graph indicates the melting range or not?

A. I don't remember. I would have to check.

Q. If the melting range were 10 degrees, that would not be a very pure sample, correct?

MR. POLLACK: Objection to form.

A. You see the point is that, I have to go back and check, but from what I remember, the range that's observed above there in DSC does not directly correlate to the degree range that one typically sees on recording a melting point on a hot plate apparatus. So the

width there that you see is not necessarily the same thing that I would expect to see if I were recording a melting point with a melting point apparatus.

Q. Do you know if a melting point apparatus is more accurate than a DSC?

A. My understanding is that a DSC is more accurate for obtaining the number of 107.06 that we see there, but again, I would have to go back and check to see what the significance is of the width of the peak that you're describing.

Q. So sitting here today, you can't say for certain how pure the sample is, correct?

A. Well, sitting here today, what I can say is that the DSC shows a melting temperature of 107 degrees, and when I compare that 107 degrees melting point of the form B material to the information in the '393, I conclude that this material is, at least it's pure, if not more pure than the material obtained in the '393.

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Q. But other than statement you don't know any other evidence to support that, correct?

A. I think the evidence that I have to support that is the melting temperature of 107 degrees that is clear from -- to me from figure 21 for the form B material.

Q. Is it fair to say that a more narrow melting point range is more pure than a broad melting point range?

A. When those melting points are obtained with a melting point machine, typically what one does is to correlate the tightness of the melting point range to the purity of the material.

But -- excuse me -- in the case of the DSC measurement, I don't know what the significance -- I don't remember what the significance is of the distance at the top of the peak.

Q. So you don't know the melting point range for this sample, correct?

A. No. All I know is that the

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DSC is showing a melting point of 107 degrees.

Which is higher than the melting points that were described in the '393 for the same material.

Q. And based on Phares, there is no specific level of purity disclosed for the material, correct?

A. Well, the primary measure of purity in Phares in my opinion is the 107-degree melting point for the form B material, which is, as I mentioned before, is higher than the melting point that is described in the '393 for the form B material.

From that I would conclude that the material here is at least as pure if not more pure than the material described in the '393 patent.

Q. Phares does not disclose a specific level of purity. You're only basing your analysis on the DSC, correct?

A. I don't remember any other description of purity in the -- in Phares

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other than this melting point. But given two samples of the same polymorphic material, if one is higher melting than the other, I would assume that that compound would be the purer.

I would note, I would really know that that compound would be the purer. I can't think of any examples where two samples of the same material and the same polymorph where the lower melting material would be more pure.

In my experience, the higher the melting material is the more pure.

Q. And two samples --

MR. DELAFIELD: Strike that.

Q. If one sample had a high melting point impurity and it -- as opposed to another sample that did not have high melting point impurity, is it possible to have a higher melting point even if the overall purity is lower?

A. So it turns out that the way melting point depression works is that even if the additive or the impurity has

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a higher melting point itself, what it tends to do is to disrupt or disorganize the crystal structure of the -- of the primary component, to such an extent that ironically, even though it has a higher melting point by itself it can reduce and typically does reduce the melting point of the primary material.

So typically impurities do lower melting point.

Q. But you're not aware of any evidence in this case that that is necessarily true for treprostinil or treprostinil diethanolamine, correct?

MR. POLLACK: Objection to form.

A. I'm sorry, I don't understand your question.

Q. You didn't cite any documents or prior art that showed that a higher melting point was a higher purity with regard to the treprostinil or treprostinil diethanolamine, correct?

MR. POLLACK: Objection to

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form.

A. I think that's a general teaching for one of skill would understand that the higher the melting point -- it may even be cited in some of the references that I supplied in some of these general textbooks, but I'm not positive. But in certainly any organic chemistry textbook, it would explain that the higher melting point the purer the sample is.

Assuming, of course, the same polymorph.

(Winkler Exhibit 13, copy of a Journal of Organic Chemistry paper entitled, "The Intramolecular Asymmetric Pauson-Khand Cyclization as a Novel and General Stereoselective Route to Benzidene Prostacyclins: Synthesis of UT-15 (Treprostinil)," [SteadyMed-Exhibit 1004], marked for identification, this date.)

THE WITNESS: Thank you.

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Q. You've been handed what's has been marked Exhibit 13 which is a copy of a Journal of Organic Chemistry paper entitled, "The intramolecular Asymmetric Pauson-Khand Cyclization as a Novel and General Stereoselective Route to Benzidene Prostacyclins: Synthesis of UT-15 (Treprostinil)."

Do you recognize this document?

A. Yes, I do.

Q. And is this one of the documents that you relied upon in your declaration?

A. Yes, it is.

Q. So if you turn to page 13, which is the last page in the document, and at the bottom of the left column it begins the final step in the synthesis for UT-15 compound 7. Do you see that? On the very last page?

A. I'm sorry, could you repeat that, please?

Q. Yes. If you could turn to the

very last page, 13?

A. Yes.

Q. And at the bottom of the left column, starts, the final step for the synthesis of UT-15?

A. Yes.

Q. Do you see that?

A. Yes, I do.

Q. And that continues on to the next column and at the bottom of the right column, right above "Acknowledgment," it says -- let's see. Purity 99.7 percent, I think you cite that number in your declaration?

A. Yes, I do.

Q. Now, do you know if that number refers to the total related impurities or the assay?

A. Well, the way it's described here, I think one of skill would assume, as I did, that this refers to the assay.

Q. Is there anything discussing the assay here?

A. No, there is not.

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Q. So it could be the total related impurities, correct?

MR. POLLACK: Objection to form.

A. Again, my assumption in reading this is that this is an assay for the treprostinil itself.

Q. But earlier today we saw several documents discussing the purity of the treprostinil in terms of the total related substances, correct?

A. Yes, we did.

Q. And so if one number is reporting total related substances and another is reporting assay, you can't really compare those numbers, right?

A. Well, I don't think that's true. I think what I can certainly compare here is that when I look at the 99.7, especially given the fact that there is no discussion of related impurities, I would presume here that this 99.7 refers to an HPLC assay of the treprostinil. I think that's what one of

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the skill would assume here.

Q. But there is also no discussion of assay, correct?

A. Excuse me.

MR. POLLACK: Objection to form. You can answer.

A. There is no discussion, I don't think that there is any discussion in the text of the assay conditions for the method that was used to establish purity.

So I assume it's just the area under of the curve for the treprostinil.

Q. So you assume it's that but you're not sure, right?

A. Well, like I said, in reading this, I would read this an HPLC assay.

(Winkler Exhibit 14, Japanese Patent Application 56-122328, [SteadyMed-Exhibit 1007], marked for identification, this date.)

Q. You've been handed what's been marked as Exhibit 14, which is a Japanese patent application 56-122328, which is

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referred to as the Kawakami reference.

Do you recognize this document?

A. Yes, I do.

Q. And is this a document that you relied on in your declaration?

A. Yes, it is.

Q. If you turn to page 4, at the top it says, "This reaction has an excellent yield but has a serious drawback of typically producing an unnecessary 7Z isomer as a byproduct," and then it cites a paper. Do you see that?

A. Yes, I do.

Q. And then it goes on to say, "In addition, the properties of the two are extremely similar for 7E, and 0.17 for 7Z; making separation and purification very difficult." Do you see that?

A. Yes, I do.

Q. Do you agree that it's typically difficult to separate and

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purify isomers?

A. I think that very much depends on the isomers.

Q. With respect to the prostacyclin and prostaglandin isomers?

A. I think it would be difficult for me make that kind of broad generalization. I think sometimes it's very difficult and sometimes it's quite straightforward.

Q. With respect to prostacyclin and prostaglandin --

A. Excuse me.

Q. -- isomers it's your opinion that it can be easy or it can be hard basically?

A. I think it depends on the isomers in question.

Q. It goes on to say that, "Also, the melting point of this compound is fairly low and crystallization is therefore severely impeded by the admixing of trace impurities." Do you see that?

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A. Yes, I do.

Q. So essentially it's saying that even trace impurities can greatly affect the outcome of the --

MR. DELAFIELD: Strike that.

Q. It's saying that even trace impurities can affect the overall purity in terms of crystallization, right?

A. I think what it's saying is that the crystallization is severely impeded by the admixing of trace impurities. That's how I read this.

THE WITNESS: Excuse me.

Q. So in some cases even trace impurities can be important to analyze and remove, correct?

A. I'm sorry, could you repeat that please?

Q. So in some cases even trace impurities need to be removed, correct?

A. I think all this teaches me is trace impurities can impede crystallization, in some cases, including the case that's shown here. That's the

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conclusion that I think a person of skill or a I, myself, would reach here.

THE WITNESS: Excuse me.

MR. DELAFIELD: Bless you.

Q. So this paper doesn't disclose treprostinil, correct?

A. Well, this paper describes a methanoprostacyclin derivative. So in other words, it's a compound that is replated to treprostinil.

Q. But none of the compounds have the three-ring structure that's formed treprostinil, correct?

A. None of the compounds in this paper or in this patent I think -- that's actually not true.

There are some compounds that are described in this patent that have as many as five rings.

But the compound that is shown in the -- in this scheme, compounds two and two prime, I think has shown each have two rings.

Some of the compounds under

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formula I, for example, on page 5 can have five rings, as I count them, depending on the nature of R-1.

Q. So let me rephrase.

None of the compounds disclosed in this paper has three fused rings; is that more accurate?

A. I think it is true that none of the compounds have three fused rings, although I should say add that the notion of taking carboxylic acid, preparing the amine salt as a purification technique and then regenerating the acid is not something that I would necessarily think would be dependent on the number of rings in the structure in terms of its efficacy, because I've seen this procedure used on any of a number of compounds with any of a number of different rings.

Q. But you agree that the paper doesn't disclose any structures of three fused rings, correct?

A. Excuse me. I agree that the

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paper does not disclose any structures with three fused rings.

Q. Now, the separation procedure described is in reference to separating Z and E isomers, correct?

A. That is correct.

Q. And it's not in reference to separating stereoisomers, correct?

A. That is not correct.

Q. Why is that?

A. Because enantiomers are stereoisomers.

Q. Stereoisomers require a chiral center, correct?

A. No, that is not true.

Q. So this paper does not include separation of diastereomers, correct?

A. Actually compound 2 and compound 2 prime by the definition that I use in teaching stereochemistry, and that I've been using for, for over 30 years, two and two prime are in fact diastereomeric compounds.

Q. Do two and two prime have

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different chiral centers?

A. Two and two prime do not have different chiral centers or different stereo centers is the terminology that we typically use now.

Q. So to clarify, this paper doesn't describe the separation of compounds with different stereo centers, correct?

A. The paper does not describe the separation of compounds with different stereo centers, but it does describe the separation of diastereoisomers or stereoisomers, more general.

Q. And the only difference there is whether it's E or Z at the double bond at the top of the ring, correct?

A. That is correct.

MR. POLLACK: Would this be a good time for a break?

MR. DELAFIELD: Getting close. So just a little bit longer.

THE WITNESS: A break would be

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great.

MR. POLLACK: Do you want a break?

MR. DELAFIELD: Okay.

MR. POLLACK: We've been going over an hour and a half.

THE VIDEOGRAPHER: The time is 3:48 p.m. and we're off the record.

(A brief recess was taken.)

THE VIDEOGRAPHER: This begins media unit number 4. The time is 4:03 p.m., and we're back on the record.

Q. I just have a couple more questions. If you could turn back to your CV, Exhibit 1.

A. It's got to be here somewhere. Yep.

Q. On the first page, I was just curious what is the "Philadelphia Organic Chemists Club"?

A. The Philadelphia Organic Chemists Club is a consortium of organic chemists in the Delaware Valley area. So

it's been in existence for a long time and it -- like I said, it's basically a consortium of the pharmaceutical companies in the area and academics in the area.

Q. And what was the award for?

A. The award was in recognition of my research accomplishments.

MR. DELAFIELD: All right. I don't have any more questions.

MR. POLLACK: I have a very short redirect.

EXAMINATION BY

MR. POLLACK:

Q. If you could pull out Winkler deposition Exhibit 13, and that's the document also known as SteadyMed Exhibit 1004.

A. Yes.

Q. And if you could turn to page 13?

A. Yes.

Q. Are there any -- is there any information stated here regarding how the

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purity of 99.7 percent was determined?

A. Well, at the end of the experimental procedure for the preparation of UT-15, that is compound 7 in Moriarty, starting about three quarters of the way down, the paragraph on the right side of page 13, you can see that after the C13 MMR data, it describes a UV Landham Acts for the compound, as well as HPLC information.

And so it actually indicates the column that was used and the dimensions of the column. It indicates the flow rate that was used. And it also indicates the mobile phases, mobile phase A and mobile phase B, as well as the retention time of the treprostinil, treprostinil under these conditions.

Q. So what does that tell us about how the 99.7 percent was determined?

A. So that simply tells us what conditions they were using in the HPLC to determine this purity.

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Q. And what equipment, what piece of equipment was used to determine this purity?

A. Well, sir, this is indicating that the purity was determined by HPLC.

Q. Okay. And is that, what does that tell you about whether or not it's from assay or related impurities, what does that tell you about what method was used?

MR. DELAFIELD: Objection to form.

A. Well, I think this would indicate to me that, as I had indicated before, that the purity is being determined by the HPLC assay method.

MR. POLLACK: No further questions.

MR. DELAFIELD: I have one quick question, following up on that.

EXAMINATION BY

MR. DELAFIELD:

Q. If you recall we discussed two

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ways purities were determined in the documents we looked at; the assay and the total related substances. Do you recall that?

A. Yes, I do.

Q. And you also recall that HPLC was used for both of those determinations, correct?

A. Yes, I do.

MR. DELAFIELD: Okay. I have no further questions.

THE VIDEOGRAPHER: The time is 4:07 p.m., June 14, 2016, and this completes today's video deposition of Jeffrey D. Winkler.

(Time noted: 4:07 p.m.)

STATE OF _____)

) :ss

COUNTY OF _____)

I, JEFFREY D. WINKLER, Ph.D., the witness herein, having read the foregoing testimony of the pages of this deposition, do hereby certify it to be a true and correct transcript, subject to the corrections, if any, shown on the attached page.

_____

JEFFREY D. WINKLER, Ph.D.

Sworn and subscribed to before me,

this _____ day of _____, 2016.

_____

Notary Public

C E R T I F I C A T E

STATE OF NEW YORK)

: ss.

COUNTY OF NEW YORK)

I, Jennifer Ocampo-Guzman, a Notary Public within and for the State of New York, do hereby certify:

That JEFFREY D. WINKLER, Ph.D., the witness whose deposition is hereinbefore set forth, was duly sworn and that such deposition is a true record of the testimony given by the witness.

I further certify that I am not related to any of the parties to this action by blood or marriage, and that I am in no way interested in the outcome of this matter.

IN WITNESS WHEREOF, I have hereunto set my hand this 15th day of June 2016.

J. Ocampo-Guzman

JENNIFER OCAMPO-GUZMAN, CRR, CLR

1

2 ----------I N D E X ----------

3 WITNESS EXAMINATION BY PAGE

4 JEFFREY WINKLER MR. DELAFIELD 7, 208

5 MR. POLLACK 206

6 ---------- EXHIBITS ----------
WINKLER FOR I.D.
7

25

EXHIBITS (Continued):

INSTRUCTIONS TO WITNESS

Please read your deposition over carefully and make any necessary corrections. You should state the reason in the appropriate space on the errata sheet for any corrections that are made.

After doing so, please sign the errata sheet and date it.

You are signing same subject to the changes you have noted on the errata sheet, which will be attached to your deposition.

It is imperative that you return the original errata sheet to the deposing attorney within thirty (30) days of receipt of the deposition transcript by you. If you fail to do so, the deposition transcript may be deemed to be accurate and may be used in court.

E R R A T A

I wish to make the following changes,
for the following reasons:

PAGE LINE

___ ___ CHANGE:_____

REASON:_____

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REASON:_____

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REASON:_____

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REASON:_____

_____ _____

WITNESS' SIGNATURE DATE

ERRATA

I wish to make the following changes, for the following reasons:

Page, Line	Change	Reason
P10, line 15	delete "the"	Transcription error
P12, line 4	Add a semicolon after career	Transcription error
P13, line 21	"T-H-R-E-O" instead of "30, P-H-R-E-O."	Transcription error
P59, line 16	Replace "0.7%" with "0.07%"	Transcription error
P75, line 3	"Samples" should be "examples"	Transcription error
P88, line 3	"essentially auspicious" should be "essentially suspicious"	Transcription error
P98, line 13	"CV is did he staled at" should be "CV as is stated is"	Transcription error
P112, line 15	"perform" should be "form"	Transcription error
P120, line 18	"compliments" should be "components"	Transcription error
P120, line 25	"affect" should be "effect"	Transcription error
P126, line 24	should read "carboxylate salt, purifying that salt, and"	Transcription error
P127, line 12	there should be a comma after "acids"	Transcription error
P130, line 10	should read "if the API is" instead of "if the API"	Transcription error
P135, line 23	should read "reactants and products" instead of "reactants in products."	Transcription error
P159, line 3	"chem" should be "10"	Transcription error
P161, line 3	"starting tip" should read "starting materials"	Transcription error
P162, line 20	"of formula" should be "a formula"	Transcription error
P166, line 4	"synthetic re" should be "synthetic route"	Transcription error
P173, line 8	"pulse" should be "plus"	Transcription error
P188, line 24	"it's pure" should be "as pure"	Transcription error
P201, line 11	"replated" should be "related"	Transcription error
P203, line 12	"enantiomers" should be "diastereomers"	Transcription error
P207, line 10	"Landham Acts" should be "lambda max"	Transcription error

Jeffrey D. Winkler, Ph.D.

6-27-16
Date

Electronic Acknowledgement Receipt	
EFS ID:	26384965
Application Number:	14849981
International Application Number:	
Confirmation Number:	6653
Title of Invention:	PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
First Named Inventor/Applicant Name:	Hitesh BATRA
Customer Number:	22428
Filer:	Stephen Bradford Maebius/Karen Strawderman
Filer Authorized By:	Stephen Bradford Maebius
Attorney Docket Number:	080618-1581
Receipt Date:	19-JUL-2016
Filing Date:	10-SEP-2015
Time Stamp:	10:02:30
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Miscellaneous Incoming Letter	NtfRltdProc.pdf	53198 08c659f20e41d0d20e983c0f7895439d5a5c981f	no	2
Warnings:					

Information:					
2	Miscellaneous Incoming Letter	5-12-2016PublicInstitutionofIPR.pdf	1598383 2ba7afcfd5fe312bc9a184844d1168e5597b8576	no	53
Warnings:					
Information:					
3	Miscellaneous Incoming Letter	7-13-2016PublicPatentOwnerResponsetoPetition.pdf	343563 2c0e7f3990fb732195bd9542442cf0eb65000ff9	no	57
Warnings:					
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4	Miscellaneous Incoming Letter	Exhibit2020Public.pdf	350553 ef25158b9db44265e9fe4ac6e347b626f61d5b87	no	51
Warnings:					
Information:					
5	Miscellaneous Incoming Letter	Exhibit2021.pdf	1918078 89bcdd1c343dd9da762d4f932a4ed900dfc519e1	no	66
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13	Miscellaneous Incoming Letter	Exhibit2029.pdf	636267 de0d387dc5e8691a295db465819e7540dad50357	no	3
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14	Miscellaneous Incoming Letter	Exhibit2030.pdf	1444440 cbe4c905c2174ef7ee42ebc533e49aad79ab3f7	no	8
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		Total Files Size (in bytes):	87679381		

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New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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Courtesy Reminder for
Application Serial No: 14/849,981

Attorney Docket No: 080618-1581
Customer Number: 22428
Date of Electronic Notification: 02/25/2016

This is a courtesy reminder that new correspondence is available for this application. If you have not done so already, please review the correspondence. The official date of notification of the outgoing correspondence will be indicated on the form PTOL-90 accompanying the correspondence.

An email notification regarding the correspondence was sent to the following email address(es) associated with your customer number:
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Atty. Dkt. No. 080618-1581

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor Name:	Hitesh BATRA
Title:	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
Appl. No.:	14/849,981
Filing Date:	9/10/2015
Examiner:	Yevgeny Valenrod
Art Unit:	1672
Confirmation Number:	6653

NOTIFICATION OF RELATED PROCEEDINGS

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

Applicant hereby updates the Office concerning the status of a related proceeding styled *Steadymed Ltd. (Petitioner), v. United Therapeutics Corporation (Patent Owner)*, Case IPR2016-00006, US Patent 8,497,393, which involves the issued parent of the above-captioned patent application. Other documents from the above-identified Inter Partes Review (IPR) were submitted in the present application with an Information Disclosure Statement filed on October 13, 2015, for the Examiner's consideration. The purpose of this notice is to provide a copy of Patent Owner's Preliminary Response Under 35 U.S.C. § 313 and 37 C.F.R. § 42.107, Patent Owner Exhibit List and Exhibits 2002 and 2007-2016 as filed on January 14, 2016 from the IPR

proceeding. Certain information in the Preliminary Response is redacted and certain exhibits are not provided due to their filing under seal in the IPR proceeding.

Respectfully submitted,

Date Feb. 26, 2016

By /Stephen B. Maebius/

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 672-5569
Facsimile: (202) 672-5399

Stephen B. Maebius
Attorney for Applicant
Registration No. 35,264

Paper _____

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

STEADYMED LTD.,

Petitioner,

v.

UNITED THERAPEUTICS CORPORATION,

Patent Owner.

Case IPR2016-00006
Patent 8,497,393

Patent Owner Preliminary Response Under 35 U.S.C. § 313 and 37 C.F.R. § 42.107

4827-9995-8060.1

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CASES

STATUTES

RULES

REGULATIONS

I. INTRODUCTION

United Therapeutics Corporation ("Patent Owner") submits this preliminary response under 35 U.S.C. § 313 responsive to the petition for *inter partes* review ("IPR") of claims 1-22 of U.S. Patent No. 8,497,393 ("the '393 patent") filed by SteadyMed LTD. ("Petitioner"). This preliminary response is timely filed within three months of the Board's notice, Paper 3 mailed October 14, 2015, indicating that the petition was accorded a filing date. For the reasons set forth herein and in the accompanying exhibits, Petitioner's petition for IPR should be denied.

II. DEVELOPMENT OF REMODULIN®

Patent Owner holds approved New Drug Application No. 21-272 for Remodulin® (treprostinil) Injection, which Patent Owner markets and sells as Remodulin®. Remodulin® is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1), a rare, fatal disease affecting the pulmonary vasculature. Remodulin® was the second drug to receive FDA approval for the treatment of PAH. Ex. 2002.

When a compound exists in multiple stereoisomeric forms, "[i]t is extremely important to the proper biological function of a drug" to obtain the specific stereoisomer that produces the desired activity, as "other stereoisomers may have

no biological effect or a deleterious biological effect." Ex. 2013[1] at p. 15, ll. 8-17. Treprostinil, the active ingredient of Remodulin®, is a complex prostacyclin analogue compound containing five chiral centers; consequently, thirty-two stereoisomers of the molecule are possible. Ex. 2013, at p. 11, l. 18 – p. 12, l. 18. Only one particular stereoisomer, treprostinil, is able to mimic the function of a natural hormone, prostacyclin, because it has the same configuration at the five chiral centers as the natural hormone prostacyclin. Ex. 2013, at p. 15, ll. 1-8, p. 19, ll. 14-25.

No sample of treprostinil is 100% pure. Ex. 2013, at p. 12, ll. 16-17, p. 41, ll. 22-25. Each sample of treprostinil carries with it characteristic impurities, including other stereoisomers, arising, *inter alia*, from the synthetic process used to form it. Ex. 2013, at p. 132, l. 21- p. 133, l. 2.

[1] In May of 2014, Dr. Williams and Dr. Aristroff provided expert testimony on behalf of United Therapeutics Corporation in *United Therapeutics Corp. v. Sandoz, Inc.*, 3:13-cv-00316-PGS-LHG (D.N.J.), and Ex. 2013 comprises the trial transcript relating to that testimony. While the '393 patent itself was not at issue in that case, Dr. Williams and Dr. Aristoff offered opinions concerning certain subject matter that is relevant to the Board's consideration of the '393 patent.

The '393 patent, entitled "Process To Prepare Treprostinil, The Active Ingredient in REMODULIN®," appears in FDA's Orange Book for Remodulin® and also other products. The claims of the '393 patent are product-by-process claims that resulted from the inventors' discovery that a combination of processes unexpectedly provides a physically different and improved final product with significantly reduced overall impurities and a distinct and unexpected impurity profile.

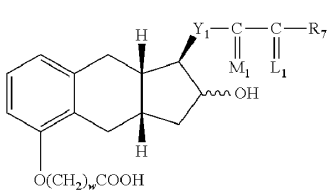
In fact, when the FDA approved the Patent Owner's implementation of the new process steps covered by the '393 patent, the FDA adopted a higher purity specification reflecting the physically changed nature of the product as explained below in Section IX.

III. THE '393 PATENT

The '393 patent issued from U.S. Patent Application No. 13/548,446, filed July 13, 2012, which is a continuation of U.S. Patent Application No. 12/334,731 (now U.S. Patent No. 8,242,305; "'305 patent;" Ex. 2007) filed December 15, 2008, which claims priority to U.S. Provisional Patent Application No. 61/014,232, filed December 17, 2007. Ex. 2008. The '393 patent contains twenty-two product-by-process claims, including two independent claims, directed to an improved treprostinil product.

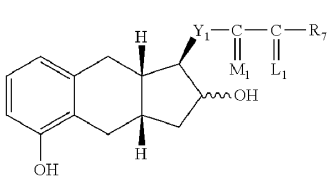
Claim 1 of the '393 patent recites:

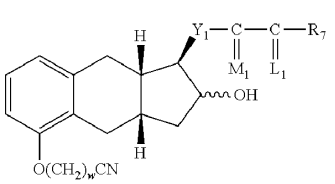
A product comprising a compound of formula I



or a pharmaceutically acceptable salt thereof, wherein said product is prepared by a process comprising

(a) alkylating a compound of structure II with an alkylating agent to produce a compound of formula III,

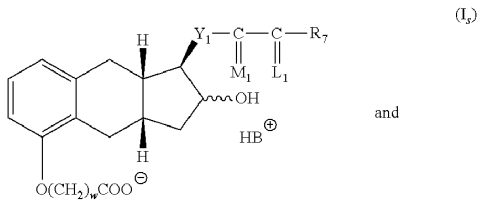




wherein [recitation of Markush groups for the specified structures]…,

(b) hydrolyzing the product of formula III of step (a) with a base,

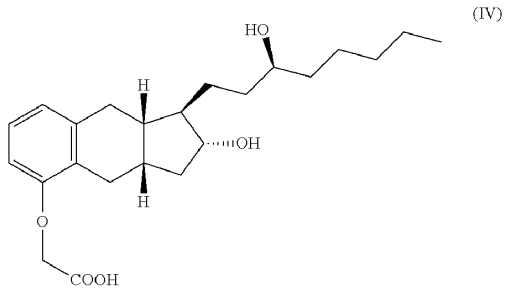
(c) contacting the product of step (h) [sic: (b)][2] with a base B to form a salt of formula I_s.



(d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula I.

Claim 9 of the '393 patent recites:

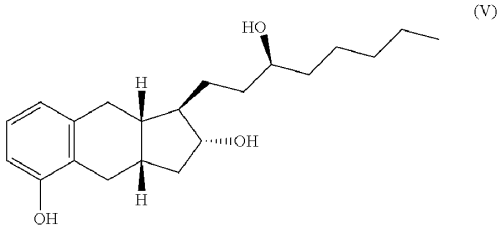
A product comprising a compound having formula IV



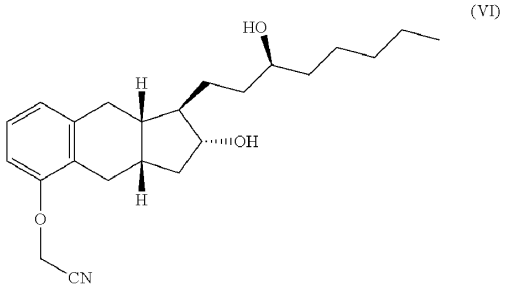
[2] The reference to step "(h)" is an obvious typographical error in claim 1 the '393 patent. The "(h)" should have been "(b)", as indicated in the specification of the '393 patent which correctly recites "(b)". Ex. 1001, p. 4, left column. A person of ordinary skill in the art would recognize that the claims should be read as reciting step (b), as Petitioner's expert has expressly acknowledged (Ex. 1009, ¶ 51) which acknowledgement the Petition has adopted (Pet. at pp. 24-25, and 27, citing ¶ 51).

or a pharmaceutically acceptable salt thereof, wherein the product is prepared by the process comprising

(a) alkylating a compound of formula V with an alkylating agent to produce a compound of formula VI,



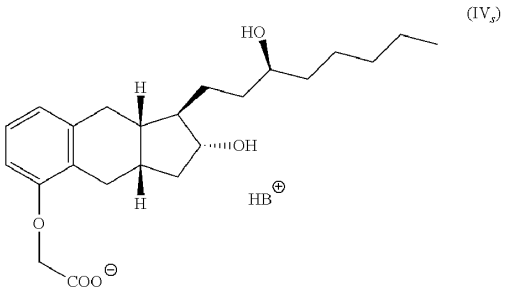
(V)



(VI)

(b) hydrolyzing the product of formula VI of step (a) with a base,

(c) contacting the product of step (h) [sic: (b)][3] with a base B to form a salt of formula IV_s, and



(IV_s)

[3] See preceding footnote.

(d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula IV

As the specification of the '393 patent explains, there was a need "for an efficient process to synthesize treprostinil compounds on a large scale suitable for commercial production." Ex. 1001. Col. 1 ll.58-61. The '393 patent claims are directed to improved treprostinil products with higher purity that are novel and nonobvious to a person of ordinary skill in the art ("POSA"). Ex. 1001. Col. 5 ll. 46-47.

IV. THE PROSECUTION HISTORIES OF THE '393 PATENT AND RELATED APPLICATIONS ALREADY ADDRESS AND REJECT PETITIONER'S ARGUMENTS

A. Moriarty and Phares were both considered by the Examiner during prosecution of the '393 patent

Petitioner relies heavily on Moriarty (Moriarty *et al.*, J. Org. Chem. 2004, 1890-1902; Ex. 1004) and Phares (International Publication No. WO 2005/007081; Ex. 1005), but these references already were considered by the Examiner during original prosecution. Specifically, the Examiner considered these references in the context of rejections under 35 U.S.C. § 102 and 35 U.S.C. § 103, which were overcome, as discussed in more detail below. This is reflected on the face of the patent, which includes Moriarty (Ex. 1004) and Phares (Ex. 1005) as References Cited, and in the prosecution history of the '393 Patent and related patents.

The Examiner's prior consideration of these references undermines any reasonable likelihood that Petitioner will prevail in this IPR with respect to any claim. The Examiner has already considered these references and found neither anticipation nor obviousness. By now asking the Board to consider very similar arguments about the same references in the hopes they will reach the opposite conclusion, Petitioner places unjustified and redundant demands upon the Office's resources. The additional references cited by Petitioner (Kawakami and Ege) add no significant teachings, and the basic arguments underlying the petition already have been thoroughly addressed by the Office.

B. The Examiner considered Moriarty during prosecution of the '393 patent and ultimately found no anticipation

As originally filed, the application resulting in the '393 patent contained 21 claims. Ex. 1002. The Examiner rejected originally filed claims 1-21 as anticipated by Moriarty. Ex. 1002 at pp. 293-296. The Examiner initially found that Moriarty discloses a "compound 7" that has the same structure as the claimed product and a purity of 99.7%. Ex. 1002 at p. 295. According to the Examiner, "[s]ince the claims were product by process claims, the patentability of the product did not depend on the method of its production." *Id.* Applicants submitted a response explaining that the impurity profile of the claimed invention was different as compared to Moriarty's product. The Examiner issued a final action

maintaining the rejection because Applicants evidence was not presented as a declaration. Ex. 1002 at pp. 325-330.

In response, Patent Owner submitted "a declaration under 37 C.F.R. § 1.132 by Dr. David Walsh." Ex. 1002, at pp. 346-350. Dr. Walsh provided data from representative Certificates of Analysis with impurity profiles for treprostinil prepared according to the process corresponding to Moriarty, treprostinil diethanolamine prepared according to the process specified in claim 1 or 10 [issued claim 9], and treprostinil as the free acid prepared according to the process specified in claim 1 or 10 [issued claim 9]. *Id.* Dr. Walsh concluded that the claimed treprostinil differed from the treprostinil produced by Moriarty:

> "[E]ach of treprostinil as the free acid and treprostinil diethanolamine prepared according to the process specified in claim 1 or 10 [issued claim 9] of the present application is physically different from treprostinil prepared according to the process of 'Moriarty' at least because neither of them contains a detectable amount of any of benzindene triol, treprostinil methyl ester, 1AU90 treprostinil stereoisomer and 2AU90 treprostinil stereoisomer, each of which were present in detectable amounts in treprostinil produced according to the process of 'Moriarty.'"

Ex. 1002, at pp. 347-349. He further noted that in these representative examples, the "treprostinil diethanolamine prepared according to claims 1 or 10 of the present

application has only one impurity, treprostinil stereoisomer 3AU90, in a detectable amount" and that "treprostinil as the free acid prepared according to claims 1 or 10 of the present has only three impurities, treprostinil ethyl ester, treprostinil dimers 750W93 and 751W93." Ex. 1002, at pp. 348-349.

The Examiner subsequently allowed claims 1-23 (claim 8 was later canceled by Patent Owner), which issued as claims 1-22 in the '393 patent. Ex. 1002, at pp. 359, 370-376. Thus, the Examiner fully considered Moriarty's impact on patentability and determined that the claims are patentable over Moriarty.

C. The Examiner considered Phares combined with Moriarty during prosecution of the '393 patent and ultimately found no obviousness

The Examiner also considered Phares during prosecution of the application leading to the '393 patent and asserted an obviousness rejection based upon the combination of Moriarty in view of Phares. Ex. 1002, at pp. 122-123. Specifically, the Examiner stated that "[t]he instant invention amounts to addition of a purification step via crystallization." Ex. 1002, at p. 123. This is effectively the same as one of Petitioner's arguments. Petition at section VIII.B.2. Patent Owner provided a detailed response to this rejection, which is detailed below in this Preliminary Response. *See* Ex. 1002, at pp. 176-183; *see infra* Section IV.D.

D. The Examiner considered Phares alone and in combination with Moriarty during prosecution of a related continuation application and found no anticipation or obviousness

Phares was also cited under 35 U.S.C. §§ 102 and 103 during prosecution of a continuation application of the '393 patent, U.S. Patent Application No. 13/910,583, filed June 05, 2013 (now U.S. Patent No. 8,748,657; "the '657 patent;" Ex. 2009). The '657 patent contains seven product-by-process claims, including one independent claim.

Claim 1 of the '657 patent recites:

> A process for producing a pharmaceutical composition comprising treprostinil, comprising providing a starting batch of treprostinil having one or more impurities resulting from prior alkylation and hydrolysis steps, forming a salt of treprostinil by combining the starting batch and a base, isolating the treprostinil salt, and preparing a pharmaceutical solution from the isolated salt comprising treprostinil or a pharmaceutically acceptable salt thereof from the isolated treprostinil salt, whereby a level of one or more impurities found in the starting batch of treprostinil is lower in the pharmaceutical composition, and wherein said alkylation is alkylation of benzindene triol.

The Examiner asserted that "Phares discloses a method of producing a pharmaceutical composition comprising combining a starting batch of treprostinil

which comprises treprostinil, ethanol and water with diethanolamine to produce treprostinil diethanolamine salt … Since the process steps of claim 1 are the same as the process steps described by Phares et al, the purity of the Phares salt is inherently the same as the instantly claimed purity of claims 3 and 10." Ex. 2010, at pp. 164-167 (Office Action mailed July 19, 2013).

In response, Patent Owner amended claim 1 to recite "the starting batch of treprostinil has one or more impurities resulting from prior alkylation and hydrolysis steps." Patent Owner explained that "Phares neither anticipates nor renders obvious amended claim 1 or any claim depending from it because Phares discloses more than one process for providing a starting batch of treprostinil and because Phares does not provide evidence of whether salt formation can remove any impurities from a given type of treprostinil starting material." Ex. 2010, at pp. 149-155. At that time, Patent Owner explained to the Examiner that Phares provides at least two routes for producing the diethanolamine salt of treprostinil. One of those routes prepares treprostinil without prior alkylation and hydrolysis as recited in steps (a) and (b) of the '393 independent claims, and the other route employs prior alkylation and hydrolysis. Ex. 2010, at pp. 151-154.

Patent Owner further explained why Phares does not inherently result in the claimed product :

> [T]here are several different processes for preparing a starting batch of treprostinil, only one of which leads to treprostinil having one or more impurities resulting from prior alkylation and hydrolysis steps. Therefore, Phares does not inherently and necessarily result in a process in which the same kind or amount of impurities are present in the starting batch and in which the level of one or more such impurities resulting from prior alkylation and hydrolysis steps is reduced in the final product as required by claim 1. For this reason alone, Phares cannot anticipate the present claims based on inherency.

Ex. 2010, at p. 153. The "Examiner agree[d] with the applicant that the amended claims are not anticipated by Phares" (Final Office Action mailed August 20, 2013). Ex. 2010, at pp. 138-144.

Having conceded novelty over Phares, the Examiner then asserted that the pending claims were unpatentable under 35 U.S.C. § 103 over Phares in view of Moriarty. Ex. 2010, at p. 140. Although the claims of the '657 patent and the '393 patent are not identical, the issues raised by the Petitioner for the '393 patent with regard to Phares and Moriarty are indistinguishable from the issues raised by the Examiner during the prosecution of the '657 patent.

In response, the Patent Owner stated in a Request for Continued Examination (RCE) that Phares does not teach forming a salt intermediate in a

process that allows reduction of one or more impurities resulting from prior alkylation and hydrolysis steps. Ex. 2010, at pp. 39-43. Since Moriarty does not teach or suggest forming an intermediate salt to remove impurities, even if Phares and Moriarty were combined, Patent Owner noted there still would have been no motivation to perform the claimed process. *Id.* Following an agreement to cancel certain product claims, the Examiner then directly issued a Notice of Allowance for remaining process claims 1-7 based on the earlier arguments. Ex. 2010, at pp. 5-8.

E. The Board should exercise its discretion to decline to institute trial

Because Petitioner's arguments are a rehashed version of issues already considered and rejected by the Office, the Board should exercise its discretion under 35 U.S.C. § 325(d) to decline to institute trial. *See* 35 U.S.C. § 325(d); *Prism Pharma Co., Ltd. v. Choongwai Pharma Corp.*, IPR No. 2014-00315 (Paper 14, July 8, 2014) (Because "[t]he same prior art . . . and arguments substantially the same as Petitioner's current contention . . . were presented previously to the Office" during prosecution, Examiner considered, the same prior art and substantially the same arguments" during prosecution, the Board chose to "exercise [its] discretion and deny the Petition under 35 U.S.C. § 325(d)"); *Universal Remote Control, Inc. v. Universal Electronics, Inc.*, IPR No. 2014-01084 (Paper 26, December 18, 2015) ("[I]n determining whether to institute an *inter partes* review

we may take into account whether a prior art reference was presented previously to the Office and have discretion to deny a petition on that basis, *see* 35 U.S.C. § 325(d)….").

Phares and Moriarty were considered and applied by the Examiner during original prosecution of the '393 patent in the same way presented by Petitioner and Patent Owner distinguished those references. Petitioner does not cast Phares or Moriarty in a new light or present any persuasive evidence to supplement the record that was previously in front of the Office. Consequently, the facts in this case are like those in *Funai Electric* and the result should be the same – exercising the Board's discretion under § 325(d) and declining to institute trial. *Funai Electric Co. v. Gold Charm Ltd.*, IPR No. 2015-01491 (Paper 15 at 19-20, December 28, 2015).

V. CLAIM CONSTRUCTION

Patent Owner disagrees with Petitioner's proposed construction of the term "product" found in claims 1, 9, and 22, "A product comprising a compound of formula I/IV or a pharmaceutically acceptable salt thereof" in claims 1 and 9, and "A process comprising" and "the process comprising" in claims 1 and 9. "[O]nly those terms need be construed that are in controversy, and only to the extent necessary to resolve the controversy." *Vivid Tech., Inc. v. Am. Sci. & Eng'g., Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999); *Eli Lilly and Company., v. Los Angeles*

Biomedical Research Institute At Harbor-Ucla Medical Center, IPR2014-00693 (Paper 45, October 22, 2015). Accordingly, Patent Owner focuses claim construction on the contested terms. *Gechter v. Davidson*, 116 F.3d 1454, 1460 (Fed. Cir. 1997); *accord Aero Prods. Int'l, Inc. v. Intex Rec. Corp.*, 466 F.3d 1000, 1012 n.6 (Fed. Cir. 2006) (appropriate to focus on disputed limitations), *citing Scripps Clinic & Research Found. v. Genentech, Inc.*, 927 F.2d 1565, 1580 (Fed. Cir. 1991).

A. Legal Standard

"[C]laim construction begins with, and remains focused on, the language of the claims." *Biagro W. Sales, Inc. v. Grow-More, Inc.*, 423 F.3d 1296, 1302 (Fed. Cir. 2005) (internal citations omitted). Claim terms are generally given their plain and ordinary meaning. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312-13 (Fed. Cir. 2005) (*en banc*). "[T]he ordinary and customary meaning of a claim term is the meaning that the term would have to a [POSA] in question at the time of the invention, i.e., as of the effective filing date of the patent application." *Id.* at 1313. Indeed, there is "a 'heavy presumption' that a claim term carries its ordinary and customary meaning." *Teleflex, Inc. v. Ficosa N. Am. Corp.*, 299 F.3d 1313, 1325 (Fed. Cir. 2002); *DSW, Inc. v. Shoe Pavilion, Inc.*, 537 F.3d 1342, 1347 (Fed. Cir. 2008) ("[A]bsent contravening evidence from the specification or prosecution history, plain and unambiguous claim language controls the construction

analysis."). Absent a disclaimer of subject matter (*i.e.*, a clear or unmistakable surrender of subject matter in the patent specification or prosecution history) or lexicography explicitly defining a claim term, the plain meaning of the claim controls. *Toshiba Corp. v. Imation Corp.*, 681 F.3d 1358, 1369 (Fed. Cir. 2012).

If a claim term is construed, the Board should construe claim terms such that they have the "broadest reasonable construction in light of the specification of the patent in which it appears." 42 C.F.R. § 42.100(b).

B. "Product"

Petitioner proposed that the term "product" be construed as "a chemical composition." Patent Owner, however, submits that "product" means "a substance resulting from a chemical reaction," which is the "broadest reasonable construction in light of the specification of the patent in which it appears." 42 C.F.R. § 42.100(b). Moreover, this definition is also consistent with the plain and ordinary meaning of the term as used in the context of the '393 patent as well as the intrinsic and extrinsic evidence. In particular, the claims and specification of the '393 patent consistently use the word "product" to refer to a substance resulting from a chemical reaction. Ex. 1001, at Col. 5:45-46 ("the product of the process according to the present invention has higher purity"); Col. 7:16-20 ("a compound of formula XI, which is a cyclization product of a compound of formula X"); Col. 17:37-40 ("This process provides better quality of final product."); and claims 1-22. This

usage is in line with how a POSA would understand the term "product," as the real world product of a chemical reaction, particularly in the context of these product-by-process claims.

In the prosecution history, Patent Owner distinguished the "product" of the claimed invention from the prior art on the basis that both the chemical process steps recited in the claims "and the products resulting from those steps are different than the chemical process and product of" the prior art, noting specifically that the "product" of the claims lacks certain impurities found in the product prepared by the prior art process. Ex. 1002, at p. 315. The Examiner found that the prior art and specification lacked sufficient evidence about impurities in question to support a finding "that the process by which the instantly claimed product is prepared results in a product that is different from the product of" the prior art. Ex. 1002, at p. 328. The Examiner stated that evidence of "data demonstrating the difference between the two products" should be presented in the form of a declaration. Ex. 1002, at pp. 328-329. Accordingly, Dr. David Walsh submitted a declaration providing evidence from representative "product batch[es]" to show that the product of the '393 claims is physically different from treprostinil produced according to the prior art process at least because the product of the '393 claims lacks certain impurities found in treprostinil made by the prior art process. Ex. 1002, at pp. 346-350. Thus, during prosecution, the Patent Owner and Examiner

explicitly discussed the "product" of the claims as a real world substance that results from employing a specific chemical process, as differentiated from the substance obtained from employing a different chemical process. Such usage is consistent with the plain and ordinary meaning of this term and with Patent Owner's proposed construction.

Patent Owner's construction also comports with how a POSA would understand these terms in the context of the '393 patent. Indeed, well-known chemistry textbooks specifically define "product" as "a substance resulting from a chemical reaction; it is shown to the right of the arrow in a chemical equation." Ex. 2011, Zumdahl, *Chemistry*, pp. A25, A36 (1986); *see also* Ex. 2012, Brown, et al., *Chemistry: The Central Science*, pp. G-2, G-10 (9th ed. 2003). Several other references also similarly define or describe a "product" to indicate it is the result of a chemical reaction. Ex. 2014, Suchocki, et al., *Conceptual Chemistry*, p. G-6 (2001).

Simply put, the "product" claimed in a product-by-process claim is necessarily a substance that results from the process specified in that claim. In the case of the '393 patent, wherein the claims specify the process of a certain chemical reaction, the claimed "product" must be understood to be "a substance resulting from a chemical reaction." Patent Owner's proffered definitions, for both the term

"product" and for other related terms that contain this word, comport with this understanding.

Petitioner's definition of "product" as "a chemical composition" is unreasonably broad, as it erroneously removes from the term its identity as a product made by a specified process (*i.e.*, a chemical reaction). In doing so, Petitioner's definition disregards both the intrinsic evidence and the nature of a product-by-process claim. Under Petitioner's over-expansive construction, the term "product" would refer not only to the substance created by a chemical reaction, but also the starting materials, solvents, catalysts, and glassware involved in performing that reaction. Such an unreasonable definition would render the claims nonsensical. The invention of the claims of the '393 patent is not merely "a chemical composition" but a specific, real world substance that results from the chemical process specified in the claims and thus possesses the characteristics that result from employing that process.

C. "A product comprising a compound of formula I/IV or a pharmaceutically acceptable salt thereof"

Petitioner proposed that the term "A product comprising a compound of formula I/IV or a pharmaceutically acceptable salt thereof" be construed as "a chemical composition that includes, but is not limited to, a compound of Formula I, or a pharmaceutically acceptable salt thereof, and that may also include other non-

mentioned substances (including impurities), additives, or carriers, without limitation as to the types of or relative amounts thereof." Petition at p. 11.

Patent Owner submits that this term means "a substance resulting from a chemical reaction constituted primarily of formula I/IV or a pharmaceutically acceptable salt thereof." This construction is consistent with how a POSA would understand the term in the context of the patent. The '393 patent is directed toward prostaglandin products, including specifically treprostinil, which are made by a process that results in both high yield and high purity. Ex. 1001. Col. 1:58-60 ("Because Treprostinil, and other prostacyclin derivatives are of great importance from a medicinal point of view, a need exists for an efficient process to synthesize these compounds on a large scale suitable for commercial production."), Ex. 1001. Col. 5:36-49. Indeed, as detailed above with respect to the term "product," the very high purity of the claimed product, which constituted an improvement over the prior art product, was explicitly identified during the prosecution of the '393 patent. *See* section V.B. In light of this, a POSA would understand that the substances described by this term would be substances primarily constituted, respectively, of formula I and formula IV.

Petitioner's proposed construction should be rejected, as it is not a reasonable construction of the term. With respect to the term "product," which is nested within this term, the points made above apply here with equal force, rendering Petitioner's

construction unreasonably overbroad. *See* section V.B. With respect to the remainder of this term, Petitioner's construction is both unreasonable and improperly overbroad. As an initial, matter, Petitioner seeks to construe two terms – one term containing a reference to "Formula I" and the other containing a reference to "Formula IV" – with a single construction that would only refer to "Formula I," inexplicably reading Formula IV out of the term entirely. This is nonsensical and thus inherently unreasonable.

Moreover, Petitioner's construction is unreasonable in that it seeks to broaden the term to encompass "other non-mentioned substances (including impurities), additives, or carriers, *without limitation as to the types or relative amounts thereof*" [emphasis added]. This construction is contradicted by the nature of the claims themselves and finds no support in the specification. The claims at issue are product-by-process claims that claim a real-world product created by a specified chemical process. Thus, the claimed product must have the characteristics, including the characteristic types and amount of impurities that result from the claimed process. During prosecution, Patent Owner pointed to these characteristics as distinguishing the claimed subject matter from the prior art. Ex. 1002, at pp. 315, 344. Petitioner's construction contradicts this inherent limitation of the claims. Additionally, the word "comprising" is defined in the specification as simply meaning "including but not limited to." It does not provide any support for

Petitioner's contradictory construction of these terms as encompassing other substances "without limitation as to the types or relative amounts thereof." Ex. 1001. Col. 4, ll. 22-25. By attempting to introduce the phrase "without limitation as to the types or relative amounts thereof" into these claims terms, Petitioner's construction would render the term unreasonably broad, contradicting the inherent limitations of product-by-process claims that would be understood by one of ordinary skill in the art. Accordingly, Petitioner's proposed construction should be rejected.

D. "A process comprising" and "the process comprising"

Petitioner proposed that the terms "A process comprising" and "the process comprising" be construed as "a process that includes, but is not limited to, the recited process steps, and may include, without limitation, any other non-recited steps." Petitioner's proposed construction repeats the words "a process," and thus effectively only seek to construe the word "comprising." Yet the word "comprising" is a well-understood term with no ambiguity. The Federal Circuit has noted that "[i]n the patent claim context the term 'comprising' is well understood to mean 'including but not limited to.'" *CIAS, Inc. v. Alliance Gaming Corp.,* 504 F.3d 1356, 1360 (Fed. Cir. 2007). This well-understood meaning is consistent the patent specification's definition of "comprising" to mean "including but not limited to." Ex. 1001. Col. 4, ll. 22-25. Accordingly, Patent Owner submits that the terms

"a process comprising" and "the process comprising" have an indisputable meaning: "a/the process including but not limited to."

Petitioner asserted that its construction was supported by Patent Owner's definition of "comprising" as meaning "including but not limited to" and that "other non-mentioned … steps may be present." Petition at p. 16. Yet Petitioner's proposed phrase "and may include, without limitation, any other non-recited steps" is unsupported by the patent specification. Petition at p. 17. In particular, the phrase "without limitation" in Petitioner's proposed construction threatens to swallow the essential elements of the claim. As such, Petitioner's proposed construction should be rejected.

The Board should adopt the Patent Owner's construction of the terms "Product"; "A product comprising a compound of formula I/IV or a pharmaceutically acceptable salt thereof"; and "A process comprising" and "the process comprising," by applying the "broadest reasonable construction in light of the specification of the patent in which it appears" standard. 42 C.F.R. § 42.100(b).

VI. STANDARD OF REVIEW

The Board may not grant a petition for IPR unless the Board "determines that the information presented in the petition filed under section 311 and any

response filed under section 313 shows that there is a reasonable likelihood that the petitioner would prevail." 35 U.S.C. § 314(a).

Importantly, § 314(a) requires the Board's determination to be based on "information presented in the petition." Likewise, the petitioner has a statutory obligation under § 312(a)(3) to identify "with particularity, each claim challenged, the grounds on which the challenge to each claim is based, and the evidence that supports the grounds for the challenge to each claim." Thus, it the responsibility of the Petitioner in the first instance, not the Board, to present information adequate to justify institution on any grounds.

Equally important is § 314(a)'s requirement that the Board's determination take into account "information presented in . . . any *response* filed under section 313." (emphasis added) In other words, the Board's determination must be based on the totality of the written evidence presented at the pre-trial stage.

Ultimately, the focus of the inquiry under § 314(a) is whether the petitioner "would prevail"—i.e., *win on the merits* based exclusively on the "information presented in the petition . . . and any response."

VII. THE PETITION SHOULD BE DENIED BECAUSE IT RAISES ISSUES ALREADY ADDRESSED IN PROSECUTION

As indicated above, the core issues presented in the Petition have been extensively addressed in prosecution of applications related to the '393 patent. The

Board should use its discretion under 35 U.S.C. § 325(d) to deny some or all of the Grounds in the Petition because the same or substantially the same issues were addressed during prosecution.

For Grounds 2 and 3, the first alternative (*i.e.,* over Moriarty and Phares, and for Ground 3, Ege) should be denied under § 325(d) because the same or substantially the same prior art was considered by the Office during prosecution. *See* IPR2015-00525, Paper No. 12, p. 17 (denying institution of petition that raised arguments already considered by Examiner); IPR2015-01491, Paper 15, pp. 19-20 (same). The USPTO explicitly considered Moriarty and Phares in combination, and by Petitioner's own admission, Ege is nothing more than a first-year organic chemistry textbook. Thus, the same or substantially the same prior art has already been considered. Furthermore, while Patent Owner acknowledges that the Board has in the past declined to exercise the discretion afforded by § 325(d) when Petitioner submits evidence in the form of a declaration along with previously-considered prior art, in the case of at least claims 6, 15, 21, and 22, Petitioner relies on nothing more than conclusory statements in three paragraphs of the Winkler declaration. As stated in 37 C.F.R. § 42.65(a), "testimony that does not disclose the underlying facts or data on which the opinion is based is entitled to little or no weight." Thus, for at least these claims, Petitioner has provided no evidence of

probative value that is any different than what was already before the Patent Office during prosecution.

VIII. GROUND 1: THE PETITION SHOULD BE DENIED BECAUSE PETITIONER HAS FAILED TO PROVIDE ANY EVIDENCE THAT A SINGLE EMBODIMENT OF PHARES WOULD INHERENTLY RESULT IN THE SAME PRODUCT AS THAT CLAIMED IN ANY OF CLAIMS 1-5, 7-9, 11-14 OR 16-20 OF THE '393 PATENT

Petitioner asserts in Ground 1 that Phares anticipates claims 1-5, 7-9, 11-14, and 16-20 of the '393 patent under 35 U.S.C. 102(b). Petitioner's arguments are misplaced for two primary reasons.

First, Petitioner is unable to identify a single embodiment in Phares that would anticipate any claim of the '393 patent. Instead, Petitioner cobbles together disclosure from four disparate portions of Phares covering multiple distinct embodiments (pp. 24, 41-42, 85-93, and 99 of Ex. 1005). At the same time, Petitioner selectively ignores other portions in the Phares disclosure that suggest the four disparate portions of Phares should not be cobbled together to a single allegedly anticipatory embodiment. Petition at pp. 22-24 and 33-34. Of the four regions, three (pp. 24, 85-93, and 99) relate to step (c), and only one (pp. 41-42) relates to steps (a)-(b) of claims 1 and 9. This patchwork approach to anticipation is improper because "[t]he identical invention must be shown in as complete detail as is contained in the …claim." *Richardson v. Suzuki Motor*, 868 F.2d 1226 (Fed. Cir. 1989). To anticipate, "[the] reference must clearly and unequivocally

disclose the claimed [invention] or direct those skilled in the art to the [invention] without *any* need for picking, choosing, and combining various disclosures not directly related to each other by the teachings of the cited reference". *In re Arkley*, 455 F.2d 586, 587 (CCPA 1972) (emphasis in original), *see also Sanofi-Synthelabo v. Apotex Inc.*, 550 F.3d 1075 (Fed. Cir. 2008)(*citing Arkley*). Moreover, if the teachings of the prior art can be practiced in a way that yields a product lacking the allegedly inherent property, the prior art in question does not inherently anticipate. *See Glaxo Inc. v. Novopharm Ltd.,* 52 F.3d 1043, 1047–48 (Fed. Cir. 1995).

Second, even if Phares is effectively rewritten as argued by Petitioner, Phares does not teach each and every element of the challenged claims. Specifically, Petitioner is forced to rely on inherency because Petitioner concedes that Phares lacks express disclosure of certain claim elements. *E.g.*, Petition at 24-25 and 28. Proving inherency, however, is a high burden. "The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic." *In re Rijckaert*, 9 F.3d 1531 (Fed. Cir. 1993). In the context of an IPR, the Board requires more than conclusory statements in an expert declaration that something is inherent, and the Board has declined to institute when petitioner has not carried its burden to show a result is inherent based on objective evidence. *See* IPR2014-01116, Paper No. 12, p. 10 (quoting 37 C.F.R. § 42.65(a): "testimony that does not disclose the

underlying facts or data on which the opinion is based is entitled to little or no weight"). As shown below, Petitioner has not provided such objective evidence of inherency in this case.

A. Petitioner cannot pick and choose from unrelated portions of Phares to establish anticipation

In attempting to show inherent anticipation, Petitioner cites four different portions of Phares, Ex. 1005, as teaching the combined elements of claims 1 and 9. Inherent anticipation requires that the undisclosed feature must "necessarily and inevitably" flow from practice of what is disclosed in the prior art reference. *Schering Corp. v. Geneva Pharms., Inc.*, 339 F.3d 1373, 1378 (Fed. Cir. 2003). Yet Petitioner does not, and indeed cannot, show that these elements in Phares "necessarily and inevitably" give rise to the treprostinil synthesis required by claims 1 and 9 of the '393 patent: first, because there would be no reason to combine the disparate portions of Phares identified by Petitioner, which cover different subject matter; and second, because Phares explicitly points to methods of practicing its teachings which would not lead to the invention of the '393 patent. While Petitioner cites three portions of Phares, specifically Ex. 1005, at pp. 24, 85-93, and 99, as teaching a salt formed by step (c) (discussed in detail below), Petitioner only cites one portion of Phares, specifically Ex. 1005, at pp. 41-42, as teaching steps (a) and (b). Yet Phares (Ex. 1005) at pp. 41-42 is not concerned

with the synthesis of treprostinil itself, but instead with the synthesis of *the enantiomer* of treprostinil. Ex. 1005, at pp. 41-42 (Specifically noting that "*(-)-treprostinil* can be synthesized as follows" and then summarizing that "the *enantiomer* of the commercial drug (+)-Treprostinil was synthesized." [emphasis added]). Accordingly, there is no reason to connect this portion of Phares, which discloses a synthesis for the *enantiomer* of treprostinil, with the other portions relied upon by Petitioner, which all relate to treprostinil itself. Further, Petitioner does not provide any evidence that this same synthesis was in fact used to make the starting treprostinil material associated with any of the three portions of Phares Petitioner cites as disclosing step (c).

Moreover, Petitioner ignores other parts of Phares that disclose different ways of making treprostinil that do *not* include steps (a) and (b). For example, Phares states that "[c]ompounds of the present invention can also be provided by modifying the compounds found in US Patent Nos. 4,306,075 and 5,153,222 in like manner." Ex. 1005, at p. 11. The method of making treprostinil disclosed in U.S. Patent No. 4,306,075 is diagrammed in Moriarty at "Scheme 2." Ex. 1004, at p. 4 (see footnote 26 citing "US 4306075"). This scheme does not involve steps (a) and (b) of claims 1 and 9 of the '393 patent. Thus, Phares explicitly provides that treprostinil can be made by methods that do not include steps (a) and (b). When "the teachings of the prior art can be practiced in a way that yields a product

lacking the allegedly inherent property, the prior art in question does not inherently anticipate." *United Therapeutics Corp. v. Sandoz, Inc.*, 2014 U.S. Dist. LEXIS 121573, *80-81 (D.N.J. Aug. 29, 2014) (*citing Glaxo Inc. v. Novopharm Ltd.*, 52 F.3d 1043, 1047-48 (Fed. Cir. 1995)). Likewise here, these disparate portions of Phares cannot be combined to inherently anticipate the invention of the '393 patent. As discussed above, this same issue of combining disparate portions was addressed in a similar way during prosecution of an application related to the '393 patent and ultimately led to the Examiner's decision to withdraw an anticipation rejection over Phares.

B. Phares does not anticipate step (c) of the '393 patent claims

The first portion in Phares cited by Petitioner for teaching step (c) is p. 24 of Ex. 1005, which reads: "Treprostinil acid [of unknown origin] is dissolved in a 1:1 molar ratio mixture of ethanol:water and diethanolamine is added and dissolved. The solution is heated and acetone is added as an antisolvent during cooling." This describes an example of how to make treprostinil diethanolamine from a starting material of treprostinil acid. This example, however, provides no detail whatsoever about how the starting treprostinil acid was made or where it comes from. Consequently, this lack of disclosure fails to demonstrate inherent anticipation for lack of evidence. Nothing on Phares' p. 24 shows that the treprostinil acid was made using steps (a) and (b).

The second portion in Phares cited by Petitioner for teaching step (c) is pp. 85-93 of Ex. 1005. This portion of Phares relates to a clinical study of sustained release capsules and tablets of treprostinil diethanolamine and to a polymorph characterization study of treprostinil diethanolamine. Again, there is no indication in this portion of Phares what process was actually used to make the starting "treprostinil acid" for the treprostinil diethanolamine that is the subject of these pages.

The third portion in Phares cited by Petitioner for teaching step (c) is p. 99 of Ex. 1005, which is claim 49 directed to the diethanolamine salt of treprostinil. Again, there is no indication in this portion of Phares what process was used to make the starting treprostinil acid leading to the treprostinil diethanolamine that is the subject of the claim.

Because the portions of Phares relied upon by Petitioner do not necessarily describe a treprostinil acid made using steps (a) and (b), these portions of Phares cannot constitute an anticipatory disclosure. Indeed, as discussed below and as disclosed by Phares itself, treprostinil acid can be made in a variety of ways, which in turn, impact the composition of the final product.

C. Petitioner has not shown that step (c) would necessarily lead to the same final product if made from different starting treprostinil materials

As stated in the '393 patent itself, treprostinil free acid can be made in different ways. Treprostinil was first disclosed in U.S. Patent No. 4,306,075 ("the '075 patent") and was produced by a method that does not include steps (a) and (b). This alternative process of the '075 patent for making a starting treprostinil material is one of the references cited in Phares. This method resulted in a mixture of diastereomers and a physically different form of treprostinil. Ex. 1004, at pp. 3-4. Later in U.S. Patent No. 4,668,814 ("the '814 patent" Ex. 2015), a slightly better scheme for synthesizing an impure treprostinil product was developed. This new route included an alkylation and hydrolysis step similar to steps (a) and (b) of the '393 patent (Ex. 2015, at Col. 30-32), producing a physically different form of treprostinil, though this scheme also resulted in a mix of diastereomers and could not be scaled up. Ex. 2013, at p. 178, ll. 8-22, p. 193, l. 21-p. 195, l. 8; p. 197, l. 20-p. 198, l.3; p. 219, l. 15-p. 220, l. 4; p. 338, l. 14-p. 339, l. 2. As referenced above, Moriarty was a synthesis that reduced impurities, increased yields, and resulted in a different impurity profile. Ex. 1002, at pp. 346-350. Each method was an improvement over the previous one and each resulted in a different product with different impurity profiles. Thus, at the time of the '393 patent, there existed at least three prior art methods to obtain an impure treprostinil product.

During prosecution, Patent Owner demonstrated that the final treprostinil product from the '393 patent is physically different than that of Moriarty. Thus, even if the Moriarty treprostinil was used for Phares, Petitioner has failed to provide any evidence that the final Phares treprostinil product would necessarily be the same as the products claimed in the '393 patent. Specifically, the declaration of Dr. Walsh submitted during original prosecution shows that certain impurities in representative examples are reduced below detectable amounts by step (c), while others are still present in detectable amounts, such as treprostinil stereoisomer 3AU90. Ex. 1002, at pp. 346-350. Both the type of impurity, as well as the relative amount of that impurity in the starting treprostinil material, may impact the impurity profile of the final product after step (c), yet there is absolutely no disclosure of any specific impurities or total amount of impurities in Phares and Petitioner has failed to provide any further evidence on this point.

Phares simply does not disclose what starting treprostinil material is used. Thus, Phares cannot inherently anticipate the final treprostinil product of the '393 patent because each method would result in a distinct impurity profile. Indeed, the particular process by which a treprostinil product is made will affect the impurity profile and total amount of impurities in the final product, and thus each process may result in a structurally different treprostinil product. Ex. 2013, at p. 207, ll. 19-24. Petitioner has failed to show that performing step (c) on a starting

treprostinil material with a different impurity profile than a starting treprostinil material made a different way would *necessarily* lead to an identical product after step (c). For this reason alone, there can be no inherent anticipation based on a teaching of a treprostinil salt product that does not identify the source of its starting treprostinil material, as is the case with Petitioner's reliance on each of the three separate portions of Phares discussed above.

Additionally, Petitioner fails to identify any specific purity in Phares that would anticipate any claim of the '393 patent. Instead, Petitioner relies on melting point alone as a proxy for a certain purity, but melting point does not disclose any specific impurity level and instead may demonstrate a different form, or polymorph, of treprostinil diethanolamine altogether. Petition at pp. 27-28. Just because Phares discloses a higher melting point does not mean that it is necessarily a "higher purity" or even necessarily the same polymorph of treprostinil diethanolamine. While Petitioner admits that Phares and the '393 patent cite different melting point ranges for treprostinil diethanolamine, it ignores the fact that different melting points can result in different forms or polymorphs of treprostinil diethanolamine. *Id.*; *see also* Ex. 1005, pp.88-93; Ex. 1001, Example 3 and 4. Given that both Phares and the '393 patent provide different melting points for the treprostinil diethanolamine polymorph, Petitioner has not carried its burden to show that these materials are the same form, let alone the same purity.

Moreover, despite providing an expert declaration, Petitioner provides no additional evidence regarding the purity, melting point, or polymorph structure of either Phares or the '393 patent. *Glaxo Inc.*, 52 F.3d at 1047-48 (finding no inherent anticipation where testing evidence demonstrated that the prior art example could yield crystals of either the claimed polymorph or a different polymorph). On this additional basis, Phares cannot inherently anticipate the claims of the '393 patent. For these reasons, Petitioner's petition for IPR should be denied as to Ground 1.

IX. THE FDA ACCEPTED A NEW PURITY SPECIFICATION WHEN PATENT OWNER IMPLEMENTED CLAIMS 1 AND 10 OF THE '393 PATENT

Ex. 2004 is a process validation report (Protocol No. "VAL-00131"), which states at p. 3 that it applies to "production of treprostinil diethanolamine intermediate (UT-15C-I), a chemical intermediate used for the production of active pharmaceutical ingredients treprostinil (UT-15) and treprostinil diethanolamine (UT-15C)." Ex. 2004, at pp. 5-7 shows that [redacted].

Ex. 2005 is a Process Optimization Report that provides results for batches resulting from step (d) of claims 1 and 10 in the '393 patent, which was performed on specific batches of the diethanolamine salt intermediate produced by steps (a)-(c) [redacted].

Ex. 2005, at p. 3 states that "[redacted]" The percent yield and purity levels of the final treprostinil product are compared to the former process in a chart on Ex. 2005, at p. 3, further demonstrating the differences that result in the final treprostinil product when all of steps (a)-(d) of claims 1 and 10 of the '393 patent are performed.

Ex. 2006 is a letter from Patent Owner to the FDA, which references the VAL-00131 report of Ex. 2004 and states as follows:

[redacted]

Ex. 2006, at p. 2. In addition, Ex. 2006, at p. 3 states as follows:

In all lots, the total unidentified impurity level (%AUC) decreased from triol to UT-15C intermediate. [redacted]

Finally, Ex. 2006, at pp. 3-4 states that, when the new process was implemented, "it was observed that the purity of the treprostinil improved close to 100%", and the letter proposes that "the range of the specification for the HPLC assay for treprostinil be shifted from [redacted]% to [redacted]% [redacted]."

The FDA subsequently approved the Patent Owner's proposed implementation of the '393 process and the increased purity standard. Ex. 2003.

X. GROUNDS 2 AND 3 OF THE PETITION SHOULD BE DENIED BECAUSE THE TRANSLATOR'S DECLARATION FOR KAWAKAMI IS INSUFFICEINT

All Grounds relying on Kawakami should be denied because Petitioner relies on an improper translation of the Japanese-language reference. Ex. 1011, at p. 1. When a party relies on a document or is required to produce a document in a language other than English, a translation of the document into English and an affidavit attesting to the accuracy of the translation must be filed with the document. 37 C.F.R. § 41.154(b). However, the declarant, Boris Levine, states that another individual (James Dowdle) carried out the translation. The declaration does not indicate that the declarant understands Japanese, but rather that someone else, James Dowdle, knows that language. The actual translator did not submit

declaration. Thus, the declaration is objectionable under Federal Rule of Evidence 602 because the declarant lacks personal knowledge of the relevant facts, e.g., the accuracy of the translation. The declaration is also objectionable as irrelevant under Federal Rule of Evidence 402 because the accuracy of the translation cannot be determined. The Levine declaration is of no probative value because the declarant has no personal knowledge regarding the accuracy of the translation, and any belief the declarant may have is not founded on evidence because he had no way of determining whether Mr. Dowdle's translation was accurate. *See*, 37 C.F.R. § 1.68. Petitioner's use of this declarant also means that the real translator is shielded from cross-examination, contrary to what is required by the IPR rules and Trial Practice Guide. For these reasons, the translation of Kawakami, and therefore Kawakami itself, should not be included in evidence and Grounds 2 and 3 should be denied on this basis alone.

XI. GROUND 2 SHOULD BE DENIED BECAUSE IT FAILS TO ESTABLISH A REASONABLE LIKELIHOOD OF SUCCESS THAT ANY OF CLAIMS 1-5, 7-9, 11-14, OR 16-20 WOULD HAVE BEEN OBVIOUS

Petitioner asserts that claims 1-5, 7-9, 11-14, and 16-20 are rendered obvious under 35 U.S.C. § 103 when considering Moriarty in view of either Phares or Kawakami. Petition at p. 4. Petitioner, therefore, has asserted Ground 2 in the alternative. Either Moriarty in view of Phares, or Moriarty in view of Kawakami is

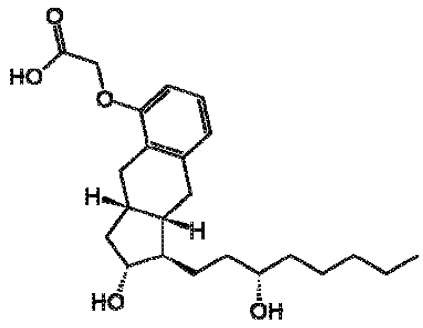
asserted against claims 1-5, 7-9, 11-14, and 16-20. Patent Owner addresses the deficiencies of each alternative in turn below.

A. Petitioner fails to establish a motivation to combine Moriarty with Kawakami with a reasonable expectation of success

Even if the Board accepts the defective declaration for Kawakami, Petitioner has failed to establish that the '393 patent would have been obvious in view of any Kawakami combination. Simply put, Kawakami is directed to entirely different compounds with entirely different impurity profiles. Nothing in Kawakami comes close to addressing the treprostinil product of the '393 patent much less how a POSA would or would not go about synthesizing or purifying the product. Thus, a POSA would have no motivation to combine Moriarty with Kawakami and no reasonable expectation of success of obtaining the same high purity treprostinil product of the '393 patent.

As previously described, Moriarty fails to disclose the high purity treprostinil product of the '393 patent, much less the same impurity profile. Kawakami is asserted as allegedly remedying these deficiencies. However, Petitioner does not establish a motivation or reasonable expectation of success of forming a salt of the compounds in Moriarty with a purity profile of the products in the present claims. Petitioner fails to establish that Kawakami provides a reasonable expectation that the purity profile of the products in the present claims

can be obtained. The Petition relies on the Winkler declaration to provide motivation to combine, but the relied-upon portion of the declaration merely states that Kawakami discloses prostacyclin compounds, and treprostinil is a prostacyclin compound.



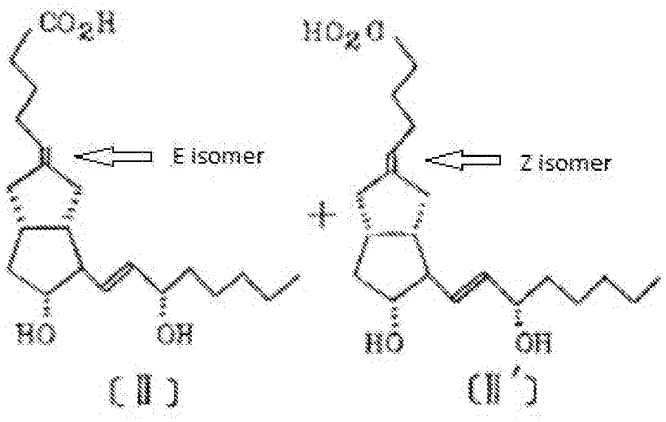
Treprostinil

"prostacyclin compound" in Kawakami

There are myriad "prostacyclin compounds" with widely-varying structures. Treprostinil's core structure and side chains are entirely different from those found in the "prostacyclin compounds" in Kawakami. Indeed, the alleged "prostacyclin compound" disclosed in Kawakami is a two ring structure, yet the core three ring structure of treprostinil is key to its pharmaceutical usefulness (Ex. 2013, at pp. 15, ll. 1-17) and is also present in every structure of every step of the '393 patent. *See, e.g.*, '393 patent claim 1. Other than the Winkler Declaration's conclusory statement that Kawakami's compounds are "prostacyclin compounds (of which treprostinil is an example)," Petitioner offers no basis from which to draw any

conclusion about whether an impurity reduction step in Kawakami would possibly have any relevance to a process to synthesize and or purify a totally different structure such as treprostinil.

To illustrate this point further, Kawakami is directed to purifying E- and Z-isomers of "prostacyclin compounds" from one another. In order for the E- and Z-isomers to exist, the "prostacyclin compound" must have an alkene. For example, Kawakami discusses separating a mixture of the following compounds:



Treprostinil, on the other hand, contains no mixture of E/Z isomers. In fact, it cannot because it does not contain an alkene capable of E/Z isomerization. Petitioner has failed to provide a factual basis as to how or why the separation of E/Z isomers of an alkene would provide a motivation to combine or reasonable expectation of success in a compound not containing an alkene capable of E/Z isomerization, such as treprostinil.

For these reasons, a POSA would have no motivation to look at Kawakami in order to arrive at the claimed invention of the '393 patent.

B. Moriarty in view of Phares does not render the '393 patent obvious

As explained above for Ground 1, Phares fails to disclose the synthetic route or purity of the claimed treprostinil product. Moriarty adds nothing to cure these deficiencies. Moriarty was considered during prosecution and disclosed multiple routes to synthesize the treprostinil formula. (Ex. 1004) Those same routes were also disclosed on the face of the '393 patent itself. Specifically, Moriarty discloses three distinct routes. *See, supra*, Section VIII.C. While Moriarty itself was an improvement over the previous methods by reducing the level of total impurities, reducing specific types of impurities and increasing the yield of the treprostinil product (Ex. 2013, at pp. 177, ll. 24–pp. 178, ll. 5, pp. 196, ll. 3–11, pp. 197, ll. 20–23, pp. 218, ll. 21–pp. 219, ll. 9, pp. 311, ll. 15–17), the '393 patent unexpectedly reduced the impurity level in the claimed treprostinil product even more. Petitioner, however, ignores this evidence, and states that "Moriarty discloses the synthesis (Ex. 1004, at p. 6) of treprostinil which is Formula 7 on p. 3" and that "formation of salts by the reaction of carboxylic acids with bases is a common reaction in organic chemistry." But this misses the point. The claimed invention is not the discovery that carboxylic acids react with bases, but rather that

compounds of Formula (I), and in particular treprostinil or a salt thereof, can be obtained with a superior purity profile compared to the prior art.

Specifically, Patent Owner discovered that performing step (c) on a product that resulted from steps (a) and (b) provided a product with reduced impurities. This discovery was not disclosed or suggested in Moriarty and resulted in a significant improvement in the treprostinil product. *See, supra*, Section IV.D.

Moreover, Patent Owner established at that time that, when "treprostinil acid made by the type of process disclosed in Moriarty 2004 was analyzed by the applicants, it was found to contain small amounts of 4 different impurities in a representative sample (benzindene triol, treprostinil methyl ester, and 2 different stereoisomers of treprostinil)." Each of these impurities, however, is reduced or eliminated in a product produced by the process according to claims 1 or 9 of the '393 patent. *See supra*, Section IV.D, Ex. 1002, at pp. 346-350. Petitioner argues that the salt formation step would have been obvious to reduce or remove acidic or basic impurities, but these reduced or removed impurities are neither strongly acidic nor basic as they are either diastereomers of treprostinil – which is very weakly acidic – or similarly neutral ester and triol impurities. The '393 patent therefore not only reduced the weakly acidic impurities present from the already improved Moriarty process, but also unexpectedly reduced or eliminated non-acidic impurities as well. Thus, even under Petitioner's broad and erroneous

understanding of the standard for obviousness, it was unexpected that the salt formation step would remove these additional impurities.

XII. GROUND 3 SHOULD BE DENIED BECAUSE THE PETITION FAILS TO ESTABLISH THAT IT WOULD HAVE BEEN OBVIOUS TO COMBINE THE REFERENCES WITH A REASONABLE EXPECTATION OF SUCCESS

Petitioner asserts that claims 6, 10, 15, 21 and 22[4] are rendered obvious under 35 U.S.C. § 103 over Moriarty with Phares or Kawakami, and in further combination with Ege. Petition, p. 53. Petitioner has asserted Ground 3 in the alternative. Either Moriarty in view of Phares and in further combination with

[4] These claims require that the product is produced with the optional step (d), and claim 22 requires that the product is produced with an additional step after step (d) wherein the product comprises a pharmaceutically acceptable salt formed from the product of step (d). Thus, claims 6, 10, 15, and 21 require the free acid of a compound of Formula (I) or treprostinil, while claim 22 recites a salt form of a compound of Formula (I) that has been purified through the salt-formation step (c) followed by the acid-formation step (d). Thus, in addition to the many reasons why these claims are not rendered obvious as described herein, these additional steps are similarly not disclosed in any of the prior art references asserted by Petitioner and for this additional reason would not have been obvious over the prior art.

Ege, or Moriarty in view of Kawakami and in further combination with Ege is asserted against claims 6, 10, 15, 21 and 22. Thus, each of the combinations asserted in Ground 3 requires Ege. Ege, however, does not disclose any of the missing claim elements from these previously addressed obviousness combinations.

A. Ege is not relevant to the '393 patent

Ege provides no additional support for any of these alleged obviousness combinations as it is merely an undergraduate chemistry textbook with only generalized descriptions of carboxylic acids and related synthetic procedures. Ege discloses nothing about any prostacyclin derivative, much less treprostinil free acid. Indeed, Ege fails to disclose anything about the synthesis of pharmaceuticals. Ege merely shows it was known to form a free acid from treatment of the corresponding carboxylate salt with a strong acid. But this fact alone provides no reason why one of ordinary skill in the art, based on any reference, would conduct a "carboxylate salt formation and regeneration of the neutral carboxylic acid" step with a reasonable expectation of obtaining the claimed product.

In fact, Ege actually suggests this "carboxylate salt formation and regeneration of the neutral carboxylic acid" step would be relatively useless as a means for purifying treprostinil:

> Carboxylic acids that have low solubility in water, such as benzoic acid, are converted to water-soluble salts by reaction with aqueous base (p. 95). Protonation of the carboxylate anion by a strong acid regenerates the water-insoluble acid. These properties of carboxylic acids are *useful in separating them from reaction mixtures containing neutral and basic compounds*.

Ex. 1008, p. 8 (emphasis added). However, other compounds containing carboxylic-acids are not "neutral and basic compounds." Thus, Ege would not create an expectation of success for separating one carboxylic-acid compound (*e.g.,* treprostinil free acid) from other carboxylic-acid containing compounds (*e.g.,* different stereoisomers of treprostinil free acid). If anything, Ege would teach away or discourage the use of salt formation for purifying a mixture of compounds that includes other carboxylic-acid containing compounds as impurities.

B. Moriarty in view of Phares with Ege Fails To Establish Obviousness

In the first alternative for Ground 3 (Moriarty, Phares and Ege), Petitioner fails to establish a reasonable likelihood that claims 6, 10, 15, 21, and 22 are unpatentable as obvious.

1. Petitioner fails to provide a motivation to combine Moriarty, Phares, and Ege or an expectation of success for obtaining the free-acid product of claims 6, 10, 15, and 21

Claims 6, 10, 15, and 21 are to the free acid of Formula (I) or treprostinil. As mentioned above, out of Moriarty, Phares and Ege, only Moriarty discloses free acid treprostinil with any particularity. However, the free acid treprostinil in Moriarty was analyzed by Patent Owner, and representative samples were found to contain small amounts of four different impurities, including two different stereoisomers of treprostinil.

As explained previously, the claimed free-acid compounds, including treprostinil, produced by the processes of claims 6, 10, 15, and 21 provided a new product that induced FDA to adopt a new purity standard for treprostinil free acid due to the excellent purity of the final product. Furthermore, Patent Owner demonstrated that treprostinil free acid made by the claimed methods provided a compound without many of the impurities included in the free acid treprostinil of the Moriarty process, including the two different stereoisomers of treprostinil.

Neither Phares nor Ege provide a reason that a POSA would include a "carboxylate salt formation and regeneration of the neutral carboxylic acid" step. *See* Petition, p. 54. Phares merely discloses forming a salt from treprostinil free acid of undisclosed origin. *See* Section VIII.B, *supra*. There is no suggestion that

this salt should then be converted *back* to the free acid (*e.g.*, there is no suggestion of using the salt formation as a purification method).

As discussed above, the impurities in representative examples of Moriarty include two different stereoisomers of treprostinil free acid. Ege suggests that a "carboxylate salt formation and regeneration of the neutral carboxylic acid" step would not remove these compounds from the product. Thus, a POSA looking to make the free acid product of claims 6, 10, 15, and 21, such as treprostinil free acid, would have understood Moriarty, Phares, and Ege to suggest simply making the treprostinil free acid product of Moriarty, and not undergoing the additional time and expense of a "carboxylate salt formation and regeneration of the neutral carboxylic acid" step because Ege actually teaches away from the usefulness of this step.

Petitioner provides no additional evidence to augment or strengthen the position taken in the Petition by adding Ege. Although Petitioner submitted the Winkler declaration with the Petition, the only declaratory "evidence" relied upon in the Petition for claims 6, 15, and 21 is the conclusory statements made in paragraphs 84, 86, and 88, which are entitled to little or no weight. *See* 37 C.F.R. § 42.65(a) ("Expert testimony that does not disclose the underlying facts or data on which the opinion is based is entitled to little or no weight.").

In sum, even though Phares discloses forming a salt from treprostinil free acid, and Ege generally discusses that carboxylate salt formation was known in the art, there would have been no motivation or expectation of success in using these teachings on the already-formed free acid disclosed in Moriarty, and Petitioner has failed to establish that a POSA would have carried out steps necessary to inherently obtain the claimed products. Thus, Petitioner fails to establish a reasonable likelihood that claims 6, 10, 15 and 21 are unpatentable as obvious.

2. Petitioner fails to provide a motivation to combine Moriarty, Phares and Ege or an expectation of success for obtaining the salt product of claim 22

As noted above, claim 22 recites a salt form of a compound of Formula (I) that has been purified through the salt-formation step (c) followed by the acid-formation step (d). In essence, this claim requires a salt product of the free acid that has a novel purity profile, as discussed above.

For the reasons outlined above, Petitioner has failed to establish that a POSA would have had a motivation or a reasonable expectation that subjecting a free acid compound such as treprostinil to a "carboxylate salt formation and regeneration of the neutral carboxylic acid" step, which was shown by Patent Owner (and evidenced by the FDA's actions) to produce a significantly different final product. Petitioner has likewise failed to show that a POSA would be motivated to then turn around and make a salt of the significantly different final product. Again,

Petitioner provides no additional evidence to augment or strengthen the position taken in the Petition, and instead cites to the conclusory statements made in paragraphs 84, 86 and 88 of the Winkler declaration.

C. Moriarty in view of Kawakami with Ege

Much like the first alternative for Ground 3, the second alternative – over Moriarty, Kawakami and Ege – fails to establish a reasonable likelihood that claims 6, 10, 15, 21, and 22 are unpatentable as obvious.

1. Petitioner fails to provide a motivation to combine Moriarty, Kawakami and Ege or an expectation of success for obtaining the free-acid product of claims 6, 10, 15, and 21

As noted throughout this Preliminary Response, the treprostinil free acid in Moriarty has a different purity profile than treprostinil free acid encompassed by the present claims. This difference in product was so significant that FDA changed its protocol for analyzing treprostinil free acid once this new product was introduced. *See, supra*, Section II.

Kawakami allegedly discloses purification of a compound containing a carboxylic acid by forming the acid addition salt and then reforming the carboxylic acid. Petition, pg. 53. Kawakami allegedly discloses that the resulting product is of "fairly high purity." *Id.* Petitioner, however, fails to establish that a POSA would reasonably expect the teachings of Kawakami to extend to the products in

Moriarty. Specifically, Petitioner offers no evidence that a POSA would expect that the purification of a particular compound in Kawakami to a "fairly high purity" would suggest that the products in Moriarty (containing structurally unrelated stereoisomers of treprostinil free acid and other impurities) could be purified using the same process. Again, despite submitting the Winkler declaration with the Petition, the only "evidence" relied upon in the Petition for claims 6, 15, and 21 is the conclusory statements made in paragraphs 84, 86, and 88. This provides no evidence as to why Kawakami (separation of E/Z isomers of an alkene) would be applicable to the products in Moriarty or why Ege does not directly teach away from Petitioner's conclusion.

2. Petitioner fails to provide a motivation to combine Moriarty, Kawakami, and Ege or an expectation of success for obtaining the salt product of claim 22

As noted above, claim 22 recites a salt form of a compound of Formula (I) that has been purified through the salt-formation step (c) followed by the acid-formation step (d). In essence, this claim requires a salt product of the free acid that has a novel purity profile, as discussed above.

For the reasons outlined above, Petitioner has failed to establish that a POSA would have had a motivation or a reasonable expectation that subjecting a free acid compound such as treprostinil to a "carboxylate salt formation and regeneration of the neutral carboxylic acid" step, which was shown by Patent Owner (and

evidenced by FDA's actions) to produce a significantly different final product. Petitioner has likewise failed to show that a POSA would be motivated to then turn around and make a salt of the significantly different final product. Again, Petitioner provides no additional evidence to augment or strengthen the position taken in the Petition, and instead cites to the conclusory statements made in paragraphs 84, 86 and 88 of the Winkler declaration.

D. Petitioner provides no evidence that the product of the '393 patent would be "inherently produced"

Petitioners attempt to create a new legal theory out of whole cloth by alleging that a hypothetical combination of prior art references would inherently create the same product as the '393 patent. Specifically, Petitioner has not asserted that the free acid and salt products of claims 6, 10, 15, 21, and 22 would have been obvious from the product in Moriarty, Phares/Kawakami, and Ege.[5] Instead, Petitioner asserts an inherency position whereby it would have been obvious to conduct the salt-formation step (c) followed by the acid-formation step (d) (and a further salt-formation step for the purposes of claim 22), and the resulting product would have inherently been the same as that which is claimed.

[5] Indeed, Patent Owner established during prosecution that the free acid and salt products of claims 6, 10, 15, 21, and 22 were patentably distinct from the products in Moriarty and Phares. Ex. 1002.

Petitioner has set forth an inherency rationale that "a [POSA] would want to form the treprostinil diethanolamine salt, purify it, and then convert it back to its free form (i.e., treprostinil) in order to obtain excellent crystallinity and increased purity." Petition, p. 54. Basically, Petitioner's rationale relies on the inherent production of the claimed product flowing from the assertion that it would have been obvious to conduct the salt-formation step (c) followed by the acid-formation step (d) (and a further salt-formation step for the purposes of claim 22). This position, however, has no basis in law as inherency stems from *what must necessarily be present in the prior art*, not what might possibly be present based on an alleged obviousness combination. *See, e.g., Atlas Powder Co. v. Ireco Inc.,* 190 F.3d 1342, 1345-46 (Fed. Cir. 1999). As discussed for anticipation, Petitioner failed to provide a shred of evidence that any prior art reference contained any specific impurity profile or impurity level, much less that any prior art reference necessarily matched the impurity profile or impurity level of the '393 patent. For obviousness, Petitioner asserts that new hypothetical products made by combining prior art references would also result in the same treprostinil products claimed in the '393 patent. This argument however, has absolutely no evidentiary support or legal support. For these additional reasons, the petition for IPR should be denied should be denied with respect to Ground 3.

XIII. SECONDARY CONSIDERATIONS WOULD REBUT ANY POSSIBLE CASE OF OBVIOUSNESS

Petitioner has not established a *prima facie* case of obviousness. Thus, Patent Owner is not obligated to provide evidence of objective indicia of non-obviousness. Nonetheless, objective indicia of non-obviousness confirm that the '393 patent would not have been obvious and, in fact, represents a surprising solution to the problem of minimizing impurities and providing a safer and purer treprostinil product.

A. Long-felt unmet need

At the time of the invention, there was a long-felt need to have a more efficient synthesis to produce treprostinil in a more pure form and in a cost-effective manner. Treprostinil has five chiral centers resulting in 32 possible diastereomers, so the potential for diastereomeric impurities is high; only the treprostinil stereoisomer has the desired pharmaceutical effect. Ex. 2013, at pp. 11, ll. 18-25, pp. 15, ll. 1-pp. 16, ll. 8, pp. 19, ll. 14-25. Treprostinil is also a very potent drug so any diastereomeric impurities would also potentially be potent and could potentially have deleterious effects. *Id*. Thus, there was a desire to reduce the amount of impurities as much as possible and the product of the '393 patent further reduces impurities over the previous treprostinil products made by the prior art.

B. Unexpected results

The results of the claimed inventions in the '393 were unexpected. The use of a salt form of treprostinil to further purify the treprostinil acid in a cheaper and better way than the previously used methods of purification was an unexpected result. Moreover, it was unexpected that the salt purification step reduced not only diastereomeric impurities, but also non-acidic impurities as well. *See, supra*, Section XI.B.1. Thus, a person of skill in the art would not have expected the results of the '393 patent to be so successful.

C. Commercial Success

The '393 patent is used in the current production of Remodulin® and has reduced the amount of solvents and purification steps used to make Remodulin® and has thereby reduced the cost of making Remodulin® and increased efficiency. Ex. 2006, pp. 64-66. Remodulin is a commercially successful product that competes well against other alternatives such as Flolan. The commercial success of Remodulin® is reflected in its total revenue and relevant market share. Specifically, Remodulin® generated approximately $553.7 million, $491.2 million and $458.0 million in revenues for the years ended December 31, 2014, 2013 and 2012, respectively. Ex. 2016, p. 6.

D. Copying

The non-obviousness of the '393 patent is evidenced by the actions of several generic pharmaceutical companies who have attempted to copy Remodulin® and Tyvaso®. *See, e.g.*, *United Therapeutics Corp. v. Sandoz, Inc.*, Civil Action No. 3:14-cv-05499-PGS-LHG (D.N.J. 2014); *United Therapeutics Corp. v. Teva Pharma*, Civil Action No. 3:14-cv-05498-PGS-LHG (D.N.J. 2014); *United Therapeutics Corp. v. Watson Laboratories, Inc.*, Civil Action No. 15-cv-5723 (D.N.J. 2015). Treprostinil is marketed under the trade names Remodulin® for infusion and Tyvaso® for inhalation. The '393 patent product and process is currently used in the production of Remodulin® and Tyvaso®. *See, supra*, Section II.

XIV. CONCLUSION

For the foregoing reasons, SteadyMed's Petition should be denied. The issues raised have already been addressed by the Office, so denying the Petition is appropriate under 35 U.S.C. § 325(d). Even if the Board does not exercise its discretion, the Petition should be denied because Petitioner has failed to demonstrate a likelihood of success on the merits.

Respectfully submitted,

Date: Jan. 14, 2016

/Stephen B. Maebius/
Stephen B. Maebius
Reg. No. 35,264

CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of the foregoing Patent Owner Preliminary Response was served on counsel of record for Petitioner on January 14, 2016 by delivering a copy via email to Stuart Pollack and Lisa Haile (the counsel of record for the Petitioner) at the following address:

Steadymed-IPR@dlapiper.com

Date: Jan. 14, 2016 signature: /Stephen B. Maebius/
Stephen B. Maebius

Paper _____

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

STEADYMED LTD.
Petitioner

v.

UNITED THERAPEUTICS CORPORATION
Patent Owner

U.S. Patent No. 8,497,393
Issue Date: Jul. 30, 2013
Title: PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®

Case IPR2016-00006

Patent Owner's Exhibit List

Mail Stop "PATENT BOARD"
Patent Trial and Appeal Board
U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

4825-0169-9884.1

Ex #	Exhibit Description
2001	November 19, 2015 Conference Call Before the Panel
2002	Remodulin Label
2003	FDA Approval Letter
2004	Process Validation Report: (Protocol No.: "VAL 00131")
2005	Process Optimization Report
2006	UTC Letter of January 2009 to FDA
2007	U.S. Patent No. 8,242,305; the '305 patent;
2008	U.S. Provisional Patent Application No. 61/014,232
2009	U.S. Patent No. 8,748,657; the '657 patent
2010	The '657 patent prosecution history
2011	Zumdahl, Chemistry, pp. A25, A36 (1986)
2012	Brown, et al., Chemistry: The Central Science, pp. G-2, G-10 (9th ed. 2003)
2013	Trial testimony of Dr. Williams and Dr. Aristoff
2014	Suchocki, et al., Conceptual Chemistry, p. G-6 (2001)
2015	U.S. Patent No. 4,668,814; the '814 patent

2016	UTC Form 10K 2014 Annual Report

Respectfully submitted,

Date: Jan. 14, 2016

/Stephen B. Maebius/
Stephen B. Maebius
Registration No. 35,264
Counsel for Patent Owner

CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of the foregoing Patent Owner's Exhibit List and a copy of each listed exhibit except for Exhibit Nos. 2003-2006 (which are filed under seal) were served on counsel of record for the Petitioner on Jan. 14, 2016 by delivering a copy via email to Stuart Pollack and Lisa Haile (the counsel of record for the Petitioner) at the following address: Steadymed-IPR@dlapiper.com.

Date: Jan. 14, 2016

/Stephen B. Maebius/
Stephen B. Maebius
Registration No. 35,264
Counsel for Patent Owner

4825-0169-9884.1

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use REMODULIN safely and effectively. See full prescribing information for REMODULIN.

REMODULIN® (treprostinil) Injection, for subcutaneous or intravenous use
Initial U.S. Approval: May 2002

----------RECENT MAJOR CHANGES----------

Dosage and Administration (2.1, 2.5) 12/2014

----------INDICATIONS AND USAGE----------

Remodulin is a prostacyclin vasodilator indicated for:

- Treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to diminish symptoms associated with exercise. Studies establishing effectiveness included patients with NYHA Functional Class II-IV symptoms and etiologies of idiopathic or heritable PAH (58%), PAH associated with congenital systemic-to-pulmonary shunts (23%), or PAH associated with connective tissue diseases (19%) (1.1)
- Patients who require transition from Flolan®, to reduce the rate of clinical deterioration. The risks and benefits of each drug should be carefully considered prior to transition. (1.2)

----------DOSAGE AND ADMINISTRATION----------

PAH in patients with NYHA Class II-IV symptoms:

- Initial dose for patients new to prostacyclin infusion therapy: 1.25 ng/kg/min; increase based on clinical response (increments of 1.25 ng/kg/min per week for the first 4 weeks of treatment, later 2.5 ng/kg/min per week). Avoid abrupt cessation. (2.2, 2.3)
- Mild to moderate hepatic insufficiency: Decrease initial dose to 0.625 ng/kg/min.
- Severe hepatic insufficiency: No studies performed. (2.4)

Transition from Flolan:

Increase the Remodulin dose gradually as the Flolan dose is decreased, based on constant observation of response. (2.6)

Administration:

Continuous subcutaneous infusion (undiluted) is the preferred mode. Use intravenous (IV) infusion (dilution required) if subcutaneous infusion is not tolerated. (2.1, 2.5)

----------DOSAGE FORMS AND STRENGTHS----------

- Remodulin is supplied in 20 mL vials containing 20, 50, 100, or 200 mg of treprostinil (1, 2.5, 5 or 10 mg/mL). (3)

----------CONTRAINDICATIONS----------

None

----------WARNINGS AND PRECAUTIONS----------

- For intravenous infusion use an indwelling central venous catheter. This route is associated with the risk of blood stream infections (BSIs) and sepsis, which may be fatal. (5.1)
- Do not abruptly lower the dose or withdraw dosing. (5.2)

----------ADVERSE REACTIONS----------

Most common adverse reactions (incidence >3%) reported in clinical studies with Remodulin: subcutaneous infusion site pain and reaction, headache, diarrhea, nausea, jaw pain, vasodilatation, edema, and hypotension. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact United Therapeutics Corp. at 1-866-458-6479 or contact FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**.**

----------DRUG INTERACTIONS----------

- Blood pressure lowering drugs (e.g., diuretics, antihypertensive agents, or vasodilators): Risk of increased reduction in blood pressure (7.1)
- Remodulin inhibits platelet aggregation. Potential for increased risk of bleeding, particularly among patients on anticoagulants. (7.2)
- Remodulin dosage adjustment may be necessary if inhibitors or inducers of CYP2C8 are added or withdrawn. (7.6)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 12/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

1.1 Pulmonary Arterial Hypertension

Remodulin is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to diminish symptoms associated with exercise. Studies establishing effectiveness included patients with NYHA Functional Class II-IV symptoms and etiologies of idiopathic or heritable PAH (58%), PAH associated with congenital systemic-to-pulmonary shunts (23%), or PAH associated with connective tissue diseases (19%) *[see Clinical Studies (14.1)]*.

It may be administered as a continuous subcutaneous infusion or continuous intravenous (IV) infusion; however, because of the risks associated with chronic indwelling central venous catheters, including serious blood stream infections (BSIs), reserve continuous intravenous infusion for patients who are intolerant of the subcutaneous route, or in whom these risks are considered warranted *[see Warnings and Precautions 5.1]*.

1.2 Pulmonary Arterial Hypertension in Patients Requiring Transition from Flolan®

In patients with pulmonary arterial hypertension requiring transition from Flolan (epoprostenol sodium), Remodulin is indicated to diminish the rate of clinical deterioration. Consider the risks and benefits of each drug prior to transition.

2 DOSAGE AND ADMINISTRATION

2.1 General

Remodulin can be administered without further dilution for subcutaneous administration, or diluted for intravenous infusion with Sterile Diluent for Remodulin or similar approved high-pH glycine diluent (e.g. Sterile Diluent for Flolan or Sterile Diluent for Epoprostenol Sodium), Sterile Water for Injection, or 0.9% Sodium Chloride Injection prior to administration. See Table 1 below for storage and administration time limits for the different diluents.

Table 1. Selection of Diluent

Route	Diluent	Storage limits	Administration limits
SC	None	See section 16	72 hours at 37°C
IV	Sterile Diluent for Remodulin Sterile Diluent for Flolan Sterile Diluent for Epoprostenol Sodium	14 days at room temperature	48 hours at 40 °C
	Sterile water for injection 0.9% Sodium Chloride for injection	4 hours at room temperature or 24 hours refrigerated	48 hours at 40°C

2.2 Initial Dose for Patients New to Prostacyclin Infusion Therapy

Remodulin is indicated for subcutaneous (SC) or intravenous (IV) use only as a continuous infusion. Remodulin is preferably infused subcutaneously, but can be administered by a central intravenous line if the subcutaneous route is not tolerated, because of severe site pain or reaction. The infusion rate is initiated at 1.25 ng/kg/min. If this initial dose cannot be tolerated because of systemic effects, reduce the infusion rate to 0.625 ng/kg/min.

2.3 Dosage Adjustments

The goal of chronic dosage adjustments is to establish a dose at which PAH symptoms are improved, while minimizing excessive pharmacologic effects of Remodulin (headache, nausea, emesis, restlessness, anxiety and infusion site pain or reaction).

The infusion rate should be increased in increments of 1.25 ng/kg/min per week for the first four weeks of treatment and then 2.5 ng/kg/min per week for the remaining duration of infusion, depending on clinical response. Dosage adjustments may be undertaken more often if tolerated. Avoid abrupt cessation of infusion *[see Warnings and Precautions (5.4)]*. Restarting a Remodulin infusion within a few hours after an interruption can be done using the same dose rate. Interruptions for longer periods may require the dose of Remodulin to be re-titrated.

2.4 Patients with Hepatic Insufficiency

In patients with mild or moderate hepatic insufficiency, decrease the initial dose of Remodulin to 0.625 ng/kg/min ideal body weight. Remodulin has not been studied in patients with severe hepatic insufficiency *[see Warnings and Precautions (5.3), Use In Specific Populations (8.6)* and *Clinical Pharmacology (12.3)]*.

2.5 Administration

Inspect parenteral drug products for particulate matter and discoloration prior to administration whenever solution and container permit. If either particulate matter or discoloration is noted, do not use.

Subcutaneous Infusion

Remodulin is administered subcutaneously by continuous infusion without further dilution, via a subcutaneous catheter, using an infusion pump designed for subcutaneous drug delivery. To avoid potential interruptions in drug delivery, the patient must have immediate access to a backup infusion pump and subcutaneous infusion sets. The ambulatory infusion pump used to administer Remodulin should: (1) be small and lightweight, (2) be adjustable to approximately 0.002 mL/hr, (3) have occlusion/no delivery, low battery, programming error and motor malfunction alarms, (4) have delivery accuracy of ±6% or better and (5) be positive pressure driven. The reservoir should be made of polyvinyl chloride, polypropylene or glass.

Remodulin is administered subcutaneously by continuous infusion at a calculated subcutaneous infusion rate (mL/hr) based on a patient's dose (ng/kg/min), weight (kg), and the vial strength (mg/mL) of Remodulin being used. During use, a single reservoir (syringe) of undiluted Remodulin can be administered up to 72 hours at 37°C. The subcutaneous infusion rate is calculated using the following formula:

$$\textbf{Subcutaneous Infusion Rate (mL/hr)} = \frac{\textbf{Dose} \text{ (ng/kg/min)} \times \textbf{Weight} \text{ (kg)} \times \textbf{0.00006*}}{\textbf{Remodulin Vial Strength} \text{ (mg/mL)}}$$

**Conversion factor of 0.00006 = 60 min/hour x 0.000001 mg/ng*

Example calculations for ***Subcutaneous Infusion*** are as follows:

Example 1:

For a 60 kg person at the recommended initial dose of 1.25 ng/kg/min using the 1 mg/mL Remodulin, the infusion rate would be calculated as follows:

$$\textbf{Subcutaneous Infusion Rate (mL/hr)} = \frac{\textbf{1.25} \text{ ng/kg/min} \times \textbf{60} \text{ kg} \times \textbf{0.00006}}{\textbf{1} \text{ mg/mL}} = \textbf{0.005} \text{ mL/hr}$$

Example 2:

For a 65 kg person at a dose of 40 ng/kg/min using the 5 mg/mL Remodulin, the infusion rate would be calculated as follows:

$$\textbf{Subcutaneous Infusion Rate (mL/hr)} = \frac{\textbf{40} \text{ ng/kg/min} \times \textbf{65} \text{ kg} \times \textbf{0.00006}}{\textbf{5} \text{ mg/mL}} = \textbf{0.031} \text{ mL/hr}$$

Intravenous Infusion

Diluted Remodulin is administered intravenously by continuous infusion via a surgically placed indwelling central venous catheter using an infusion pump designed for intravenous drug delivery. If clinically necessary, a temporary peripheral intravenous cannula, preferably placed in a large vein, may be used for short term administration of Remodulin. Use of a peripheral intravenous infusion for more than a few hours may be associated with an increased risk of thrombophlebitis. To avoid potential interruptions in drug delivery, the patient must have immediate access to a backup infusion pump and infusion sets. The ambulatory infusion pump used to administer Remodulin should: (1) be small and lightweight, (2) have occlusion/no delivery, low battery, programming error and motor malfunction alarms, (3) have delivery accuracy of ±6% or better of the hourly dose, and (4) be positive pressure driven. The reservoir should be made of polyvinyl chloride, polypropylene or glass.

Infusion sets with an in-line 0.22 or 0.2 micron pore size filter should be used.

Diluted Remodulin has been shown to be stable at ambient temperature when stored for up to 14 days using high-pH glycine diluent at concentrations as low as 0.004 mg/mL (4,000 ng/mL).

Select the intravenous infusion rate to allow for a desired infusion period length of up to 48 hours between system changeovers. Typical intravenous infusion system reservoirs have volumes of 50 or 100 mL. With this selected intravenous infusion rate (mL/hr) and the patient's dose (ng/kg/min) and weight (kg), the diluted intravenous Remodulin concentration (mg/mL) can be calculated using the following formula:

Step 1

$$\textbf{Diluted Intravenous Remodulin Concentration (mg/mL)} = \frac{\textbf{Dose} \text{ (ng/kg/min)} \times \textbf{Weight} \text{ (kg)} \times \textbf{0.00006}}{\textbf{Intravenous Infusion Rate} \text{ (mL/hr)}}$$

The volume of Remodulin Injection needed to make the required diluted intravenous Remodulin concentration for the given reservoir size can then be calculated using the following formula:

Step 2

$$\text{Volume of Remodulin Injection (mL)} = \frac{\text{Diluted Intravenous Remodulin Concentration (mg/mL)}}{\text{Remodulin Vial Strength (mg/mL)}} \times \text{Total Volume of Diluted Remodulin Solution in Reservoir (mL)}$$

The calculated volume of Remodulin Injection is then added to the reservoir along with the sufficient volume of diluent to achieve the desired total volume in the reservoir.

Example calculations for ***Intravenous Infusion*** are as follows:

Example 3:

For a 60 kg person at a dose of 5 ng/kg/min, with a predetermined intravenous infusion rate of 1 mL/hr and a reservoir of 50 mL, the diluted intravenous Remodulin concentration would be calculated as follows:

Step 1

$$\text{Diluted Intravenous Remodulin Concentration (mg/mL)} = \frac{\mathbf{5}\text{ ng/kg/min} \times \mathbf{60}\text{ kg} \times \mathbf{0.00006}}{\mathbf{1}\text{ mL/hr}} = \mathbf{0.018}\text{ mg/mL (18,000 ng/mL)}$$

The volume of Remodulin Injection (using 1 mg/mL Vial Strength) needed for a total diluted Remodulin concentration of 0.018 mg/mL and a total volume of 50 mL would be calculated as follows:

Step 2

$$\text{Volume of Remodulin Injection (mL)} = \frac{\mathbf{0.018}\text{ mg/mL}}{\mathbf{1}\text{ mg/mL}} \times \mathbf{50}\text{ mL} = \mathbf{0.9}\text{ mL}$$

The diluted intravenous Remodulin concentration for the person in Example 3 would thus be prepared by adding 0.9 mL of 1 mg/mL Remodulin Injection to a suitable reservoir along with a sufficient volume of diluent to achieve a total volume of 50 mL in the reservoir. The pump flow rate for this example would be set at 1 mL/hr.

Example 4:

For a 75 kg person at a dose of 30 ng/kg/min, with a predetermined intravenous infusion rate of 2 mL/hr, and a reservoir of 100 mL, the diluted intravenous Remodulin concentration would be calculated as follows:

Step 1

$$\text{Diluted Intravenous} = \frac{\mathbf{30}\text{ ng/kg/min} \times \mathbf{75}\text{ kg} \times \mathbf{0.00006}}{} = \mathbf{0.0675}\text{ mg/mL (67,500 ng/mL)}$$

$$\text{Remodulin Concentration (mg/mL)} = \frac{\text{Remodulin Concentration (mg/mL)}}{\text{2 mL/hr}}$$

The volume of Remodulin Injection (using 2.5 mg/mL Vial Strength) needed for a total diluted Remodulin concentration of 0.0675 mg/mL and a total volume of 100 mL would be calculated as follows:

Step 2

$$\text{Volume of Remodulin Injection (mL)} = \frac{\textbf{0.0675} \text{ mg/mL}}{\textbf{2.5} \text{ mg/mL}} \times \textbf{100} \text{ mL} = \textbf{2.7} \text{ mL}$$

The diluted intravenous Remodulin concentration for the person in Example 4 would thus be prepared by adding 2.7 mL of 2.5 mg/mL Remodulin Injection to a suitable reservoir along with a sufficient volume of diluent to achieve a total volume of 100 mL in the reservoir. The pump flow rate for this example would be set at 2 mL/hr.

2.6 Patients Requiring Transition from Flolan

Transition from Flolan to Remodulin is accomplished by initiating the infusion of Remodulin and increasing it, while simultaneously reducing the dose of intravenous Flolan. The transition to Remodulin should take place in a hospital with constant observation of response (e.g., walk distance and signs and symptoms of disease progression). Initiate Remodulin at a recommended dose of 10% of the current Flolan dose, and then escalate as the Flolan dose is decreased (see Table 2 for recommended dose titrations).

Patients are individually titrated to a dose that allows transition from Flolan therapy to Remodulin while balancing prostacyclin-limiting adverse events. Increases in the patient's symptoms of PAH should be first treated with increases in the dose of Remodulin. Side effects normally associated with prostacyclin and prostacyclin analogs are to be first treated by decreasing the dose of Flolan.

Table 2: Recommended Transition Dose Changes

Step	Flolan Dose	Remodulin Dose
1	Unchanged	10% Starting Flolan Dose
2	80% Starting Flolan Dose	30% Starting Flolan Dose
3	60% Starting Flolan Dose	50% Starting Flolan Dose
4	40% Starting Flolan Dose	70% Starting Flolan Dose
5	20% Starting Flolan Dose	90% Starting Flolan Dose
6	5% Starting Flolan Dose	110% Starting Flolan Dose
7	0	110% Starting Flolan Dose + additional 5-10% increments as needed

3 DOSAGE FORMS AND STRENGTHS

20-mL vial containing 20 mg treprostinil (1 mg per mL).

20-mL vial containing 50 mg treprostinil (2.5 mg per mL).
20-mL vial containing 100 mg treprostinil (5 mg per mL).
20-mL vial containing 200 mg treprostinil (10 mg per mL).

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Catheter-Related Bloodstream Infection

Chronic intravenous infusions of Remodulin are delivered using an indwelling central venous catheter. This route is associated with the risk of blood stream infections (BSIs) and sepsis, which may be fatal. Therefore, continuous subcutaneous infusion (undiluted) is the preferred mode of administration.

In an open-label study of IV treprostinil (n=47), there were seven catheter-related line infections during approximately 35 patient years, or about 1 BSI event per 5 years of use. A CDC survey of seven sites that used IV treprostinil for the treatment of PAH found approximately 1 BSI (defined as any positive blood culture) event per 3 years of use. Administration of IV Remodulin with a high pH glycine diluent has been associated with a lower incidence of BSIs when compared to neutral diluents (sterile water, 0.9% sodium chloride) when used along with catheter care guidelines.

5.2 Worsening PAH upon Abrupt Withdrawal or Sudden Large Dose Reduction

Avoid abrupt withdrawal or sudden large reductions in dosage of Remodulin, which may result in worsening of PAH symptoms.

5.3 Patients with Hepatic or Renal Insufficiency

Titrate slowly in patients with hepatic or renal insufficiency, because such patients will likely be exposed to greater systemic concentrations relative to patients with normal hepatic or renal function *[see Dosage and Administration (2.4, 2.5), Use In Specific Populations (8.6, 8.7), and Clinical Pharmacology (12.3)]*.

5.4 Effect of Other Drugs on Treprostinil

Co-administration of a cytochrome P450 (CYP) 2C8 enzyme inhibitor (e.g., gemfibrozil) increases exposure (both C_{max} and AUC) to treprostinil. Co-administration of a CYP2C8 enzyme inducer (e.g., rifampin) decreases exposure to treprostinil *[see Drug Interactions (7.5)* and *Clinical Pharmacology (12.3)]*.

6 ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere in labeling: Infections associated with intravenous administration *[see Warnings and Precautions (5.1)]*.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse Events with Subcutaneously Administered Remodulin

Patients receiving Remodulin as a subcutaneous infusion reported a wide range of adverse events, many potentially related to the underlying disease (dyspnea, fatigue, chest pain, right ventricular heart failure, and pallor). During clinical trials with subcutaneous infusion of Remodulin, infusion site pain and reaction were the most common adverse events among those treated with Remodulin. Infusion site reaction was defined as any local adverse event other than pain or bleeding/bruising at the infusion site and included symptoms such as erythema, induration or rash. Infusion site reactions were sometimes severe and could lead to discontinuation of treatment.

Table 3: Percentages of subjects reporting subcutaneous infusion site adverse events

	Reaction		Pain	
	Placebo	Remodulin	Placebo	Remodulin
Severe	1	38	2	39
Requiring narcotics*	NA†	NA†	1	32
Leading to discontinuation	0	3	0	7

* based on prescriptions for narcotics, not actual use

† medications used to treat infusion site pain were not distinguished from those used to treat site reactions

Other adverse events included diarrhea, jaw pain, edema, vasodilatation and nausea, and these are generally considered to be related to the pharmacologic effects of Remodulin, whether administered subcutaneously or intravenously.

Adverse Reactions during Chronic Dosing

Table 4 lists adverse reactions defined by a rate of at least 3% more frequent in patients treated with subcutaneous Remodulin than with placebo in controlled trials in PAH.

Table 4: Adverse Reactions in Controlled 12-Week Studies of Subcutaneous Remodulin and at least 3% more frequent than on Placebo.

Adverse Reaction	Remodulin (N=236) Percent of Patients	Placebo (N=233) Percent of Patients
Infusion Site Pain	85	27
Infusion Site Reaction	83	27
Headache	27	23
Diarrhea	25	16
Nausea	22	18
Rash	14	11
Jaw Pain	13	5
Vasodilatation	11	5
Edema	9	3

Reported adverse reactions (at least 3% more frequent on drug than on placebo) are included except those too general to be informative, and those not plausibly attributable to the use of the drug, because they were associated with the condition being treated or are very common in the treated population.

While hypotension occurred in both groups, the event was experienced twice as frequently in the Remodulin group as compared to the placebo group (4% in Remodulin treatment group verses 2% in placebo-controlled group). As a potent vasodilator, hypotension is possible with the administration of Remodulin.

The safety of Remodulin was also studied in a long-term, open-label extension study in which 860 patients were dosed for a mean duration of 1.6 years, with a maximum exposure of 4.6 years. Twenty-nine (29%) percent achieved a dose of at least 40 ng/kg/min (max: 290 ng/kg/min). The safety profile during this chronic dosing study was similar to that observed in the 12-week placebo controlled study except for the following suspected adverse drug reactions (occurring in at least 3% of patients): anorexia, vomiting, infusion site infection, asthenia, and abdominal pain.

Adverse Events Attributable to the Drug Delivery System

In controlled studies of Remodulin administered subcutaneously, there were no reports of infection related to the drug delivery system. There were 187 infusion system complications reported in 28% of patients (23% Remodulin, 33% placebo); 173 (93%) were pump related and 14 (7%) related to the infusion set. Eight of these patients (4 Remodulin, 4 Placebo) reported non-serious adverse events resulting from infusion system complications. Adverse events resulting from problems with the delivery systems were typically related to either symptoms of excess Remodulin (e.g., nausea) or return of PAH symptoms (e.g., dyspnea). These events were generally resolved by correcting the delivery system pump or infusion set problem such as replacing the syringe or battery, reprogramming the pump, or straightening a crimped infusion line**.** Adverse events resulting from problems with the delivery system did not lead to clinical instability or rapid deterioration. In addition to these adverse events due to the drug delivery system during subcutaneous administration, the following adverse events may be attributable to the IV mode of infusion including arm swelling, paresthesias, hematoma and pain *[see Warnings and Precautions (5.1)]*.

6.2 Post-Marketing Experience

In addition to adverse reactions reported from clinical trials, the following events have been identified during post-approval use of Remodulin. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The following events have been chosen for inclusion because of a combination of their seriousness, frequency of reporting, and potential connection to Remodulin. These events are thrombophlebitis associated with peripheral intravenous infusion, thrombocytopenia bone pain, pruritus and dizziness. In addition, generalized rashes, sometimes macular or papular in nature, and cellulitis have been infrequently reported.

7 DRUG INTERACTIONS

Pharmacokinetic/pharmacodynamic interaction studies have been conducted with treprostinil administered subcutaneously (Remodulin) and orally (treprostinil diethanolamine).

Pharmacodynamics

7.1 Antihypertensive Agents or Other Vasodilators

Concomitant administration of Remodulin with diuretics, antihypertensive agents or other vasodilators may increase the risk of symptomatic hypotension.

7.2 Anticoagulants

Since treprostinil inhibits platelet aggregation, there may be an increased risk of bleeding, particularly among patients receiving anticoagulants.

Pharmacokinetics

7.3 Bosentan

In a human pharmacokinetic study conducted with bosentan (250 mg/day) and an oral formulation of treprostinil (treprostinil diethanolamine), no pharmacokinetic interactions between treprostinil and bosentan were observed.

7.4 Sildenafil

In a human pharmacokinetic study conducted with sildenafil (60 mg/day) and an oral formulation of treprostinil (treprostinil diethanolamine), no pharmacokinetic interactions between treprostinil and sildenafil were observed.

7.5 Effect of Treprostinil on Cytochrome P450 Enzymes

In vitro studies of human hepatic microsomes showed that treprostinil does not inhibit cytochrome P450 (CYP) isoenzymes CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A. Additionally, treprostinil does not induce cytochrome P450 isoenzymes CYP1A2, CYP2B6, CYP2C9, CYP2C19, and CYP3A. Thus Remodulin is not expected to alter the pharmacokinetics of compounds metabolized by CYP enzymes.

7.6 Effect of Cytochrome P450 Inhibitors and Inducers on Treprostinil

Human pharmacokinetic studies with an oral formulation of treprostinil (treprostinil diethanolamine) indicated that co-administration of the cytochrome P450 (CYP) 2C8 enzyme inhibitor gemfibrozil increases exposure (both C_{max} and AUC) to treprostinil. Co-administration of the CYP2C8 enzyme inducer rifampin decreases exposure to treprostinil. It has not been determined if the safety and efficacy of treprostinil by the parenteral (subcutaneously or intravenously) route are altered by inhibitors or inducers of CYP2C8 *[see Warnings and Precautions (5.4)]*.

Remodulin has not been studied in conjunction with Flolan or Tracleer® (bosentan).

7.7 Effect of Other Drugs on Treprostinil

Drug interaction studies have been carried out with treprostinil (oral or subcutaneous) co-administered with acetaminophen (4 g/day), warfarin (25 mg/day), and fluconazole (200 mg/day), respectively in healthy volunteers. These studies did not show a clinically significant effect on the pharmacokinetics of treprostinil. Treprostinil does not affect the pharmacokinetics or pharmacodynamics of warfarin. The pharmacokinetics of R- and S- warfarin and the INR in healthy subjects given a single 25 mg dose of warfarin were unaffected by continuous subcutaneous infusion of treprostinil at an infusion rate of 10 ng/kg/min.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B - In pregnant rats, continuous subcutaneous infusions of treprostinil during organogenesis and late gestational development, at rates as high as 900 ng treprostinil/kg/min (about 117 times the starting human rate of infusion, on a ng/m^2 basis and about 16 times the average rate achieved in clinical trials), resulted in no evidence of harm to the fetus. In pregnant rabbits, effects of continuous subcutaneous infusions of treprostinil during organogenesis were limited to an increased incidence of fetal skeletal variations (bilateral full rib or right rudimentary rib on lumbar 1) associated with maternal toxicity (reduction in body weight and food consumption) at an infusion rate of 150 ng treprostinil/kg/min (about 41 times the starting human rate of infusion, on a ng/m^2 basis, and 5 times the average rate used in clinical trials). In rats, continuous subcutaneous infusion of treprostinil from implantation to the end of lactation, at rates of up to 450 ng treprostinil/kg/min, did not affect the growth and development of offspring. Animal reproduction studies are not always predictive of human response.

8.2 Labor and Delivery

No treprostinil treatment-related effects on labor and delivery were seen in animal studies. The effect of treprostinil sodium on labor and delivery in humans is unknown.

8.3 Nursing Mothers

It is not known whether treprostinil is excreted in human milk or absorbed systemically after ingestion. Many drugs are excreted in human milk.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established. Clinical studies of Remodulin did not include sufficient numbers of patients aged ≤16 years to determine whether they respond differently from older patients.

8.5 Geriatric Use

Clinical studies of Remodulin did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Patients with Hepatic Insufficiency

Remodulin clearance is reduced in patients with hepatic insufficiency. In patients with mild or moderate hepatic insufficiency, decrease the initial dose of Remodulin to 0.625 ng/kg/min ideal body weight, and monitor closely. Remodulin has not been studied in patients with severe hepatic insufficiency *[see Dosage and Administration (2.4), Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)]*.

8.7 Patients with Renal Insufficiency

No studies have been performed in patients with renal insufficiency. No specific advice about dosing in patients with renal impairment can be given *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

Signs and symptoms of overdose with Remodulin during clinical trials are extensions of its dose-limiting pharmacologic effects and include flushing, headache, hypotension, nausea, vomiting, and diarrhea. Most events were self-limiting and resolved with reduction or withholding of Remodulin.

In controlled clinical trials, seven patients received some level of overdose and in open-label follow-on treatment seven additional patients received an overdose; these occurrences resulted from accidental bolus administration of Remodulin, errors in pump programmed rate of administration, and prescription of an incorrect dose. In only two cases did excess delivery of Remodulin produce an event of substantial hemodynamic concern (hypotension, near-syncope).

One pediatric patient was accidentally administered 7.5 mg of Remodulin via a central venous catheter. Symptoms included flushing, headache, nausea, vomiting, hypotension and seizure-like activity with loss of consciousness lasting several minutes. The patient subsequently recovered.

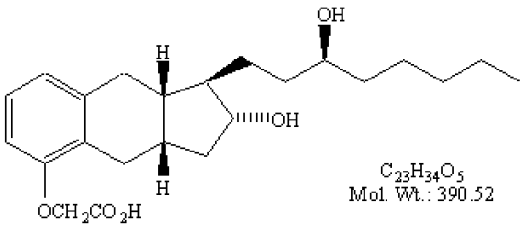
11 DESCRIPTION

Remodulin (treprostinil) Injection is a sterile solution of treprostinil formulated for subcutaneous or intravenous administration. Remodulin is supplied in 20 mL multidose vials in four strengths, containing 20 mg, 50 mg, 100 mg, or 200 mg (1 mg/mL, 2.5 mg/mL, 5 mg/mL or 10 mg/mL) of treprostinil. Each mL also contains 5.3 mg sodium chloride (except for the 10 mg/mL strength which contains 4.0 mg sodium chloride), 3 mg metacresol, 6.3 mg sodium citrate, and water for injection. Sodium hydroxide and hydrochloric acid may be added to adjust pH between 6.0 and 7.2.

Treprostinil is chemically stable at room temperature and neutral pH.

Treprostinil is (1R,2R,3aS,9aS)-[[2,3,3a,4,9,9a-Hexahydro-2-hydroxy-1-[(3S)-3-hydroxyoctyl]-1H-benz[f]inden-5-yl]oxy]acetic acid. Treprostinil has a molecular weight of 390.52 and a molecular formula of $C_{23}H_{34}O_5$.

The structural formula of treprostinil is:



Sterile Diluent for Remodulin is a high-pH (pH~10.4) glycine diluent supplied in a 50 mL vial containing 50 mL of Sterile Diluent for Remodulin. Each vial contains 94 mg glycine, 73.3 mg sodium chloride, sodium hydroxide (to adjust pH), and water for injection.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The major pharmacologic actions of treprostinil are direct vasodilation of pulmonary and systemic arterial vascular beds, and inhibition of platelet aggregation.

12.2 Pharmacodynamics

In animals, the vasodilatory effects reduce right and left ventricular afterload and increase cardiac output and stroke volume. Other studies have shown that treprostinil causes a dose-related negative inotropic and lusitropic effect. No major effects on cardiac conduction have been observed.

Treprostinil produces vasodilation and tachycardia. Single doses of treprostinil up to 84 mcg by inhalation produce modest and short-lasting effects on QTc, but this is apt to be an artifact of the rapidly changing heart rate. Treprostinil administered by the subcutaneous or intravenous routes has the potential to generate concentrations many-fold greater than those generated via the inhaled route; the effect on the QTc interval when treprostinil is administered parenterally has not been established.

12.3 Pharmacokinetics

The pharmacokinetics of continuous subcutaneous Remodulin are linear over the dose range of 1.25 to 125 ng/kg/min (corresponding to plasma concentrations of about 15 pg/mL to 18,250 pg/mL) and can be described by a two-compartment model. Dose proportionality at infusion rates greater than 125 ng/kg/min has not been studied.

Subcutaneous and intravenous administration of Remodulin demonstrated bioequivalence at steady state at a dose of 10 ng/kg/min.

Absorption

Remodulin is relatively rapidly and completely absorbed after subcutaneous infusion, with an absolute bioavailability approximating 100%. Steady-state concentrations occurred in approximately 10 hours. Concentrations in patients treated with an average dose of 9.3 ng/kg/min were approximately 2,000 pg/mL.

Distribution

The volume of distribution of the drug in the central compartment is approximately 14L/70 kg ideal body weight. Remodulin at *in vitro* concentrations ranging from 330-10,000 mcg/L was 91% bound to human plasma protein.

Metabolism and Excretion

Treprostinil is substantially metabolized by the liver, primarily by CYP2C8. In a study conducted in healthy volunteers using [^{14}C] treprostinil, 78.6% and 13.4% of the subcutaneous dose was recovered in the urine and feces, respectively, over 10 days. Only 4% was excreted as unchanged treprostinil in the urine. Five metabolites were detected in the urine, ranging from 10.2% to 15.5% and representing 64.4% of the dose administered. Four of the metabolites are products of oxidation of the 3-hydroxyloctyl side chain and one is a glucuroconjugated derivative (treprostinil glucuronide). The identified metabolites do not appear to have activity.

The elimination of treprostinil (following subcutaneous administration) is biphasic, with a terminal elimination half-life of approximately 4 hours using a two compartment model. Systemic clearance is approximately 30 L/hr for a 70 kg person.

Based on in vitro studies treprostinil does not inhibit or induce major CYP enzymes *[see Drug Interactions (7.5)]*.

Special Populations

Hepatic Insufficiency

In patients with portopulmonary hypertension and mild (n=4) or moderate (n=5) hepatic insufficiency, Remodulin at a subcutaneous dose of 10 ng/kg/min for 150 minutes had a C_{max} that was 2-fold and 4-fold, respectively, and an AUC_{0-} that was 3-fold and 5-fold, respectively, values observed in healthy subjects. Clearance in patients with hepatic insufficiency was reduced by up to 80% compared to healthy adults.

Renal Insufficiency

No studies have been performed in patients with renal insufficiency, so no specific advice about dosing in such patients can be given. Although only 4% of the administered dose is excreted unchanged in the urine, the five identified metabolites are all excreted in the urine.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies have not been performed to evaluate the carcinogenic potential of treprostinil. *In vitro* and *in vivo* genetic toxicology studies did not demonstrate any mutagenic or clastogenic effects of treprostinil. Treprostinil did not affect fertility or mating performance of male or female rats given continuous subcutaneous infusions at rates of up to 450 ng treprostinil/kg/min [about 59 times the recommended starting human rate of infusion (1.25 ng/kg/min) and about 8 times the average rate (9.3 ng/kg/min) achieved in clinical trials, on a ng/m^2 basis]. In this study, males were dosed from 10 weeks prior to mating and through the 2-week mating period. Females were dosed from 2 weeks prior to mating until gestational day 6.

14 CLINICAL STUDIES

14.1 Clinical Trials in Pulmonary Arterial Hypertension (PAH)

Two 12-week, multicenter, randomized, double-blind studies compared continuous subcutaneous infusion of Remodulin to placebo in a total of 470 patients with NYHA Class II (11%), III (81%), or IV (7%) pulmonary arterial hypertension (PAH). PAH was idiopathic/heritable in 58% of patients, associated with connective tissue diseases in 19%, and the result of congenital systemic-to-pulmonary shunts in 23%. The mean age was 45 (range 9 to 75 years). About 81% were female and 84% were Caucasian. Pulmonary hypertension had been diagnosed for a mean of 3.8 years. The primary endpoint of the studies was change in 6-minute walking distance, a standard measure of exercise capacity. There were many assessments of symptoms related to heart failure, but local discomfort and pain associated with Remodulin may have substantially unblinded those assessments. The 6-minute walking distance and an associated subjective measurement of shortness of breath during the walk (Borg dyspnea score) were administered by a person not participating in other aspects of the study. Remodulin was administered as a subcutaneous infusion, described in Section 2, DOSAGE AND ADMINISTRATION, and the dose averaged 9.3 ng/kg/min at Week 12. Few subjects received doses > 40 ng/kg/min. Background therapy,

determined by the investigators, could include anticoagulants, oral vasodilators, diuretics, digoxin, and oxygen but not an endothelin receptor antagonist or epoprostenol. The two studies were identical in design and conducted simultaneously, and the results were analyzed both pooled and individually.

Hemodynamic Effects

As shown in Table 5, chronic therapy with Remodulin resulted in small hemodynamic changes consistent with pulmonary and systemic vasodilation.

Table 5: Hemodynamics during Chronic Administration of Remodulin in Patients with PAH in 12-Week Studies

Hemodynamic Parameter	Baseline		Mean change from baseline at Week 12	
	Remodulin (N=204-231)	Placebo (N=215-235)	Remodulin (N=163-199)	Placebo (N=182-215)
CI ($L/min/m^2$)	2.4 ± 0.88	2.2 ± 0.74	+0.12 ± 0.58*	-0.06 ± 0.55
PAPm (mmHg)	62 ± 17.6	60 ± 14.8	-2.3 ± 7.3*	+0.7 ± 8.5
RAPm (mmHg)	10 ± 5.7	10 ± 5.9	-0.5 ± 5.0*	+1.4 ± 4.8
PVRI ($mmHg/L/min/m^2$)	26 ± 13	25 ± 13	-3.5 ± 8.2*	+1.2 ± 7.9
SVRI ($mmHg/L/min/m^2$)	38 ± 15	39 ± 15	-3.5 ± 12*	-0.80 ± 12
SvO_2 (%)	62 ± 100	60 ± 11	+2.0 ± 10*	-1.4 ± 8.8
SAPm (mmHg)	90 ± 14	91 ± 14	-1.7 ± 12	-1.0 ± 13
HR (bpm)	82 ± 13	82 ± 15	-0.5 ± 11	-0.8 ± 11

*Denotes statistically significant difference between Remodulin and placebo, $p<0.05$.
CI = cardiac index; PAPm = mean pulmonary arterial pressure; PVRI = pulmonary vascular resistance indexed; RAPm = mean right atrial pressure; SAPm = mean systemic arterial pressure; SVRI = systemic vascular resistance indexed; SvO2 = mixed venous oxygen saturation; HR = heart rate.

Clinical Effects

The effect of Remodulin on 6-minute walk, the primary end point of the 12-week studies, was small and did not achieve conventional levels of statistical significance. For the combined populations, the median change from baseline on Remodulin was 10 meters and the median change from baseline on placebo was 0 meters from a baseline of approximately 345 meters. Although it was not the primary endpoint of the study, the Borg dyspnea score was significantly improved by Remodulin during the 6-minute walk, and Remodulin also had a significant effect, compared with placebo, on an assessment that combined walking distance with the Borg dyspnea score. Remodulin also consistently improved indices of dyspnea, fatigue and signs and symptoms of pulmonary hypertension, but these indices were difficult to interpret in the context of incomplete blinding to treatment assignment resulting from infusion site symptoms.

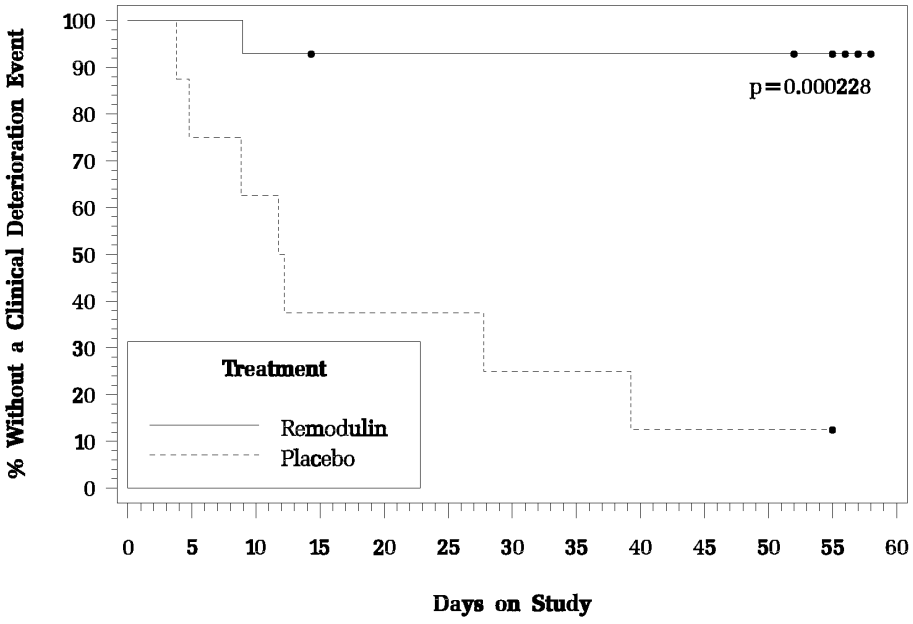
14.2 Flolan-To-Remodulin Transition Study

In an 8-week, multicenter, randomized, double-blind, placebo-controlled study, patients on stable doses of Flolan were randomly withdrawn from Flolan to placebo or Remodulin. Fourteen

Remodulin and 8 placebo patients completed the study. The primary endpoint of the study was the time to clinical deterioration, defined as either an increase in Flolan dose, hospitalization due to PAH, or death. No patients died during the study.

During the study period, Remodulin effectively prevented clinical deterioration in patients transitioning from Flolan therapy compared to placebo (Figure 1). Thirteen of 14 patients in the Remodulin arm were able to transition from Flolan successfully, compared to only 1 of 8 patients in the placebo arm (p=0.0002).

Figure 1: Time to Clinical Deterioration for PAH Patients Transitioned from Flolan to Remodulin or Placebo in an 8-Week Study



16 HOW SUPPLIED / STORAGE AND HANDLING

Remodulin is supplied in 20-mL multidose vials as sterile solutions in water for injection, individually packaged in cartons. Unopened vials of Remodulin are stable until the date indicated when stored at 25°C (77°F), with excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. A single vial of Remodulin should be used for no more than 30 days after the initial introduction into the vial.

Remodulin Injection is supplied as:

Remodulin	Concentration	NDC 66302-xxx-xx
20 mg / 20 mL	1 mg/ mL	101-01
50 mg / 20 mL	2.5 mg/ mL	102-01
100 mg / 20 mL	5 mg/ mL	105-01
200 mg / 20 mL	10 mg/ mL	110-01

Sterile Diluent for Remodulin is supplied separately as:
50 mL vial, carton of 1 (NDC 66302-150-50).

17 PATIENT COUNSELING INFORMATION

Patients receiving Remodulin should be given the following information: Remodulin is infused continuously through a subcutaneous or surgically placed indwelling central venous catheter, via an infusion pump. Patients receiving intravenous infusion should use an infusion set with an in-line filter. Therapy with Remodulin will be needed for prolonged periods, possibly years, and the patient's ability to accept and care for a catheter and to use an infusion pump should be carefully considered. In order to reduce the risk of infection, aseptic technique must be used in the preparation and administration of Remodulin. Additionally, patients should be aware that subsequent disease management may require the initiation of an alternative intravenous prostacyclin therapy, Flolan (epoprostenol sodium).

REMODULIN manufactured for:

United Therapeutics Corp.
Research Triangle Park, NC 27709

US008242305B2

(12) **United States Patent**
Batra et al.

(10) **Patent No.: US 8,242,305 B2**
(45) **Date of Patent: Aug. 14, 2012**

(54) **PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 567 days.

(21) Appl. No.: **12/334,731**

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(51) **Int. Cl.**
C07C 62/00 (2006.01)
C07C 65/00 (2006.01)

(52) **U.S. Cl.** **562/466**

(58) **Field of Classification Search** ..... None
See application file for complete search history.

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(57) **ABSTRACT**

This present invention relates to an improved process to prepare prostacyclin derivatives. One embodiment provides for an improved process to convert benzindene triol to treprostinil via salts of treprostinil and to purify treprostinil.

28 Claims, No Drawings

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PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority from U.S. Provisional Patent Application 61/014,232, filed Dec. 17, 2007, the entire contents of which are incorporated herein by reference.

BACKGROUND

The present invention relates to a process for producing prostacyclin derivatives and novel intermediate compounds useful in the process.

Prostacyclin derivatives are useful pharmaceutical compounds possessing activities such as platelet aggregation inhibition, gastric secretion reduction, lesion inhibition, and bronchodilation.

Treprostinil, the active ingredient in Remodulin®, was first described in U.S. Pat. No. 4,306,075. Treprostinil, and other prostacyclin derivatives have been prepared as described in Moriarty, et al in *J. Org. Chem.* 2004, 69, 1890-1902, *Drug of the Future,* 2001, 26(4), 364-374, U.S. Pat. Nos. 6,441,245, 6,528,688, 6,765,117 and 6,809,223. Their teachings are incorporated by reference to show how to practice the embodiments of the present invention.

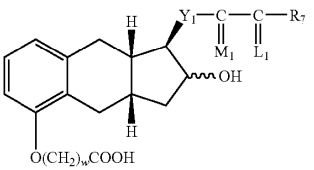
U.S. Pat. No. 5,153,222 describes use of treprostinil for treatment of pulmonary hypertension. Treprostinil is approved for the intravenous as well as subcutaneous route, the latter avoiding septic events associated with continuous intravenous catheters. U.S. Pat. Nos. 6,521,212 and 6,756,033 describe administration of treprostinil by inhalation for treatment of pulmonary hypertension, peripheral vascular disease and other diseases and conditions. U.S. Pat. No. 6,803,386 discloses administration of treprostinil for treating cancer such as lung, liver, brain, pancreatic, kidney, prostate, breast, colon and head-neck cancer. U.S. patent application publication No. 2005/0165111 discloses treprostinil treatment of ischemic lesions. U.S. Pat. No. 7,199,157 discloses that treprostinil treatment improves kidney functions. U.S. patent application publication No. 2005/0282903 discloses treprostinil treatment of neuropathic foot ulcers. U.S. application Ser. No. 12/028,471 filed Feb. 8, 2008, discloses treprostinil treatment of pulmonary fibrosis. U.S. Pat. No. 6,054,486 discloses treatment of peripheral vascular disease with treprostinil. U.S. patent application Ser. No. 11/873,645 filed Oct. 17, 2007 discloses combination therapies comprising treprostinil. U.S. publication No. 2008/0200449 discloses delivery of treprostinil using a metered dose inhaler. U.S. publication No. 2008/0280986 discloses treatment of interstitial lung disease with treprostinil. U.S. application Ser. No. 12/028,471 filed Feb. 8, 2008 discloses treatment of asthma with treprostinil. U.S. Pat. Nos. 7,417,070, 7,384,978 and U.S. publication Nos. 2007/0078095, 2005/0282901, and 2008/0249167 describe oral formulations of treprostinil and other prostacyclin analogs.

Because Treprostinil, and other prostacyclin derivatives are of great importance from a medicinal point of view, a need exists for an efficient process to synthesize these compounds on a large scale suitable for commercial production.

SUMMARY

The present invention provides in one embodiment a process for the preparation of a compound of formula I, hydrate, solvate, prodrug, or pharmaceutically acceptable salt thereof.

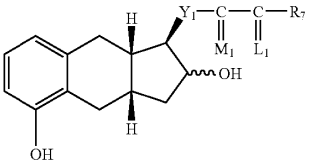
(I)



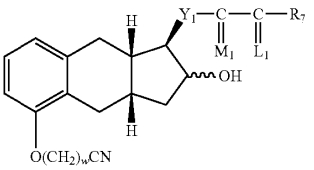
The process comprises the following steps:

(a) alkylating a compound of structure II with an alkylating agent to produce a compound of formula III,

(II)



(III)



wherein

w=1, 2, or 3;

Y_1 is trans-CH═CH—, cis-CH═CH—, —CH_2 $(CH_2)_m$—, or —C≡C—; m is 1, 2, or 3;

R_7 is

(1) —C_pH_{2p}—CH_3, wherein p is an integer from 1 to 5, inclusive,

(2) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3) alkyl, or (C_1-C_3) alkoxy, with the proviso that not more than two substituents are other than alkyl, with the proviso that R_7 is phenoxy or substituted phenoxy, only when R_3 and R_4 are hydrogen or methyl, being the same or different,

(3) phenyl, benzyl, phenylethyl, or phenylpropyl optionally substituted on the aromatic ring by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3)alkyl, or (C_1-C_3) alkoxy, with the proviso that not more than two substituents are other than alkyl,

(4) cis-CH═CH—CH_2—CH_3,

(5) —$(CH_2)_2$—CH(OH)—CH_3, or

(6) —$(CH_2)_3$—CH═$C(CH_3)_2$;

wherein —$C(L_1)$-R_7 taken together is

(1) (C_4-C_7)cycloalkyl optionally substituted by 1 to 3 (C_1-C_5)alkyl;

(2) 2-(2-furyl)ethyl,

(3) 2-(3-thienyl)ethoxy, or

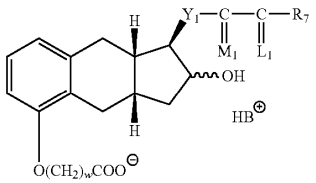
(4) 3-thienyloxymethyl;

M_1 is α-OH:β-R_5 or α-R_5:β-OH or α-OR_1:β-R_5 or α-R_5:β-OR_2, wherein R_5 is hydrogen or methyl, R_2 is an alcohol protecting group, and

L_1 is α-R_3:β-R_4, α-R_4:β-R_3, or a mixture of α-R_3:β-R_4 and α-R_4:β-R_3, wherein R_3 and R_4 are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R_3 and R_4 is fluoro only when the other is hydrogen or fluoro.

(b) hydrolyzing the product of step (a) with a base,

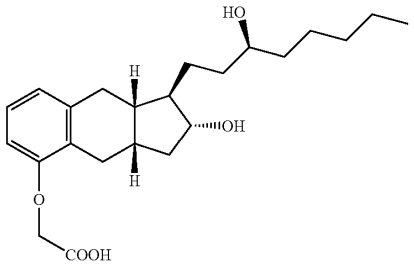
(c) contacting the product of step (b) with a base B to for a salt of formula I_s



(I_s)

(d) reacting the salt from step (c) with an acid to form the compound of formula I.

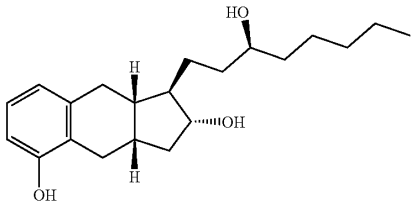
The present invention provides in another embodiment a process for the preparation of a compound of formula IV.



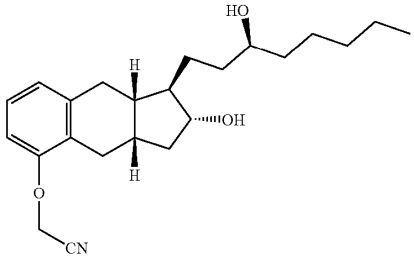
(IV)

The process comprises the following steps:

(a) alkylating a compound of structure V with an alkylating agent to produce a compound of formula VI,



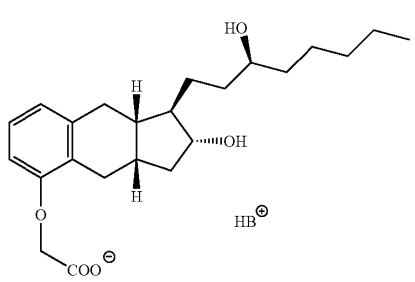
(V)



(VI)

(b) hydrolyzing the product of step (a) with a base,

(c) contacting the product of step (b) with a base B to for a salt of formula IV_s, and



(IV_s)

(d) reacting the salt from step (b) with an acid to form the compound of formula IV.

DETAILED DESCRIPTION

The various terms used, separately and in combinations, in the processes herein described are defined below.

The expression "comprising" means "including but not limited to." Thus, other non-mentioned substances, additives, carriers, or steps may be present. Unless otherwise specified, "a" or "an" means one or more.

C_{1-3}-alkyl is a straight or branched alkyl group containing 1-3 carbon atoms. Exemplary alkyl groups include methyl, ethyl, n-propyl, and isopropyl.

C_{1-3}-alkoxy is a straight or branched alkoxy group containing 1-3 carbon atoms. Exemplary alkoxy groups include methoxy, ethoxy, propoxy, and isopropoxy.

C_{4-7}-cycloalkyl is an optionally substituted monocyclic, bicyclic or tricyclic alkyl group containing between 4-7 carbon atoms. Exemplary cycloalkyl groups include but not limited to cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl.

Combinations of substituents and variables envisioned by this invention are only those that result in the formation of stable compounds. The term "stable", as used herein, refers to compounds which possess stability sufficient to allow manufacture and which maintains the integrity of the compound for a sufficient period of time to be useful for the purposes detailed herein.

As used herein, the term "prodrug" means a derivative of a compound that can hydrolyze, oxidize, or otherwise react under biological conditions (in vitro or in vivo) to provide an active compound. Examples of prodrugs include, but are not limited to, derivatives of a compound that include biohydrolyzable groups such as biohydrolyzable amides, biohydrolyzable esters, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, and biohydrolyzable phosphate analogues (e.g., monophosphate, diphosphate or triphosphate).

As used herein, "hydrate" is a form of a compound wherein water molecules are combined in a certain ratio as an integral part of the structure complex of the compound.

As used herein, "solvate" is a form of a compound where solvent molecules are combined in a certain ratio as an integral part of the structure complex of the compound.

"Pharmaceutically acceptable" means in the present description being useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes being useful for veterinary use as well as human pharmaceutical use.

"Pharmaceutically acceptable salts" mean salts which are pharmaceutically acceptable, as defined above, and which possess the desired pharmacological activity. Such salts

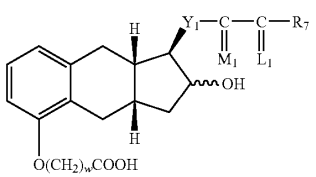
include acid addition salts formed with organic and inorganic acids, such as hydrogen chloride, hydrogen bromide, hydrogen iodide, sulfuric acid, phosphoric acid, acetic acid, glycolic acid, malcic acid, malonic acid, oxalic acid, methanesulfonic acid, trifluoroacetic acid, fumaric acid, succinic acid, tartaric acid, citric acid, benzoic acid, ascorbic acid and the like. Base addition salts may be formed with organic and inorganic bases, such as sodium, ammonia, potassium, calcium, ethanolamine, diethanolamine, N-methylglucamine, choline and the like. Included in the invention are pharmaceutically acceptable salts or compounds of any of the formulae herein.

Depending on its structure, the phrase "pharmaceutically acceptable salt," as used herein, refers to a pharmaceutically acceptable organic or inorganic acid or base salt of a compound. Representative pharmaceutically acceptable salts include, e.g., alkali metal salts, alkali earth salts, ammonium salts, water-soluble and water-insoluble salts, such as the acetate, amsonate (4,4-diaminostilbene-2,2-disulfonate), benzenesulfonate, benzonate, bicarbonate, bisulfate, bitartrate, borate, bromide, butyrate, calcium, calcium edetate, camsylate, carbonate, chloride, citrate, clavulariate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexafluorophosphate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, N-methylglucamine ammonium salt, 3-hydroxy-2-naphthoate, oleate, oxalate, palmitate, pamoate (1,1-methene-bis-2-hydroxy-3-naphthoate, einbonate), pantothenate, phosphate/diphosphate, picrate, polygalacturonate, propionate, p-toluenesulfonate, salicylate, stearate, subacetate, succinate, sulfate, sulfosalicylate, suramate, tannate, tartrate, teoclate, tosylate, triethiodide, and valerate salts.

The present invention provides for a process for producing treprostinil and other prostacyclin derivatives and novel intermediate compounds useful in the process. The process according to the present invention provides advantages on large-scale synthesis over the existing method. For example, the purification by column chromatography is eliminated, thus the required amount of flammable solvents and waste generated are greatly reduced. Furthermore, the salt formation is a much easier operation than column chromatography. Moreover, it was found that the product of the process according to the present invention has higher purity. Therefore the present invention provides for a process that is more economical, safer, faster, greener, easier to operate, and provides higher purity.

One embodiment of the present invention is a process for the preparation of a compound of formula I, or a hydrate, solvate, prodrug, or pharmaceutically acceptable salt thereof.

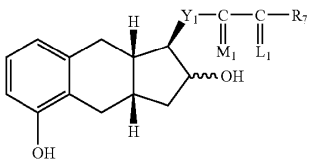
(I)



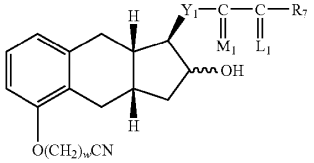
The process comprises the following steps:

(a) alkylating a compound of formula II with an alkylating agent to produce a compound of formula III,

(II)



(III)



wherein

w=1, 2, or 3;

Y_1 is trans-CH═CH—, cis-CH═CH—, —$CH_2(CH_2)_m$—, or —C≡C—; m is 1, 2, or 3;

R_7 is

(1) —C_pH_{2p}—CH_3, wherein p is an integer from 1 to 5, inclusive,

(2) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3) alkyl, or (C_1-C_3) alkoxy, with the proviso that not more than two substituents are other than alkyl, with the proviso that R_7 is phenoxy or substituted phenoxy, only when R_3 and R_4 are hydrogen or methyl, being the same or different,

(3) phenyl, benzyl, phenylethyl, or phenylpropyl optionally substituted on the aromatic ring by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3)alkyl, or (C_1-C_3) alkoxy, with the proviso that not more than two substituents are other than alkyl,

(4) cis-CH═CH—CH_2—CH_3,

(5) —$(CH_2)_2$—CH(OH)—CH_3, or

(6) —$(CH_2)_3$—CH—$C(CH_3)_2$;

wherein —$C(L_1)$-R_7 taken together is

(1) (C_4-C_7)cycloalkyl optionally substituted by 1 to 3 (C_1-C_5)alkyl;

(2) 2-(2-furyl)ethyl,

(3) 2-(3-thienyl)ethoxy, or

(4) 3-thienyloxymethyl;

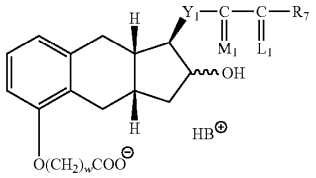
M_1 is x-OH:β-R_5 or α-R_5:β-OH or α-OR_1:β-R_5 or α-R_5:β-OR_2, wherein R_5 is hydrogen or methyl, R_2 is an alcohol protecting group, and

L_1 is α-R_3:β-R_4, α-R_4:β-R_3, or a mixture of α-R_3:β-R_4 and α-R_4:β-R_3, wherein R_3 and R_4 are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R_3 and R_4 is fluoro only when the other is hydrogen or fluoro.

(b) hydrolyzing the product of step (a) with a base,

(c) contacting the product of step (b) with a base B to for a salt of formula I_s

(Is)

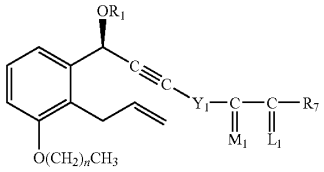


(d) reacting the salt from step (c) with an acid to form the compound of formula I.

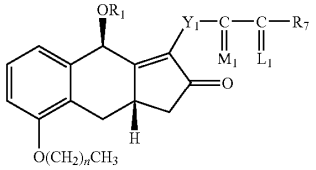
In one embodiment, the compound of formula I is at least 90.0%, 95.0%, 99.0%.

The compound of formula II can be prepared from a compound of formula XI, which is a cyclization product of a compound of formula X as described in U.S. Pat. No. 6,441,245.

(X)



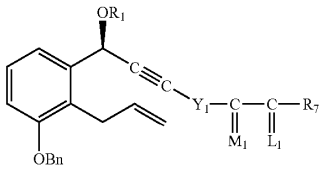
(XI)



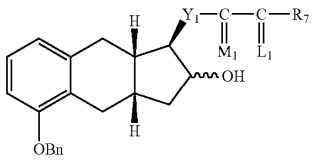
Wherein n is 0, 1, 2, or 3.

The compound of formula II can be prepared alternatively from a compound of formula XIII, which is a cyclization product of a compound of formula XII as described in U.S. Pat. No. 6,700,025.

(XII)

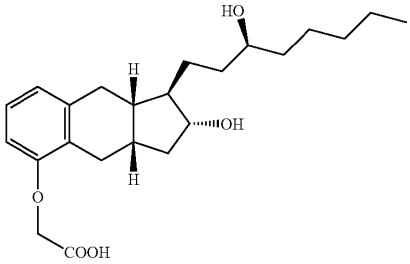


(XIII)



One embodiment of the present invention is a process for the preparation of a compound having formula IV, or a hydrate, solvate, or pharmaceutically acceptable salt thereof.

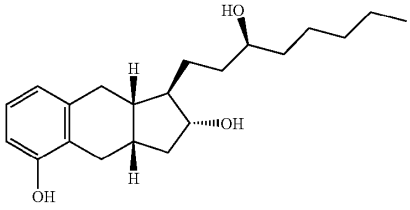
(IV)



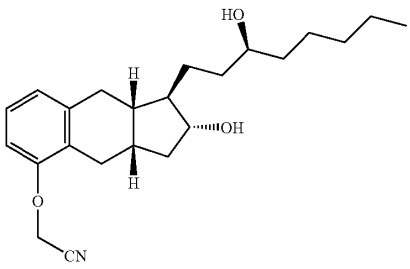
The process comprises

(a) alkylating a compound of structure V with an alkylating agent such as $ClCH_2CN$ to produce a compound of formula VI,

(V)

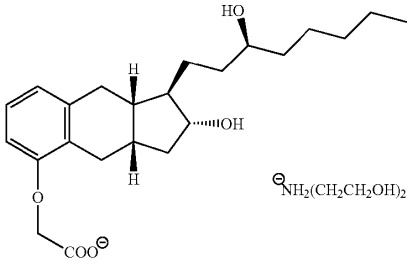


(VI)



(b) hydrolyzing the product of step (a) with a base such as KOH,

(c) contacting the product of step (b) with a base B such as diethanolamine to for a salt of the following structure, and



(d) reacting the salt from step (b) with an acid such as HCl to form the compound of formula IV.

In one embodiment, the purity of compound of formula IV is at least 90.0%, 95.0%, 99.0%, 99.5%.

In one embodiment, the process further comprises a step of isolating the salt of formula IV_s.

In one embodiment, the base B in step (c) may be ammonia, N-methylglucamine, procaine, tromethanine, magnesium, L-lysine, L-arginine, or triethanolamine.

The following abbreviations are used in the description and/or appended claims, and they have the following meanings:

"MW" means molecular weight.

"Eq." means equivalent.

"TLC" means thin layer chromatography.

"HPLC" means high performance liquid chromatography.

"PMA" means phosphomolybdic acid.

"AUC" means area under curve.

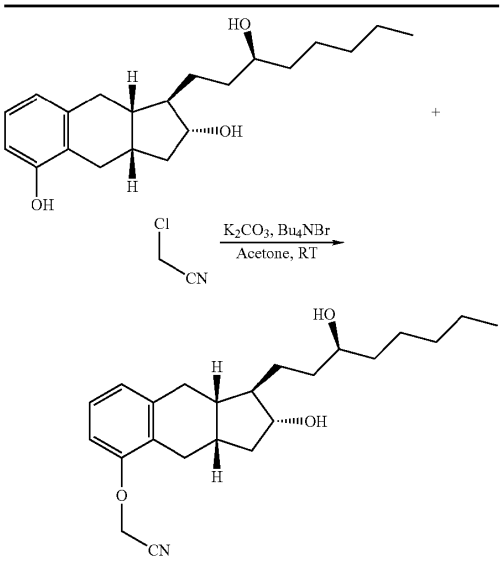
In view of the foregoing considerations, and specific examples below, those who are skilled in the art will appreciate that how to select necessary reagents and solvents in practicing the present invention.

The invention will now be described in reference to the following Examples. These examples are not to be regarded as limiting the scope of the present invention, but shall only serve in an illustrative manner.

EXAMPLES

Example 1

Alkylation of Benzindene Triol

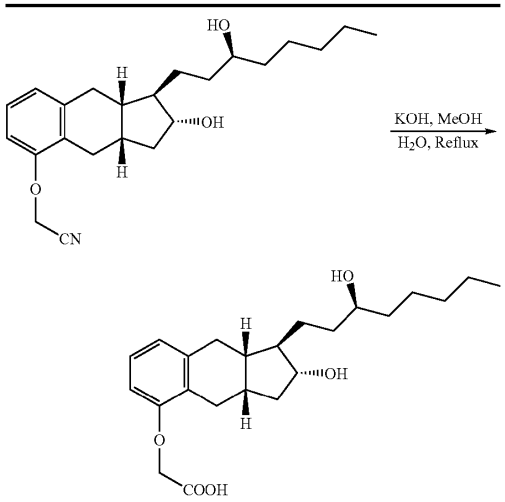


Name	MW	Amount	Mol.	Eq.
Benzindene Triol	332.48	1250 g	3.76	1.00
K_2CO_3 (powder)	138.20	1296 g	9.38	2.50
$ClCH_2CN$	75.50	567 g	7.51	2.0
Bu_4NBr	322.37	36 g	0.11	0.03
Acetone	—	29 L	—	—
Celite ® 545	—	115 g	—	—

A 50-L, three-neck, round-bottom flask equipped with a mechanical stirrer and a thermocouple was charged with benzindene triol (1250 g), acetone (19 L) and K_2CO_3 (powdered) (1296 g), chloroacetonitrile (567 g), tetrabutylammonium bromide (36 g). The reaction mixture was stirred vigorously at room temperature (23±2° C.) for 16-72 h. The progress of the reaction was monitored by TLC. (methanol/CH_2Cl_2; 1:9 and developed by 10% ethanolic solution of PMA). After completion of reaction, the reaction mixture was filtered with/without Celite pad. The filter cake was washed with acetone (10 L). The filtrate was concentrated in vacuo at 50-55° C. to give a light-brown, viscous liquid benzindene nitrile. The crude benzindene nitrile was used as such in the next step without further purification.

Example 2

Hydrolysis of Benzindene Nitrile



Name	MW	Amount	Mol.	Eq.
Benzindene Nitrile	371.52	1397 g*	3.76	1.0
KOH	56.11	844 g	15.04	4.0
Methanol	—	12 L	—	—
Water	—	4.25 L	—	—

*Note:
This weight is based on 100% yield from the previous step. This is not isolated yield.

A 50-L, cylindrical reactor equipped with a heating/cooling system, a mechanical stirrer, a condenser, and a thermocouple was charged with a solution of benzindene nitrile in methanol (12 L) and a solution of KOH (844 g of KOH dissolved in 4.25 L of water). The reaction mixture was stirred and heated to reflux (temperature 72.2° C.). The progress of the reaction was monitored by TLC (for TLC purpose, 1-2 mL of reaction mixture was acidified with 3M HCl to pH 1-2 and extracted with ethyl acetate. The ethyl acetate extract was used for TLC; Eluent: methanol/CH_2Cl_2; 1:9, and developed by 10% ethanolic solution of PMA). After completion of the reaction (~5 h), the reaction mixture was cooled to −5 to 10° C. and quenched with a solution of hydrochloric acid (3M, 3.1 L) while stirring. The reaction mixture was concentrated in vacuo at 50-55° C. to obtain approximately 12-14 L of condensate. The condensate was discarded.

The aqueous layer was diluted with water (7-8 L) and extracted with ethyl acetate (2×6 L) to remove impurities soluble in ethyl acetate. To aqueous layer, ethyl acetate (22 L) was added and the pH of reaction mixture was adjusted to 1-2

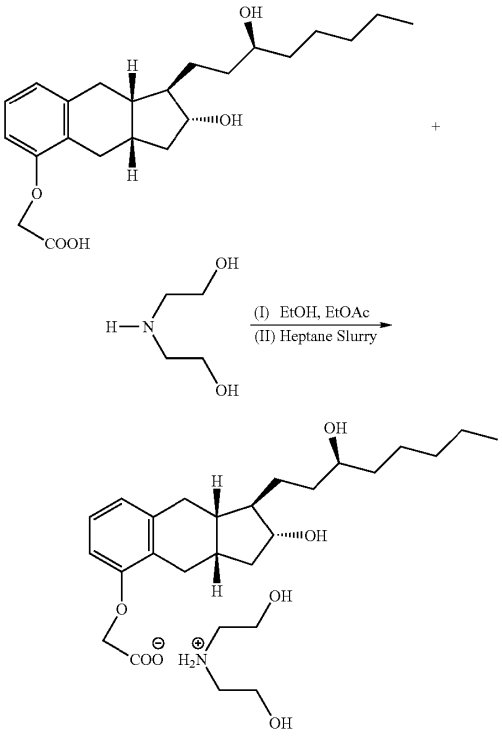
by adding 3M HCl (1.7 L) with stirring. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2×11 L). The combined organic layers were washed with water (3×10 L) and followed by washing with a solution of $NaHCO_3$ (30 g of $NaHCO_3$ dissolved in 12 L of water). The organic layer was further washed with saturated solution of NaCl (3372 g of NaCl dissolved in water (12 L)) and dried over anhydrous Na_2SO_4 (950-1000 g), once filtered.

The filtrate was transferred into a 72-L reactor equipped with mechanical stirrer, a condenser, and a thermocouple. To the solution of treprostinil in reactor was added activated carbon (110-130 g). The suspension was heated to reflux (temperature 68-70° C.) for at least one hour. For filtration, a pad of Celite® 545 (300-600 g) was prepared in sintered glass funnel using ethyl acetate. The hot suspension was filtered through the pad of Celite® 545. The Celite® 545 was washed with ethyl acetate until no compound was seen on TLC of the washings.

The filtrate (pale-yellow) was reduced to volume of 35-40 L by evaporation in vacuo at 50-55° C. for direct use in next step.

Example 3

Conversion of Treprostinil to Treprostinil Diethanolamine Salt (1:1)



Name	MW	Amount	Mol	Eq
Treprostinil	390.52	1464 g*	3.75	1.0
Diethanolamine	105.14	435 g	4.14	1.1
Ethanol	—	5.1 L	—	—
Ethyl acetate	—	35 L**	—	—
Treprostinil Diethanolamine Salt (seed)	—	12 g	—	—

*Note:
This weight is based on 100% yield from benzindene triol. It is not isolated yield. The treprostinil was carried from previous step in ethyl acetate solution and used as such for this step.
**Note:
The total volume of ethyl acetate should be in range 35-36 L (it should be 7 times the volume of ethanol used). Approximately 35 L of ethyl acetate was carried over from previous step and additional 1.0 L of ethyl acetate was used for rinsing the flask.

A 50-L, cylindrical reactor equipped with a heating/cooling system, a mechanical stirrer, a condenser, and a thermocouple was charged with a solution of treprostinil in ethyl acetate (35-40 L from the previous step), anhydrous ethanol (5.1 L) and diethanolamine (435 g). While stirring, the reaction mixture was heated to 60-75° C., for 0.5-1.0 h to obtain a clear solution. The clear solution was cooled to 55±5° C. At this temperature, the seed of polymorph B of treprostinil diethanolamine salt (~12 g) was added to the clear solution. The suspension of polymorph B was stirred at this temperature for 1 h. The suspension was cooled to 20±2° C. overnight (over a period of 16-24 h). The treprostinil diethanolamine salt was collected by filtration using Aurora filter equipped with filter cloth, and the solid was washed with ethyl acetate (2×8 L). The treprostinil diethanolamine salt was transferred to a HDPE/glass container for air-drying in hood, followed by drying in a vacuum oven at 50±5° C. under high vacuum.

At this stage, if melting point of the treprostinil diethanolamine salt is more than 104° C., it was considered polymorph B. There is no need of recrystallization. If it is less than 104° C., it is recrystallized in EtOH-EtOAc to increase the melting point.

Data on Treprostinil Diethanolamine Salt (1:1)

Batch No.	Wt. of Benzindene Triol (g)	Wt. of Treprostinil Diethanolamine Salt (1:1) (g)	Yield (%)	Melting point (° C.)
1	1250	1640	88.00	104.3-106.3
2	1250	1528	82.00*	105.5-107.2
3	1250	1499	80.42**	104.7-106.6
4	1236	1572	85.34	105-108

*Note:
In this batch, approximately 1200 mL of ethyl acetate solution of treprostinil before carbon treatment was removed for R&D carbon treatment experiments.
**Note:
This batch was recrystallized, for this reason yield was lower.

Example 4

Heptane Slurry of Treprostinil Diethanolamine Salt (1:1)

Name	Batch No.	Amount	Ratio
Treprostinil Diethanolamine Salt	1	3168 g	1
Heptane	—	37.5 L	12
Treprostinil Diethanolamine Salt	2	3071 g	1
Heptane	—	36.0 L	12

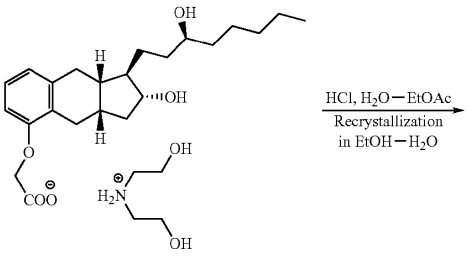
A 50-L, cylindrical reactor equipped with a heating/cooling system, a mechanical stirrer, a condenser, and a thermocouple was charged with slurry of treprostinil diethanolamine salt in heptane (35-40 L). The suspension was heated to 70-80° C. for 16-24 h. The suspension was cooled to 22±2° C. over a period of 1-2 h. The salt was collected by filtration using Aurora filter. The cake was washed with heptane (15-30 L) and the material was dried in Aurora filter for 1 h. The salt was transferred to trays for air-drying overnight in hood until a constant weight of treprostinil diethanolamine salt was obtained. The material was dried in oven under high vacuum for 2-4 h at 50-55° C.

Analytical Data on and Treprostinil Diethanolamine Salt (1:1)

Test	Batch 1	Batch 2
IR	Conforms	Conforms
Residue on Ignition (ROI)	<0.1% w/w	<0.1% w/w
Water content	0.1% w/w	0.0% w/w
Melting point	105.0-106.5° C.	104.5-105.5° C.
Specific rotation $[\alpha]^{25}_{589}$	+34.6°	+35°
Organic volatile impurities		
Ethanol	Not detected	Not detected
Ethyl acetate	Not detected	<0.05% w/w
Heptane	<0.05% w/w	<0.05% w/w
HPLC (Assay)	100.4%	99.8%
Diethanolamine	Positive	Positive

Example 5

Conversion of Treprostinil Diethanolamine Salt (1:1) to Treprostinil



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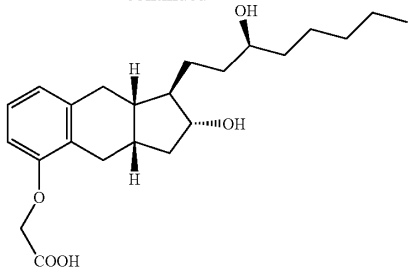


A 250-mL, round-bottom flask equipped with magnetic stirrer was charged with treprostinil diethanolamine salt (4 g) and water (40 mL). The mixture was stirred to obtain a clear solution. To the clear solution, ethyl acetate (100 mL) was added. While stirring, 3M HCl (3.2 mL) was added slowly until pH 1 was attained. The mixture was stirred for 10 minutes and organic layer was separated. The aqueous layer was extracted with ethyl acetate (2×100 mL). The combined organic layers was washed with water (2×100 mL), brine (1×50 mL) and dried over anhydrous Na_2SO_4. The ethyl acetate solution of treprostinil was filtered and the filtrate was concentrated under vacuum at 50° C. to give off-white solid. The crude treprostinil was recrystallized from 50% ethanol in water (70 mL). The pure treprostinil was collected in a Buchner funnel by filtration and cake was washed with cold 20% ethanolic solution in water. The cake of treprostinil was air-dried overnight and further dried in a vacuum oven at 50° C. under high vacuum to afford 2.9 g of treprostinil (Yield 91.4%, purity (HPLC, AUC, 99.8%).

Analytical Data on Treprostinil from Treprostinil Diethanolamine Salt (1:1) to Treprostinil

Batch No.	Yield	Purity (HPLC)
1	91.0%	99.8% (AUC)
2	92.0%	99.9% (AUC)
3	93.1%	99.7% (AUC)
4	93.3%	99.7% (AUC)
5	99.0%	99.8% (AUC)
6	94.6%	99.8% (AUC)

Example 6

Comparison of the Former Process and a Working Example of the Process According to the Present Invention

Step No.	Steps	Former Process (Batch size: 500 g)	Working example of the Process according to the present invention (Batch size: 5 kg)
		Nitrile	
1	Triol weight	500 g	5,000 g
2	Acetone	20 L (1:40 wt/wt)	75 L (1:15 wt/wt)
3	Potassium carbonate	1,300 g (6.4 eq)	5,200 g (2.5 eq)
4	Chloroacetonitrile	470 g (4.2 eq)	2,270 g (2 eq)
5	Tetrabutylammonium bromide	42 g (0.08 eq)	145 g (0.03 eq)
6	Reactor size	72-Liter	50- gallon

-continued

Step No.	Steps	Former Process (Batch size: 500 g)	Working example of the Process according to the present invention (Batch size: 5 kg)
7	Reflux time	8 hours	No heating, Room temperature (r.t.) 45 h
8	Hexanes addition before filtration	Yes (10 L)	No
9	Filter	Celite	Celite
10	Washing	Ethyl acetate (10 L)	Acetone (50 L)
11	Evaporation	Yes	Yes
12	Purification	Silica gel column Dichloromethane: 0.5 L Ethyl acetate: 45 L Hexane: 60 L	No column
13	Evaporation after column	Yes	No
14	Yield of nitrite	109-112%	Not checked
		Treprostinil (intermediate)	
15	Methanol	7.6 L (50-L reactor)	50 L (50-gal reactor)
16	Potassium hydroxide	650 g (8 eq)	3,375 g (4 eq)
17	Water	2.2 L	17 L
18	% of KOH	30%	20%
19	Reflux time	3-3.5 h	4-5 h
20	Acid used	2.6 L (3 M)	12 L (3 M)
21	Removal of impurities	3 × 3 L Ethyl acetate	2 × 20 L Ethyl acetate
22	Acidification	0.7 L	6.5 L
23	Ethyl acetate extraction	5 × 17 L = 35 L	90 + 45 + 45 = 180 L
24	Water washing	2 × 8 L	3 × 40 L
25	Sodium bicarbonate washing	Not done	120 g in 30 L water + 15 L brine
26	Brine washing	Not done	1 × 40 L
27	Sodium sulfate	1 kg	Not done
28	Sodium sulfate filtration	Before charcoal, 6 L ethyl acetate	N/A
29	Charcoal	170 g, reflux for 1.5 h, filter over Celite, 11 L ethyl acetate	Pass hot solution (75° C.) through charcoal cartridge and clean filter, 70 L ethyl acetate
30	Evaporation	Yes, to get solid intermediate treprostinil	Yes, adjust to 150 L solution
		Treprostinil Diethanolamine Salt	
31	Salt formation	Not done	1,744 g diethanolamine, 20 L ethanol at 60-75° C.
32	Cooling	N/A	To 20° C. over weekend; add 40 L ethyl acetate; cooled to 10° C.
33	Filtration	N/A	Wash with 70 L ethyl acetate
34	Drying	N/A	Air-dried to constant wt., 2 days
		Treprostinil (from 1.5 kg Treprostinil diethanolamine salt)	
35	Hydrolysis	N/A	15 L water + 25 L ethyl acetate + HCl
36	Extraction	N/A	2 × 10 L ethyl acetate
37	Water wash	N/A	3 × 10 L
38	Brine wash	N/A	1 × 10 L
39	Sodium sulfate	N/A	1 kg, stir
40	Filter	N/A	Wash with 6 L ethyl acetate
41	Evaporation	N/A	To get solid, intermediate Treprostinil
42	Crude drying on tray	1 or 3 days	Same
43	Ethanol & water for cryst.	5.1 L + 5.1 L	10.2 L + 10.2 L (same %)
44	Crystallization in	20-L rotavap flask	50-L jacketed reactor
45	Temperature of crystallization	2 h r.t., fridge −0° C. 24 h	50° C. to 0° C. ramp, 0° C. overnight
46	Filtration	Buchner funnel	Aurora filter
47	Washing	20% (10 L) cooled ethanol-water	20% (20 L) cooled ethanol-water
48	Drying before oven	Buchner funnel (20 h) Tray (no)	Aurora filter (2.5 h) Tray (4 days)
49	Oven drying	15 hours, 55° C.	6-15 hours, 55° C.

-continued

Step No.	Steps	Former Process (Batch size: 500 g)	Working example of the Process according to the present invention (Batch size: 5 kg)
50	Vacuum	<−0.095 mPA	<5 Torr
51	UT-15 yield weight	~535 g	~1,100 g
52	% yield from triol)	~91%	~89%
53	Purity	~99.0%	99.9%

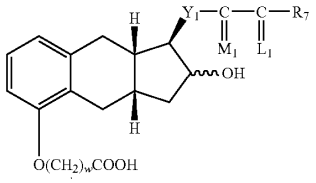
The quality of treprostinil produced according to this invention is excellent. The purification of benzindene nitrile by column chromatography is eliminated. The impurities carried over from intermediate steps (i.e. alkylation of triol and hydrolysis of benzindene nitrile) are removed during the carbon treatment and the salt formation step. Additional advantages of this process are: (a) crude treprostinil salts can be stored as raw material at ambient temperature and can be converted to treprostinil by simple acidification with diluted hydrochloric acid, and (b) the treprostinil salts can be synthesized from the solution of treprostinil without isolation. This process provides better quality of final product as well as saves significant amount of solvents and manpower in purification of intermediates.

Although the foregoing refers to particular preferred embodiments, it will be understood that the present invention is not so limited. It will occur to those of ordinary skill in the art that various modifications may be made to the disclosed embodiments and that such modifications are intended to be within the scope of the present invention.

All of the publications, patent applications and patents cited in this specification are incorporated herein by reference in their entirety.

What is claimed is:

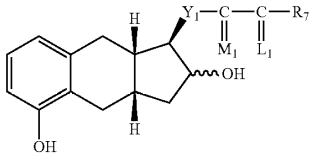
1. A process for the preparation of a compound of formula I



(I)

comprising

(a) alkylating a compound of structure II with an alkylating agent to produce a compound of formula III,



(II)

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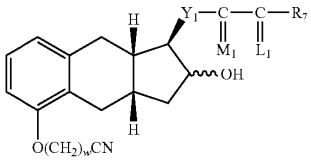


(III)

wherein

w=1, 2, or 3;

Y_1 is trans-CH═CH—, cis-CH═CH—, —CH_2 $(CH_2)_m$—, or —C≡C—; m is 1, 2, or 3;

R_7 is

(1) —C_pH_{2p}—CH_3, wherein p is an integer from 1 to 5, inclusive,

(2) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3) alkyl, or (C_1-C_3) alkoxy, with the proviso that not more than two substituents are other than alkyl, with the proviso that R_7 is phenoxy or substituted phenoxy, only when R_3 and R_4 are hydrogen or methyl, being the same or different,

(3) phenyl, benzyl, phenylethyl, or phenylpropyl optionally substituted on the aromatic ring by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3)alkyl, or (C_1-C_3) alkoxy, with the proviso that not more than two substituents are other than alkyl,

(4) cis-CH═CH—CH_2—CH_3,

(5) —$(CH_2)_2$—CH(OH)—CH_3, or

(6) —$(CH_2)_3$—CH═$C(CH_3)_2$;

—$C(L_1)$-R_7 taken together is

(1) (C_4-C_7)cycloalkyl optionally substituted by 1 to 3 (C_1-C_5)alkyl;

(2) 2-(2-furyl)ethyl,

(3) 2-(3-thienyl)ethoxy, or

(4) 3-thienyloxymethyl;

M_1 is α-OH:β-R_5 or α-R_5:β-OH or α-OR_1:β-R_5 or α-R_5:β-OR_2, wherein R_5 is hydrogen or methyl, R_2 is an alcohol protecting group, and

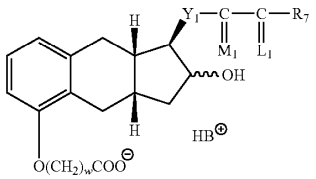
L_1 is α-R_3:β-R_4, α-R_4:β-R_3, or a mixture of α-R_3:β-R_4 and α-R_4:β-R_3, wherein R_3 and R_4 are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R_3 and

R_4 is fluoro only when the other is hydrogen or fluoro,

(b) hydrolyzing the product of formula III of step (a) with a base,

(c) contacting the product of step (b) with a base B to form a salt of formula I_s,

(Is)



(d) reacting the salt formed in step (c) with an acid to form the compound of formula I.

2. The process of claim **1**, which does not include purifying the compound of formula (III) produced in step (a).

3. The process according to claim **2**, wherein the product of step (d) has the purity of compound of formula I of at least 90.0%.

4. The process according to claim **1**, further comprising a step of isolating the salt of formula I_s.

5. The process according to claim **1**, wherein the alkylating agent is $Cl(CH_2)_wCN$, $Br(CH_2)_wCN$, or $I(CH_2)_wCN$.

6. The process according to claim **1**, wherein the base in step (b) is KOH or NaOH.

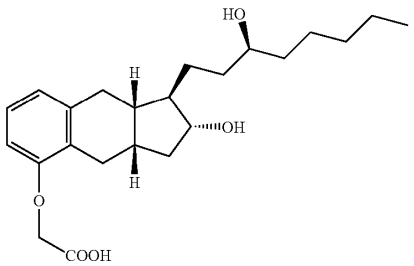
7. The process according to claim **1**, wherein the base B in step (c) is selected from the group consisting of ammonia, N-methylglucamine, procaine, tromethanine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.

8. The process according to claim **1**, wherein the acid in step (d) is HCl or H_2SO_4.

9. The process according to claim **1**, wherein Y_1 is $—CH_2CH_2—$; M_1 is α-OH:β-H or α-H:β-OH; $—C(L_1)-R_7$ taken together is $—(CH_2)_4CH_3$; and w is 1.

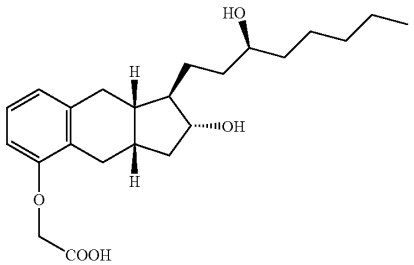
10. The process according to claim **1**, wherein the compound of formula I is a compound of formula IV,

(IV)



11. A process for the preparation of a compound having formula IV

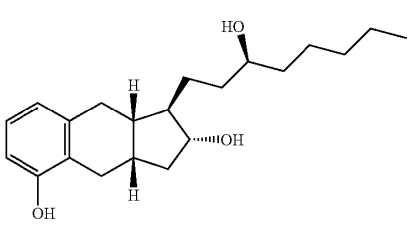
(IV)



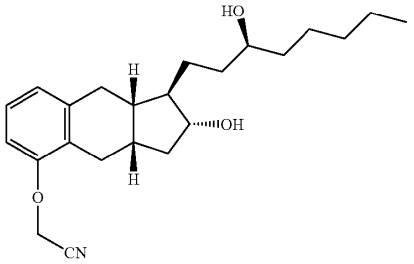
comprising

(a) alkylating a compound of formula V with an alkylating agent to produce a compound of formula VI,

(V)



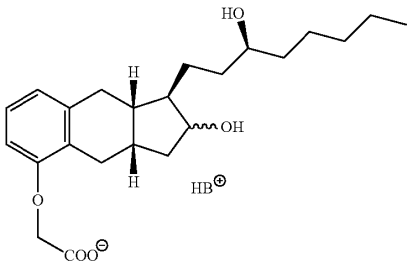
(VI)



(b) hydrolyzing the product of formula VI of step (a) with a base,

(c) contacting the product of step (b) with a base B to form a salt of formula IV_s, and

(IVs)



(d) reacting the salt formed in step (c) with an acid to form the compound of formula IV.

12. The process of claim **11**, which does not include purifying the compound of formula (VI) produced in step (a).

13. The process according to claim **12**, wherein the product of step (d) has the purity of the compound of formula IV of at least 90.0%.

14. The process according to claim **11**, further comprising a step of isolating the salt of formula IV_s.

15. The process according to claim **11**, wherein the alkylating agent is $ClCH_2CN$.

16. The process according to claim **11**, wherein the base in step (b) is KOH.

17. The process according to claim **11**, wherein the base B in step (c) is selected from a group consisting of ammonia, N-methylglucamine, procaine, tromethanine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.

18. The process according to claim **17**, wherein the base B is diethanolamine.

19. The process according to claim **11**, wherein the acid in step (d) is HCl.

20. The process of claim **2**, wherein the product of step (d) has the purity of compound of formula I of at least 95%.

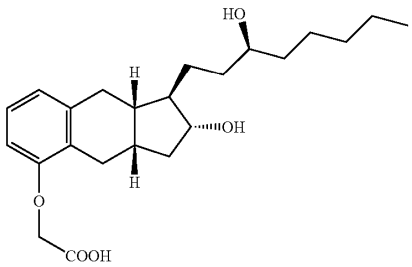
21. The process of claim **12**, wherein the product of step (d) has the purity of compound of formula I of at least 95%.

22. The process of claim **12**, wherein the base B in step (c) is selected from a group consisting of ammonia, N-methylglucamine, procaine, tromethanine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.

23. The process of claim **22**, wherein the base B is diethanolamine.

24. A process for the preparation of a compound having formula IV, or pharmaceutically acceptable salt thereof

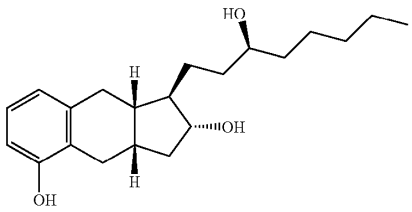
(IV)



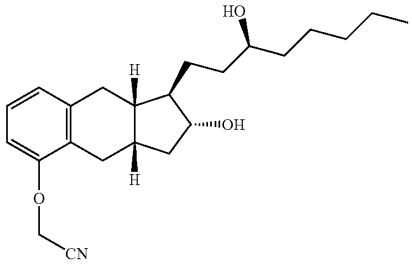
comprising

(a) alkylating a compound of formula V with an alkylating aent to produce a compound of formula VI,

(V)



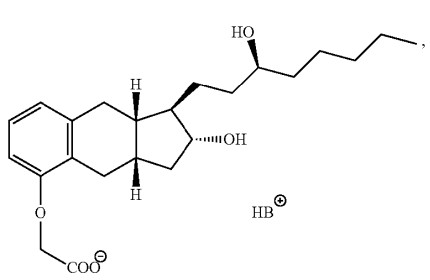
(VI)



(b) hydrolyzing the product of formula VI of step (a) with a base, and

(c) contacting the product of step (b) with a base B to form a salt of formula IV_s

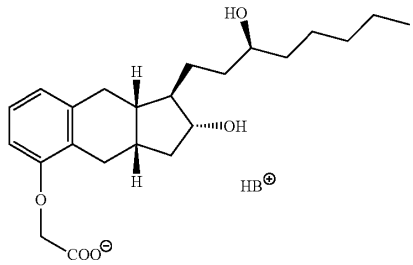
(IV_s)



wherein the process does not comprise purifying the compound of formula (VI) produced in step (a).

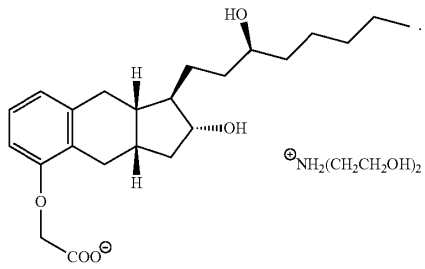
25. The process according to claim **24**, wherein the base B in step (c) is selected from a group consisting of ammonia, N-methylglucamine, procaine, tromethanine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine and wherein the compound produced is a compound of the formula IV_s,

IV_S



wherein the base B is selected from a group consisting of ammonia, N-methylglucamine, procaine, tromethanine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.

26. The process according to claim **25**, wherein the base B is diethanolamine and wherein the compound produced is a compound of the following formula:



27. The process according to claim 1, wherein the base in step (b) is KOH or NaOH and wherein the base B in step (c) is selected from the group consisting of ammonia, N-methylglucamine, procaine, tromethanine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.

28. The process according to claim 11, wherein the base in step (b) is KOH or NaOH and wherein the base B in step (c) is selected from the group consisting of ammonia, N-methylglucamine, procaine, tromethanine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO.	: 8,242,305 B2
APPLICATION NO.	: 12/334731
DATED	: August 14, 2012
INVENTOR(S)	: Hitesh Batra et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Claims

Replace the term "tromethanine" with --tromethamine-- as follows:

Col. 19, claim 17, line 26;
Col. 21, claim 22, line 10;
Col. 22, claim 25, line 25;
Col. 23, claim 27, line 4; and
Col. 24, claim 28, line 2.

Signed and Sealed this
Twenty-fifth Day of February, 2014

Michelle K. Lee

Michelle K. Lee
Deputy Director of the United States Patent and Trademark Office

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
61/014,232	12/17/2007		105	080618-0570		

CONFIRMATION NO. 1248

22428
FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

FILING RECEIPT

OC00000027520062

Date Mailed: 01/03/2008

Receipt is acknowledged of this provisional patent application. It will not be examined for patentability and will become abandoned not later than twelve months after its filing date. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please write to the Office of Initial Patent Examination's Filing Receipt Corrections. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Applicant(s)

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Sudersan M. Tuladhar, Silver Spring, MD;
Raju Penmasta, Herndon, VA;
David A. Walsh, Palmyra, VA;

Power of Attorney: The patent practitioners associated with Customer Number 22428

If Required, Foreign Filing License Granted: 01/02/2008
The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 61/014,232**
Projected Publication Date: None, application is not eligible for pre-grant publication
Non-Publication Request: No
Early Publication Request: No
**** SMALL ENTITY ****
Title

Process to prepare treprostinil, the active ingredient in remodulin®

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing

of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

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Title 37, Code of Federal Regulations, 5.11 & 5.15

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Atty. Dkt. No. 080618-0570

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Hitesh BATRA et al.

Title: AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®

Appl. No.: Unassigned

Filing Date: 12/17/2007

PROVISIONAL PATENT APPLICATION TRANSMITTAL

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Transmitted herewith for filing under 37 C.F.R. § 1.53(c) is the provisional patent application of:

Hitesh BATRA
Sudersan M. TULADHAR
Raju PENMASTA
David A. WALSH

[**X**] Applicant claims small entity status under 37 CFR 1.27(c)(1).

Enclosed are:

[**X**] Cover page, Description, Claims, and Abstract (28 pages).

[**X**] Application Data Sheet (37 CFR 1.76).

The adjustment to the number of sheets for EFS-Web filing follows:

Number of Sheets		**EFS-Web Adjustment**	**Number of Sheets for EFS-Web**
27	x	75%	21

WASH_2157918.1

The filing fee is calculated below:

						Rate		Fee Totals
Basic Fee						$210.00		$210.00
Size Fee	21	- 100	=	0	x	$260.00		$0.00
Surcharge under 37 CFR 1.16(e) for late payment of filing fee					+	$50.00	=	$0.00
						SUBTOTAL:	=	$210.00
[X]	Small Entity Fees Apply (subtract ½ of above):						=	$105.00
						TOTAL FILING FEE:	=	$105.00
Assignment Recordation Fee:					+	$40.00	=	$0.00
						TOTAL FEE	=	$105.00

The above-identified fees of $105.00 are being paid by credit card via EFS-Web.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by the credit card payment instructions in EFS-Web being incorrect or absent, resulting in a rejected or incorrect credit card transaction, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741.

Please direct all correspondence to the undersigned attorney or agent at the address indicated below.

Respectfully submitted,

Date December 17, 2007

By _____

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Stephen B. Maebius
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Registration No. 35,264

Application Data Sheet

Application Information	
Application Type::	Provisional
Subject Matter::	Utility
Suggested classification::	
Suggested Group Art Unit::	
CD-ROM or CD-R?::	None
Computer Readable Form (CRF)?::	No
Title::	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
Attorney Docket Number::	080618-0570
Request for Early Publication?::	No
Request for Non-Publication?::	No
Suggested Drawing Figure::	
Total Drawing Sheets::	0
Small Entity?::	Yes
Petition included?::	No
Secrecy Order in Parent Appl.?::	No

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Representative Information

Representative Customer Number::	22428	

Domestic Priority Information

Application::	**Continuity Type::**	**Parent Application::**	**Parent Filing Date::**

Foreign Priority Information

Country::	Application number::	Filing Date::	Priority Claimed::

Assignee Information

Assignee Name:: United Therapeutics Corporation

U.S. PATENT APPLICATION

for

AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®

Inventors: Hitesh Batra

Sudersan M. Tuladhar

Raju Penmasta

David A. Walsh

AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®

BACKGROUND OF THE INVENTION

[0001] The present invention relates to a process for producing prostacyclin derivatives and novel intermediate compounds useful in the process.

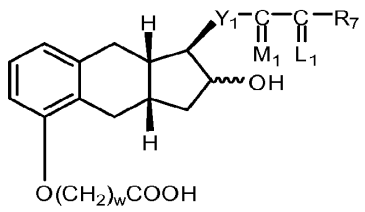
[0002] Prostacyclin derivatives are useful pharmaceutical compounds possessing activities such as platelet aggregation inhibition, gastric secretion reduction, lesion inhibition, and bronchodilation.

[0003] Treprostinil, the active ingredient in Remodulin®, and other prostacyclin derivatives have been prepared as described in Moriarty, et al in *J. Org. Chem.* 2004, 69, 1890-1902, U.S. Pat. Nos. 6,441,245, 6,528,688, 6,700,025, and 6,809,223. Their teachings are incorporated by reference to show how to practice the embodiments of the present invention.

[0004] It is evident that these compounds are of great importance from a medicinal point of view. There is, therefore, a need for an efficient process to synthesize these compounds on a large scale suitable for commercial production.

SUMMARY OF THE INVENTION

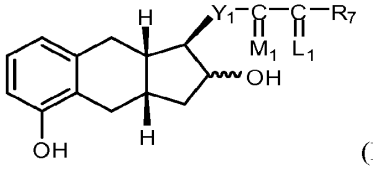
[0005] The present invention provides in one embodiment a process for the preparation of a compound of formula I, hydrate, solvate, prodrug, or pharmaceutically acceptable salt thereof.



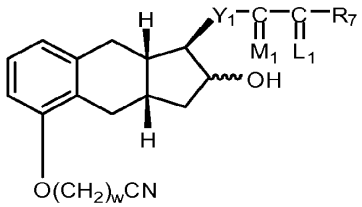
(I)

[0006] The process comprises the following steps:

(a) alkylating a compound of structure II with an alkylating agent to produce a compound of formula III,



(II)



(III)

wherein

w= 1, 2, or 3;

Y_1 is trans-CH=CH-, cis-CH=CH-, $-CH_2(CH_2)_m-$, or -C≡C-; m is 1, 2, or 3;

R_7 is

(1) $-C_pH_{2p}-CH_3$, wherein p is an integer from 1 to 5, inclusive,

(2) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3) alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl, with the proviso that R_7 is phenoxy or substituted phenoxy, only when R_3 and R_4 are hydrogen or methyl, being the same or different,

(3) phenyl, benzyl, phenylethyl, or phenylpropyl optionally substituted on the aromatic ring by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3)alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl,

(4) cis-CH=CH-CH_2-CH_3,

(5) $-(CH_2)_2$-CH(OH)-CH_3, or

(6) $-(CH_2)_3$-CH=$C(CH_3)_2$;

wherein $-C(L_1)-R_7$ taken together is

(1) (C_4-C_7)cycloalkyl optionally substituted by 1 to 3 (C_1-C_5)alkyl;

(2) 2-(2-furyl)ethyl,

(3) 2-(3-thienyl)ethoxy, or

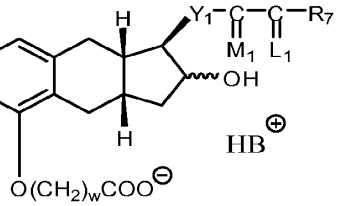
(4) 3-thienyloxymethyl;

M_1 is α-OH:β-R_5 or α-R_5:β-OH or α-OR_1:β-R_5 or α-R_5:β-OR_2, wherein R_5 is hydrogen or methyl, R_2 is an alcohol protecting group, and

L_1 is α-R_3:β-R_4, α-R_4:β-R_3, or a mixture of α-R_3:β-R_4 and α-R_4:β-R_3, wherein R_3 and R_4 are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R_3 and R_4 is fluoro only when the other is hydrogen or fluoro.

(b) hydrolyzing the product of step (a) with a base,

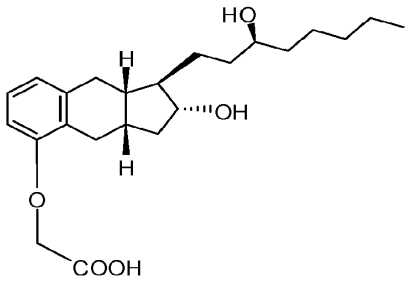
(c) contacting the product of step (b) with a base B to for a salt of formula I_s



(I_s)

(d) reacting the salt from step (c) with an acid to form the compound of formula I.

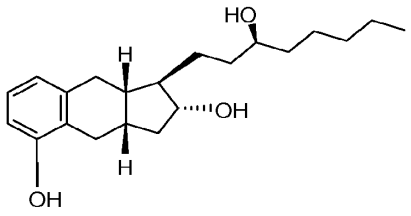
[0007] The present invention provides in another embodiment a process for the preparation of a compound of formula IV.



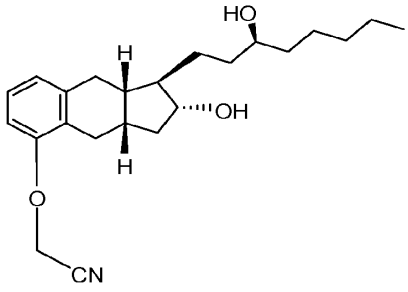
(IV)

[0008] The process comprises the following steps:

(a) alkylating a compound of structure V with an alkylating agent to produce a compound of formula VI,



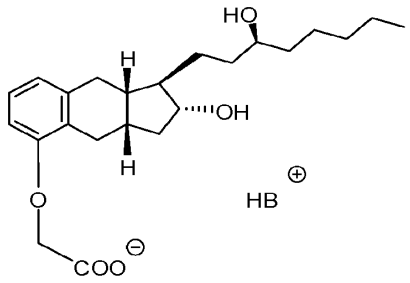
(V)



(VI)

(b) hydrolyzing the product of step (a) with a base,

(c) contacting the product of step (b) with a base B to for a salt of formula IV_s, and



(IV_S)

(d) reacting the salt from step (b) with an acid to form the compound of formula IV.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0009] The various terms used, separately and in combinations, in the processes herein described are defined below.

[0010] The expression "comprising" means "including but not limited to." Thus, other non-mentioned substances, additives, carriers, or steps may be present. Unless otherwise specified, "a" or "an" means one or more.

[0011] C_{1-3}-alkyl is a straight or branched alkyl group containing 1-3 carbon atoms. Exemplary alkyl groups include methyl, ethyl, n-propyl, and isopropyl.

[0012] C_{1-3}-alkoxy is a straight or branched alkoxy group containing 1-3 carbon atoms. Exemplary alkoxy groups include methoxy, ethoxy, propoxy, and isopropoxy.

[0013] C_{4-7}-cycloalkyl is an optionally substituted monocyclic, bicyclic or tricyclic alkyl group containing between 4-7 carbon atoms. Exemplary cycloalkyl groups include but not limited to cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl.

[0014] Combinations of substituents and variables envisioned by this invention are only those that result in the formation of stable compounds. The term "stable", as used herein, refers to compounds which possess stability sufficient to allow manufacture and which maintains the integrity of the compound for a sufficient period of time to be useful for the purposes detailed herein.

[0015] As used herein, the term "prodrug" means a derivative of a compound that can hydrolyze, oxidize, or otherwise react under biological conditions (*in vitro* or *in vivo*) to provide an active compound. Examples of prodrugs include, but are not limited to,

derivatives of a compound that include biohydrolyzable groups such as biohydrolyzable amides, biohydrolyzable esters, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable urcides, and biohydrolyzable phosphate analogues (*e.g.*, monophosphate, diphosphate or triphosphate).

[0016] As used herein, "hydrate" is a form of a compound wherein water molecules are combined in a certain ratio as an integral part of the structure complex of the compound.

[0017] As used herein, "solvate" is a form of a compound where solvent molecules are combined in a certain ratio as an integral part of the structure complex of the compound.

[0018] "Pharmaceutically acceptable" means in the present description being useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes being useful for veterinary use as well as human pharmaceutical use.

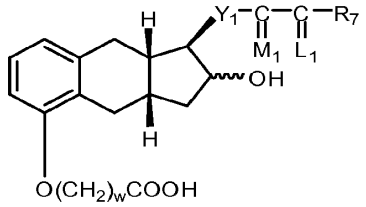
[0019] "Pharmaceutically acceptable salts" mean salts which are pharmaceutically acceptable, as defined above, and which possess the desired pharmacological activity. Such salts include acid addition salts formed with organic and inorganic acids, such as hydrogen chloride, hydrogen bromide, hydrogen iodide, sulfuric acid, phosphoric acid, acetic acid, glycolic acid, maleic acid, malonic acid, oxalic acid, methanesulfonic acid, trifluoroacetic acid, fumaric acid, succinic acid, tartaric acid, citric acid, benzoic acid, ascorbic acid and the like. Base addition salts may be formed with organic and inorganic bases, such as sodium, ammonia, potassium, calcium, ethanolamine, diethanolamine, N-methylglucamine, choline and the like. Included in the invention are pharmaceutically acceptable salts or compounds of any of the formulae herein.

[0020] Depending on its structure, the phrase "pharmaceutically acceptable salt," as used herein, refers to a pharmaceutically acceptable organic or inorganic acid or base salt of a compound. Representative pharmaceutically acceptable salts include, *e.g.*, alkali metal salts, alkali earth salts, ammonium salts, water-soluble and water-insoluble salts, such as the acetate, amsonate (4,4-diaminostilbene-2, 2 -disulfonate), benzenesulfonate, benzonate, bicarbonate, bisulfate, bitartrate, borate, bromide, butyrate, calcium, calcium edetate, camsylate, carbonate, chloride, citrate, clavulariate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexafluorophosphate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride,

hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, N-methylglucamine ammonium salt, 3-hydroxy-2-naphthoate, oleate, oxalate, palmitate, pamoate (1,1-methene-bis-2-hydroxy-3-naphthoate, einbonate), pantothenate, phosphate/diphosphate, picrate, polygalacturonate, propionate, p-toluenesulfonate, salicylate, stearate, subacetate, succinate, sulfate, sulfosalicylate, suramate, tannate, tartrate, teoclate, tosylate, triethiodide, and valerate salts.

[0021] The present invention provides for a process for producing treprostinil and other prostacyclin derivatives and novel intermediate compounds useful in the process. The process according to the present invention provides advantages on large-scale synthesis over the existing method. For example, the purification by column chromatography is eliminated, thus the required amount of flammable solvents and waste generated are greatly reduced. Furthermore, the salt formation is a much easier operation than column chromatography. Moreover, it was found that the product of the process according to the present invention has higher purity. Therefore the present invention provides for a process that is more economical, safer, faster, greener, easier to operate, and provides higher purity.

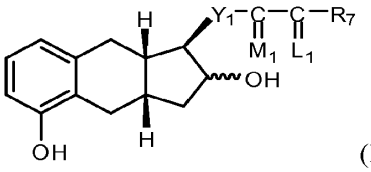
[0022] One embodiment of the present invention is a process for the preparation of a compound of formula I, or a hydrate, solvate, prodrug, or pharmaceutically acceptable salt thereof.



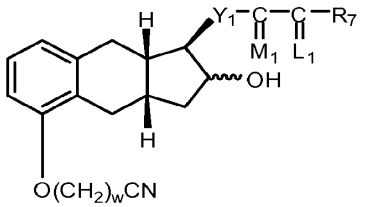
(I)

[0023] The process comprises the following steps:

(a) alkylating a compound of formula II with an alkylating agent to produce a compound of formula III,



(II)



(III)

wherein

w= 1, 2, or 3;

Y_1 is trans-CH=CH-, cis-CH=CH-, $-CH_2(CH_2)_m-$, or -C≡C-; m is 1, 2, or 3;

R_7 is

(1) $-C_pH_{2p}-CH_3$, wherein p is an integer from 1 to 5, inclusive,

(2) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3) alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl, with the proviso that R_7 is phenoxy or substituted phenoxy, only when R_3 and R_4 are hydrogen or methyl, being the same or different,

(3) phenyl, benzyl, phenylethyl, or phenylpropyl optionally substituted on the aromatic ring by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3)alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl,

(4) cis-CH=CH-CH_2-CH_3,

(5) $-(CH_2)_2$-CH(OH)-CH_3, or

(6) $-(CH_2)_3$-CH=$C(CH_3)_2$;

wherein $-C(L_1)-R_7$ taken together is

(1) (C_4-C_7)cycloalkyl optionally substituted by 1 to 3 (C_1-C_5)alkyl;

(2) 2-(2-furyl)ethyl,

(3) 2-(3-thienyl)ethoxy, or

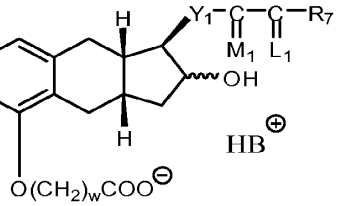
(4) 3-thienyloxymethyl;

M_1 is α-OH:β-R_5 or α-R_5:β-OH or α-OR_1:β-R_5 or α-R_5:β-OR_2, wherein R_5 is hydrogen or methyl, R_2 is an alcohol protecting group, and

L_1 is α-R_3:β-R_4, α-R_4:β-R_3, or a mixture of α-R_3:β-R_4 and α-R_4:β-R_3, wherein R_3 and R_4 are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R_3 and R_4 is fluoro only when the other is hydrogen or fluoro.

(b) hydrolyzing the product of step (a) with a base,

(c) contacting the product of step (b) with a base B to for a salt of formula I_s

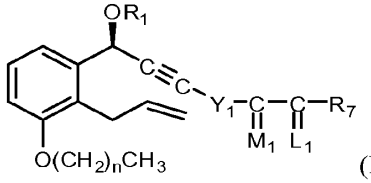


(I_s)

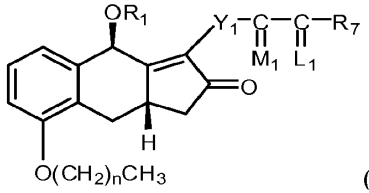
(d) reacting the salt from step (c) with an acid to form the compound of formula I.

[0024] In one embodiment, the compound of formula I is at least 90.0%, 95.0%, 99.0%.

[0025] The compound of formula II can be prepared from a compound of formula XI, which is a cyclization product of a compound of formula X as described in U.S. Pat. No. 6,441,245.



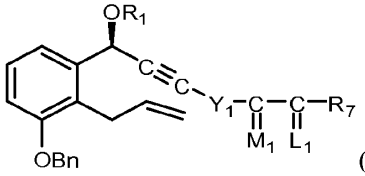
(X)



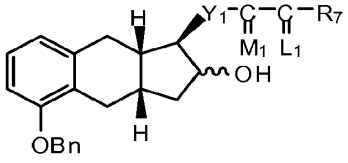
(XI)

Wherein n is 0, 1, 2, or 3.

[0026] The compound of formula II can be prepared alternatively from a compound of formula XIII, which is a cyclization product of a compound of formula XII as described in U.S. Pat. No. 6,700,025.

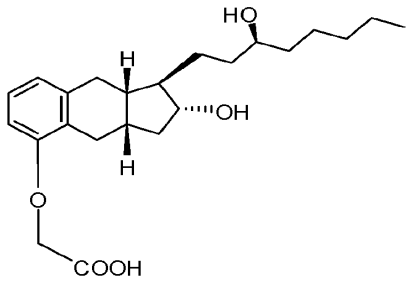


(XII)



(XIII)

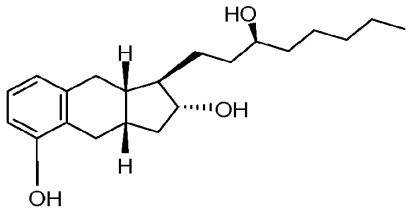
[0027] One embodiment of the present invention is a process for the preparation of a compound having formula IV, or a hydrate, solvate, or pharmaceutically acceptable salt thereof.



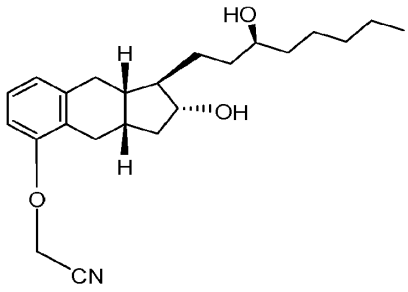
(IV)

[0028] The process comprises

(a) alkylating a compound of structure V with an alkylating agent such as $ClCH_2CN$ to produce a compound of formula VI,



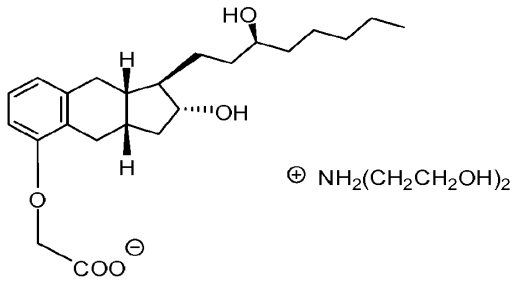
(V)



(VI)

(b) hydrolyzing the product of step (a) with a base such as KOH,

(c) contacting the product of step (b) with a base B such as diethanolamine to for a salt of the following structure, and



(d) reacting the salt from step (b) with an acid such as HCl to form the compound of formula IV.

[0029] In one embodiment, the purity of compound of formula IV is at least 90.0%, 95.0%, 99.0%, 99.5%.

[0030] In one embodiment, the process further comprises a step of isolating the salt of formula IV_S.

[0031] In one embodiment, the base B in step (c) may be ammonia, N-methylglucamine, procaine, tromethanine, magnesium, L-lysine, L-arginine, or triethanolamine.

[0032] The following abbreviations are used in the description and/or appended claims, and they have the following meanings:

"MW" means molecular weight.

"Eq." means equivalent.

"TLC" means thin layer chromatography.

"HPLC" means high performance liquid chromatography.

"PMA" means phosphomolybdic acid.

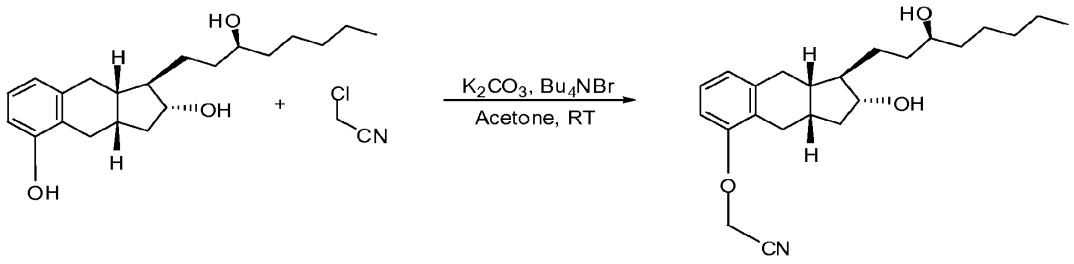
"AUC" means area under curve.

[0033] In view of the foregoing considerations, and specific examples below, those who are skilled in the art will appreciate that how to select necessary reagents and solvents in practicing the present invention.

[0034] The invention will now be described in reference to the following Examples. These examples are not to be regarded as limiting the scope of the present invention, but shall only serve in an illustrative manner.

EXAMPLES

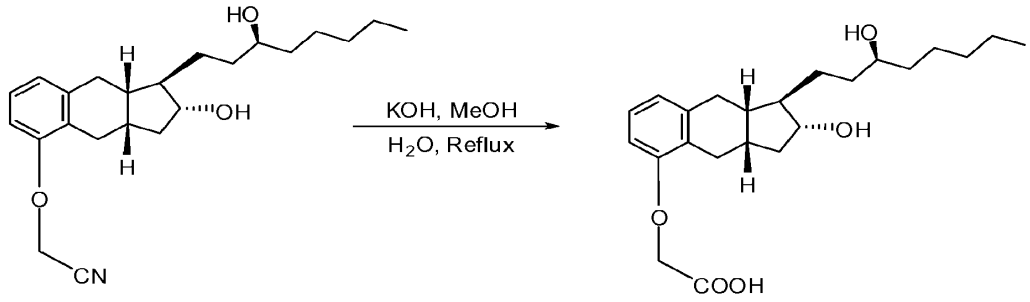
Example 1. Alkylation of Benzindene Triol



Name	MW	Amount	Mol.	Eq.
Benzindene Triol	332.48	1250 g	3.76	1.00
K_2CO_3 (powder)	138.20	1296 g	9.38	2.50
$ClCH_2CN$	75.50	567 g	7.51	2.0
Bu_4NBr	322.37	36 g	0.11	0.03
Acetone	--	29 L	--	--
Celite®545	--	115 g	--	--

[0035] A 50-L, three-neck, round-bottom flask equipped with a mechanical stirrer and a thermocouple was charged with benzindene triol (1250 g), acetone (19 L) and K_2CO_3 (powdered) (1296 g), chloroacetonitrile (567 g), tetrabutylammonium bromide (36 g). The reaction mixture was stirred vigorously at room temperature (23±2°C) for 16-72 h. The progress of the reaction was monitored by TLC. (methanol/CH_2Cl_2; 1:9 and developed by 10% ethanolic solution of PMA). After completion of reaction, the reaction mixture was filtered with/without Celite pad. The filter cake was washed with acetone (10L). The filtrate was concentrated *in vacuo* at 50-55°C to give a light-brown, viscous liquid benzindene nitrile. The crude benzindene nitrile was used as such in the next step without further purification.

Example 2. Hydrolysis of Benzindene Nitrile



Name	MW	Amount	Mol.	Eq.
Benzindene Nitrile	371.52	1397 g*	3.76	1.0
KOH	56.11	844 g	15.04	4.0
Methanol	--	12 L	--	--
Water	--	4.25 L	--	--

*Note: This weight is based on 100% yield from the previous step. This is not isolated yield.

[0036] A 50-L, cylindrical reactor equipped with a heating/cooling system, a mechanical stirrer, a condenser, and a thermocouple was charged with a solution of benzindene nitrile in methanol (12 L) and a solution of KOH (844 g of KOH dissolved in 4.25 L of water). The reaction mixture was stirred and heated to reflux (temperature 72.2°C). The progress of the reaction was monitored by TLC (for TLC purpose, 1-2 mL of reaction mixture was acidified with 3M HCl to pH 1-2 and extracted with ethyl acetate. The ethyl acetate extract was used for TLC; Eluent: methanol/CH_2Cl_2; 1:9, and developed by 10% ethanolic solution of PMA). After completion of the reaction (~5 h), the reaction mixture was cooled to -5 to 10°C and quenched with a solution of hydrochloric acid (3M, 3.1 L) while stirring. The reaction mixture was concentrated *in vacuo* at 50-55°C to obtain approximately 12-14 L of condensate. The condensate was discarded.

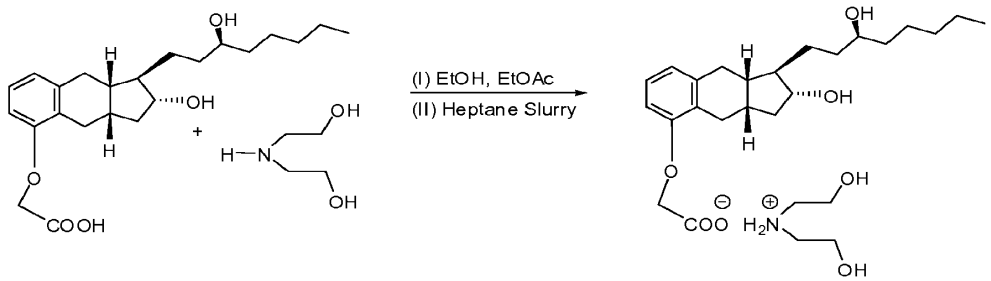
[0037] The aqueous layer was diluted with water (7-8 L) and extracted with ethyl acetate (2 × 6 L) to remove impurities soluble in ethyl acetate. To aqueous layer, ethyl acetate (22 L) was added and the pH of reaction mixture was adjusted to 1-2 by adding 3M HC1 (1.7 L) with stirring. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 × 11 L). The combined organic layers were washed with water (3 × 10 L) and followed by washing with a solution of $NaHCO_3$ (30 g of $NaHCO_3$ dissolved in 12 L of water). The organic layer was further washed with saturated solution of NaCl (3372 g of NaCl dissolved in water (12 L)) and dried over anhydrous Na_2SO_4 (950-1000 g), once filtered.

[0038] The filtrate was transferred into a 72-L reactor equipped with mechanical stirrer, a condenser, and a thermocouple. To the solution of treprostinil in reactor was added activated carbon (110-130 g). The suspension was heated to reflux (temperature 68-70°C) for at least one hour. For filtration, a pad of Celite®545 (300-600 g) was prepared in sintered glass

funnel using ethyl acetate. The hot suspension was filtered through the pad of Celite®545. The Celite®545 was washed with ethyl acetate until no compound was seen on TLC of the washings.

[0039] The filtrate (pale-yellow) was reduced to volume of 35-40 L by evaporation *in vacuo* at 50-55°C for direct use in next step.

Example 3. Conversion of Treprostinil to Treprostinil Diethanolamine Salt (1:1)



Name	MW	Amount	Mol	Eq
Treprostinil	390.52	1464 g*	3.75	1.0
Diethanolamine	105.14	435 g	4.14	1.1
Ethanol	--	5.1 L	--	--
Ethyl acetate	--	35L**	--	--
Treprostinil Diethanolamine Salt (seed)	--	12 g	--	--

*Note: This weight is based on 100% yield from benzindene triol. It is not isolated yield. The treprostinil was carried from previous step in ethyl acetate solution and used as such for this step.

**Note: The total volume of ethyl acetate should be in range of 35-36 L (it should be 7 times the volume of ethanol used). Approximately 35 L of ethyl acetate was carried over from previous step and additional 1.0 L of ethyl acetate was used for rinsing the flask.

[0040] A 50-L, cylindrical reactor equipped with a heating/cooling system, a mechanical stirrer, a condenser, and a thermocouple was charged with a solution of treprostinil in ethyl acetate (35-40 L from the previous step), anhydrous ethanol (5.1 L) and diethanolamine (435 g). While stirring, the reaction mixture was heated to 60-75°C, for 0.5-1.0 h to obtain a

clear solution. The clear solution was cooled to 55±5°C. At this temperature, the seed of polymorph B of treprostinil diethanolamine salt (~12 g) was added to the clear solution. The suspension of polymorph B was stirred at this temperature for 1 h. The suspension was cooled to 20±2°C overnight (over a period of 16-24 h). The treprostinil diethanolamine salt was collected by filtration using Aurora filter equipped with filter cloth, and the solid was washed with ethyl acetate (2 × 8 L). The treprostinil diethanolamine salt was transferred to a HDPE/glass container for air-drying in hood, followed by drying in a vacuum oven at 50±5°C under high vacuum.

[0041] At this stage, if melting point of the treprostinil diethanolamine salt is more than 104°C, it was considered polymorph B. There is no need of recrystallization. If it is less than 104°C, it is recrystallized in EtOH-EtOAc to increase the melting point.

Data on Treprostinil Diethanolamine Salt (1:1)

Batch No.	Wt. of Benzindene Triol (g)	Wt. of Treprostinil Diethanolamine Salt (1:1) (g)	Yield (%)	Melting point (°C)
1	1250	1640	88.00	104.3-106.3
2	1250	1528	82.00*	105.5-107.2
3	1250	1499	80.42**	104.7-106.6
4	1236	1572	85.34	105-108

**Note*: In this batch, approximately 1200 mL of ethyl acetate solution of treprostinil before carbon treatment was removed for R&D carbon treatment experiments.

***Note*: This batch was recrystallized, for this reason yield was lower.

Example 4. Heptane Slurry of Treprostinil Diethanolamine Salt (1:1)

Name	Batch No.	Amount	Ratio
Treprostinil Diethanolamine Salt	1	3168 g	1
Heptane	--	37.5 L	12

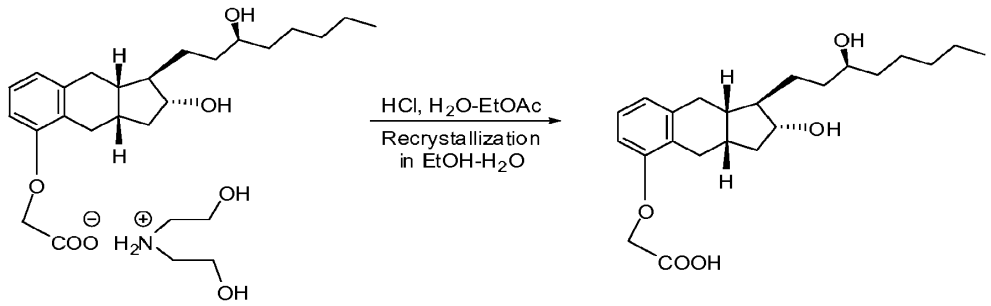
Name	Batch No.	Amount	Ratio
Treprostinil Diethanolamine Salt	2	3071 g	1
Heptane	--	36.0 L	12

[0042] A 50-L, cylindrical reactor equipped with a heating/cooling system, a mechanical stirrer, a condenser, and a thermocouple was charged with slurry of treprostinil diethanolamine salt in heptane (35-40 L). The suspension was heated to 70-80°C for 16-24 h. The suspension was cooled to 22±2°C over a period of 1-2 h. The salt was collected by filtration using Aurora filter. The cake was washed with heptane (15-30 L) and the material was dried in Aurora filter for 1 h. The salt was transferred to trays for air-drying overnight in hood until a constant weight of treprostinil diethanolamine salt was obtained. The material was dried in oven under high vacuum for 2-4 h at 50-55°C.

Analytical data on and Treprostinil Diethanolamine Salt (1:1)

Test	Batch 1	Batch 2
IR	Conforms	Conforms
Residue on Ignition (ROI)	<0.1% w/w	<0.1% w/w
Water content	0.1% w/w	0.0% w/w
Melting point	105.0-106.5°C	104.5-105.5°C
Specific rotation $[\alpha]^{25}_{589}$	+34.6°	+35°
Organic volatile impurities		
• Ethanol	• Not detected	• Not detected
• Ethyl acetate	• Not detected	• <0.05% w/w
• Heptane	• <0.05% w/w	• <0.05% w/w
HPLC (Assay)	100.4%	99.8%
Diethanolamine	Positive	Positive

Example 5. Conversion of Treprostinil Diethanolamine Salt (1:1) to Treprostinil



[0043] A 250-mL, round-bottom flask equipped with magnetic stirrer was charged with treprostinil diethanolamine salt (4 g) and water (40 mL). The mixture was stirred to obtain a clear solution. To the clear solution, ethyl acetate (100 mL) was added. While stirring, 3M HC1 (3.2 mL) was added slowly until pH ~1 was attained. The mixture was stirred for 10 minutes and organic layer was separated. The aqueous layer was extracted with ethyl acetate (2 × 100 mL). The combined organic layers was washed with water (2 × 100 mL), brine (1 × 50 mL) and dried over anhydrous Na_2SO_4. The ethyl acetate solution of treprostinil was filtered and the filtrate was concentrated under vacuum at 50°C to give off-white solid. The crude treprostinil was recrystallized from 50% ethanol in water (70 mL). The pure treprostinil was collected in a Buchner funnel by filtration and cake was washed with cold 20% ethanolic solution in water. The cake of treprostinil was air-dried overnight and further dried in a vacuum oven at 50°C under high vacuum to afford 2.9 g of treprostinil (Yield 91.4%, purity (HPLC, AUC, 99.8%).

Analytical data on Treprostinil from Treprostinil Diethanolamine Salt (1:1) to Treprostinil

Batch No.	Yield	Purity (HPLC)
1	91.0%	99.8% (AUC)
2	92.0%	99.9% (AUC)
3	93.1%	99.7% (AUC)
4	93.3%	99.7% (AUC)
5	99.0 %	99.8% (AUC)
6	94.6%	99.8% (AUC)

Example 6. Comparison of the former process and a working example of the process according to the present invention

Step No.	Steps	Former Process (Batch size: 500g)	Working example of the Process according to the present invention (Batch size: 5 kg)
Nitrile			
1	Triol weight	500 g	5,000 g
2	Acetone	20 L (1:40 wt/wt)	75 L (1:15 wt/wt)
3	Potassium carbonate	1,300 g (6.4 eq)	5,200 g (2.5 eq)
4	Chloroacetonitrile	470 g (4.2 eq)	2,270 g (2 eq)
5	Tetrabutylammoniu m bromide	42 g (0.08 eq)	145 g (0.03 eq)
6	Reactor size	72-Liter	50- gallon
7	Reflux time	8 hours	No heating, Room temperature (r.t.) 45 h
8	Hexanes addition before filtration	Yes (10 L)	No
9	Filter	Celite	Celite
10	Washing	Ethyl acetate (10 L)	Acetone (50 L)
11	Evaporation	Yes	Yes
12	Purification	Silica gel column Dichloromethane:0.5 L Ethyl acetate: 45 L Hexane: 60 L	No column
13	Evaporation after column	Yes	No
14	Yield of nitrite	109-112 %	Not checked
Treprostinil (intermediate)			
15	Methanol	7.6 L (50-L reactor)	50 L (50-gal reactor)
16	Potassium hydroxide	650 g (8 eq)	3,375g (4 eq)
17	Water	2.2 L	17 L
18	% of KOH	30%	20%

19	Reflux time	3-3.5 h	4-5 h
20	Acid used	2.6 L (3 M)	12 L (3 M)
21	Removal of impurities	3 × 3 L Ethyl acetate	2 × 20 L Ethyl acetate
22	Acidification	0.7 L	6.5 L
23	Ethyl acetate extraction	5 × 17 L = 35 L	90+45+45 = 180 L
24	Water washing	2 × 8 L	3 × 40 L
25	Sodium bicarbonate washing	Not done	120 g in 30L water + 15 L brine
26	Brine washing	Not done	1 × 40 L
27	Sodium sulfate	1 kg	Not done
28	Sodium sulfate filtration	Before charcoal, 6 L ethyl acetate	N/A
29	Charcoal	170 g, reflux for 1.5 h, filter over Celite, 11 L ethyl acetate	Pass hot solution (75°C) through charcoal cartridge and clean filter, 70 L ethyl acetate
30	Evaporation	Yes, to get solid intermediate treprostinil	Yes, adjust to 150 L solution
Treprostinil Diethanolamine Salt			
31	Salt formation	Not done	1,744 g dicthanolamine, 20 L ethanol at 60-75°C.
32	Cooling	N/A	To 20°C over weekend; add 40 L ethyl acetate; cooled to 10°C
33	Filtration	N/A	Wash with 70 L ethyl acetate
34	Drying	N/A	Air-dried to constant wt., 2 days
Treprostinil (from 1.5 kg Treprostinil diethanolamine salt)			
35	Hydrolysis	N/A	15 L water + 25 L ethyl acetate + HCl
36	Extraction	N/A	2 × 10 L ethyl acetate
37	Water wash	N/A	3 × 10 L
38	Brine wash	N/A	1 × 10 L

39	Sodium sulfate	N/A	1 kg, stir
40	Filter	N/A	Wash with 6 L ethyl acetate
41	Evaporation	N/A	To get solid, intermediate Treprostinil
42	Crude drying on tray	1 or 3 days	Same
43	Ethanol & water for cryst.	5.1 L + 5.1 L	10.2 L + 10.2 L (same %)
44	Crystallization in	20-L rotavap flask	50-L jacketed reactor
45	Temperature of crystallization	2 h r.t., fridge -0°C 24 h	50°C to 0°C ramp, 0°C overnight
46	Filtration	Buchner funnel	Aurora filter
47	Washing	20% (10 L) cooled ethanol-water	20% (20 L) cooled ethanol-water
48	Drying before oven	Buchner funnel (20 h) Tray (no)	Aurora filter (2.5 h) Tray (4 days)
49	Oven drying	15 hours, 55°C	6-15 hours, 55°C
50	Vacuum	<-0.095 mPA	< 5 Torr
51	UT-15 yield weight	~ 535 g	~ 1,100 g
52	% yield from triol)	~ 91%	~ 89%
53	Purity	~ 99.0%	99.9%

[0044] The quality of treprostinil produced according to this invention is excellent. The purification of benzindene nitrile by column chromatography is eliminated. The impurities carried over from intermediate steps (i.e. alkylation of triol and hydrolysis of benzindene nitrile) are removed during the carbon treatment and the salt formation step. Additional advantages of this process are: (a) crude treprostinil salts can be stored as raw material at ambient temperature and can be converted to treprostinil by simple acidification with diluted hydrochloric acid, and (b) the treprostinil salts can be synthesized from the solution of treprostinil without isolation. This process provides better quality of final product as well as saves significant amount of solvents and manpower in purification of intermediates.

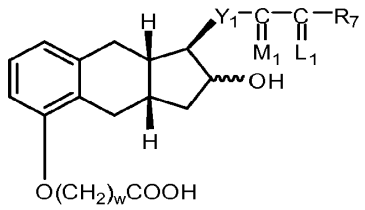
[0045] Although the foregoing refers to particular preferred embodiments, it will be understood that the present invention is not so limited. It will occur to those of ordinary skill

in the art that various modifications may be made to the disclosed embodiments and that such modifications are intended to be within the scope of the present invention.

[0046] All of the publications, patent applications and patents cited in this specification are incorporated herein by reference in their entirety.

WHAT IS CLAIMED IS:

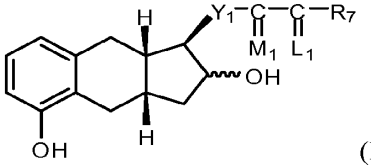
1. A process for the preparation of a compound of formula I, a hydrate, solvate, prodrug, or pharmaceutically acceptable salt thereof



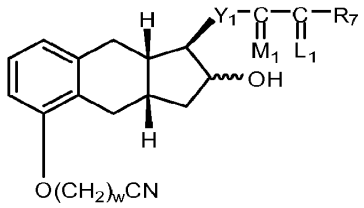
(I)

comprising

(a) alkylating a compound of structure II with an alkylating agent to produce a compound of formula III,



(II)



(III)

wherein

w=1, 2, or 3;

Y_1 is trans-CH=CH-, cis-CH=CH-, $-CH_2(CH_2)_m-$, or -C≡C-; m is 1, 2, or 3;

R_7 is

(1) $-C_pH_{2p}-CH_3$, wherein p is an integer from 1 to 5, inclusive,

(2) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3) alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl, with the proviso that R_7 is phenoxy or substituted phenoxy, only when R_3 and R_4 are hydrogen or methyl, being the same or different,

(3) phenyl, benzyl, phenylethyl, or phenylpropyl optionally substituted on the aromatic ring by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3)alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl,

(4) cis-CH=CH-CH_2-CH_3,

(5) $-(CH_2)_2-CH(OH)-CH_3$, or

(6) $-(CH_2)_3-CH=C(CH_3)_2$;

$-C(L_1)-R_7$ taken together is

(1) (C_4-C_7)cycloalkyl optionally substituted by 1 to 3 (C_1-C_5)alkyl;

(2) 2-(2-furyl)ethyl,

(3) 2-(3-thienyl)ethoxy, or

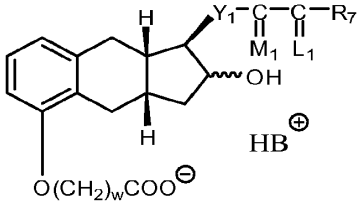
(4) 3-thienyloxymethyl;

M_1 is α-OH:β-R_5 or α-R_5:β-OH or α-OR_1:β-R_5 or α-R_5:β-OR_2, wherein R_5 is hydrogen or methyl, R_2 is an alcohol protecting group, and

L_1 is α-R_3:β-R_4, α-R_4:β-R_3, or a mixture of α-R_3:β-R_4 and α-R_4:β-R_3, wherein R_3 and R_4 are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R_3 and R_4 is fluoro only when the other is hydrogen or fluoro.

(b) hydrolyzing the product of formula III of step (a) with a base,

(c) contacting the product of step (b) with a base B to for a salt of formula I_s,



(I_s)

(d) reacting the salt from step (c) with an acid to form the compound of formula I.

2. The process according to claim 1, wherein the purity of compound of formula I is at least 90.0%, 95%, or 99.0%.

3. The process according to claim 1, further comprising a step of isolating the salt of formula I_s.

4. The process according to claim 1, wherein the alkylating agent is $Cl(CH_2)_wCN$, $Br(CH_2)_wCN$, or $I(CH_2)_wCN$.

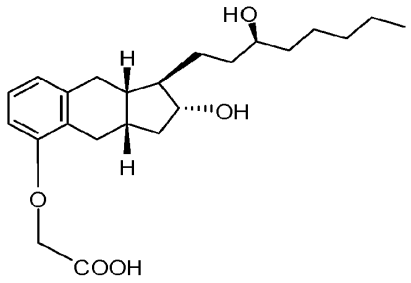
5. The process according to claim 1, wherein the base in step (b) is KOH or NaOH.

6. The process according to claim 1, wherein the base B in step (c) is selected from the group consisting of ammonia, N-methylglucamine, procaine, tromethanine, magnesium, L-lysine, L-arginine, tricthanolamine, and dicthanolamine.

7. The process according to claim 1, wherein the acid in step (d) is HCl or H_2SO_4.

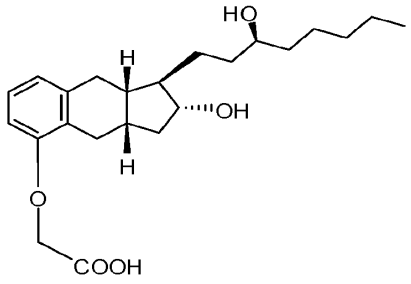
8. The process according to claim 1, wherein Y_1 is $-CH_2CH_2-$; M_1 is α-OH:β-H or α-H:β-OH; $-C(L_1)-R_7$ taken together is $-(CH_2)_4CH_3$; and w is 1.

9. The process according to claim 1, wherein the compound of formula I is a compound of formula IV.



(IV)

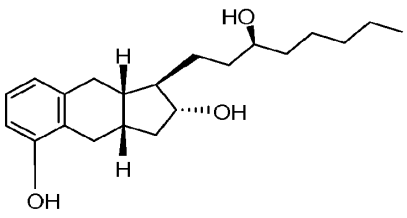
10. A process for the preparation of a compound having formula IV, a hydrate, solvate, prodrug, or pharmaceutically acceptable salt thereof



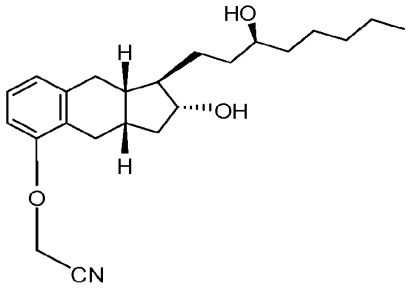
(IV)

comprising

(a) alkylating a compound of formula V with an alkylating agent to produce a compound of formula VI,



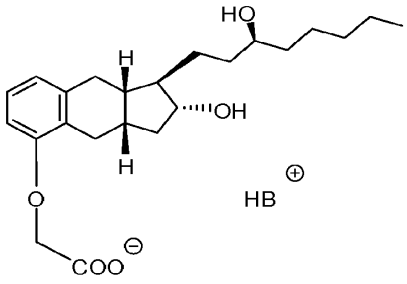
(V)



(VI)

(b) hydrolyzing the product of formula VI of step (a) with a base,

(c) contacting the product of step (b) with a base B to form a salt of formula IV_s, and



(IV_s)

(d) reacting the salt from step of formula IV_s with an acid to form the compound of formula IV.

11. The process according to claim 10, wherein the purity of compound of formula IV is at least 90.0%, 95.0%, 99.0%, or 99.5%.

12. The process according to claim 10, further comprising a step of isolating the salt of formula IV_s.

13. The process according to claim 10, wherein the alkylating agent is $ClCH_2CN$.

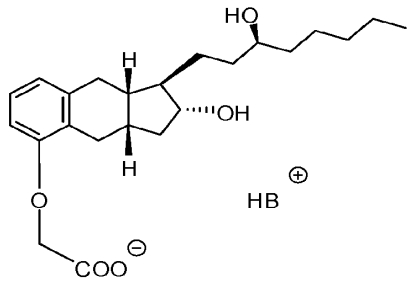
14. The process according to claim 10, wherein the base in step (b) is KOH.

15. The process according to claim 10, wherein the base B in step (c) is selected from a group consisting of ammonia, N-methylglucamine, procaine, tromethanine, magnesium, L-lysine, L-arginine, tricthanolamine, and dicthanolamine.

16. The process according to claim 15, wherein the base B is diethanolamine.

17. The process according to claim 10, wherein the acid in step (d) is HCl.

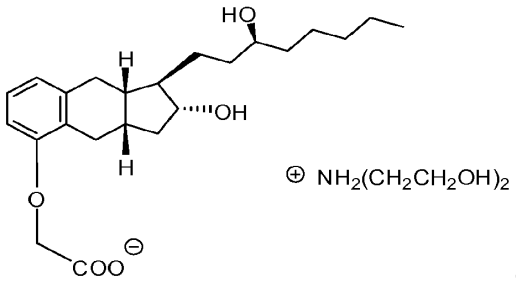
18. A process as claimed in claim 1, wherein the compound produced is a compound of the formula IV_s,



IV_s

wherein the base B is selected from a group consisting of ammonia, N-methylglucamine, procaine, tromethanine, magnesium, L-lysine, L-arginine, tricthanolamine, and diethanolamine.

19. A process as claimed in claim 1, wherein the compound produced is a compound of the following formula:



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ABSTRACT

This present invention relates to an improved process to prepare prostacyclin derivatives. One embodiment provides for an improved process to convert benzindene triol to treprostinil via salts of treprostinil and to purify treprostinil.

Electronic Patent Application Fee Transmittal	
Application Number:	
Filing Date:	
Title of Invention:	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
First Named Inventor/Applicant Name:	Hitesh Batra
Filer:	Paul D. Strain/Karen Walker
Attorney Docket Number:	080618-0570
Filed as Small Entity	

Provisional Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Provisional Application filing fee	2005	1	105	105
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**105**

Electronic Acknowledgement Receipt	
EFS ID:	2600535
Application Number:	61014232
International Application Number:	
Confirmation Number:	1248
Title of Invention:	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
First Named Inventor/Applicant Name:	Hitesh Batra
Customer Number:	22428
Filer:	Paul D. Strain
Filer Authorized By:	
Attorney Docket Number:	080618-0570
Receipt Date:	17-DEC-2007
Filing Date:	
Time Stamp:	16:25:23
Application Type:	Provisional

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Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$105
RAM confirmation Number	1792
Deposit Account	190741
Authorized User	ABEGGLEN,RICK L.
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)	

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	Claims		22	26	
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New Applications Under 35 U.S.C. 111
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National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

US008748657B2

(12) **United States Patent**
Batra et al.

(10) **Patent No.: US 8,748,657 B2**
(45) **Date of Patent: Jun. 10, 2014**

(54) **PROCESS TO PREPARE TREPROSTINIL**

(71) Applicant: **United Therapeutics Corporation**, Silver Spring, MD (US)

(72) Inventors: **Hitesh Batra**, Herndon, VA (US); **Sudersan M. Tuladhar**, Silver Spring, MD (US); **Raju Penmasta**, Herndon, VA (US); **David A. Walsh**, Palmyra, VA (US)

(73) Assignee: **United Therapeutics Corporation**, Silver Spring, MD (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **13/910,583**

(22) Filed: **Jun. 5, 2013**

(65) **Prior Publication Data**

US 2013/0267734 A1 Oct. 10, 2013

Related U.S. Application Data

(63) Continuation of application No. 13/548,446, filed on Jul. 13, 2012, now Pat. No. 8,497,393, which is a continuation of application No. 12/334,731, filed on Dec. 15, 2008, now Pat. No. 8,242,305.

(60) Provisional application No. 61/014,232, filed on Dec. 17, 2007.

(51) **Int. Cl.**

C07C 51/08	(2006.01)
C07C 51/41	(2006.01)
A01N 37/10	(2006.01)
C07C 405/00	(2006.01)
C07C 59/72	(2006.01)
C07C 39/12	(2006.01)
C07C 39/17	(2006.01)

(52) **U.S. Cl.**

CPC ***C07C 51/08*** (2013.01); ***C07C 51/41*** (2013.01); *C07D 59/60* (2013.01); *C07C 59/72* (2013.01); ***C07C 405/0075*** (2013.01); *C07C 39/12* (2013.01); *C07C 39/17* (2013.01); *A01N 37/10* (2013.01)

USPC **562/466**; 514/733

(58) **Field of Classification Search**

CPC C07C 51/08; C07C 51/41; C07C 59/60; C07C 59/72; C07C 405/0075; C07C 39/12; C07C 39/17

USPC 562/466; 514/569

See application file for complete search history.

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Primary Examiner — Yevegeny Valenrod

(74) *Attorney, Agent, or Firm* — Foley & Lardner LLP

(57) **ABSTRACT**

This present invention relates to an improved process to prepare prostacyclin derivatives. One embodiment provides for an improved process to convert benzindene triol to treprostinil via salts of treprostinil and to purify treprostinil.

7 Claims, No Drawings

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PROCESS TO PREPARE TREPROSTINIL

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a Continuation of U.S. application Ser. No. 13/548,446, filed Jul. 13, 2013, which is a Continuation of U.S. application Ser. No. 12/334,731, filed Dec. 15, 2008, which claims priority from U.S. Provisional Patent Application 61/014,232, filed Dec. 17, 2007, the entire contents of which are incorporated herein by reference.

BACKGROUND

The present invention relates to a process for producing prostacyclin derivatives and novel intermediate compounds useful in the process.

Prostacyclin derivatives are useful pharmaceutical compounds possessing activities such as platelet aggregation inhibition, gastric secretion reduction, lesion inhibition, and bronchodilation.

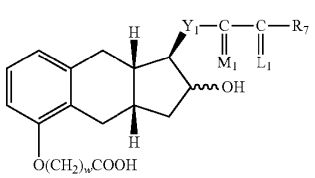
Treprostinil, the active ingredient in Remodulin®, was first described in U.S. Pat. No. 4,306,075. Treprostinil, and other prostacyclin derivatives have been prepared as described in Moriarty, et al in *J. Org. Chem.* 2004, 69, 1890-1902, *Drug of the Future,* 2001, 26(4), 364-374, U.S. Pat. Nos. 6,441,245, 6,528,688, 6,765,117 and 6,809,223. Their teachings are incorporated by reference to show how to practice the embodiments of the present invention.

U.S. Pat. No. 5,153,222 describes use of treprostinil for treatment of pulmonary hypertension. Treprostinil is approved for the intravenous as well as subcutaneous route, the latter avoiding septic events associated with continuous intravenous catheters. U.S. Pat. Nos. 6,521,212 and 6,756,033 describe administration of treprostinil by inhalation for treatment of pulmonary hypertension, peripheral vascular disease and other diseases and conditions. U.S. Pat. No. 6,803,386 discloses administration of treprostinil for treating cancer such as lung, liver, brain, pancreatic, kidney, prostate, breast, colon and head-neck cancer. U.S. patent application publication No. 2005/0165111 discloses treprostinil treatment of ischemic lesions. U.S. Pat. No. 7,199,157 discloses that treprostinil treatment improves kidney functions. U.S. patent application publication No. 2005/0282903 discloses treprostinil treatment of neuropathic foot ulcers. U.S. application Ser. No. 12/028,471 filed Feb. 8, 2008, discloses treprostinil treatment of pulmonary fibrosis. U.S. Pat. No. 6,054,486 discloses treatment of peripheral vascular disease with treprostinil. U.S. patent application Ser. No. 11/873,645 filed Oct. 17, 2007 discloses combination therapies comprising treprostinil. U.S. publication No. 2008/0200449 discloses delivery of treprostinil using a metered dose inhaler. U.S. publication No. 2008/0280986 discloses treatment of interstitial lung disease with treprostinil. U.S. application Ser. No. 12/028,471 filed Feb. 8, 2008 discloses treatment of asthma with treprostinil. U.S. Pat. Nos. 7,417,070, 7,384,978 and U.S. publication Nos. 2007/0078095, 2005/0282901, and 2008/0249167 describe oral formulations of treprostinil and other prostacyclin analogs.

Because Treprostinil, and other prostacyclin derivatives are of great importance from a medicinal point of view, a need exists for an efficient process to synthesize these compounds on a large scale suitable for commercial production.

SUMMARY

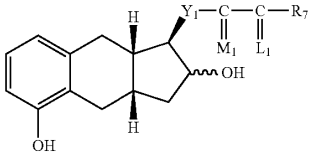
The present invention provides in one embodiment a process for the preparation of a compound of formula I, hydrate, solvate, prodrug, or pharmaceutically acceptable salt thereof.



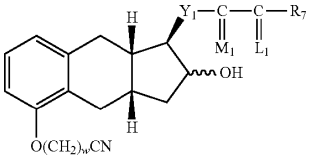
(I)

The process comprises the following steps:

(a) alkylating a compound of structure II with an alkylating agent to produce a compound of formula III,



(II)



(III)

wherein

w=1, 2, or 3;

Y_1 is trans-CH—CH—, cis-CH—CH—, —$CH_2(CH_2)_m$—, or —C≡C—; m is 1, 2, or 3;

R_7 is

(1) —C_pH_{2p}—CH_3, wherein p is an integer from 1 to 5, inclusive,

(2) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3) alkyl, or (C_1-C_3) alkoxy, with the proviso that not more than two substituents are other than alkyl, with the proviso that R_7 is phenoxy or substituted phenoxy, only when R_3 and R_4 are hydrogen or methyl, being the same or different,

(3) phenyl, benzyl, phenylethyl, or phenylpropyl optionally substituted on the aromatic ring by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3)alkyl, or (C_1-C_3) alkoxy, with the proviso that not more than two substituents are other than alkyl,

(4) cis-CH=CH—CH_2—CH_3,

(5) —$(CH_2)_2$—CH(OH)—CH_3, or

(6) —$(CH_2)_3$—CH=$C(CH_3)_2$;

wherein —$C(L_1)$-R_7 taken together is

(1) (C_4-C_7)cycloalkyl optionally substituted by 1 to 3 (C_1-C_5)alkyl;

(2) 2-(2-furyl)ethyl,

(3) 2-(3-thienyl)ethoxy, or

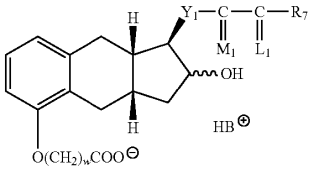
(4) 3-thienyloxymethyl;

M_1 is α-OH:β-R_5 or α-R_5:β-OH or α-OR_1:β-R_5 or α-R_5:β-OR_2, wherein R_5 is hydrogen or methyl, R_2 is an alcohol protecting group, and

L_1 is α-R_3:β-R_4, α-R_4:β-R_3, or a mixture of α-R_3:β-R_4 and α-R_4:β-R_3, wherein R_3 and R_4 are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R_3 and R_4 is fluoro only when the other is hydrogen or fluoro.

(b) hydrolyzing the product of step (a) with a base,

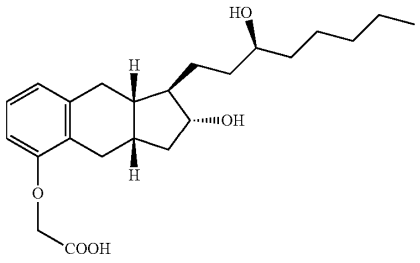
(c) contacting the product of step (b) with a base B to for a salt of formula I_s



(I_s)

(d) reacting the salt from step (c) with an acid to form the compound of formula I.

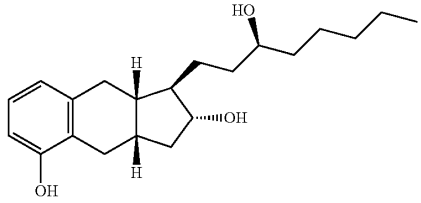
The present invention provides in another embodiment a process for the preparation of a compound of formula IV.



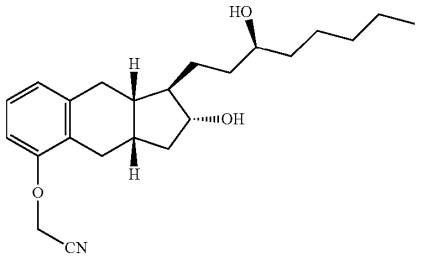
(IV)

The process comprises the following steps:

(a) alkylating a compound of structure V with an alkylating agent to produce a compound of formula VI,



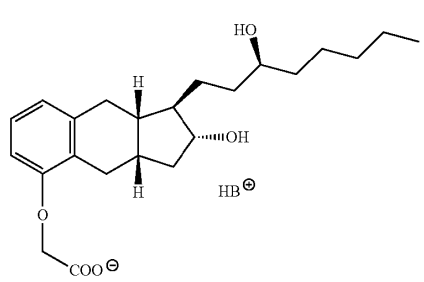
(V)



(VI)

(b) hydrolyzing the product of step (a) with a base,

(c) contacting the product of step (b) with a base B to for a salt of formula IV_s, and



(IV_s)

(d) reacting the salt from step (b) with an acid to form the compound of formula IV.

DETAILED DESCRIPTION

The various terms used, separately and in combinations, in the processes herein described are defined below.

The expression "comprising" means "including but not limited to." Thus, other non-mentioned substances, additives, carriers, or steps may be present. Unless otherwise specified, "a" or "an" means one or more.

C_{1-3}-alkyl is a straight or branched alkyl group containing 1-3 carbon atoms. Exemplary alkyl groups include methyl, ethyl, n-propyl, and isopropyl.

C_{1-3}-alkoxy is a straight or branched alkoxy group containing 1-3 carbon atoms. Exemplary alkoxy groups include methoxy, ethoxy, propoxy, and isopropoxy.

C_{4-7}-cycloalkyl is an optionally substituted monocyclic, bicyclic or tricyclic alkyl group containing between 4-7 carbon atoms. Exemplary cycloalkyl groups include but not limited to cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl.

Combinations of substituents and variables envisioned by this invention are only those that result in the formation of stable compounds. The term "stable", as used herein, refers to compounds which possess stability sufficient to allow manufacture and which maintains the integrity of the compound for a sufficient period of time to be useful for the purposes detailed herein.

As used herein, the term "prodrug" means a derivative of a compound that can hydrolyze, oxidize, or otherwise react under biological conditions (in vitro or in vivo) to provide an active compound. Examples of prodrugs include, but are not limited to, derivatives of a compound that include biohydrolyzable groups such as biohydrolyzable amides, biohydrolyzable esters, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, and biohydrolyzable phosphate analogues (e.g., monophosphate, diphosphate or triphosphate).

As used herein, "hydrate" is a form of a compound wherein water molecules are combined in a certain ratio as an integral part of the structure complex of the compound.

As used herein, "solvate" is a form of a compound where solvent molecules are combined in a certain ratio as an integral part of the structure complex of the compound.

"Pharmaceutically acceptable" means in the present description being useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes being useful for veterinary use as well as human pharmaceutical use.

"Pharmaceutically acceptable salts" mean salts which are pharmaceutically acceptable, as defined above, and which possess the desired pharmacological activity. Such salts

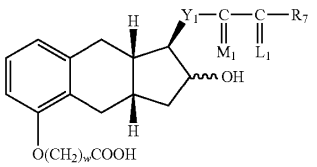
include acid addition salts formed with organic and inorganic acids, such as hydrogen chloride, hydrogen bromide, hydrogen iodide, sulfuric acid, phosphoric acid, acetic acid, glycolic acid, malcic acid, malonic acid, oxalic acid, methanesulfonic acid, trifluoroacetic acid, fumaric acid, succinic acid, tartaric acid, citric acid, benzoic acid, ascorbic acid and the like. Base addition salts may be formed with organic and inorganic bases, such as sodium, ammonia, potassium, calcium, ethanolamine, diethanolamine, N-methylglucamine, choline and the like. Included in the invention are pharmaceutically acceptable salts or compounds of any of the formulae herein.

Depending on its structure, the phrase "pharmaceutically acceptable salt," as used herein, refers to a pharmaceutically acceptable organic or inorganic acid or base salt of a compound. Representative pharmaceutically acceptable salts include, e.g., alkali metal salts, alkali earth salts, ammonium salts, water-soluble and water-insoluble salts, such as the acetate, amsonate (4,4-diaminostilbene-2,2-disulfonate), benzenesulfonate, benzonate, bicarbonate, bisulfate, bitartrate, borate, bromide, butyrate, calcium, calcium edetate, camsylate, carbonate, chloride, citrate, clavulariate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexafluorophosphate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, N-methylglucamine ammonium salt, 3-hydroxy-2-naphthoate, oleate, oxalate, palmitate, pamoate (1,1-methene-bis-2-hydroxy-3-naphthoate, einbonate), pantothenate, phosphate/diphosphate, picrate, polygalacturonate, propionate, p-toluenesulfonate, salicylate, stearate, subacetate, succinate, sulfate, sulfosalicylate, suramate, tannate, tartrate, teoclate, tosylate, triethiodide, and valerate salts.

The present invention provides for a process for producing treprostinil and other prostacyclin derivatives and novel intermediate compounds useful in the process. The process according to the present invention provides advantages on large-scale synthesis over the existing method. For example, the purification by column chromatography is eliminated, thus the required amount of flammable solvents and waste generated are greatly reduced. Furthermore, the salt formation is a much easier operation than column chromatography. Moreover, it was found that the product of the process according to the present invention has higher purity. Therefore the present invention provides for a process that is more economical, safer, faster, greener, easier to operate, and provides higher purity.

One embodiment of the present invention is a process for the preparation of a compound of formula I, or a hydrate, solvate, prodrug, or pharmaceutically acceptable salt thereof.

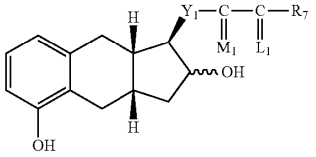
(I)



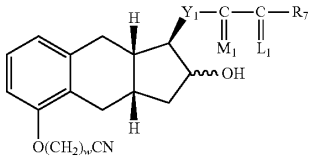
The process comprises the following steps:

(a) alkylating a compound of formula II with an alkylating agent to produce a compound of formula III,

(II)



(III)



wherein

w=1, 2, or 3;

Y_1 is trans-CH=CH—, cis-CH=CH—, —$CH_2(CH_2)_m$—, or —C≡C—; m is 1, 2, or 3;

R_7 is

(1) —C_pH_{2p}—CH_3, wherein p is an integer from 1 to 5, inclusive,

(2) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3) alkyl, or (C_1-C_3) alkoxy, with the proviso that not more than two substituents are other than alkyl, with the proviso that R_7 is phenoxy or substituted phenoxy, only when R_3 and R_4 are hydrogen or methyl, being the same or different,

(3) phenyl, benzyl, phenylethyl, or phenylpropyl optionally substituted on the aromatic ring by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3)alkyl, or (C_1-C_3) alkoxy, with the proviso that not more than two substituents are other than alkyl,

(4) cis-CH=CH—CH_2—CH_3,

(5) —$(CH_2)_2$—CH(OH)—CH_3, or

(6) —$(CH_2)_3$—CH=$C(CH_3)_2$;

wherein —$C(L_1)$-R_7 taken together is

(1) (C_4-C_7)cycloalkyl optionally substituted by 1 to 3 (C_1-C_5)alkyl;

(2) 2-(2-furyl)ethyl,

(3) 2-(3-thienyl)ethoxy, or

(4) 3-thienyloxymethyl;

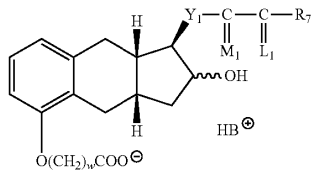
M_1 is α-OH:β-R_5 or α-R_5:β-OH or α-OR_1:β-R_5 or α-R_5:β-OR_2, wherein R_5 is hydrogen or methyl, R_2 is an alcohol protecting group, and

L_1 is α-R_3:β-R_4, α-R_4:β-R_3, or a mixture of α-R_3:β-R_4 and α-R_4:β-R_3, wherein R_3 and R_4 are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R_3 and R_4 is fluoro only when the other is hydrogen or fluoro.

(b) hydrolyzing the product of step (a) with a base,

(c) contacting the product of step (b) with a base B to for a salt of formula I_S.

(I_S)

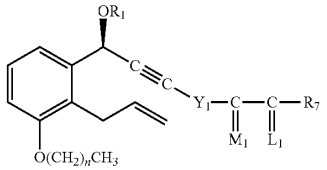


(d) reacting the salt from step (c) with an acid to form the compound of formula I.

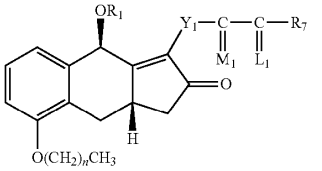
In one embodiment, the compound of formula I is at least 90.0%, 95.0%, 99.0%.

The compound of formula II can be prepared from a compound of formula XI, which is a cyclization product of a compound of formula X as described in U.S. Pat. No. 6,441,245.

(X)



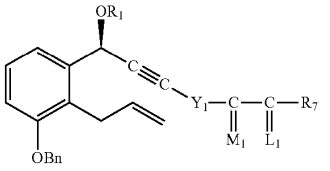
(XI)



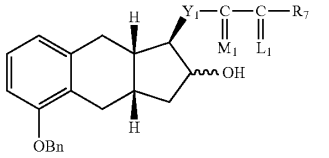
Wherein n is 0, 1, 2, or 3.

The compound of formula II can be prepared alternatively from a compound of formula XIII, which is a cyclization product of a compound of formula XII as described in U.S. Pat. No. 6,700,025.

(XII)

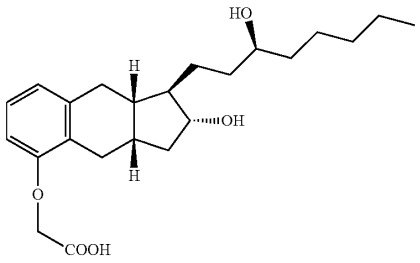


(XIII)



One embodiment of the present invention is a process for the preparation of a compound having formula IV, or a hydrate, solvate, or pharmaceutically acceptable salt thereof.

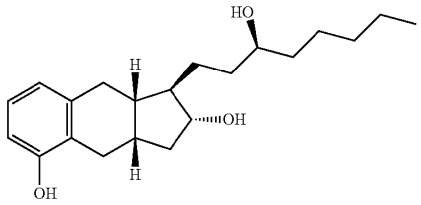
(IV)



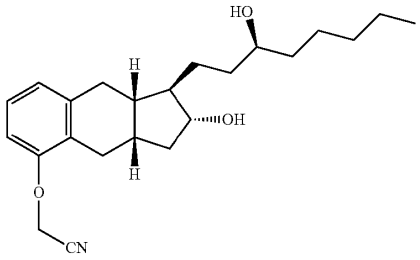
The process comprises

(a) alkylating a compound of structure V with an alkylating agent such as $ClCH_2CN$ to produce a compound of formula VI,

(V)

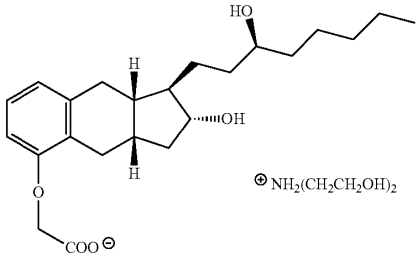


(VI)



(b) hydrolyzing the product of step (a) with a base such as KOH,

(c) contacting the product of step (b) with a base B such as diethanolamine to for a salt of the following structure, and



(d) reacting the salt from step (b) with an acid such as HCl to form the compound of formula IV.

In one embodiment, the purity of compound of formula IV is at least 90.0%, 95.0%, 99.0%, 99.5%.

In one embodiment, the process further comprises a step of isolating the salt of formula IV_s.

In one embodiment, the base B in step (c) may be ammonia, N-methylglucamine, procaine, tromethanine, magnesium, L-lysine, L-arginine, or triethanolamine.

The following abbreviations are used in the description and/or appended claims, and they have the following meanings.

"MW" means molecular weight.

"Eq." means equivalent.

"TLC" means thin layer chromatography.

"HPLC" means high performance liquid chromatography.

"PMA" means phosphomolybdic acid.

"AUC" means area under curve.

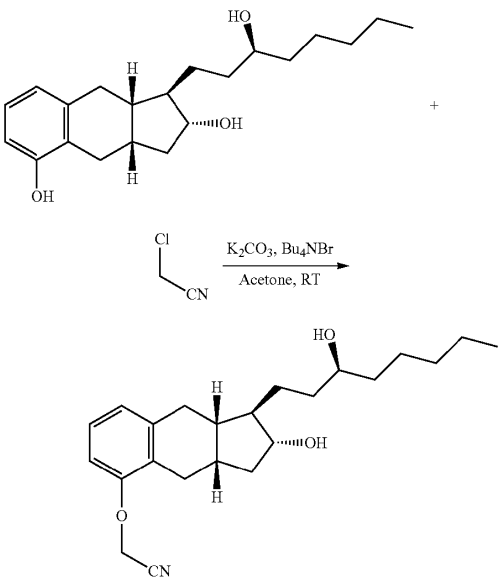
In view of the foregoing considerations, and specific examples below, those who are skilled in the art will appreciate that how to select necessary reagents and solvents in practicing the present invention.

The invention will now be described in reference to the following Examples. These examples are not to be regarded as limiting the scope of the present invention, but shall only serve in an illustrative manner.

EXAMPLES

Example 1

Alkylation of Benzindene Triol

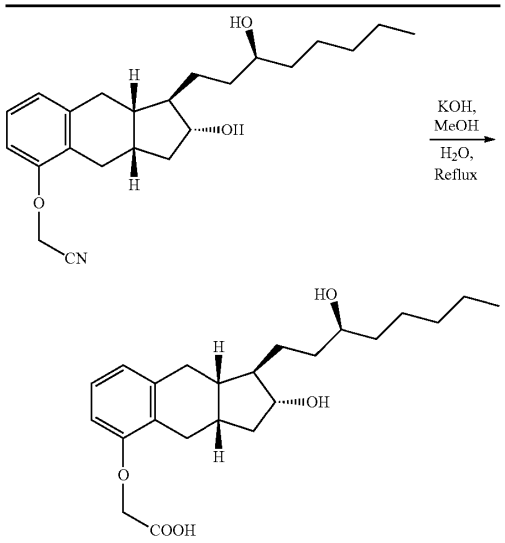


Name	MW	Amount	Mol.	Eq.
Benzindene Triol	332.48	1250 g	3.76	1.00
K_2CO_3 (powder)	138.20	1296 g	9.38	2.50
$ClCH_2CN$	75.50	567 g	7.51	2.0
Bu_4NBr	322.37	36 g	0.11	0.03
Acetone	—	29 L	—	—
Celite ® 545	—	115 g	—	—

A 50-L, three-neck, round-bottom flask equipped with a mechanical stirrer and a thermocouple was charged with benzindene triol (1250 g), acetone (19 L) and K_2CO_3 (powdered) (1296 g), chloroacetonitrile (567 g), tetrabutylammonium bromide (36 g). The reaction mixture was stirred vigorously at room temperature (23±2° C.) for 16-72 h. The progress of the reaction was monitored by TLC. (methanol/CH_2Cl_2; 1:9 and developed by 10% ethanolic solution of PMA). After completion of reaction, the reaction mixture was filtered with/without Celite pad. The filter cake was washed with acetone (10 L). The filtrate was concentrated in vacuo at 50-55° C. to give a light-brown, viscous liquid benzindene nitrile. The crude benzindene nitrile was used as such in the next step without further purification.

Example 2

Hydrolysis of Benzindene Nitrile



Name	MW	Amount	Mol.	Eq.
Benzindene Nitrile	371.52	1397 g*	3.76	1.0
KOH	56.11	844 g	15.04	4.0
Methanol	—	12 L	—	—
Water	—	4.25 L	—	—

*Note:
This weight is based on 100% yield from the previous step. This is not isolated yield.

A 50-L, cylindrical reactor equipped with a heating/cooling system, a mechanical stirrer, a condenser, and a thermocouple was charged with a solution of benzindene nitrile in methanol (12 L) and a solution of KOH (844 g of KOH dissolved in 4.25 L of water). The reaction mixture was stirred and heated to reflux (temperature 72.2° C.). The progress of the reaction was monitored by TLC (for TLC purpose, 1-2 mL of reaction mixture was acidified with 3M HCl to pH 1-2 and extracted with ethyl acetate. The ethyl acetate extract was used for TLC; Eluent: methanol/CH_2Cl_2; 1:9, and developed by 10% ethanolic solution of PMA). After completion of the reaction (~5 h), the reaction mixture was cooled to −5 to 10° C. and quenched with a solution of hydrochloric acid (3M, 3.1 L) while stirring. The reaction mixture was concentrated in vacuo at 50-55° C. to obtain approximately 12-14 L of condensate. The condensate was discarded.

The aqueous layer was diluted with water (7-8 L) and extracted with ethyl acetate (2×6 L) to remove impurities soluble in ethyl acetate. To aqueous layer, ethyl acetate (22 L) was added and the pH of reaction mixture was adjusted to 1-2 by adding 3M HCl (1.7 L) with stirring. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2×11 L). The combined organic layers were washed with water (3×10 L) and followed by washing with a solution

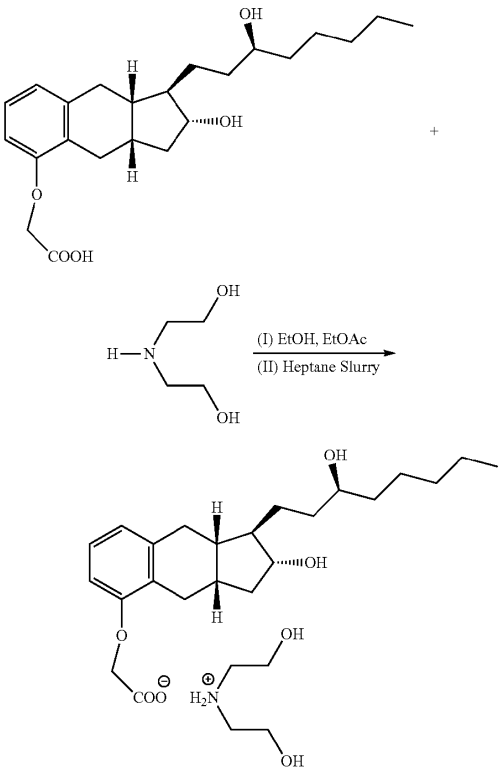
of $NaHCO_3$ (30 g of $NaHCO_3$ dissolved in 12 L of water). The organic layer was further washed with saturated solution of NaCl (3372 g of NaCl dissolved in water (12 L)) and dried over anhydrous Na_2SO_4 (950-1000 g), once filtered.

The filtrate was transferred into a 72-L reactor equipped with mechanical stirrer, a condenser, and a thermocouple. To the solution of treprostinil in reactor was added activated carbon (110-130 g). The suspension was heated to reflux (temperature 68-70° C.) for at least one hour. For filtration, a pad of Celite° 545 (300-600 g) was prepared in sintered glass funnel using ethyl acetate. The hot suspension was filtered through the pad of Celite® 545. The Celite° 545 was washed with ethyl acetate until no compound was seen on TLC of the washings.

The filtrate (pale-yellow) was reduced to volume of 35-40 L by evaporation in vacuo at 50-55° C. for direct use in next step.

Example 3

Conversion of Treprostinil to Treprostinil Diethanolamine Salt (1:1)



Name	MW	Amount	Mol	Eq
Treprostinil	390.52	1464 g*	3.75	1.0
Diethanolamine	105.14	435 g	4.14	1.1
Ethanol	—	5.1 L	—	—
Ethyl acetate	—	35 L**	—	—
Treprostinil Diethanolamine Salt (seed)	—	12 g	—	—

*Note:
This weight is based on 100% yield from benzindene triol. It is not isolated yield. The treprostinil was carried from previous step in ethyl acetate solution and used as such for this step.
**Note:
The total volume of ethyl acetate should be in range of 35-36 L (it should be 7 times the volume of ethanol used). Approximately 35 L of ethyl acetate was carried over from previous step and additional 1.0 L of ethyl acetate was used for rinsing the flask.

A 50-L, cylindrical reactor equipped with a heating/cooling system, a mechanical stirrer, a condenser, and a thermocouple was charged with a solution of treprostinil in ethyl acetate (35-40 L from the previous step), anhydrous ethanol (5.1 L) and diethanolamine (435 g). While stirring, the reaction mixture was heated to 60-75° C., for 0.5-1.0 h to obtain a clear solution. The clear solution was cooled to 55±5° C. At this temperature, the seed of polymorph B of treprostinil diethanolamine salt (~12 g) was added to the clear solution. The suspension of polymorph B was stirred at this temperature for 1 h. The suspension was cooled to 20±2° C. overnight (over a period of 16-24 h). The treprostinil diethanolamine salt was collected by filtration using Aurora filter equipped with filter cloth, and the solid was washed with ethyl acetate (2×8 L). The treprostinil diethanolamine salt was transferred to a HDPE/glass container for air-drying in hood, followed by drying in a vacuum oven at 50±5° C. under high vacuum.

At this stage, if melting point of the treprostinil diethanolamine salt is more than 104° C., it was considered polymorph B. There is no need of recrystallization. If it is less than 104° C., it is recrystallized in EtOH-EtOAc to increase the melting point.

Data on Treprostinil Diethanolamine Salt (1:1)

Batch No.	Wt. of Benzindene Triol (g)	Wt. of Treprostinil Diethanolamine Salt (1:1) (g)	Yield (%)	Melting point (° C.)
1	1250	1640	88.00	104.3-106.3
2	1250	1528	82.00*	105.5-107.2
3	1250	1499	80.42**	104.7-106.6
4	1236	1572	85.34	105-108

*Note: In this batch, approximately 1200 mL of ethyl acetate solution of treprostinil before carbon treatment was removed for R&D carbon treatment experiments.
**Note: This batch was recrystallized, for this reason yield was lower.

Example 4

Heptane Slurry of Treprostinil Diethanolamine Salt (1:1)

Name	Batch No.	Amount	Ratio
Treprostinil Diethanolamine Salt	1	3168 g	1
Heptane	—	37.5 L	12
Treprostinil Diethanolamine Salt	2	3071 g	1
Heptane	—	36.0 L	12

A 50-L, cylindrical reactor equipped with a heating/cooling system, a mechanical stirrer, a condenser, and a thermocouple was charged with slurry of treprostinil diethanolamine salt in heptane (35-40 L). The suspension was heated to

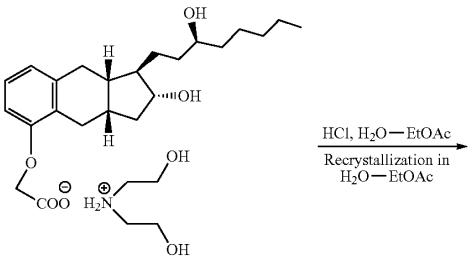
70-80° C. for 16-24 h. The suspension was cooled to 22±2° C. over a period of 1-2 h. The salt was collected by filtration using Aurora filter. The cake was washed with heptane (15-30 L) and the material was dried in Aurora filter for 1 h. The salt was transferred to trays for air-drying overnight in hood until a constant weight of treprostinil diethanolamine salt was obtained. The material was dried in oven under high vacuum for 2-4 h at 50-55° C.

Analytical data on and Treprostinil Diethanolamine Salt (1:1)

Test	Batch 1	Batch 2
IR	Conforms	Conforms
Residue on Ignition (ROI)	<0.1% w/w	<0.1% w/w
Water content	0.1% w/w	0.0% w/w
Melting point	105.0-106.5° C.	104.5-105.5° C.
Specific rotation $[\alpha]^{25}_{589}$	+34.6°	+35°
Organic volatile impurities		
Ethanol	Not detected	Not detected
Ethyl acetate	Not detected	<0.05% w/w
Heptane	<0.05% w/w	<0.05% w/w
HPLC (Assay)	100.4%	99.8%
Diethanolamine	Positive	Positive

Example 5

Conversion of Treprostinil Diethanolamine Salt (1:1) to Treprostinil



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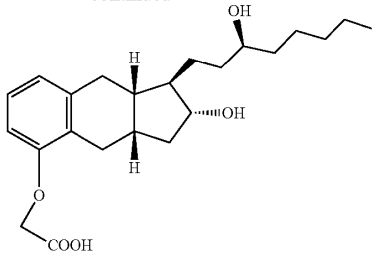

A 250-mL, round-bottom flask equipped with magnetic stirrer was charged with treprostinil diethanolamine salt (4 g) and water (40 mL). The mixture was stirred to obtain a clear solution. To the clear solution, ethyl acetate (100 mL) was added. While stirring, 3M HCl (3.2 mL) was added slowly until pH ~1 was attained. The mixture was stirred for 10 minutes and organic layer was separated. The aqueous layer was extracted with ethyl acetate (2×100 mL). The combined organic layers was washed with water (2×100 mL), brine (1×50 mL) and dried over anhydrous Na_2SO_4. The ethyl acetate solution of treprostinil was filtered and the filtrate was concentrated under vacuum at 50° C. to give off-white solid. The crude treprostinil was recrystallized from 50% ethanol in water (70 mL). The pure treprostinil was collected in a Buchner funnel by filtration and cake was washed with cold 20% ethanolic solution in water. The cake of treprostinil was air-dried overnight and further dried in a vacuum oven at 50° C. under high vacuum to afford 2.9 g of treprostinil (Yield 91.4%, purity (HPLC, AUC, 99.8%).

Analytical data on Treprostinil from Treprostinil Diethanolamine Salt (1:1) to Treprostinil

Batch No.	Yield	Purity (HPLC)
1	91.0%	99.8% (AUC)
2	92.0%	99.9% (AUC)
3	93.1%	99.7% (AUC)
4	93.3%	99.7% (AUC)
5	99.0%	99.8% (AUC)
6	94.6%	99.8% (AUC)

Example 6

Comparison of the Former Process and a Working Example of the Process According to the Present Invention

Step No.	Steps	Former Process (Batch size: 500 g)	Working example of the Process according to the present invention (Batch size: 5 kg)
		Nitrile	
1	Triol weight	500 g	5,000 g
2	Acetone	20 L (1:40 wt/wt)	75 L (1:15 wt/wt)
3	Potassium carbonate	1,300 g (6.4 eq)	5,200 g (2.5 eq)
4	Chloroacetonitrile	470 g (4.2 eq)	2,270 g (2 eq)
5	Tetrabutylammonium bromide	42 g (0.08 eq)	145 g (0.03 eq)
6	Reactor size	72-Liter	50-gallon
7	Reflux time	8 hours	No heating,

-continued

Step No.	Steps	Former Process (Batch size: 500 g)	Working example of the Process according to the present invention (Batch size: 5 kg)
			Room temperature (r.t.) 45 h
8	Hexanes addition before filtration	Yes (10 L)	No
9	Filter	Celite	Celite
10	Washing	Ethyl acetate (10 L)	Acetone (50 L)
11	Evaporation	Yes	Yes
12	Purification	Silica gel column Dichloromethane: 0.5 L Ethyl acetate: 45 L Hexane: 60 L	No column
13	Evaporation after column	Yes	No
14	Yield of nitrite	109-112%	Not checked
		Treprostinil (intermediate)	
15	Methanol	7.6 L (50-L reactor)	50 L (50-gal reactor)
16	Potassium hydroxide	650 g (8 eq)	3,375 g (4 eq)
17	Water	2.2 L	17 L
18	% of KOH	30%	20%
19	Reflux time	3-3.5 h	4-5 h
20	Acid used	2.6 L (3M)	12 L (3M)
21	Removal of impurities	3 × 3 L Ethyl acetate	2 × 20 L Ethyl acetate
22	Acidification	0.7 L	6.5 L
23	Ethyl acetate extraction	5 × 17 L = 35 L	90 + 45 + 45 = 180 L
24	Water washing	2 × 8 L	3 × 40 L
25	Sodium bicarbonate washing	Not done	120 g in 30 L water + 15 L brine
26	Brine washing	Not done	1 × 40 L
27	Sodium sulfate	1 kg	Not done
28	Sodium sulfate filtration	Before charcoal, 6 L ethyl acetate	N/A
29	Charcoal	170 g, reflux for 1.5 h, filter over Celite, 11 L ethyl acetate	Pass hot solution (75° C.) through charcoal cartridge and clean filter, 70 L ethyl acetate
30	Evaporation	Yes, to get solid intermediate treprostinil	Yes, adjust to 150 L solution
		Treprostinil Diethanolamine Salt	
31	Salt formation	Not done	1,744 g diethanolamine, 20 L ethanol at 60-75° C.
32	Cooling	N/A	To 20° C. over weekend; add 40 L ethyl acetate; cooled to 10° C.
33	Filtration	N/A	Wash with 70 L ethyl acetate
34	Drying	N/A	Air-dried to constant wt., 2 days
		Treprostinil (from 1.5 kg Treprostinil diethanolamine salt)	
35	Hydrolysis	N/A	15 L water + 25 L ethyl acetate + HCl
36	Extraction	N/A	2 × 10 L ethyl acetate
37	Water wash	N/A	3 × 10 L
38	Brine wash	N/A	1 × 10 L
39	Sodium sulfate	N/A	1 kg, stir
40	Filter	N/A	Wash with 6 L ethyl acetate
41	Evaporation	N/A	To get solid, intermediate Treprostinil
42	Crude drying on tray	1 or 3 days	Same
43	Ethanol & water for cryst.	5.1 L + 5.1 L	10.2 L + 10.2 L (same %)
44	Crystallization in	20-L rotavap flask	50-L jacketed reactor
45	Temperature of crystallization	2 h r.t., fridge −0° C. 24 h	50° C. to 0° C. ramp, 0° C. overnight
46	Filtration	Buchner funnel	Aurora filter
47	Washing	20% (10 L) cooled ethanol-water	20% (20 L) cooled ethanol-water
48	Drying before oven	Buchner funnel (20 h) Tray (no)	Aurora filter (2.5 h) Tray (4 days)
49	Oven drying	15 hours, 55° C.	6-15 hours, 55° C.

-continued

Step No.	Steps	Former Process (Batch size: 500 g)	Working example of the Process according to the present invention (Batch size: 5 kg)
50	Vacuum	<−0.095 mPA	<5 Torr
51	UT-15 yield weight	~535 g	~1,100 g
52	% yield from triol)	~91%	~89%
53	Purity	~99.0%	99.9%

The quality of treprostinil produced according to this invention is excellent. The purification of benzindene nitrile by column chromatography is eliminated. The impurities carried over from intermediate steps (i.e. alkylation of triol and hydrolysis of benzindene nitrile) are removed during the carbon treatment and the salt formation step. Additional advantages of this process are: (a) crude treprostinil salts can be stored as raw material at ambient temperature and can be converted to treprostinil by simple acidification with diluted hydrochloric acid, and (b) the treprostinil salts can be synthesized from the solution of treprostinil without isolation. This process provides better quality of final product as well as saves significant amount of solvents and manpower in purification of intermediates.

Although the foregoing refers to particular preferred embodiments, it will be understood that the present invention is not so limited. It will occur to those of ordinary skill in the art that various modifications may be made to the disclosed embodiments and that such modifications are intended to be within the scope of the present invention.

All of the publications, patent applications and patents cited in this specification are incorporated herein by reference in their entirety.

What is claimed is:

1. A process for producing a pharmaceutical composition comprising treprostinil, comprising providing a starting batch of treprostinil having one or more impurities resulting from prior alkylation and hydrolysis steps, forming a salt of treprostinil by combining the starting batch and a base, isolating the treprostinil salt, and preparing a pharmaceutical solution from the isolated salt comprising treprostinil or a pharmaceutically acceptable salt thereof from the isolated treprostinil salt, whereby a level of one or more impurities found in the starting batch of treprostinil is lower in the pharmaceutical composition, and wherein said alkylation is alkylation of benzindene triol.

2. The process of claim **1**, wherein the salt is isolated in crystalline form.

3. The process of claim **2**, wherein the isolated salt is at least 99.8% pure.

4. The process of claim **1**, wherein the base is selected from the group consisting of sodium, ammonia, potassium, calcium, ethanolamine, diethanolamine, N-methylglucamine, and choline.

5. The process of claim **4**, wherein the base is diethanolamine.

6. The process of claim **1**, wherein the base is combined with treprostinil that has not been previously isolated.

7. The process of claim **1**, wherein the isolated salt is stored at ambient temperature.

* * * * *

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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/910,583	06/10/2014	8748657	080618-1255	7133

22428 7590 05/21/2014

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ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

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APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
13/910,583	06/05/2013	1672	1900	080618-1255	14	1

CONFIRMATION NO. 7133

CORRECTED FILING RECEIPT

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Date Mailed: 05/13/2014

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

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Power of Attorney: The patent practitioners associated with Customer Number 22428

Domestic Priority data as claimed by applicant

This application is a CON of 13/548,446 07/13/2012 PAT 8497393
which is a CON of 12/334,731 12/15/2008 PAT 8242305
which claims benefit of 61/014,232 12/17/2007

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

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Projected Publication Date: Not Applicable

Non-Publication Request: No

Early Publication Request: No

Title

PROCESS TO PREPARE TREPROSTINIL

Preliminary Class

562

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

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This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/910,583	06/05/2013	Hitesh Batra	080618-1255	7133

22428 7590 05/12/2014
FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

EXAMINER	
VALENROD, YEVGENY	
ART UNIT	PAPER NUMBER
1672	
MAIL DATE	DELIVERY MODE
05/12/2014	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

supplemental ***Notice of Allowability***	**Application No.** 13/910,583	**Applicant(s)** BATRA ET AL.	
	Examiner YEVGENY VALENROD	**Art Unit** 1672	**AIA (First Inventor to File) Status** No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *RUSH dated 4/30/14*.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on_____.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are *1-7*. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov .
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:
   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
4. ☒ Interview Summary (PTO-413), Paper No./Mail Date *5/8/14* .
5. ☒ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/YEVGENY VALENROD/
Primary Examiner, Art Unit 1672

The present application is being examined under the pre-AIA first to invent provisions.

EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Alexey V. Saprigin on 5/8/14.

The application has been amended as follows:

The title of the application has been amended to read: "Process to Prepare Treprostinil".

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yevgeny Valenrod whose telephone number is 571-272-9049. The examiner can normally be reached on 8:30am-5:00pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/YEVGENY VALENROD/
Primary Examiner, Art Unit 1672

Examiner-Initiated Interview Summary	Application No. 13/910,583	Applicant(s) BATRA ET AL.	
	Examiner YEVGENY VALENROD	Art Unit 1672	

All participants (applicant, applicant's representative, PTO personnel):

(1) *YEVGENY VALENROD*. (3)_____.

(2) *Alexey V Saprigin*. (4)_____.

Date of Interview: *08 May 2014*.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☒ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☐102 ☐103 ☒Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: *none*.

Identification of prior art discussed: *none*.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

A proposed amendment to the title of the application was discussed and agreed upon .

Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/YEVGENY VALENROD/ Primary Examiner, Art Unit 1672	

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

22428 7590 04/15/2014
FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/910,583	06/05/2013	Hitesh Batra	080618-1255	7133

TITLE OF INVENTION: PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	07/15/2014

EXAMINER	ART UNIT	CLASS-SUBCLASS
VALENROD, YEVGENY	1672	562-466000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.
1 Foley & Lardner LLP
2
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: United Therapeutics Corporation
(B) RESIDENCE: (CITY and STATE OR COUNTRY): Silver Spring, MD

Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:
☒ Issue Fee
☐ Publication Fee (No small entity discount permitted)
☐ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
☐ A check is enclosed.
☒ Payment by credit card. Form PTO-2038 is attached.
☒ The Director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number 19-0741 (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
☐ Applicant certifying micro entity status. See 37 CFR 1.29
NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
☐ Applicant asserting small entity status. See 37 CFR 1.27
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
☐ Applicant changing to regular undiscounted fee status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature /Alexey Saprigin/ For Stephen B. Maebius
Typed or printed name Stephen B. Maebius
Date 4/21/2014
Registration No. 35,264 /Reg#56,439

PTOL-85 Part B (10-13) Approved for use through 10/31/2013. OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Electronic Patent Application Fee Transmittal	
Application Number:	13910583
Filing Date:	05-Jun-2013
Title of Invention:	PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
First Named Inventor/Applicant Name:	Hitesh Batra
Filer:	Alexey V. Saprigin/Karen Walker
Attorney Docket Number:	080618-1255
Filed as Large Entity	

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Utility Appl Issue Fee	1501	1	960	960
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
		Total in USD ($)		**960**

Electronic Acknowledgement Receipt

EFS ID:	18815666
Application Number:	13910583
International Application Number:	
Confirmation Number:	7133
Title of Invention:	PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
First Named Inventor/Applicant Name:	Hitesh Batra
Customer Number:	22428
Filer:	Alexey V. Saprigin/Karen Walker
Filer Authorized By:	Alexey V. Saprigin
Attorney Docket Number:	080618-1255
Receipt Date:	21-APR-2014
Filing Date:	05-JUN-2013
Time Stamp:	15:59:31
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$960
RAM confirmation Number	2370
Deposit Account	
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

1	Issue Fee Payment (PTO-85B)	IFTM.pdf	92338 f48df2630e8b6713d595c50d608526aa86588a2d	no	1
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30694 91800765ad9b97b87ae47199e49ab359bbb1e3cd	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	123032		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

22428 7590 04/15/2014

FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

EXAMINER
VALENROD, YEVGENY

ART UNIT	PAPER NUMBER
1672	

DATE MAILED: 04/15/2014

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/910,583	06/05/2013	Hitesh Batra	080618-1255	7133

TITLE OF INVENTION: PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	07/15/2014

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

22428 7590 04/15/2014
FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/910,583	06/05/2013	Hitesh Batra	080618-1255	7133

TITLE OF INVENTION: PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	07/15/2014

EXAMINER	ART UNIT	CLASS-SUBCLASS
VALENROD, YEVGENY	1672	562-466000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
- ❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.
1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:
- ❑ Issue Fee
- ❑ Publication Fee (No small entity discount permitted)
- ❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): (**Please first reapply any previously paid issue fee shown above**)
- ❑ A check is enclosed.
- ❑ Payment by credit card. Form PTO-2038 is attached.
- ❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
- ❑ Applicant certifying micro entity status. See 37 CFR 1.29 — NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
- ❑ Applicant asserting small entity status. See 37 CFR 1.27 — NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
- ❑ Applicant changing to regular undiscounted fee status. — NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/910,583	06/05/2013	Hitesh Batra	080618-1255	7133

22428 7590 04/15/2014

FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

EXAMINER	
VALENROD, YEVGENY	
ART UNIT	PAPER NUMBER
1672	

DATE MAILED: 04/15/2014

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 0 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 0 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Examiner-Initiated Interview Summary	Application No.	Applicant(s)	
	13/910,583	BATRA ET AL.	
	Examiner	Art Unit	
	YEVGENY VALENROD	1672	

All participants (applicant, applicant's representative, PTO personnel):

(1) *YEVGENY VALENROD*. (3)_____.

(2) *Alexey V. Saprigin*. (4)_____.

Date of Interview: *01 April 2014*.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☒ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☐102 ☐103 ☒Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: *8-14*.

Identification of prior art discussed: *none*.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

A proposed Examiner's Amendment to cancel claims 8-14 was discussed and agreed upon. .

Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/YEVGENY VALENROD/ Primary Examiner, Art Unit 1672	

Notice of Allowability	Application No. 13/910,583	Applicant(s) BATRA ET AL.	
	Examiner YEVGENY VALENROD	Art Unit 1672	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *interview held 4/1/14*.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on_____.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are *1-7*. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov .
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:
   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
4. ☒ Interview Summary (PTO-413), Paper No./Mail Date *4/2/14* .
5. ☒ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/YEVGENY VALENROD/
Primary Examiner, Art Unit 1672

The present application is being examined under the pre-AIA first to invent provisions.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/17/14 has been entered.

EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Alexey V. Saprigin on 4/1/14.

The application has been amended as follows:

In the claims:

Claims 8-14 have been canceled.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yevgeny Valenrod whose telephone number is 571-272-9049. The examiner can normally be reached on 8:30am-5:00pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/YEVGENY VALENROD/
Primary Examiner, Art Unit 1672

Examiner-Initiated Interview Summary	Application No.	Applicant(s)	
	13/910,583	BATRA ET AL.	
	Examiner	Art Unit	
	YEVGENY VALENROD	1672	

All participants (applicant, applicant's representative, PTO personnel):

(1) *YEVGENY VALENROD*. (3)_____.

(2) *Alexey V. Saprigin*. (4)_____.

Date of Interview: *01 April 2014*.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☒ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☐102 ☐103 ☒Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: *8-14*.

Identification of prior art discussed: *none*.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

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Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/YEVGENY VALENROD/ Primary Examiner, Art Unit 1672	

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	13	((HITESH) near2 (BATRA)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2014/04/02 15:28
L2	11	((SUDERSAN) near2 (TULADHAR)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2014/04/02 15:28
L3	23	((RAJU) near2 (PENMASTA)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2014/04/02 15:28
L4	219	((DAVID) near2 (WALSH)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2014/04/02 15:28
L5	218	L1 or L2 or L3 or L4	US-PGPUB; USPAT	OR	OFF	2014/04/02 15:28
L6	12	L5 and treprostinil	US-PGPUB; USPAT	OR	OFF	2014/04/02 15:28
L7	845	treprostinil	US-PGPUB; USPAT	OR	OFF	2014/04/02 15:28
L8	74	L7 same diethanolamine	US-PGPUB; USPAT	OR	OFF	2014/04/02 15:28
L9	0	L8 same (crystal or crystallized)	US-PGPUB; USPAT	OR	OFF	2014/04/02 15:28
L10	10	L8 same polymorph	US-PGPUB; USPAT	OR	OFF	2014/04/02 15:28
L11	829	(562/466).CCLS.	US-PGPUB; USPAT; USOCR	OR	OFF	2014/04/02 15:28
L12	20	L7 and L11	US-PGPUB; USPAT	OR	OFF	2014/04/02 15:28
L13	14	L12 and diethanolamine	US-PGPUB; USPAT	OR	OFF	2014/04/02 15:28
L14	1350	(514/569).CCLS.	US-PGPUB; USPAT; USOCR	OR	OFF	2014/04/02 15:29
L17	516	c07c51/08.cpc.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2014/04/02 15:30

EAST Search History (Prior Art)

L18	352	c07c51/41.cpc.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2014/04/02 15:30
L19	115	c07c59/60.cpc.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2014/04/02 15:30
L20	514	c07c59/72.cpc.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2014/04/02 15:30
L21	14	c07c405/0075.cpc.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2014/04/02 15:30
L22	148	c07c39/12.cpc.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2014/04/02 15:31
L23	868	c07c39/17.cpc.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2014/04/02 15:31

EAST Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L15	2	(514/569).CCLS.	UPAD	OR	OFF	2014/04/02 15:29
L16	0	(562/466).CCLS.	UPAD	OR	OFF	2014/04/02 15:29

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. (Currently Amended) ~~In a~~ A process for producing a pharmaceutical composition comprising treprostinil, ~~the improvement~~ comprising providing ~~forming a salt of treprostinil by combining~~ a starting batch of treprostinil having one or more impurities resulting from prior alkylation and hydrolysis steps, forming a salt of treprostinil by combining the starting batch and a base, isolating the treprostinil salt, and preparing a pharmaceutical ~~composition~~ solution from the isolated salt comprising treprostinil or a pharmaceutically acceptable salt thereof from the isolated treprostinil salt, whereby a level of one or more impurities found in the starting batch of treprostinil is lower in the pharmaceutical composition, and wherein said alkylation is alkylation of benzindene triol.

2. (original) The process of claim 1, wherein the salt is isolated in crystalline form.

3. (original) The process of claim 2, wherein the isolated salt is at least 99.8% pure.

4. (original) The process of claim 1, wherein the base is selected from the group consisting of sodium, ammonia, potassium, calcium, ethanolamine, diethanolamine, N-methylglucamine, and choline.

5. (original) The process of claim 4, wherein the base is diethanolamine.

6. (original) The process of claim 1, wherein the base is combined with treprostinil that has not been previously isolated.

7. (original) The process of claim 1, wherein the isolated salt is stored at ambient temperature.

8. (currently amended) A pharmaceutical ~~composition~~ solution prepared by the process of claim 1.

9. (currently amended) A pharmaceutical ~~composition~~ solution prepared by the process of claim 2.

10. (currently amended) A pharmaceutical ~~composition~~ solution prepared by the process of claim 3.

11. (currently amended) A pharmaceutical ~~composition~~ solution prepared by the process of claim 4.

12. (currently amended) A pharmaceutical ~~composition~~ solution prepared by the process of claim 5.

13. (currently amended) A pharmaceutical ~~composition~~ solution prepared by the process of claim 6.

14. (currently amended) A pharmaceutical ~~composition~~ solution prepared by the process of claim 7.

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13910583	BATRA ET AL.
	Examiner	**Art Unit**
	YEVEGENY VALENROD	1621

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	07/17/2013	08/14/2013	04/02/2014						
	1	✓	✓	=						
	2	✓	✓	=						
	3	✓	✓	=						
	4	✓	✓	=						
	5	✓	✓	=						
	6	✓	✓	=						
	7	✓	✓	=						
	8	✓	✓	-						
	9	✓	✓	-						
	10	✓	✓	-						
	11	✓	✓	-						
	12	✓	✓	-						
	13	✓	✓	-						
	14	✓	✓	-						

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13910583	BATRA ET AL.
	Examiner	Art Unit
	YEVEGENY VALENROD	1672

CPC- SEARCHED		
Symbol	Date	Examiner
c07c 51/08; 51/41; 59/60; 59/72; 405/0075; 39/12; 39/17	4/2/2014	YV

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
562	466	4/2/2014	YV
514	569	4/2/2014	YV

SEARCH NOTES		
Search Notes	Date	Examiner
EAST search	4/2/2014	YV
Inventor search	4/2/2014	YV

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
562	466	4/2/2014	YV
514	569	4/2/2014	YV

	/YEVEGENY VALENROD/ Primary Examiner.Art Unit 1672

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13910583	BATRA ET AL.
	Examiner	**Art Unit**
	YEVEGENY VALENROD	1672

CPC							
Symbol						**Type**	**Version**
C07C		51	/	08		F	20130101
C07C		51	/	41		I	20130101
C07C		59	/	60		A	20130101
C07C		59	/	72		A	20130101
C07C		405	/	0075		I	20130101
C07C		39	/	12		A	20130101
C07C		39	/	17		A	20130101
A01N		37	/	10		A	20130101
			/				
			/				
			/				
			/				
			/				
			/				
			/				

CPC Combination Sets							
Symbol					**Type**	**Set**	**Ranking**	**Version**
			/					
			/					

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	7	
/YEVEGENY VALENROD/ Primary Examiner.Art Unit 1672	04/02/2014	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

U.S. Patent and Trademark Office — Part of Paper No. 20140402

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13910583	BATRA ET AL.
	Examiner	**Art Unit**
	YEVEGENY VALENROD	1672

US ORIGINAL CLASSIFICATION		INTERNATIONAL CLASSIFICATION										
CLASS	SUBCLASS	CLAIMED					NON-CLAIMED					
562	466	C	0	7	C	51 / 08 (2006.01.01)						
CROSS REFERENCE(S)		C	0	7	C	51 / 41 (2006.01.01)						
		A	0	1	N	37 / 10 (2006.01.01)						
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)											
514	733											

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 7	
/YEVEGENY VALENROD/ Primary Examiner.Art Unit 1672 (Primary Examiner)	04/02/2014 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure none

U.S. Patent and Trademark Office

Part of Paper No. 20140402

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13910583	BATRA ET AL.
	Examiner	**Art Unit**
	YEVEGENY VALENROD	1672

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	7	
/YEVEGENY VALENROD/ Primary Examiner.Art Unit 1672	04/02/2014	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor Name:	Hitesh BATRA
Title:	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
Appl. No.:	13/910,583
Appl. Filing Date:	06/05/2013
Examiner:	Yevgeny Valenrod
Art Unit:	1621
Confirmation Number:	7133

REQUEST FOR CONTINUED EXAMINATION (RCE) TRANSMITTAL

Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

This is a Request for Continued Examination (RCE) under 37 C.F.R. § 1.114 of the above-identified application. This RCE and the enclosed items listed below are being filed prior to the earliest of: (1) payment of the issue fee (unless a petition under 37 C.F.R. § 1.313 is granted); (2) abandonment of the application; or (3) the filing of a notice of appeal to the U.S. Court of Appeals for the Federal Circuit under 35 U.S.C. §141, or the commencement of a civil action under 35 U.S.C. §145 or §146 (unless the appeal or civil action is terminated).

1. Submission **required** under 37 C.F.R. §1.114: (check items that apply)

a. Enclosed are:

[X] Substantive Submission Under 37 C.F.R. § 1.114.

[X] US Patent 8,481,782 B2 and NPL, Aristoff et al.

The filing fee is calculated below at the large entity rate:

	Claims as Amended		Previously Paid For		Extra Claims Present		Rate		Fee Totals
RCE Fee 1.17(e):							$1,200.0 0	=	$1,200.00
Total Claims:	14	-	20	=	0	x	$80.00	=	$0.00
Independents	1	-	3	=	0	x	$420.00	=	$0.00
First presentation of any Multiple Dependent Claims:						+	$780.00	=	$0.00
CLAIMS FEE TOTAL:								=	$1,200.00

[X] Applicant hereby petitions for an extension of time under 37 C.F.R. §1.136(a) for the total number of months checked below:

[X] Extension for response filed within the first month:	$200.00	1	$200.00
		EXTENSION FEE SUBTOTAL:	$200.00
		EXTENSION FEE ALREADY PAID: -	$0.00
		EXTENSION FEE TOTAL	$200.00
		CLAIMS AND EXTENSION FEE TOTAL:	$1,400.00
		Prioritized Examination fee (Track I) under 37 C.F.R. § 1.17 (c)	$0.00
		Processing Fee (Track I) under 37 C.F.R. § 1.17 (i)	$0.00
		Publication Fee	$0.00
[ ] Suspension of action requested under 37 C.F.R. § 1.103(c)			$0.00
		TOTAL FEE:	$1,400.00

The above-identified fees of $1,400.00 are being paid by credit card via EFS-Web.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by the credit card payment instructions in EFS-Web being incorrect or absent, resulting in a rejected or incorrect credit card transaction, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741.

Please direct all correspondence to the undersigned attorney or agent at the address indicated below.

Respectfully submitted,

Date March 17, 2014

By _____

FOLEY & LARDNER LLP
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Hitesh BATRA et al.
Title:	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
Appl. No.:	13/910,583
Filing Date:	June 5, 2013
Examiner:	Yevgeny Valenrod
Art Unit:	1621
Confirmation Number:	7133

SUBSTANTIVE SUBMISSION UNDER 37 C.F.R. § 1.114

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

This paper responds to the Final Office Action dated August 20, 2013, the Advisory Action dated November 18, 2013 and the Notice of Panel Decision from Pre-Appeal Brief Review dated January 17, 2014. The present submission follows the response filed November 8, 2013 and the Pre-Appeal Brief Conference request filed December 5, 2013. Applicants petition for extension of time to make this submission timely.

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this document. **Remarks** begin on page 4 of this document.

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. (Currently Amended) ~~In a~~ A process for producing a pharmaceutical composition comprising treprostinil, ~~the improvement~~ comprising providing ~~forming a salt of treprostinil by combining~~ a starting batch of treprostinil having one or more impurities resulting from prior alkylation and hydrolysis steps, forming a salt of treprostinil by combining the starting batch and a base, isolating the treprostinil salt, and preparing a pharmaceutical ~~composition~~ solution from the isolated salt comprising treprostinil or a pharmaceutically acceptable salt thereof from the isolated treprostinil salt, whereby a level of one or more impurities found in the starting batch of treprostinil is lower in the pharmaceutical composition, and wherein said alkylation is alkylation of benzindene triol.

2. (original) The process of claim 1, wherein the salt is isolated in crystalline form.

3. (original) The process of claim 2, wherein the isolated salt is at least 99.8% pure.

4. (original) The process of claim 1, wherein the base is selected from the group consisting of sodium, ammonia, potassium, calcium, ethanolamine, diethanolamine, N-methylglucamine, and choline.

5. (original) The process of claim 4, wherein the base is diethanolamine.

6. (original) The process of claim 1, wherein the base is combined with treprostinil that has not been previously isolated.

7. (original) The process of claim 1, wherein the isolated salt is stored at ambient temperature.

8. (currently amended) A pharmaceutical ~~composition~~ solution prepared by the process of claim 1.

9. (currently amended) A pharmaceutical ~~composition~~ solution prepared by the process of claim 2.

10. (currently amended) A pharmaceutical ~~composition~~ solution prepared by the process of claim 3.

11. (currently amended) A pharmaceutical ~~composition~~ solution prepared by the process of claim 4.

12. (currently amended) A pharmaceutical ~~composition~~ solution prepared by the process of claim 5.

13. (currently amended) A pharmaceutical ~~composition~~ solution prepared by the process of claim 6.

14. (currently amended) A pharmaceutical ~~composition~~ solution prepared by the process of claim 7.

REMARKS

Applicants respectfully request reconsideration and allowance of the present application.

CLAIMS STATUS

Applicants have amended claims 1 and 8-14 to present the claimed invention in a clearer manner. Corresponding amendments have been made in the dependent claims. Support for the amended claima may be found throughout the specification as filed and in particular, for amended claim 1 on page 11. No new matter has been added.

After the amendment, claims 1-14 are pending.

CLAIM REJECTION UNDER 35 U.S.C. § 103

Claims 1-14 stand rejected as obvious over Phares (US2005/0085540) in view of Moriarty et al. (Journal of Organic Chemistry, 2004, 69, 1890-1902). Applicants respectfully traverse.

The PTO failed to establish a *prima facie* case of obviousness at least because of the reasons discussed below. At the outset, applicants emphasize that the claim amendments clearly distinguish the method over the prior art. Phares makes a solid salt of treprostinil which is itself a pharmaceutical end product. By contrast, the present claims relate to pharmaceutical solutions made from a salt intermediate that allows reduction of one or more impurities during intermediate salt formation. Moriarty does not teach or suggest forming a salt as an intermediate to remove impurities before finally making a pharmaceutical solution of treprostinil. Thus, even if Phares and Moriarty were combined, there still would have been no motivation to perform the last recited step of claim 1 as amended, namely preparing a pharmaceutical solution from the salt intermediate.

Applicants provide additional comments on why the PTO failed to establish a *prima facie* case of obviousness below.

Phares discusses synthesis of treprostinil diethanolamine (U-15C) as follows in his paragraph 0105:

"Treprostinil acid ... is dissolved in a 1:1 molar ratio mixture of ethanol:water and diethanolamine is added and dissolved. The solution is heated and acetone is added as an antisolvent during cooling."

The PTO explicitly admits that Phares does not teach all the elements of the claimed invention by stating on page 3 of the Final Office Action as follows:

"Although Phares teaches a starting batch comprising treprostinil, he fails to teach impurities resulting from prior alkylation and hydrolysis being present in said starting batch."

This admission may be fairly extended to state that Phares fails to teach impurities resulting from prior alkylation and hydrolysis being present in said starting batch, wherein said alkylation is alkylation of benzindene triol as amended claim 1 recites.

To remedy the admitted deficiencies of Phares, the PTO attempts to rely on Moriarty.

Moriarty teaches a process of making treprostinil, which involves alkylation of benzindene triol and subsequent hydrolysis.

In the Office Action, the PTO attempts to combine Phares and Moriarty in order to arrive at the claimed invention.

Applicants respectfully submit that the pending claims contain a number of "purity" elements. In particular, claim 1 recites that "a level of one or more impurities found in the starting batch of treprostinil is lower in the pharmaceutical composition." Furthermore, claim 3 recites the isolated in crystalline form salt is 99.8% pure.

Neither Phares, nor Moriarty do explicitly teach these "purity" elements of pending claims.

In order to arrive at the "purity" elements of the pending claims, the PTO relies on inherency theory, see e.g. the following assertions from page 4 of the Office Action:

"The purity limitations found in the instant claim [3 and] 10 are inherently met by the combination of the two references."

"The purity of the salt is inherently increased since the same steps directed to formation of the salt are followed in both instant claims and Phares."

The PTO failed to establish a *prima facie* case of obviousness at least because the PTO improperly relies on probabilities or possibilities in its inherency based rejection.

MPEP § 2112.IV provides the following guidelines for rejections based on inherency theory:

"IV. EXAMINER MUST PROVIDE RATIONALE OR EVIDENCE TENDING TO SHOW INHERENCY"

"The fact that a certain result or characteristic **may occur or be present** in the prior art is **not sufficient to establish** the inherency of that result or characteristic. In re Rijckaert, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); In re Oelrich, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "To establish inherency, the extrinsic evidence '**must make clear** that the missing descriptive matter **is necessarily present** in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. **Inherency, however, may not be established by probabilities or possibilities**. **The mere fact that a certain thing may result from a given set of circumstances is not sufficient**.' " In re Robertson, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (citations omitted)" (Bold underlining added)

"In relying upon the theory of inherency, the **examiner must provide a basis** in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic **necessarily** flows from the teachings of the applied prior art." Ex parte Levy, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original)" (Bold underlining added)

In the present rejection, the PTO improperly tries to establish inherency theory based on possibilities or probabilities. This is particularly clear from the following sentence bridging pages 4-5: "if one is to produce treprostinil according to the process of [Moriarty] and [to] prepare a salt according to the process of Phares the reduction in impurities would be inherent." (underlining added) The above cited sentence contains the underlined conditional "if" clause, which, at least because there are processes for producing treprostinil other than the one of Moriarty provides evidence that the PTO improperly relies on probabilities or possibilities in its inherency based rejection.

Phares does not provide any information regarding his starting batch of treprostinil. Although it is possible that Phares' starting batch of treprostinil could have been a treprostinil batch prepared by Moriarty's process, which involves alkylation of benzindene triol and hydrolysis, which batch would have one or more impurities resulting from the prior alkylation and hydrolysis steps, it is also possible that Phares' starting batch could have been an alternative treprostinil batch prepared by another process, which does not involve alkylation of benzindene triol and hydrolysis. Such alternative treprostinil batch would not have one or more impurities resulting from the prior alkylation and hydrolysis steps. For example, Phares' starting batch could have been a treprostinil batch prepared by a process disclosed in the enclosed reference, Aristoff et al., Advances in Prostaglandin, Thromboxanes, and Leukotriene Research, Vol. 11, pages 267-274, 1983. Aristoff's process does not involve alkylation of benzindene triol and hydrolysis. Therefore, the treprostinil batch prepared by Aristoff's process would not have one or more impurities resulting from the prior alkylation and hydrolysis steps. It is also possible that Phares' starting batch could have been a treprostinil batch prepare by a process presented in Scheme 3 and Example 3 (bottom of columns 19-20, top of columns 21-22) of enclosed US patent no. 8,481,782. The process of the '782 patent does not involve alkylation of benzindene triol and hydrolysis. Thus, the treprostinil batch prepared by the process presented in Scheme 3 and Example 3 of the '782 patent would not have one or more impurities resulting from the prior alkylation and hydrolysis steps. In addition, it is possible that Phares' starting batch of treprostinil could have been a treprostinil batch prepared by Moriarty's process, which involves alkylation of benzindene triol and hydrolysis, which was subsequently purified from one or more

impurities resulting from the prior alkylation and hydrolysis steps. Such a batch would not have one or more impurities resulting from the prior alkylation and hydrolysis steps.

Considering that Phares does not provide any information regarding his starting treprostinil batch, each of the scenarios discussed in the above paragraph is as possible and probable as the PTO's proposed scenario.

In sum, the PTO failed to establish a *prima facie* case of obviousness at least because it improperly relies on probabilities or possibilities in its inherency based rejection. Thus, for this reason alone, Applicants request withdrawal of the rejection.

CONCLUSION

Applicants believe that the present application is in condition for allowance. Favorable reconsideration of the application is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing or a credit card payment form being unsigned, providing incorrect information resulting in a rejected credit card transaction, or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date March 17, 2014

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US008481782B2

(12) **United States Patent**
Batra et al.

(10) **Patent No.: US 8,481,782 B2**
(45) **Date of Patent: Jul. 9, 2013**

(54) **TREPROSTINIL PRODUCTION**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 38 days.

(21) Appl. No.: **13/151,465**

(22) Filed: **Jun. 2, 2011**

(65) **Prior Publication Data**

US 2011/0319641 A1 Dec. 29, 2011

Related U.S. Application Data

(60) Provisional application No. 61/351,115, filed on Jun. 3, 2010.

(51) **Int. Cl.**
C07C 51/36 (2006.01)

(52) **U.S. Cl.**
USPC **562/466**

(58) **Field of Classification Search**
CPC C07C 51/36; C07C 59/64
USPC 562/466
See application file for complete search history.

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Primary Examiner — Rosalynd Keys

(74) *Attorney, Agent, or Firm* — Foley & Lardner LLP

(57) **ABSTRACT**

The present invention is directed to a novel method for preparing a synthetic intermediate for treprostinil via a stereoselective alkyne addition reaction. Also described are methods of preparing treprostinil comprising the alkyne addition reaction described herein as well as novel intermediates useful for synthesis prostacyclin derivatives, such as treprostinil.

23 Claims, No Drawings

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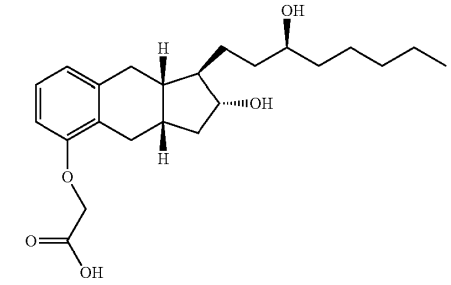
TREPROSTINIL PRODUCTION

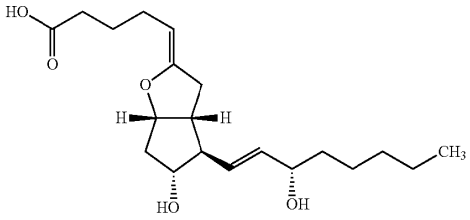
The present application claims the benefit of U.S. provisional application No. 61/351,115 filed Jun. 3, 2010, which is incorporated herein by reference in its entirety.

The present application relates to a process for producing prostacyclin derivatives, such as Treprostinil, and novel intermediate compounds useful in the process.

(+)-Treprostinil (also known as UT-15) is the active ingredient in Remodulin®, a commercial drug approved by FDA for the treatment of pulmonary arterial hypertension (PAH). It was first described in U.S. Pat. No. 4,306,075. Treprostinil is a stable analog of prostacyclin (PGI_2) belonging to a class of compounds known as benzindene prostacyclins, which are useful pharmaceutical compounds possessing activities such as platelet aggregation inhibition, gastric secretion reduction, lesion inhibition, and bronchodilation.



UT-15



PGI_2

U.S. Pat. No. 5,153,222 describes use of treprostinil for treatment of pulmonary hypertension. Treprostinil is approved for the intravenous as well as subcutaneous route, the latter avoiding potential septic events associated with continuous intravenous catheters. U.S. Pat. Nos. 6,521,212 and 6,756,033 describe administration of treprostinil by inhalation for treatment of pulmonary hypertension, peripheral vascular disease and other diseases and conditions. U.S. Pat. No. 6,803,386 discloses administration of treprostinil for treating cancer such lung, liver, brain, pancreatic, kidney, prostate, breast, colon and head-neck cancer. U.S. patent application publication No. 2005/0165111 discloses treprostinil treatment of ischemic lesions. U.S. Pat. No. 7,199,157 discloses that treprostinil treatment improves kidney functions. U.S. Pat. No. 7,879,909 discloses treprostinil treatment of neuropathic foot ulcers. U.S. publication No. 2008/0280986 discloses treprostinil treatment of pulmonary fibrosis, interstitial lung disease with treprostinil and asthma. U.S. Pat. No. 6,054,486 discloses treatment of peripheral vascular disease with treprostinil. U.S. patent application publication

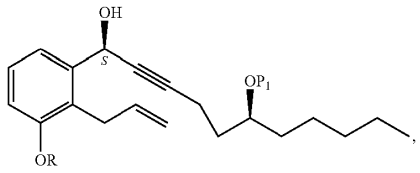
No. 2009/0036465 discloses combination therapies comprising treprostinil. U.S. publication No. 2008/0200449 discloses delivery of treprostinil using a metered dose inhaler. U.S. Pat. Nos. 7,417,070, 7,384,978 and 7,544,713 as well as U.S. publications Nos. 2007/0078095, 2005/0282901, and 2008/0249167 describe oral formulations of treprostinil and other prostacyclin analogs as well as their use for treatment of a variety of conditions. U.S. provisional application No. 61/354,949 filed Jun. 15, 2010 discloses the use of orally administered treprostinil for treatment of Raynaud's phenomenon, systemic sclerosis and digital ischemic lesions.

Treprostinil and other prostacyclin derivatives have been prepared as described in Moriarty, et al in *J. Org. Chem.* 2004, 69, 1890-1902, *Drug of the Future,* 2001, 26(4), 364-374, U.S. Pat. Nos. 4,306,075, 6,441,245, 6,528,688, 6,700,025, 6,765,117, 6,809,223 and US Publication No. 2009/0163738. The entire teaching of these documents are incorporated herein by reference in their entirety. The methods described in these patent documents, however, do not describe a feasible production method for producing stereochemically pure treprostinil because, for example, the methods require the use of expensive reagents and tedious chromatographic purification techniques. Therefore, there is a need in the art for an economical, efficient and simplified method for preparing trepostinil and its synthetic intermediates.

SUMMARY

One embodiment relates to a method of preparing a synthetic intermediate of trepostinil represented by the following structural formula:

(A)



wherein:

P_1 is an alcohol protecting group;

R is $—(CH_2)_nX$;

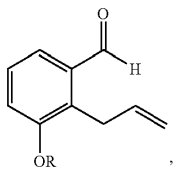
X is H, phenyl, —CN, $—OR_1$ or $COOR_1$;

R_1 is an alkyl, THP or TBDMS; and

n is 1, 2 or 3.

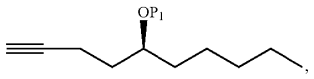
The method comprises reacting a compound represented by structural formula (I):

(I)



with a compound represented by structural formula (a):

(a)

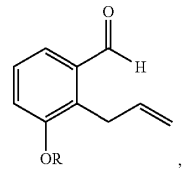


wherein R and P_1 are as described above for structural formula (A).

Another embodiment is to a method of preparing treprostinil comprising reaction 1, and optionally comprising one or more reactions 2-9 according to Scheme 2.

Yet another embodiment is a compound of formula (1):

(1)

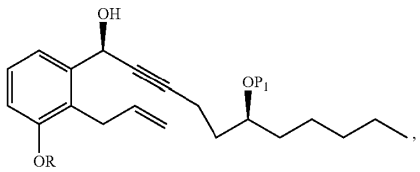


wherein R is $(CH_2)_mCO_2R_1$, m is 1, 2 or 3, and

R_1 is an alkyl group, THP, TBDMS or a substituted or unsubstituted benzyl group.

And yet another embodiment is a compound represented by structural formula (A):

(A)



wherein:

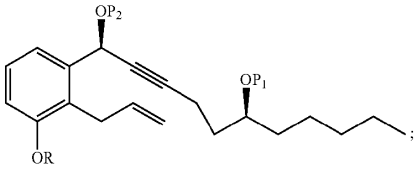
P_1 is an alcohol protecting group;

wherein R is $(CH_2)_mCO_2R_1$, m is 1, 2 or 3, and

R_1 is an alkyl group or a substituted or unsubstituted benzyl group.

And yet another embodiment is a compound represented by structural formula (4):

(4)



wherein:

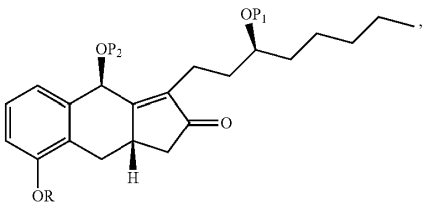
each of P_1 and P_2 is an alcohol protecting group;

wherein R is $(CH_2)_mCO_2R_1$, m is 1, 2 or 3, and

R_1 is an alkyl group, or a substituted or unsubstituted benzyl group.

And yet another embodiment is a compound represented by structural formula (5):

(5)



wherein:

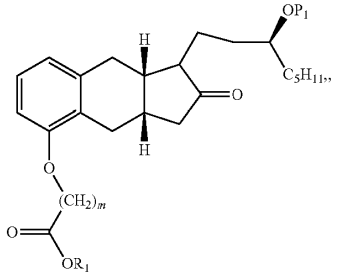
each of P_1 and P_2 is an alcohol protecting group;

wherein R is $(CH_2)_mCO_2R_1$, m is 1, 2 or 3, and

R_1 is an alkyl group, or a substituted or unsubstituted benzyl group.

And yet another embodiment is a compound represented by structural formula (6):

(6)



wherein:

P_1 is an alcohol protecting group;

wherein m is 1, 2 or 3, and

R_1 is an alkyl group, or hydrogen.

DETAILED DESCRIPTION

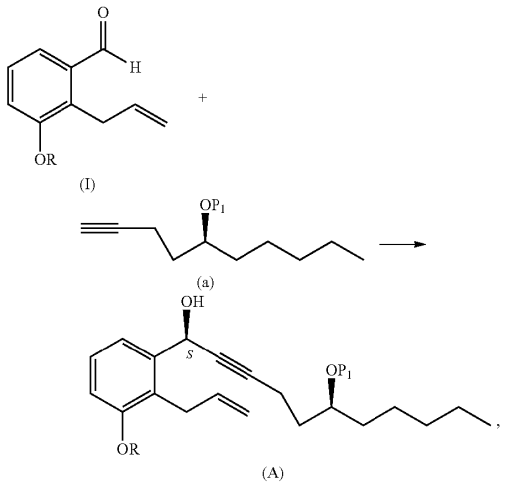
Unless otherwise specified, "a" or "an" means "one or more".

The present application is directed to methods of preparing treprostinil and synthetic intermediates useful of synthesizing treprostinil as well to synthetic intermediates themselves. The present application is also directed to methods of preparing treprostinil or a pharmaceutically acceptable salt thereof comprising the alkyne addition reaction described herein. Preferred treprostinil salts may include the sodium salt and the diethanolamine salt (see, e.g., U.S. Pat. No. 7,417,070).

In some embodiments, the present application is directed to a method of preparing a synthetic intermediate (A) of treprostinil through a stereoselective alkyne addition reaction.

One embodiment is directed to a novel method (reaction 1) for preparing a compound of structural formula (A) comprising the step of reacting an aldehyde of structural formula (I) with an alkyne of structural formula (a):

reaction 1



wherein:

P_1 is an alcohol protecting group;

R is $—(CH_2)_nX$;

X is H, phenyl, —CN, $—OR_1$ or $COOR_1$;

R_1 is an alkyl, THP, TBDMS or a substituted or unsubstituted benzyl group; and

n is 1, 2 or 3.

As used herein, "an alcohol protecting group" is a functional group that protects the alcohol group from participating in reactions that are occurring in other parts of the molecule. Suitable alcohol protecting groups are well known to those of ordinary skill in the art and include those found in T. W. Greene, *Protecting Groups in Organic Synthesis*, John Wiley & Sons, Inc. 1981, the entire teachings of which are incorporated herein by reference. Exemplary alcohol protecting groups include, but are not limited to, actetyl, benzoyl, benzyl, p-methoxyethoxymethyl ether, methoxymethyl ether, dimethoxytrityl, p-methoxybenzyl ether, trityl, silyl ether (e.g., trimethylsilyl (TMS), tert-butyldimethylsilyl (TBMDS), tert-butyldimethylsilyloxymethyl (TOM) or triisopropylsilyl (TIPS) ether), tetrahydropyranyl (THP), methyl ether and ethoxyethyl ether (EE).

An alkyl group may be a saturated straight-chain or branched aliphatic group. For example, an alkyl group may a (C1-C6)alkyl, (C1-C5)alkyl, (C1-C4)alkyl or (C1-C3)alkyl. Examples of alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isoamyl, and hexyl. An alkyl group is optionally substituted with an alkyl, a cycloalkyl (e.g., cyclopentyl or cyclohexyl), an aryl (e.g., phenyl), or heteroaryl group.

A phenyl group may be optionally substituted with one or more substituents, which may be independently selected from the group consisting of $—NO_2$, —CN, halogen (e.g., —F, —Cl, —Br or —I), (C1-C3)alkyl, halo(C1-C3)alkyl, (C1-C3)alkoxy and halo(C1-C3)alkoxy.

A substituted benzyl group may be optionally substituted at one or more meta, ortho or para positions with one or more substituents, which may be independently selected from the group consisting of $—NO_2$, —CN, halogen (e.g., —F, —Cl, —Br or —I), (C1-C3)alkyl, halo(C1-C3)alkyl, (C1-C3) alkoxy and halo(C1-C3)alkoxy.

In one embodiment, for reaction 1 described above, P_1 may be THP.

In another embodiment, R may be selected from the group consisting of methyl, benzyl, CH_2COOMe, $—CH_2COOCH_2Ph$, THP and TBDMS. Alternatively, R is methyl.

In yet another embodiment, R is methyl and P_1 is THP.

In yet another embodiments, R is $—CH_2CO_2R_1$, wherein R_1 is an alkyl group, such as a straight or branched C1-C5 alkyl group, or a substituted or unsubstituted benzyl group, and P_1 is tetrahydrofuranyl (THP), benzyl, 2,4-dinitrobenzyl, methoxymethyl (MOM), tertiarybutyldimethylsilyl (TBDMS), tertiarybutyldiphenylsilyl (TBDPS) or triethylsilyl (TES).

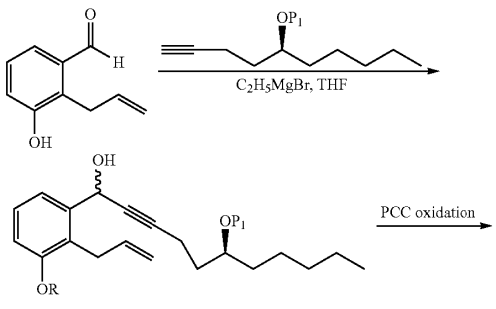
When reaction 1 is carried out in the presence of a chiral inducing agent, the reaction may yield a product having predominantly S configuration of the hydroxyl group at the benzylic carbon position. A "chiral inducing agent" is a compound that is used to create stereoselectivity at a chiral center. For example, (+)-N-methylephiderine may be used as the chiral inducing agent for reaction 1 described above. In one embodiment, at least 70%, 80%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.9% or 100% by weight of the product of reaction 1 is represented by structural formula (A), i.e., the compound prepared by reaction 1 has at least 40%, 60%, 80%, 90%, 94%, 96%, 98%, 99.0%, 99.8% or 100% chiral purity.

In some embodiments, reaction 1 may be carried out in the presence of a base and a zinc reagent. An exemplary zinc reagent includes zinc triflate ($Zn(OTf)_2$). Suitable bases that may be used include, for example, an alkali carbonate, an alkali hydroxide, an amine and an ammonium hydroxide. In some embodiments, Et_3N may be preferred as the base.

In some embodiments, reaction 1 as described in any one of the foregoing embodiments may be carried out in an organic solvent. Suitable organic solvents include, for example, ethereal solvents (e.g., diethyl ether, methyl tert-butyl ether, tetrahydrofuran, 1,4-dioxane and dimethoxyethane), aromatic solvents (e.g., benzene and toluene), chlorinated solvents (e.g., methylene chloride and 1,2-dichloroethane), alcohol solvents (e.g., methanol, ethanol, 2-propanol), dimethylformamide, dimethyl sulfoxide and acetonitrile. In one specific embodiment, reaction 1 may be carried out in toluene.

U.S. Pat. Nos. 6,700,025, 6,809,223, 6,528,668 and 6,441,245 describe a method, which may be used for preparing some of the compounds of structural formula (A). This method, depicted in Scheme 1, however, includes 3 reaction steps.

Scheme 1



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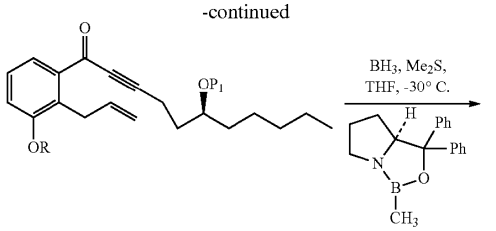
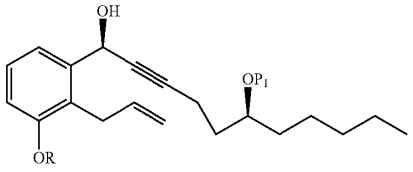


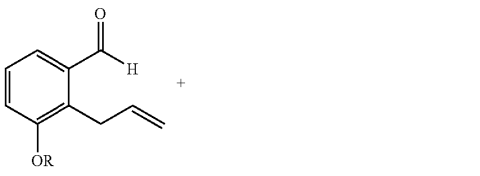


(A)

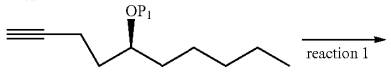
Compared to the prior art method, reaction 1 of the present invention may have one or more of the following advantages: (1) reaction 1 has high diastereoselectivity, wherein the product with greater than 95% chiral purity can be obtained. (2) the prior method requires 3-step synthesis; whereas the method (reaction 1) of the present invention only has a single step, which shortens the number of chemical steps needed; eliminates the tedious column chromatographic purifications involved in the extra two steps and saves manpower and large volume of solvents. (3) reaction 1 may be carried out at room temperature, and therefore no cryogenic reactors are needed; (4) reaction 1 is less expensive than the prior art method as the prior art method involves the use of expensive reagents as needed in the Corey asymmetric reduction. (5) reaction 1 is an eco-friendly method as it does not require the use of obnoxious borane-dimethyl sulfide complex in the Corey asymmetric reduction.

In some embodiments, the compound of structural formula (A) may be subsequently converted to a prostacyclin derivative such as treprostinil according to Scheme 2, reaction steps 2-9.

Scheme 2

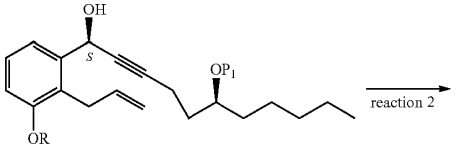


(I)



reaction 1

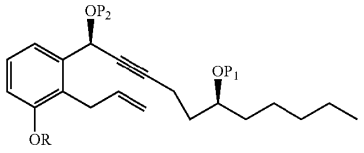
(a)



reaction 2

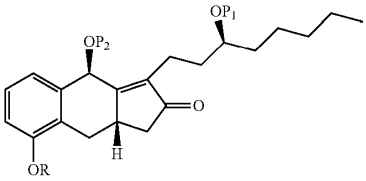
(A)

-continued



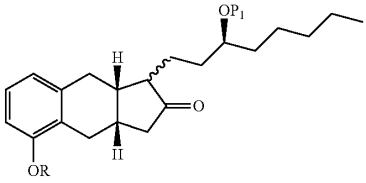
reaction 3

(II)



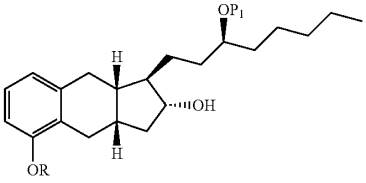
reaction 4

(III)



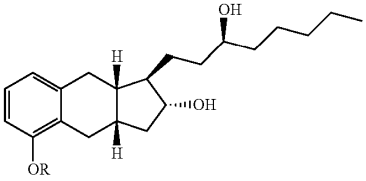
reaction 5

(IV)



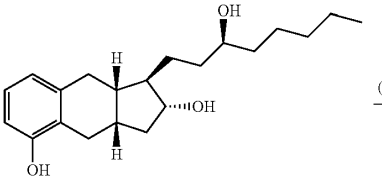
reaction 6

(V)



reaction 7

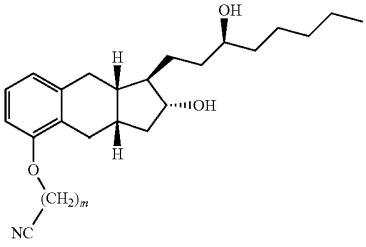
(VI)



$(X_1(CH_2)_mCN$

reaction 8

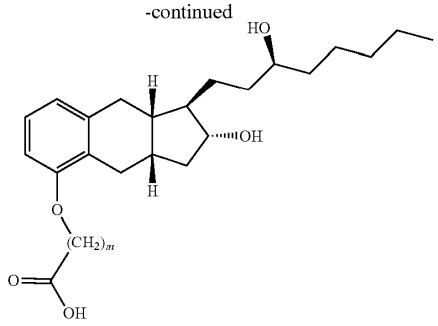
(VII)



reaction 9

(VIII)

-continued



(IX)

In Scheme 2, R and P_1 are as described above for structural formula (A); P_2 is an alcohol protecting group; and m is 1, 2, or 3.

The present application may be also directed to a method of preparing a prostacyclin derivative represented by structural formula (IX) or a pharmaceutically acceptable salt thereof comprising reaction 1. In some embodiments, the method may also optionally include one or more steps selected from the group consisting of reaction 2, reaction 3, reaction 4, reaction 5, reaction 6, reaction 7, reaction 8 and reaction 9 shown in Scheme 2 in conjunction with reaction 1 to make the prostaglandin derivative (IX). For example, the method comprises the steps of reaction 1 and reaction 3. Alternatively, the method may comprise the steps of reaction 1, reaction 3, reaction 4, reaction 5 and reaction 6. In another alternative, the method may comprise the steps of reaction 1, reaction 8 and reaction 9. In yet another alternative, the method for preparing treprostinil comprises the steps of reaction 1, reaction 2, reaction 3, reaction 4, reaction 5, reaction 6, reaction 7, reaction 8 and reaction 9.

As used herein, a "pharmaceutically acceptable salt" refers to a salt that is useful in preparing a pharmaceutical composition and is generally safe, non-toxic and neither biologically nor otherwise undesirable pharmaceutical use.

Compounds with basic groups, such as amine groups, can form pharmaceutically acceptable salts with pharmaceutically acceptable acid(s). Suitable pharmaceutically acceptable acid addition salts of the compounds of the invention include salts of inorganic acids (such as hydrochloric acid, hydrobromic, phosphoric, metaphosphoric, nitric, and sulfuric acids) and of organic acids (such as, acetic acid, benzenesulfonic, benzoic, citric, ethanesulfonic, fumaric, gluconic, glycolic, isethionic, lactic, lactobionic, maleic, malic, methanesulfonic, succinic, p-toluenesulfonic, and tartaric acids). Compounds with acidic groups such as carboxylic acids can form pharmaceutically acceptable salts with pharmaceutically acceptable base(s). Suitable pharmaceutically acceptable basic salts include ammonium salts, alkali metal salts (such as sodium and potassium salts) and alkaline earth metal salts (such as magnesium and calcium salts). Compounds with a quaternary ammonium group also contain a counteranion such as chloride, bromide, iodide, acetate, perchlorate and the like. Other examples of such salts include hydrochlorides, hydrobromides, sulfates, methanesulfonates, nitrates, maleates, acetates, citrates, fumarates, tartrates [e.g. (+)-tartrates, (−)-tartrates or mixtures thereof including racemic mixtures], succinates, benzoates and salts with amino acids such as glutamic acid. A particularly preferred salt is the diethanolamine salt of treprostinil.

In one embodiment, the prostacyclin derivative (e.g., treprostinil) prepared according to the methods described herein may have at least 40%, 60%, 80%, 90%, 94%, 96%, 98%, 99.0%, 99.8% or 100% chiral purity.

In one embodiment, the prostacyclin derivative is treprostinil represented by structural formula (IX-1) (i.e., m=1 for structural formula (IX).

In one embodiment, for structural formulas (I)-(VI) and (A), R may be selected from the group consisting of methyl, benzyl, —CH_2COOMe, —CH_2COOCH_2Ph, THP and TBDMS. More specifically, R is methyl.

In another embodiment, for structural formulas (I)-(V), (A) and (a), P_1 is THP.

In yet another embodiment, for structural formulas (II) and (III), P_2 is TBDMS.

In another embodiment, for reactions depicted in Scheme 2, R is methyl, P_1 is THP, P_2 is TBDMS and m is 1.

In one embodiment, for methods of preparing a prostacyclin derivative described herein, specific conditions and reagents for reaction 1 are as described above.

For reaction 2 depicted in Scheme 2 above, compound (A) is reacted with an alcohol protecting reagent to form the compound of structural formula (II). An "alcohol protecting reagent" is a reagent that converts a —OH group to —OP_2. In one embodiment, the alcohol protecting reagent is TBDMSCl.

In one embodiment, reaction 2 is carried out in the presence of a base. Suitable base can be used includes, but is not limited to, an alkali carbonate, an alkali hydroxide, an amine and an ammonium hydroxide. More specifically, the base is an amine. Even more specifically, the base is a mixture of imidazole and dimethylaminopyridine (DMAP).

Reaction 2 can be carried out in a suitable solvent or a solvent mixture. In one embodiment, reaction 2 is carried out in an organic solvent, such as ethereal solvents (e.g., diethyl ether, methyl tert-butyl ether, tetrahydrofuran, 1,4-dioxane and dimethoxyethane), aromatic solvents (e.g., benzene and toluene), chlorinated solvents (e.g., methylene chloride and 1,2-dichloroethane), alcohol solvents (e.g., methanol, ethanol, 2-propanol), dimethylformamide, dimethyl sulfoxide and acetonitrile. In one embodiment, the solvent is methylene chloride (CH_2Cl_2).

For reaction 3 depicted in Scheme 2, the compound of structural formula (II) is converted to the compound of structural formula (III) through a cobalt-mediated cyclization reaction. More specifically, the cyclization reaction is carried out in the presence of $CO_2(CO)_8$.

In one embodiment, reaction 3 is carried out in an organic solvent or a mixture of organic solvents. Suitable organic solvents include, but are not limited to, ethereal solvents (e.g., diethyl ether, methyl tert-butyl ether, tetrahydrofuran, 1,4-dioxane and dimethoxyethane), aromatic solvents (e.g., benzene and toluene), chlorinated solvents (e.g., methylene chloride and 1,2-dichloroethane), alcohol solvents (e.g., methanol, ethanol, 2-propanol), dimethylformamide, dimethyl sulfoxide and acetonitrile. More specifically, reaction 3 is carried out initially in CH_2Cl_2 followed by removal of the solvent by distillation. The reaction is subsequently carried out in acetonitrile.

For reaction 4 depicted in Scheme 2, the compound of structural formula (III) is hydrogenated with H_2 to form the compound of structural formula (IV). In one embodiment, the hydrogenation reaction is carried out in the presence of a hydrogenation catalyst. More specifically, the hydrogenation reaction is carried out in the presence of Pd/C. In another embodiment, the hydrogenation reaction is carried out in the presence of a base, such as a alkali carbonate (e.g., K_2CO_3).

Reaction 4 can be carried out in an organic solvent, such as ethereal solvents (e.g., diethyl ether, methyl tert-butyl ether, tetrahydrofuran, 1,4-dioxane and dimethoxyethane), aromatic solvents (e.g., benzene and toluene), chlorinated solvents (e.g., methylene chloride and 1,2-dichloroethane), alcohol solvents (e.g., methanol, ethanol, 2-propanol), dimethylformamide, dimethyl sulfoxide and acetonitrile. More specifically, the reaction is carried out in EtOH.

For reaction 5, the compound of structural formula (IV) is reacted with a reducing agent to form the compound of structural formula (V). A "reducing agent" is a reagent that can convert a carbonyl functional group to an alcohol functional group. Suitable reducing agents can be used include, but are not limited to, $NaBH_4$ and $LiAlH_4$. More specifically, the reducing agent is $NaBH_4$. In one embodiment, reaction 5 is carried out in the presence of a base, such as an alkali hydroxide (e.g. NaOH). Reaction 5 can be carried out in an organic solvent, such as those described above. More specifically, the reaction is carried out in EtOH.

For reaction 6, the compound of structural formula (V) is reacted with a strong acid, such as p-toluenesulfonic acid (pTsOH), TFA, TfOH, or hydrochloric acid, to form the compound of structural formula (VI). More specifically, the acid is pTsOH. Reaction 6 can be carried out in an organic solvent, such as those described above. More specifically, the solvent is MeOH.

For reaction 7, the compound of structural formula (VI) is reacted with Ph_2PH in the presence of a base. In one embodiment, the base is alkyllithium. More specifically, the base is nBuLi. Reaction 7 can be carried out in an organic solvent. Exemplary organic solvents are described above. In one embodiment, reaction 7 is carried out in tetrahydrofuran (THF).

For reaction 8, the compound of structural formula (VII) is reacted with $X_1(CH_2)_mCN$ to form the compound of structural formula (VIII), wherein X_1 is a leaving group and m is 1, 2 or 3. A "leaving group" is a moiety that can easily be displaced by a nucleophile. For example, a leaving group is a halide (e.g., —Cl, —Br, —I), a sulfonate group (e.g., $MeSO_2O$—, CF_3SO_2O—, $CH_3C_6H_4SO_2O$—, or $C_6H_5SO_2O$—). More specifically, X_1 is —Cl and m is 1.

In one embodiment, reaction 8 is carried out in the presence of a base, such as an alkali carbonate (e.g., K_2CO_3).

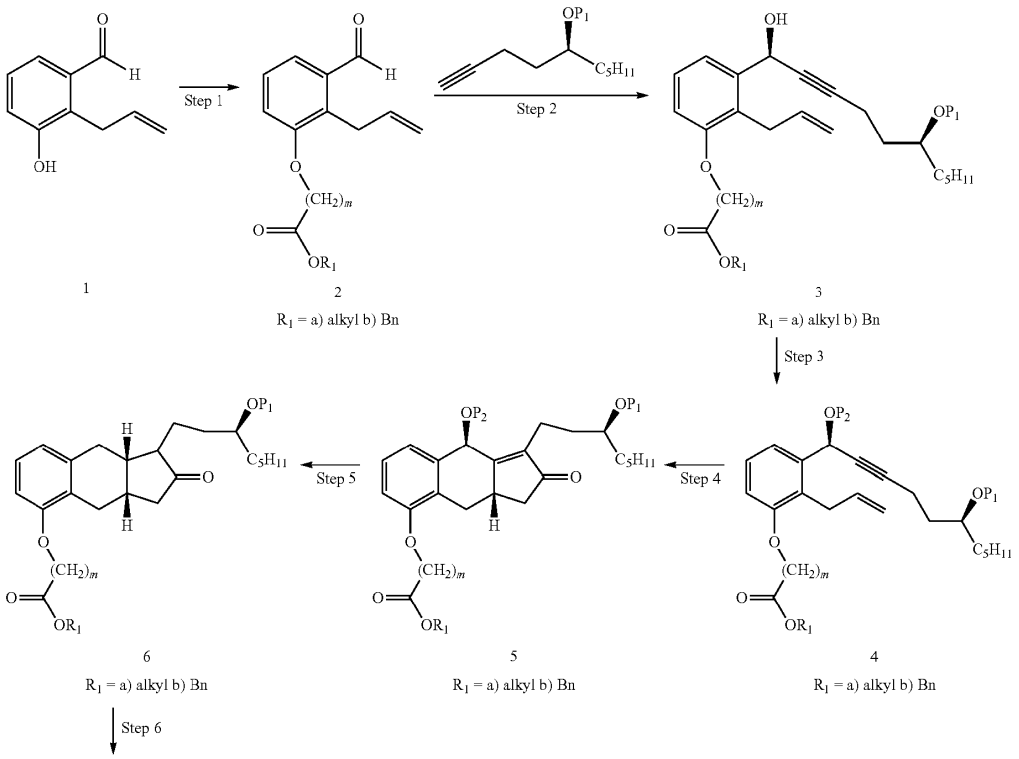
Reaction 8 can be carried out in an organic solvent, such as those described above. More specifically, the solvent is acetone.

For reaction 9, the compound of structural formula (VIII) is reacted with a base, such as an alkali hydroxide (e.g., NaOH). The reaction can be carried out in an organic solvent, such as those described above. In one embodiment, the reaction is carried out EtOH.

Also included in the present invention is the prostacyclin derivatives represented by structural formula (IX) (e.g., treprostinil) prepared by methods described herein.

In some embodiments, a prostacyclin derivative represented by structural formula (IX), such as treprostinil, or a pharmaceutically acceptable salt thereof may be prepared using one or more reactions from Scheme 3:

Scheme 3.



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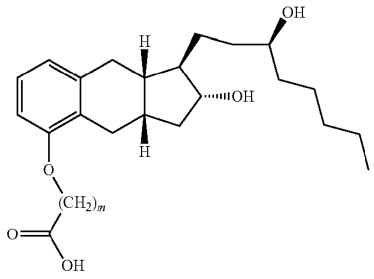


7 (treprostinil)

In Scheme 3, R_1 may be an alkyl group or a substituted or unsubstituted benzyl group, and P_1 are as described above for structural formula (A); P_2 is an alcohol protecting group; and m is 1, 2, or 3.

Compound (7) in Scheme 3 corresponds to the prostacyclin derivative represented by structural formula (IX) earlier in the disclosure, compound (2) in Scheme 3 corresponds to the compound of structural formula (A) earlier in the disclosure, while Step 2 in corresponds to reaction 1 earlier in the disclosure.

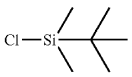
In some embodiments, a method of preparing a prostacyclin derivative represented by structural formula (IX) or a pharmaceutically acceptable salt thereof may comprising Step 2 of Scheme 3. The method may also optionally include one or more steps selected from the group consisting of Step 1, Step 3, Step 4, Step 5 and Step 6 shown in Scheme 3 in conjunction with Step 2 to make the prostaglandin derivative (IX). For example, the method comprises Step 2 and Step 3. Alternatively, the method may comprise Step 2, Step 3 and Step 4. In another alternative, the method may comprise the steps of Step 2, Step 5 and Step 6. In another alternative, the method may comprise Step 1 and Step 2. In yet another alternative, the method for preparing treprostinil may comprise Step 1, Step 2, Step 3, Step 4, Step 5 and Step 6.

The reactions of scheme 3 may be particularly useful for R is $—(CH_2)_mCO_2R_1$, wherein m=1, 2 or 3 and R_1 is an alkyl group, such as a straight or branched C1-C5 alkyl group, or a substituted or unsubstituted benzyl group. Compared to prior art methods, such as those disclosed in U.S. Pat. Nos. 6,700,025, 6,809,223, 6,528,668 and 6,441,245, the method of Scheme 3 may include fewer steps for preparing a prostacyclin derivative represented by structural formula (IX).

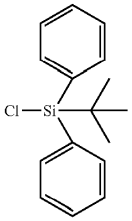
Step 1 of Scheme 3 may be performed by reacting compound 1 with R_2COOR_1, wherein R_2 may be a leaving group such as halogen, e.g. Cl, I, or Br, tosylate, mesylate or triflate, and R_1 is an alkyl group or a substituted or unsubstituted benzyl group. In some embodiments, the reaction may be carried out in the presence of a base, which may be an alkali carbonate, such as K_2CO_3. In some embodiments, the base may be potassium tertiary butoxide (t-BuOK), sodium hydride (NaH), sodium hydroxide (NaOH), lithium hydroxide (LiOH), potassium hydroxide (KOH) etc. The reaction may be carried out in a number of solvents including butanone, propanone, N,N-dimethyl formamide (DMF), dimethoxyethane (DME), dimethylsulfoxide (DMSO), tetrahydrofuran (THF), toluene and acetone.

Step 2 of Scheme 3 may be performed as described above for reaction 1 of scheme 2.

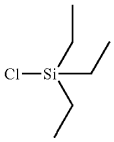
Step 3 of Scheme 3 may be performed by compound (A) with an alcohol protecting reagent to form the compound of structural formula (4). An "alcohol protecting reagent" is a reagent that converts a —OH group to $—OP_2$. In some embodiments, P_2 may be tert-butyldimethylsilyl (TBDMS), tertiarybutyldiphenylsilyl (TBDPS), triethylsilyl (TES) or triphenylmethyl (trityl group). The respective alcohol protective reagents may be TBDMSCl or TBDMSOTf for TBDMS, TESCl for TES, TBDPSCl for TBDPS and tritylchloride for trityl. In some embodiments, TBDMS may be preferred as P_2 and TBDMSCl may be preferred as the alcohol protecting reagent. Chemical formula of exemplary protective reagents is presented below.



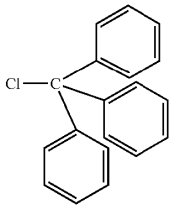
tert-butyldimethylsilyl chloride
TBDMSCl



tert-butyldiphenylsilyl chloride
TBDPSCl



triethylsilyl chloride
TESCl



trityl chloride or triphenylmethyl chloride

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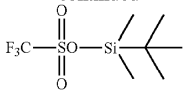


tert-butyldimethylsilyl trifluromethanesulfonate
TBDMSOTf

In one embodiment, Step 3 of Scheme 3 may be carried out in the presence of a base. Suitable base that may be used includes, but is not limited to, an alkali carbonate, an alkali hydroxide, an amine and an ammonium hydroxide. In one specific embodiment, the base may an amine, such as of imidazole, 4-dimethylaminopyridine (DMAP) or a mixture thereof.

Step 3 of Scheme 3 may be carried out in a suitable solvent or a solvent mixture. In one embodiment, Step 3 of Scheme 3 may be carried out in an organic solvent, such as ethereal solvents (e.g., diethyl ether, methyl tert-butyl ether, tetrahydrofuran, 1,4-dioxane and dimethoxyethane), aromatic solvents (e.g., benzene and toluene), chlorinated solvents (e.g., methylene chloride and 1,2-dichloroethane), dimethylformamide, dimethyl sulfoxide and acetonitrile. In one embodiment, the solvent may be methylene chloride (CH_2Cl_2).

Step 4 of Scheme 3 may be performed by converting the compound of structural formula (4) to the compound of structural formula (5). In some embodiments, such conversion may be performed by a cobalt-mediated cyclization reaction. Such cyclization reaction may be carried out, for example, in the presence of $CO_2(CO)_8$.

In one embodiment, Step 4 of Scheme 3 may be carried out in an organic solvent or a mixture of organic solvents. Suitable organic solvents include, but are not limited to, ethereal solvents (e.g., diethyl ether, methyl tert-butyl ether, tetrahydrofuran, 1,4-dioxane and dimethoxyethane), aromatic solvents (e.g., benzene and toluene), chlorinated solvents (e.g., methylene chloride and 1,2-dichloroethane), alcohol solvents (e.g., methanol, ethanol, 2-propanol), dimethylformamide, dimethyl sulfoxide and acetonitrile. In some embodiments Step 4 of Scheme 3 may be carried out in 1,2-dimethoxyethane, followed by removal of the solvent by distillation.

In some embodiments. Step 4 may be carried out using from about 2 to 15 mol % or from 3 to 12 mol % or from 5 to 10 mol % or any subrange within the above stated ranges of $CO_2(CO)_8$. In some embodiments, Step 4 may be carried out under atmosphere of carbon monoxide using from about 2 to 15 mol % or from 3 to 12 mol % or from 5 to 10 mol % or any subrange within the above stated ranges of $CO_2(CO)_8$. Such conditions may save cost and/or avoid laborious column chromatography and hence save time compared to stoichiometric Pauson-Khand cyclization such as the one used, for example, in U.S. Pat. No. 6,765,117.

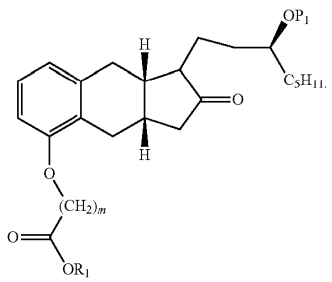
In some embodiments, the reaction of Step 4 may be carried out under atmospheric pressure. Yet in some embodiments, the reaction of step of Step 4 may be carried at a pressure that is higher than the atmospheric pressure. The use of the elevated pressure may make the reaction of Step 4 go faster compared the reaction under the atmospheric pressure. In some embodiments, the reaction of Step 4 may be carried out at a pressure ranging from 10 psi to 250 psi or from 20 psi to 250 psi or from 20 psi to 200 psi or any subrange within these ranges.

Step 5 of Scheme 3 may be performed by hydrogenating the compound of structural formula (5) to form a hydrogenated compound of formula (6) or (6'). The hydrogenation reaction may involve reacting the compound of structural formula (5) with H_2. In some embodiments, the hydrogenation reaction may be carried out in the presence of a hydrogenation catalyst. Such hydrogenation catalyst may comprise a metal hydrogenation catalyst, such as Pd. In some embodiments, the hydrogenation catalyst may be Pd/C. In some embodiments, the hydrogenation reaction may be carried out in the presence of a base, which may be a alkali carbonate, such as K_2CO_3.

Step 5 of Scheme 3 may be carried out in an organic solvent, such as ethereal solvents (e.g., diethyl ether, methyl tert-butyl ether, tetrahydrofuran, 1,4-dioxane and dimethoxyethane), aromatic solvents (e.g., benzene and toluene), chlorinated solvents (e.g., methylene chloride and 1,2-dichloroethane), alcohol solvents (e.g., methanol, ethanol, 2-propanol), dimethylformamide, dimethyl sulfoxide and acetonitrile.

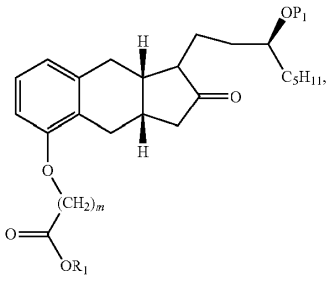
When R_1 is an alkyl group Step 5 may result in the hydrogenated compound of structural formula (6):

(6)



When R_1 is a substituted of unsubstituted benzyl group Step 5 may result in the hydrogenated compound of structural formula (6'):

(6')



which has its benzyl group cleaved as the result of hydrogenation.

Step 6 of Scheme 3 may be performed by converting the hydrogenated compound represented by structural formula (6) or (6') to a compound represented by structural formula (7) or (IX). In some embodiments, the conversion of Step 6 may be performed in the presence of a reducing agent, which may be used for the reduction of the ketone to alcohol on the cyclopentyl ring. The reducing agent may be, for example, $NaBH_4$, $NaCNBH_3$ or $LiBH_4$. In some embodiments, the reducing agent may be used together with a base, which may be used for hydrolysis of the ester group to acid. The base may be, for example, NaOH, KOH, LiOH or $Ba(OH)_2$. In some

embodiments, step 6 may be carried in the presence of an acid, which may be used to obtain a free acid from the ester group after its hydrolysis and/or to remove the protection group P_1 from the side chain. In some embodiments, the acid may be, for example, HCl, acetic acid, formic acid, trifluoroacetic acid, para-toluene sulfonic acid, dilute H_2SO_4, dilute HNO_3 or a polymer bound acidic resin, such as Amberlyst-15 or Dowex 50WX-X8. Solvents, which may be used for Step 6's conversion, may include water and/or organic solvents, such as alcohols, for example ethanol. In some embodiments, Step 6 may be performed in the presence of two or more of the reducing agent, the base and the acid. In some embodiments, Step 6 may be carried out in the presence of all three of the reducing agent, the base and the acid.

Step 6 may allow performing one or more of the following in a single pot: reduction of the ketone of compound (6) to alcohol of compound (7), hydrolysis of the ester group of compound (6) to a free acid of compound (7) and removal of the P_1 protective group of compound (6).

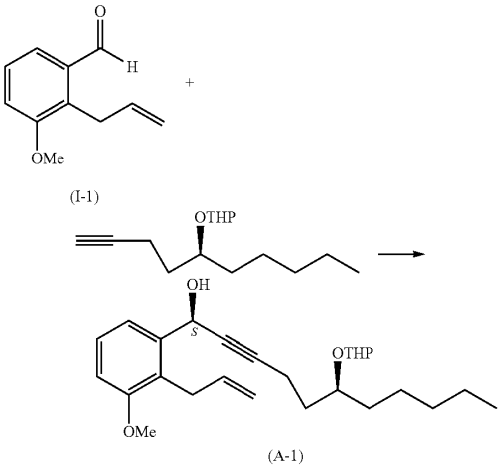
For example, conversion of compound of structural formula (6), when R_1 is an alkyl group, the conversion reaction may accomplish cleaving of the protective group P_1 and ester hydrolysis of R to a free acid in a single pot. This conversion may also include reduction of the ketone of compound (6) to alcohol of compound (7).

The present invention also relates to intermediates for synthesis a prostacyclin derivative represented by structural formula (IX), such as compounds of formulas (2), (3), (4), (5) and (6, 6') in Scheme 3.

The invention is further illustrated by, though in no way limited to, the following examples.

Example 1

Preparation of Chiral Benzyl Alcohol (A-1)



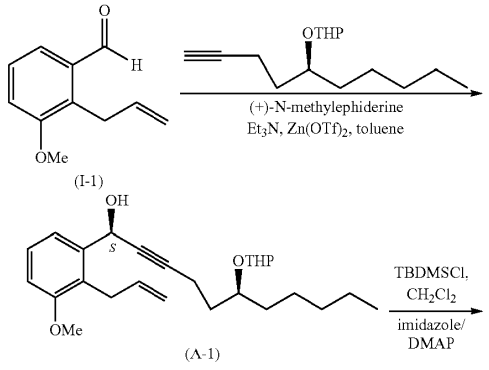
A 50-mL, two-necked, round-bottom flask equipped with a mechanical stirrer was charged with zinc triflate (2.16 g, 0.0059 mol) and (+)-N-methylephiderine (0.814 g, 0.0045 mol) in toluene (10 mL). To this mixture triethyl amine was added (0.459 g, 0.0045 mol) and this gelatinous mixture was stirred at ambient temperature for 30-60 minutes. To this mixture was then treated with a solution of alkyne (1.08 g, 0.0045 mol) in toluene (1 mL), stirred at ambient temperature for 15 minutes followed by solution of aldehyde (0.250 g, 0.0014 mol). Progress of the reaction was monitored by TLC (completion of the reaction was monitored by thin layer chromatography (TLC) using a thin layer silica gel plate; eluent: 20% ethyl acetate in hexanes). After stirring the mixture for 3 h TLC indicated completion of reaction. At this stage reaction mixture was quenched by slow addition of saturated ammonium chloride (10 mL). This was stirred for 5-10 minutes and organic layer containing desired compound was separated. Aqueous layer was washed with ethyl acetate (10 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to obtain a crude product (2.0 g). The crude product was purified by column chromatography using 250-400 mesh silica gel. A solvent gradient of ethyl acetate in hexanes (5-20%) was used to elute the product from the column. All fractions containing the desired product were combined and concentrated in vacuo to give pure chiral benzyl alcohol A-1 (0.360 g, ~87%) compound was characterized by ^1H, ^{13}C NMR, IR, LCMS and chiral HPLC data. ^1H NMR ($CDCl_3$, 300 MHz): δ 0.87 (t, 3H), 1.18-1.86 (m, 17H), 2.28 (dt, 1H), 2.34-2.45 (m, 2H), 3.40-3.53 (m, 1H), 3.54-3.62 (m, 1H), 3.63-3.75 (m, 1H), 3.81 (s, 3H, OCH_3), 3.83-3.92 (m, 1H), 4.62-4.66 (m, 1H), 4.89-5.05 (m, 2H), 5.59-5.61 (merged two s, 1H), 5.91-6.04 (m, 1H), 6.85-6.82 (d, 1H), 7.20-7.26 (m, 1H), and 7.31-7.36 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.13, 14.18, 14.98, 15.56, 19.96, 21.14, 22.71, 24.77, 25.34, 25.57, 29.51, 31.17, 31.23, 32.07, 32.19, 32.69, 33.51, 33.94, 35.13, 55.86, 60.49, 62.12, 62.18, 62.82, 75.36, 75.89, 80.20, 80.53, 86.97, 87.42, 97.31, 98.06, 110.63, 114.80, 119.18, 119.27, 125.86, 127.44, 127.50, 137.15, 140.78, 157.68; IR: 3411, 2230, 1638, 1259, 1133, 1023, 755 cm^{-1}; MS (m/z): $[M+Na]^+$ 437.35.

Example 2

Preparation of treprostinil (IX-1)

Treprostinil can be prepared according to Scheme 4. Exemplary reaction conditions for making the chiral benzyl alcohol (compound A-1) are described in Example 1. Exemplary conditions for other reactions depicted in Scheme 3 are as described in U.S. Pat. Nos. 6,700,025, 6,809,223, 6,528,668 and 6,441,245. The entire teaching of all these documents are incorporated herein by reference.

Scheme 4



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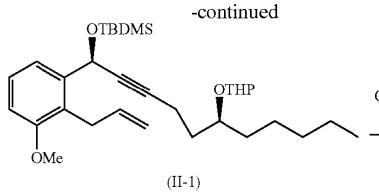
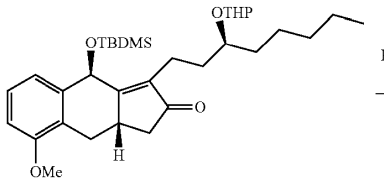


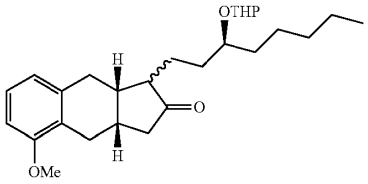
(II-1)

$Co_2(CO)_8$, CH_2Cl_2, CH_3CN



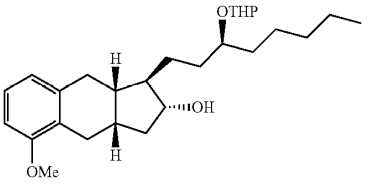
(III-1)

H_2 (80 psi), K_2CO_3, EtOH



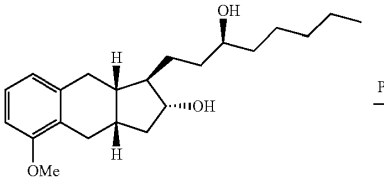
(IV-1)

$NaBH_4$, NaOH, EtOH



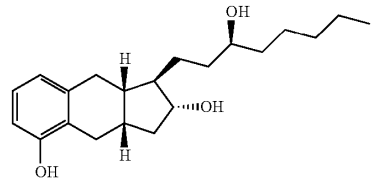
(V-1)

pTsOH/MeOH



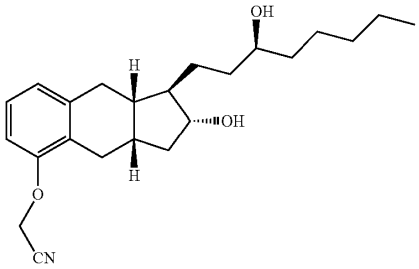
(VI-1)

nBuLi/ Ph_2PH/THF



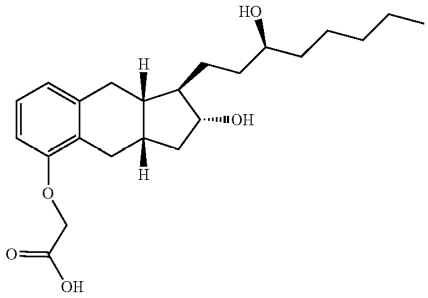
(VII-1)

$ClCH_2CN$, K_2CO_3



(VIII-1)

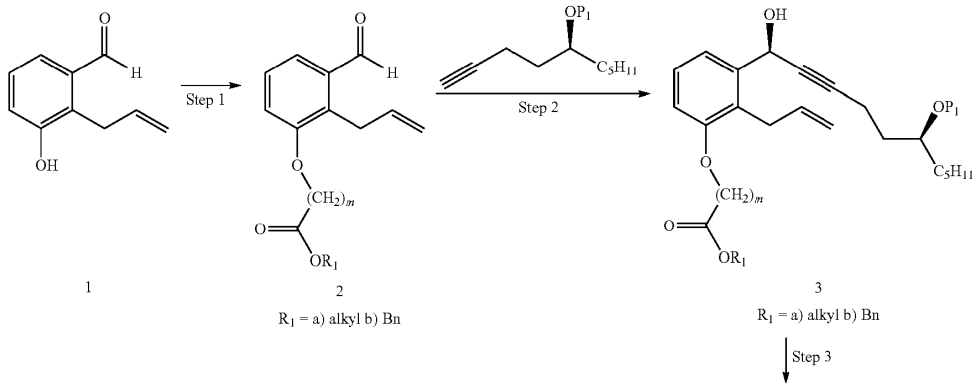
NaOH, EtOH

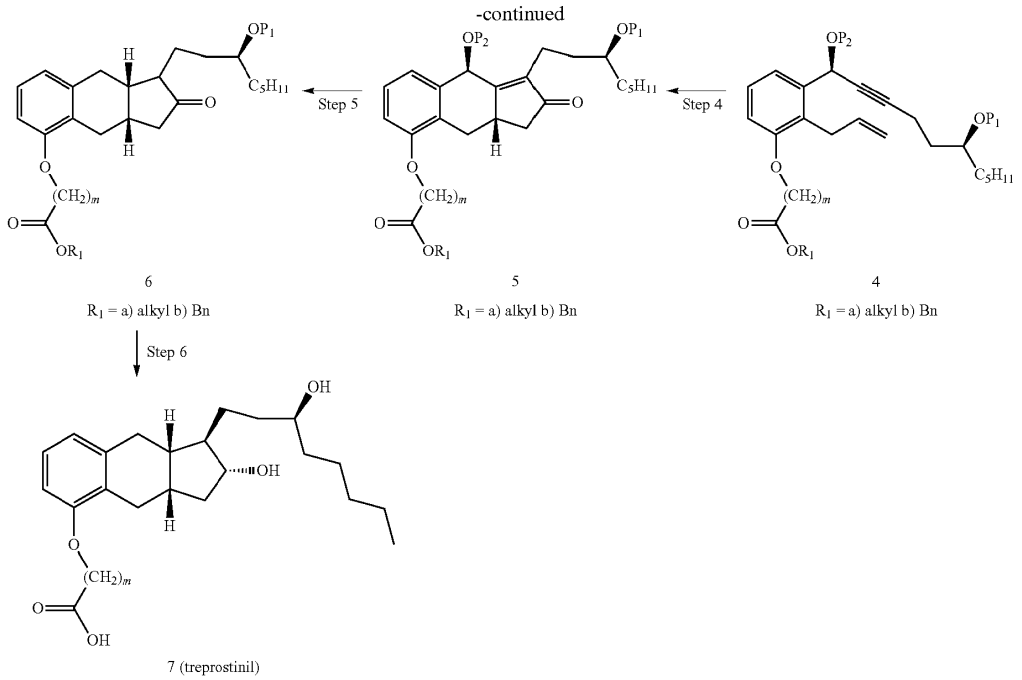


(IX-1)

Example 3

Preparation of Treprostinil





The inventors have developed a stereoselective route for the synthesis of treprostinil (7) starting from aldehyde (1) and side chain (SCiv). This route may involve direct stereoselective addition of an alkyne to starting 2-Allyl-3-[(carbomethoxy)methoxy]benzaldehyde (2) and illustrates the synthetic utility of catalytic a Pauson-Khand Cyclization (PKC) for the synthesis of a drug substance, treprostinil (7, UT-15). O-alkylation of the readily available 3-hydroxy-2-allylbenzaldehyde (Step 1->2) with methylbromoacetate provided the required starting material (2) to accomplish this synthesis. The steps in the synthesis may involve a stereoselective addition of an alkyne, and an efficient stereoselection effected in the PKC of a benzoenyne under the agency of a protective group P_1, such as benzylic OTBDMS group. This protective group can serve as a temporary stereodirecting group and may be conveniently removed via hydrogenolysis concomitantly in the catalytic hydrogenation of the enone PKC product. At the final step, reduction, P_1 cleavage and ester hydrolysis may be accomplished in one pot to obtain desired prostaglandin analog product, such as treprostinil (7).

The advantage of the present chemistry may include, but not limited to: 1) direct stereoselective addition of alkyne to aldehyde; 2) this route may also eliminate the need of four steps in the prior art synthesis of prostacyclin derivatives disclosed, for example, in Moriarty et al (U.S. Pat. No. 6,765,117). In particular, the present route may eliminate one or more of the following steps of the prior art synthesis (U.S. Pat. No. 6,765,117):

1) Grignard addition step (compound 5-compound 6 in U.S. Pat. No. 6,765,117);

2) PCC oxidation step (compound 6-compound 7 in U.S. Pat. No. 6,765,117);

3) Chiral reduction step, aka as Corey reduction (compound 7-compound 8 in U.S. Pat. No. 6,765,117);

4) demethylation of phenyl methyl ester (compound 13-compound 14 in U.S. Pat. No. 6,765,117).

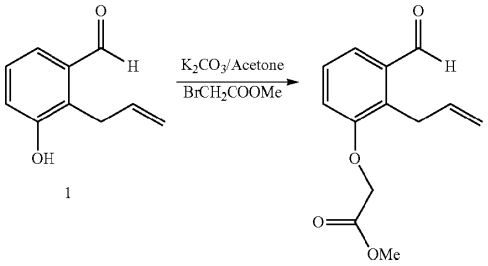
The present synthesis scheme may not only shorten the number of chemical steps to obtain treprostinil but also eliminate the tedious column chromatographic purifications required in the prior art methods, such as the one in U.S. Pat. No. 6,765,117 at intermediate steps. Such elimination of the prior art chromatographic purifications may significantly save manpower and large volumes of solvents. For example, the prior art route of U.S. Pat. No. 6,765,117 has 15 steps and requires chromatographic purifications on all them but one (compound 11-compound 12). The present synthesis has only 6 steps and may include chromatographic purification in at most three steps (steps 2, step 3 and step 4).

The present synthesis scheme may enable performing the reactions at room temperature without the need for cryogenic reactors, which are required in the prior art methods, such as the one in U.S. Pat. No. 6,765,117. For example, the prior art route of U.S. Pat. No. 6,765,117 requires cryogenic reactors in chiral reduction step (compound 7-compound 8) and in demethylation of phenyl methyl ester (compound 13-compound 14).

The present synthesis does not involve use of expensive reagents which are required in the prior art methods, such as the one in U.S. Pat. No. 6,765,117. For example, the prior art route of U.S. Pat. No. 6,765,117 in the chiral reduction step (compound 7-compound 8) used starting compound (B) for Corey reagent (B+C), which is an expensive reagent. Corey reagent (B+C) itself is also an expensive reagent.

This report provides the experimental details on the synthesis of treprostinil (7) below.

Step 1:
2-Allyl-3-[(carbomethoxy)methoxy]benzaldehyde
(2)



1 2

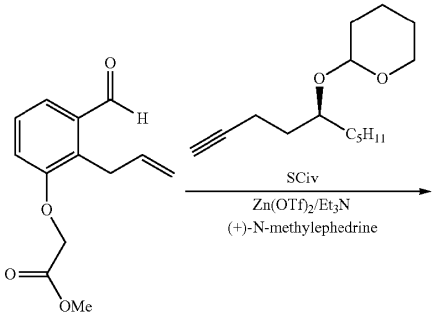
TABLE 1

Name	MW	Amount	mol
Aldehyde (1)	162.18	2.5 g	0.015
methylbromoacetate	152.97	2.5 g	0.016
K_2CO_3	138.21	6.3 g	0.045
Acetone	NA	50 ml	NA

Procedure: A 100-mL round-bottom flask equipped with a magnetic stirrer and stir bar was charged with a solution of 3-hydroxy-2-allylbenzaldehyde (1) (2.5 g in 50 mL acetone), methylbromoacetate (2.5 g, 1.10 eq.) and powdered potassium carbonate (6.3 g, 3.0 eq.). The mixture was stirred at 40° C. for four hours and progress of reaction was monitored by TLC (Note 1). After completion of the reaction, the suspension was filtered and the filtrate was evaporated in vacuo to afford a crude semi-solid mass. This was slurried in 30 mL of hexanes and stirred for 15 minutes. A solid crashed out of the hexanes and was collected by filtration to obtain compound (2) as an off-white solid; yield 3.48 g (99%), mp 46-47° C. The structure was consistent with spectral data. IR (neat) cm^{-1}: 3084, 2761, 1735, 1692; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.78 (s, 3H), 3.91 (d, 2H, J=6 Hz), 4.71 (s, 2H), 4.98 (m, 2H), 6.03 (m, 1H), 6.96 (d, 1H, J=8 Hz), 7.33 (dd, 1H, J=8 Hz), 7.52 (d, 1H, J=8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.32, 52.37, 66.01, 115.75, 117.05, 123.73, 127.55, 131.73, 135.40, 136.58, 156.23, 169.09, 192.08; MS: (M+1) 235.41.

Note 1: Completion of the reaction was monitored by TLC using a thin layer silica gel plate; eluent: 20% ethyl acetate in hexanes.

Step 2: Preparation of Chiral Benzyl Alkynol (3)



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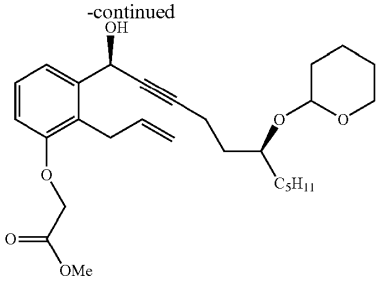


3

TABLE 2

Name	MW	Amount	mol
Aldehyde (2)	234.25	0.50 g	0.0026
Alkyne side chain (Sciv)	238.37	1.57 g	0.0065
Zinc triflate	363.51	3.17 g	0.0087
(+)-N-Methylephedrine	179.26	1.22 g	0.0068
Triethylamine	101.19	0.68 g	0.0068
Toluene	NA	10 ml	NA

Procedure: A 50-mL, two-necked, round-bottomed flask equipped with a magnetic stirrer and stir bar was charged with zinc triflate (3.17 g, 0.0087 mol) and (+)-N-methylephedrine (1.22 g, 0.0068 mol) in toluene (5 mL). To this mixture triethylamine was added (0.68 g, 0.0068 mol) and this gelatinous mixture was stirred at ambient temperature for 1-2 h. To this mixture was then added a solution of alkyne (1.57 g, 0.0065 mol) in toluene (4 mL), stirred at ambient temperature for 15-30 minutes followed by addition of a solution of aldehyde (2) (0.50 g, 0.0026 mol in 1-2 mL toluene). Progress of the reaction was monitored by TLC (Note 1). After stirring the mixture at room temperature for 16 h, TLC indicated completion of reaction. The reaction mixture was quenched by slow addition of water (10 mL). This was stirred for 5-10 minutes and organic layer containing desired compound was separated. The aqueous layer was extracted with ethyl acetate (10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and the filtrate concentrated in vacuo to obtain a crude product. The crude product was purified by column chromatography using 250-400 mesh silica gel. A solvent gradient of ethyl acetate in hexanes (5-20%) was used to elute the product from the column. All fractions containing the desired pure product were combined and concentrated in vacuo to give pure chiral benzyl alkynol (3, 700 mg, ~70%). The structure was consistent with spectral data.

^1H NMR ($CDCl_3$, 300 MHz) δ 0.84 (t, 3H, J=6 Hz), 1.25-1.82 (m, 17H), 2.28 (t, 1H, J=6 Hz), 2.34-2.42 (m, 2H), 3.42-3.52 (m, 1H), 3.61-3.74 (m, 3H), 3.78 (s, 3H), 3.81-3.95 (m, 1H), 4.61 (s, 2H), 4.68 (m, 1H), 4.94-5.01 (m, 2H), 5.62 (br s, 1H), 5.97-6.07 (m, 1H), 6.76 (d, 1H, J=8 Hz), 7.16-7.27 (m, 1H), 7.38-7.43 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 84.75, -4.38, -3.49, 14.12, 14.16, 14.84, 15.52, 18.06, 18.38, 20.04, 20.24, 22.70, 24.76, 25.25, 25.56, 25.72, 25.94, 29.67, 31.22, 31.28, 32.05, 32.11, 32.65, 33.41, 34.01, 35.08, 52.22, 62.36, 62.84, 63.09, 66.04, 75.41, 76.44, 76.68, 80.83, 81.22, 85.57, 86.01, 97.31, 98.85, 110.89, 114.80, 119.77, 119.82, 125.56, 127.11, 127.16, 136.46, 136.52, 142.66, 142.73, 155.83, 169.68; MS: (M+Na) 495.6.

Note 1: Completion of the reaction was monitored by thin layer chromatography (TLC) using a thin layer silica gel plate; eluent: 20% ethyl acetate in hexanes.

Step 3: Preparation of Chiral Benzylalkynyl tert.-butyldimethylsilyl ether (4)

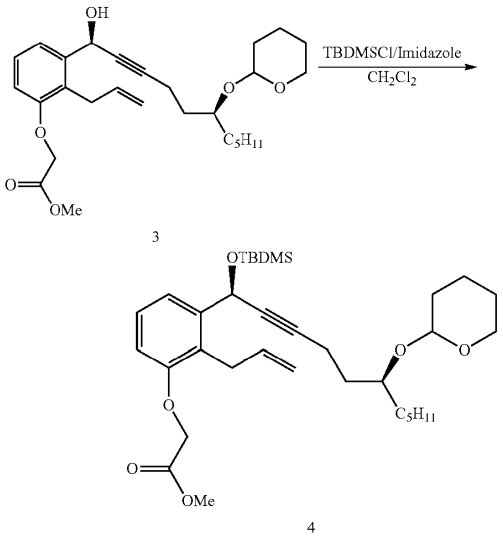


TABLE 3

Name	MW	Amount	Mol
Chiral benzylalkynol	472.62	0.680 g	0.0014
t-butyldimethylsilyl chloride	150.73	0.282 g	0.0018
Imidazole	68.0	0.127 g	0.0018
4-(Dimethylamino)pyridine	122.17	0.167 g	10 mol %
Dichloromethane	NA	30.0 mL	NA

Procedure: A 50-mL, two-necked, round-bottomed flask equipped with a magnetic stirrer and stir bar was charged with a solution of chiral benzylalkynol (3) (0.680 g, 0.0014 mol) in dichloromethane (30 mL) under argon. To this solution, imidazole (0.127 g, 0.0018 mol) and 4-(dimethylamino)pyridine (0.176 g, 10 mol %) were added while stirring at room temperature. The stirring was continued until a clear solution was obtained. To this solution t-butyldimethylsilyl chloride (0.282 g, 0.0018 mol) was added slowly while stirring. The reaction mixture was stirred at room temperature for approximately 3-4 h (Note 1). The reaction was quenched by addition of a saturated ammonium chloride solution (10 mL). The organic layer was separated and washed with brine (10 mL), dried over sodium sulfate and concentrated in vacuo. The crude product was purified by column chromatography using 250-400 mesh silica gel and eluted with a gradient solvent of ethyl acetate in hexanes (2-12%). The fractions containing the desired compound were evaporated in vacuo to yield benzyl alkynyl t-butyldimethylsilyl ether (4) as a colorless, viscous liquid (0.800 g, 94%). The structure was consistent with spectral data.

^{1}II NMR ($CDCl_3$, 300 MIIz) δ 0.07-0.13 (four merged s, 6H), 0.83 (merged t, 3H), 0.89-0.91 (two merged s, 9H), 1.24-1.84 (m, 10H), 2.18-2.34 (m, 2H), 3.39-3.69 (m, 3H), 3.78 (s, 3H), 3.81-3.91 (m, 1H), 4.55-4.56 (m, 1H), 4.62 (s, 2H), 4.96-4.98 (m, 2H), 5.57 (br s, 1H), 5.92-6.01 (m, 1H), 6.66 (d, 1H, J=8 Hz), 7.17 (two dd, 1H, J=8 Hz), 7.30 (d, 1H, J=8 Hz).

Note 1: Completion of the reaction was monitored by TLC using a thin layer silica gel plate; eluent: 20% ethyl acetate in hexanes.

Step 4: Preparation of Tricyclicenone (5)

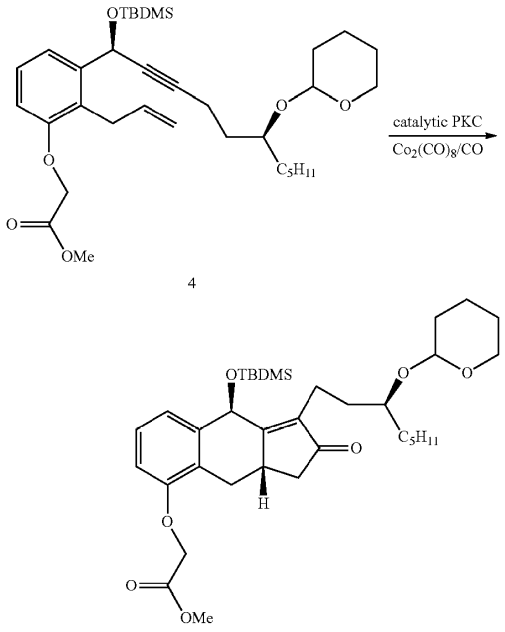


TABLE 4

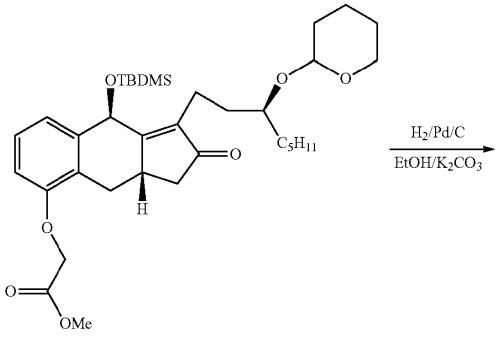
Name	MW	Amount	Mole
Benzyl alkynyl t-butyldimethylsilyl ether (4)	584.65	0.100 g	0.00017
Octacarbonyldicobalt	341.95	0.0030	5 mol %
1,2-Dimethoxyethane	NA	10 ml	NA

Procedure: A 50-mL round-bottomed flask equipped with a magnetic stirrer and stir bar was charged with a solution of benzylalkynyl tert.-butyldimethylsilyl ether (4) (0.10 g) in 1,2-DME (10 mL), and was degassed by bubbling argon through the solution for 2-3 minutes. To this solution was added $CO_2(CO)_8$ (0.003 g) and the mixture was stirred at room temperature under an atmosphere of carbon monoxide (CO, using balloon). After 30 minutes the reaction mixture was heated to 60-65° C. using an oil bath for 6 h (Note 1). After cooling to room temperature, 1,2-DME (solvent) was evaporated in vacuo to yield a crude, gummy compound that was purified by flash chromatography on silica gel using 5-20% ethyl acetate in hexanes. Fractions containing the desired compound were collected and evaporated in vacuo to yield tricyclic enone (5) (102 mg, 83%). The structure was consistent with spectral data. IR (neat) cm, 1: 2928, 1728,

1702; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.02-0.13 (m, 6H), 0.80 (merged s, 9H), 0.81-0.88 (m, 1H). 1.18-2.61 (m, 16H), 2.71 (dd, 1H, J=6 Hz), 3.32-3.60 (m, 4H), 3.79 (merged s, 3H), 3.80-3.92 (m, 1H), 4.56 (merged d, 1H), 4.60 (merged s, 2H), 5.47 and 5.53 (two s, 1H), 6.63, 1H, J=8 Hz), 6.97 (dd, 1H, J=8 Hz), 7.19 (dd, 1H, J=8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) 8 −4.20, 4.08, 14.17, 18.15, 20.13, 22.69, 24.84, 25.71, 31.27, 32.14, 33.29, 33.93, 42.19, 52.34, 62.86, 65.50, 76.68, 97.24, 110.19, 123.28, 125.74, 127.31, 137.52, 137.95, 155.18, 169.44, 209.60.

Note 1: Completion of reaction was monitored by TLC using a thin layer silica gel plate; eluant: 20% ethyl acetate in hexanes. After 3 h, TLC showed presence of starting material. At this stage extra 5 mol % cobalt catalyst was added at room temperature and reaction was again heated at 60-65° C. until completion (total reaction time 6 h)

Step 5: Preparation of Tricyclic Ketone (6)



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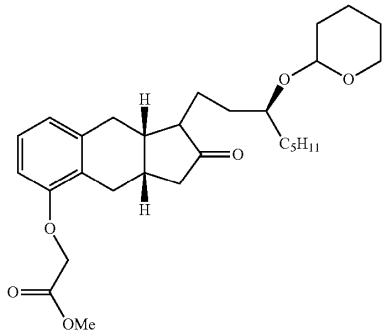


6

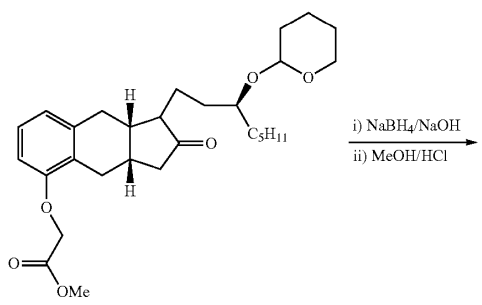
TABLE 5

Name	MW	Amount	Mole
Tricyclic enone (5)	614.90	0.10 g	NA
Palladium on charcoal (50% wet)	NA	0.01 g	NA
Potassium carbonate	NA	0.010	NA
Methanol	NA	10.0 ml	NA
Water	NA	1.00 ml	NA

Procedure: A 200-mL round-bottom flask equipped with a magnetic stirrer and stir bar was charged with a solution of tricyclic enone (5) (0.10 g) in methanol (10.0 mL) and aqueous K_2CO_3 (0.010 g in 1.0 mL water). To this solution, Pd/C (0.010 g, 50% wet) was added while stirring at room temperature. The reaction vessel was evacuated and pressurized with hydrogen gas using a balloon. The reaction mixture was hydrogenated at balloon pressure overnight (~16 h) at ambient temperature. After 16 h, the reaction was monitored by TLC, infra-red (IR) and proton NMR (Note 1). At this stage the reaction mixture was filtered through a pad of Celite (~4 g). The Celite pad was washed with methanol (~50 mL). The combined filtrates were evaporated in vacuo to give crude tricyclic ketone (6) and the crude product was purified by column chromatography using 250-400 mesh silica gel. A solvent gradient of ethyl acetate in hexanes (5-35%) was used to elute the product from column. The fractions containing desired product were evaporated in vacuo to yield tricyclic ketone (6) (0.035 g, 44%). IR (neat) cm^{-1} 2929, 1736, 1679; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.87 (br t, 3H), 1.21-3.12 (m, 27H), 3.42-3.53 (m, 1H), 3.55-3.68 (m, 1H), 3.79 (s, 3H), 3.86-3.95 (m, 1H), 4.61-4.69 (m, 1H), 4.64 (merged s, 2H), 6.53-6.56 (m, 1H), 6.74-6.81 (m, 1H), 7.06-7.08 (m, 1H).

Note 1: Completion of the hydrogenation was checked by monitoring the change in the IR carbonyl stretch frequency [starting material (tricyclic enone) ~1728 cm^{-1}, product (tricyclic ketone) −1736 cm^{-1} and proton NMR. The reaction mixture was evacuated and then purged with argon. A small aliquot of reaction mixture was sampled, filtered through a short pad of Celite, and the filtrate was evaporated in vacuo to give a thick, oily compound. The IR of the oily compound was checked for above mentioned carbonyl stretch frequency. Completion of reaction was monitored by TLC using a thin layer silica gel plate; eluent: 40% ethyl acetate in hexanes.

Step 6: Preparation of Treprostinil (7)



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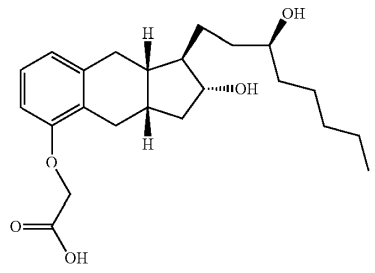


7
(treprostinil)

TABLE 6

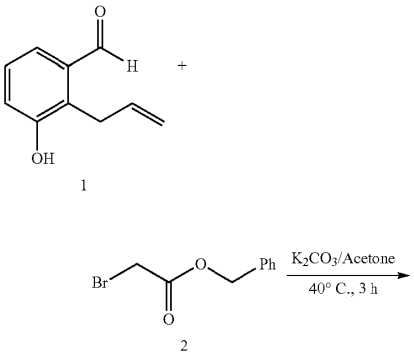
Name	MW	Amount	Mole
Tricyclic ketone (6)	486.65	0.0035 g	0.00006
Sodium hydroxide	40.0	0.030 g	0.00073
Sodium borohydride	37.8	0.004 g	0.00012
Methanol	NA	5.0 ml	NA
Water	NA	1.0 ml	NA
HCl	NA	(10%) 4-5 ml	NA

Procedure: A 200-mL round-bottom flask equipped with a magnetic stirrer and stir bar was charged with a solution of tricyclic ketone (6) (0.035 g) in methanol (5.0 mL). It was cooled to −5° C. and aqueous sodium hydroxide solution (0.030 g, 15 eq, dissolved in 1.0 mL water) was added while stirring. The reaction mixture was stirred for 30 minutes and then sodium borohydride (0.004 g in 1.0 mL water) was added and stirring was continued at −5° C. for 2 h. This was slowly allowed to warm to room temperature and stirred overnight (~16 h). The reaction mixture was quenched carefully by dropwise addition of 10% hydrochloric acid (~4-5 mL) until pH 2-3. Then the mixture was concentrated in vacuo and to this water (10 mL) and ethyl acetate (10 mL) were added and stirred for 5-10 minutes. The organic layer was separated and washed with brine (10 mL), dried over sodium sulfate and concentrated in vacuo to obtain UT-15 (7) as an off-white solid (0.021 g). The compound was characterized by spectral data and HPLC. The ^{1}HNMR and HPLC of the samples were compared with reference UT-15 and were identical; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.90 (t, 3H, 6 Hz), 1.05-1.78 (m, 13H), 2.85-2.85-2.98 (m, 1H), 2.03 2.12 (m, 1H), 2.21-2.32 (m, 1H), 2.45-2.53 (m, 1H), 2.61-2.81 (m, 3H), 3.52 (br s, 1H), 3.58-3.69 (m, 1H), 4.62 (s, 2H), 6.69 (d, 1H, J=8 Hz), 6.78 (d, 1H, J=8 Hz), 7.04 (dd, 1H, J=8 Hz).

Example 4

Preparation
2-Ally-3-(carbomethoxy)benzyloxybenzaldehyde

Reaction Scheme:



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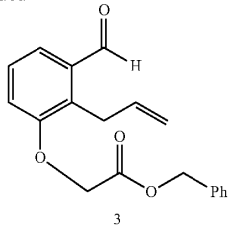


Experimental

Preparation of 2-Allyl-3-benzyloxybenzaldehyde (3)

TABLE 7

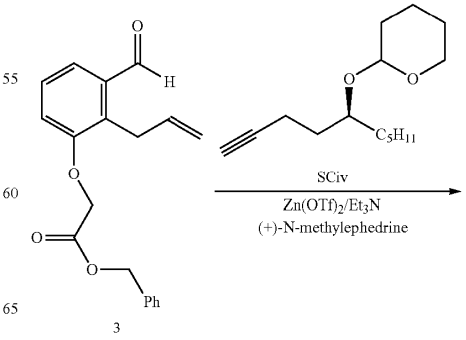
Name	Mol Wt	Amount	mol
2-Allyl-3-hydroxybenzaldehyde	162.18	1.00 g	0.006
Benzyl bromoacetate	229.08	1.53 g	0.006
Potassium carbonate	138.21	3.30 g	0.024
Acetone	NA	20 mL	NA

Experimental Procedure

To a solution of 2-allyl-3-hydroxybenzaldehyde (1) (1.00 g, 0.006 mol) in acetone (20 mL) was added powdered potassium carbonate (3.30 g) and benzyl bromoacetate (2) (1.53 g, 0.006 mol). The reaction mixture was stirred at 40° C. (oil bath temperature) for 5 h. The reaction mixture was checked by tlc (Note 1). The reaction was complete. The mixture was filtered, and the filtrate was concentrated in vacuo to get crude viscous liquid. The crude product was purified by silica gel column chromatography using a mixture of ethyl acetate and hexanes (4-10%) to get colorless viscous liquid (1.73 g, 88.7%). ^{1}H NMR ($CDCl_3$, 300 Hz) 3.89 (m, 2H), 4.74 (s, 2H), 4.95-5.00 (m, 2H), 5.22 (s, 2H), 5.97-6.06 (m, 1H), 6.97 (m, 1H), 7.29-7.34 9 m, 6H), 7.54 (m, 1H).

Note 1: Completion of the reaction was monitored by thin layer chromatography (TLC) using a thin layer silica gel plate; eluent: 10% ethyl acetate in hexanes.

Step 2: Preparation of Chiral Benzyl Alkynol (4)



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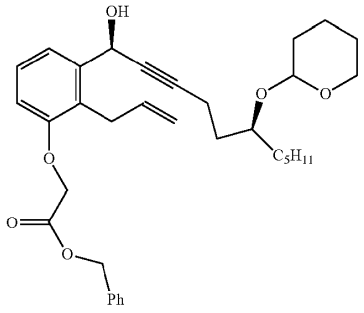


4

TABLE 8

Name	a. W	Amount	mol
Aldehyde	312.00	0.250 g	0.0008
Alkyne side chain (Sciv)	238.37	3.00 g	0.0025
Zinc triflate	363.51	1.20 g	0.0030
(+)-N-Methylephedrine	179.26	0.460 g	0.0025
Triethylamine	101.19	0.810 g	0.0025
Toluene	NA	10 mL	NA

Procedure:

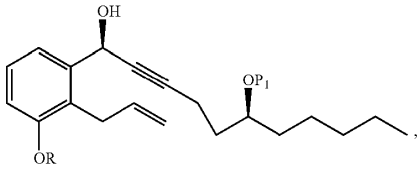
A 50-mL, two-necked, round-bottomed flask equipped with a magnetic stirrer and stir bar was charged with zinc triflate (1.20 g, 0.0030 mol) and (+)-N-methylephedrine (0.460 g, 0.0025 mol) in toluene (5 mL). To this mixture triethylamine was added (0.810 g, 0.0025 mol) and this gelatinous mixture was stirred at ambient temperature for 1-2 h. To this mixture was then added a solution of alkyne (3.00 g, 0.0025 mol) in toluene (4 mL), stirred at ambient temperature for 15-30 minutes followed by addition of a solution of aldehyde (0.250 g, 0.0008 mol in 1-2 mL toluene). Progress of the reaction was monitored by TLC (Note 1). After stirring the mixture at room temperature for 2 h, TLC indicated completion of reaction. The reaction mixture was quenched by slow addition of water (10 mL). This was stirred for 5-10 minutes and organic layer containing desired compound was separated. The aqueous layer was extracted with ethyl acetate (10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and the filtrate concentrated in vacuo to obtain a crude product. The crude product was purified by column chromatography using 250-400 mesh silica gel. A solvent gradient of ethyl acetate in hexanes (5-20%) was used to elute the product from the column. All fractions containing the desired pure product were combined and concentrated in vacuo to give pure chiral benzyl alkynol (370 mg, 84%). The structure was consistent with spectral data. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.84 (τ, 3H), 1.24-1.75 (m, 17H), 2.24-2.30 (m, 2H), 3.43-3.47 (m, 1H), 3.65-3.84 (m, 2H), 3.86-3.87 (m, 1H), 4.63-4.67 (m, 3 h), 4.95-4.97 (m, 2H), 5.21 (s, 2H), 5.60 (m, 1H), 5.95-6.04 (m, 1H), 6.70 (m, 1H), 7.18-7.36 (m, 8H).

Note 1: Completion of the reaction was monitored by thin layer chromatography (TLC) using a thin layer silica gel plate; eluent: 20% ethyl acetate in hexanes.

Additional Embodiments

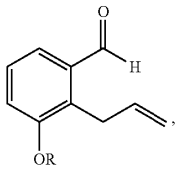
1. A method of preparing a compound represented by the following structural formula:

(A)



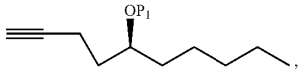
comprising reacting a compound represented by the following structural formula:

(I)



with a compound represented by the following structural formula:

(a)



wherein:

P_1 is an alcohol protecting group;

R is $—(CH_2)_1X$;

X is H, phenyl, —CN, $—OR_1$ or $COOR_1$;

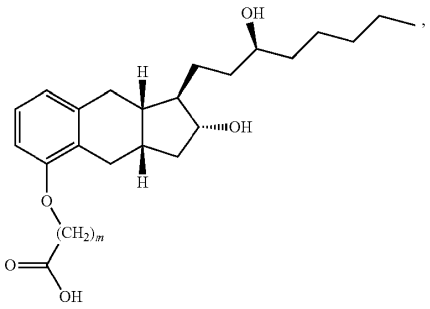
R_1 is an alkyl, THP, TBDMS or a unsubstituted or substituted benzyl group; and

n is 1, 2 or 3.

2. The method of embodiment 1, wherein R is methyl.
3. The method of embodiment 1, wherein R is $CH_2CO_2C_2H_5$.
4. The method of embodiment 1, wherein R is $CH_2CO_2CH_3$.
5. The method of embodiment 1, wherein R is CH_2CO_2Bn.
6. The method of embodiment 1, wherein P_1 is tetrahydropyranyl (THP).
7. The method of embodiment 1, wherein P_1 is tert-butyldimethylsilyl (TBDMS), tertiarybutyldiphenylsilyl (TBDPS), triethylsilyl (TES) or triphenylmethyl (trityl group).
8. The method of embodiment 7, wherein P_1 is tert-butyldimethylsilyl (TBDMS).
9. The method of embodiment 1, wherein the reaction is carried out in the presence of chiral inducing agent.
10. The method of embodiment 9, wherein the chiral inducing ligand is (+)-N-methylephederin.
11. The method of embodiment 1, wherein the reaction is carried out in the presence of a base and a zinc reagent.
12. The method of embodiment 11, wherein the base is triethylamine.
13. The method of embodiment 12, wherein the zinc reagent is zinc triflate.

14. A method of preparing a compound represented by the following structural formula:

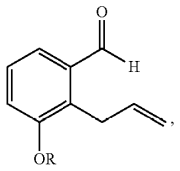
(IX)



or a pharmaceutically acceptable salt thereof, comprising:

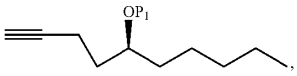
reacting a compound represented by structural formula (I):

(1)



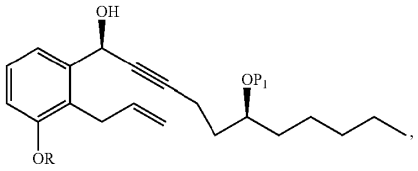
with a compound represented by structural formula (a):

(a)



to form a compound represented by structural formula (A):

(A)



wherein:

P_1 is an alcohol protecting group;

R is $—(CH_2)_1X$;

X is H, phenyl, —CN, $—OR_1$ or $COOR_1$;

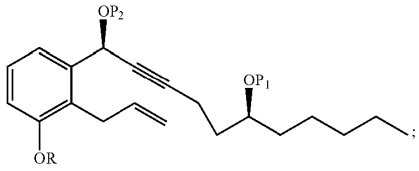
R_1 is an alkyl group, THP, TBDMS or a substituted or unsubstituted benzyl group; and

n is 1, 2 or 3.

15. The method of embodiment 14, further comprising:

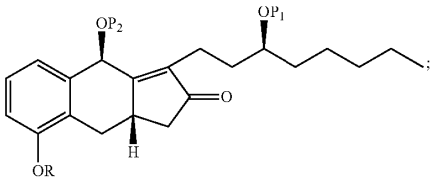
(1) reacting the compound of structural formula (A) with an alcohol protecting group to form a compound represented by structural formula (II):

(II)



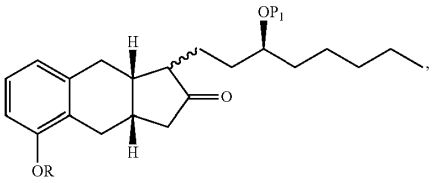
(2) converting the compound of structural formula (II) to a tricyclic compound represented by structural formula (III):

(III)



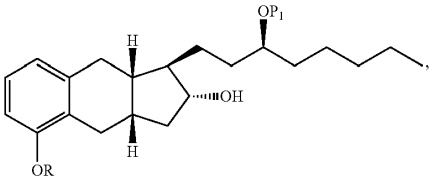
(3) hydrogenating the tricyclic compound of structural formula (III) to form a hydrogenated tricyclic compound represented by structural formula (IV):

(IV)



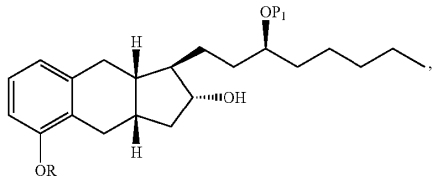
(4) reacting the compound of structural formula (IV) with a reducing agent to form a compound represented by structural formula (V):

(V)



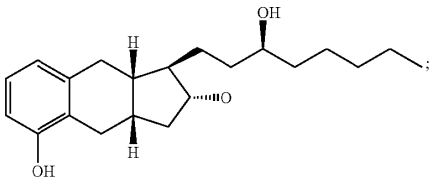
(5) deprotecting the compound of structural formula (V) to form a compound represented by structural formula (VI):

(VI)



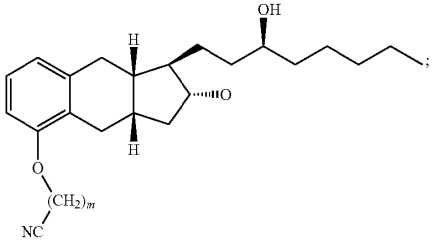
(6) converting the compound represented by structural formula (VI) to a compound represented by structural formula (VII):

(VII)



(7) reacting the compound represented by structural formula (VII) with $X_1(CH_2)_mCN$ to form a compound represented by structural formula (VIII):

(VIII)



and

(8) hydrolyzing the compound of Structural Formula (VIII) to form the compound represented by Structural Formula (IX),

wherein:

P_2 is an alcohol protecting group;

m is 1, 2 or 3; and

X_1 is a leaving group.

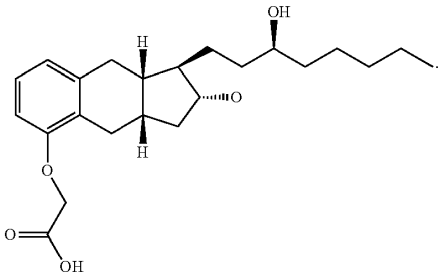
16. The method of embodiment 14, wherein R is methyl.

17. The method of embodiment 14, wherein R is $CH_2CO_2C_2H_5$.

18. The method of embodiment 14, wherein P_1 is tetrahydrofuranyl (THP).

19. The method of embodiment 14, wherein the compound of structural formula (IX) is treprostinil represented by the following structural formula:

UT-15 (IX-1)



20. The method of embodiment 14, wherein the reaction of the compound of structural formula (I) and the compound of structural formula (a) is carried out in the presence of a chiral inducing agent.

21. The method of embodiment 20, wherein the chiral inducing agent is (+)-N-methylephederin.

22. The method of embodiment 20, wherein the reaction is carried out in the presence of a base and a zinc reagent.

23. The method of embodiment 22, wherein the base is triethylamine.

24. The method of embodiment 22, wherein the zinc reagent is zinc triflate.

25. The method of embodiment 15, wherein P_2 is tert-butyldimethylsilyl (TBDMS).

26. The method of embodiment 15, wherein for step (2), the compound of structural formula (II) is converted to the compound of structural formula (III) through a cobalt-mediated cyclization reaction.

27. The method of embodiment 26, wherein the cobalt-mediated cyclization reaction is carried out in the presence of $CO_2(CO)_8$.

28. The method of embodiment 15, wherein the hydrogenation reaction of step (3) is carried out in the presence of a base.

29. The method of embodiment 28, wherein the base is K_2CO_3.

30. The method of embodiment 15, wherein the reducing agent in step (4) is $NaBH_4$.

31. The method of embodiment 15, wherein for step (5), the compound of structural formula (V) is deprotected in the presence of an acid.

32. The method of embodiment 31, wherein the acid is TsOH.

33. The method of embodiment 15, wherein for step (6), the compound of structural formula (VI) is reacted with nBuLi and Ph_2PH.

34. The method of embodiment 15, wherein for step (7), X_1 is —Cl.

35. The method of embodiment 15, wherein for step (8), the compound of structural formula (VIII) is hydrolyzed in the presence of a base.

36. The method of embodiment 35, wherein the base is NaOH.

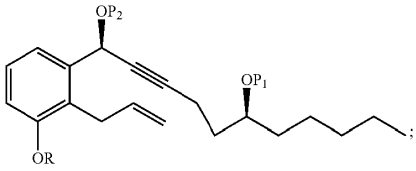
37. The method of embodiment 15, wherein the compound produced by the method is a sodium salt or a diethanolamine salt of treprostinil.

38. The method of embodiment 15, wherein R is $(CH_2)_m CO_2R_1$, wherein R_1 is an alkyl or a substituted or unsubstituted benzyl group.

39. The method embodiment 38, further comprising:

(a) reacting the compound of structural formula (A) with a second alcohol protecting group to form a compound represented by structural formula (4):

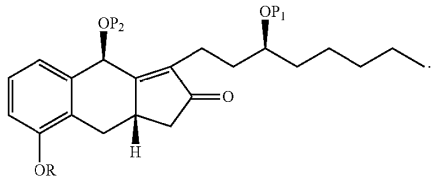
(4)



and

(b) converting the compound of structural formula (4) to a tricyclic compound represented by structural formula (5):

(5)



40. The method of embodiment 39, wherein P_2 is tert-butyldimethylsilyl (TBDMS), tertiarybutyldiphenylsilyl (TBDPS), triethylsilyl (TES) or triphenylmethyl (trityl group).

41. The method of embodiment 40, wherein P_2 is tert-butyldimethylsilyl (TBDMS).

42. The method of embodiment 39, wherein P_1 is tetrahydrofuranyl (THP), benzyl, 2,4-dinitrobenzyl, methoxymethyl (MOM), tertiarybutyldimethylsilyl (TBDMS), tertiarybutyldiphenylsilyl (TBDPS) or triethylsilyl (TES).

43. The method of embodiment 42, wherein P_1 is THP.

44. The method of embodiment 39, wherein m is 1.

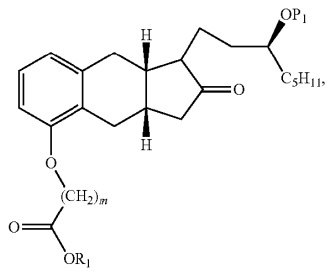
45. The method of embodiment 39, wherein for the converting step (b), the compound of structural formula (4) is converted to the compound of structural formula (5) through a cobalt-mediated cyclization reaction.

46. The method of embodiment 45, wherein the cobalt-mediated cyclization reaction is carried out in the presence of $CO_2(CO)_8$.

47. The method of embodiment 39, wherein R_1 is an alkyl group and wherein the method further comprises:

(c) hydrogenating the tricyclic compound of structural formula (5) to form a hydrogenated tricyclic compound represented by structural formula (6):

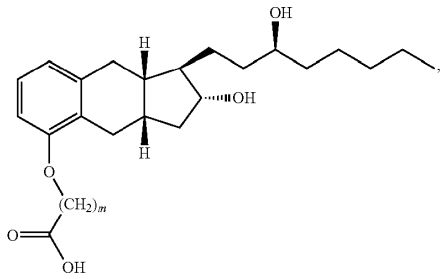
(6)



and

(d) converting the hydrogenated tricyclic compound represented by structural formula (6) to a compound represented by structural formula (IX):

(IX)



wherein said converting (d) accomplishes cleaving of the protective group P_1 and ester hydrolysis of R in a single pot.

48. The method of embodiment 47, wherein the hydrogenation reaction of step (c) is carried out in the presence of a base.

49. The method of embodiment 48, wherein the base is K_2CO_3.

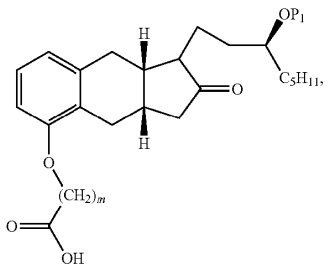
50. The method of embodiment 47, wherein R_1 is straight or branched C1-C5 alkyl.

51. The method of embodiment 50, wherein R_1 is methyl.

52. The method of embodiment 39, wherein R_1 is a substituted or unsubstituted benzyl group and wherein the method further comprises:

(c') hydrogenating the tricyclic compound of structural formula (5) to form a hydrogenated tricyclic compound represented by structural formula (6'):

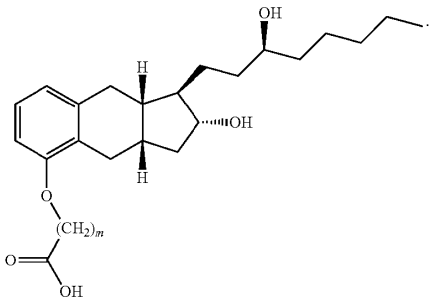
(6')



and

(d') converting the hydrogenated tricyclic compound represented by structural formula (6') to a compound represented by structural formula (IX):

(IX)



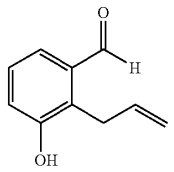
53. The method of embodiment 52, wherein the hydrogenation reaction of step (c) is carried out in the presence of a base.

54. The method of embodiment 53, wherein the base is K_2CO_3.

55. The method of embodiment 52, wherein R_1 is an unsubstituted benzyl group.

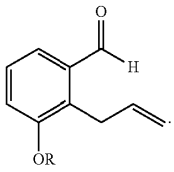
56. The method of embodiment 14, further comprising reacting compound represented by formula (1):

(1)



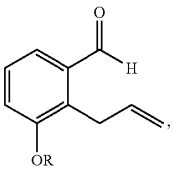
to form the compound represented by the structural formula

(I)



57. A compound of formula (1):

(1)



wherein R is $(CH_2)_mCO_2R_1$, m is 1, 2 or 3, and

R_1 is an alkyl group, THP, TBDMS or a substituted or unsubstituted benzyl group.

58. The compound of embodiment 57, wherein m is 1.

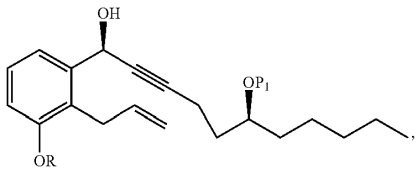
59. The compound of embodiment 57, wherein R_1 is straight or branched C1-C5 alkyl.

60. The compound of embodiment 59, where R_1 is methyl.

61. The compound of embodiment 57, wherein R_1 is unsubstituted benzyl.

62. A compound represented by structural formula (A):

(A)



wherein:

P_1 is an alcohol protecting group;

wherein R is $(CH_2)_mCO_2R_1$, m is 1, 2 or 3, and

R_1 is an alkyl group or a substituted or unsubstituted benzyl group.

63. The compound of embodiment 62, wherein m is 1.

64. The compound of embodiment 62, wherein R_1 is straight or branched C1-C5 alkyl.

65. The compound of embodiment 64, where R_1 is methyl.

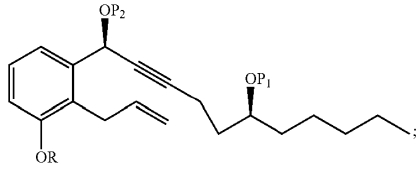
66. The compound of embodiment 62, wherein R_1 is unsubstituted benzyl.

67. The compound of embodiment 62, wherein P_1 is tetrahydrofuranyl (THP), benzyl, 2,4-dinitrobenzyl, methoxymethyl (MOM), tertiarybutyldimethylsilyl (TBDMS), tertiarybutyldiphenylsilyl (TBDPS) or triethylsilyl (TES).

68. The compound of embodiment 76, wherein P_1 is THP.

69. A compound represented by structural formula (4):

(4)



wherein:

each of P_1 and P_2 is an alcohol protecting group;

wherein R is $(CH_2)_mCO_2R_1$, m is 1, 2 or 3, and

R_1 is an alkyl group, or a substituted or unsubstituted benzyl group.

70. The compound of embodiment 69, wherein m is 1.

71. The compound of embodiment 69, wherein R_1 is straight or branched C1-C5 alkyl.

72. The compound of embodiment 71, where R_1 is methyl.

73. The compound of embodiment 62, wherein R_1 is unsubstituted benzyl.

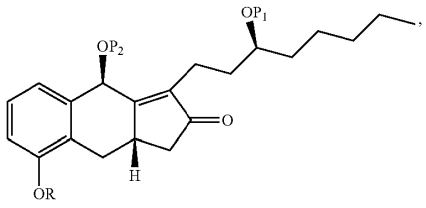
74. The compound of embodiment 62, wherein P_2 is tertbutyldimethylsilyl (TBDMS), tertiarybutyldiphenylsilyl (TBDPS), triethylsilyl (TES) or triphenylmethyl (trityl group).

75. The compound of embodiment 67, wherein P_2 is tertbutyldimethylsilyl (TBDMS).

76. The compound of embodiment 69, wherein P_1 is tetrahydrofuranyl (THP), benzyl, 2,4-dinitrobenzyl, methoxymethyl (MOM), tertiarybutyldimethylsilyl (TBDMS), tertiarybutyldipbenylsilyl (TBDPS) or triethylsilyl (TES).

77. The compound of embodiment 76, wherein P_1 is THP.

78. A compound represented by structural formula (5):



(5)

wherein:

each of P_1 and P_2 is an alcohol protecting group;

wherein R is $(CH_2)_mCO_2R_1$, m is 1, 2 or 3, and

R_1 is an alkyl group, or a substituted or unsubstituted benzyl group.

79. The compound of embodiment 78, wherein m is 1.

80. The compound of embodiment 78, wherein R_1 is straight or branched C1-C5 alkyl.

81. The compound of embodiment 80, where R_1 is methyl.

82. The compound of embodiment 78, wherein R_1 is unsubstituted benzyl.

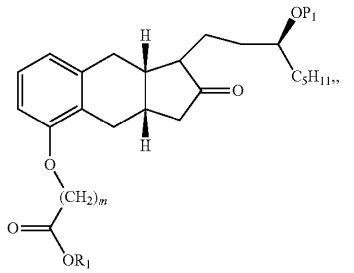
83. The compound of embodiment 78, wherein P_2 is tert-butyldimethylsilyl (TBDMS), tertiarybutyldiphenylsilyl (TBDPS), triethylsilyl (TES) or triphenylmethyl (trityl group).

84. The compound of embodiment 83, wherein P_2 is tert-butyldimethylsilyl (TBDMS).

85. The compound of embodiment 78, wherein P_1 is tetrahydrofuranyl (THP), benzyl, 2,4-dinitrobenzyl, methoxymethyl (MOM), tertiarybutyldimethylsilyl (TBDMS), tertiarybutyldiphenylsilyl (TBDPS) or triethylsilyl (TES).

86. The compound of embodiment 85, wherein P_1 is THP.

87. A compound represented by structural formula (6):



(6)

wherein:

P_1 is an alcohol protecting group;

wherein m is 1, 2 or 3, and

R_1 is an alkyl group, or hydrogen.

88. The compound of embodiment 87, wherein m is 1.

89. The compound of embodiment 87, wherein R_1 is straight or branched C1-C5 alkyl.

90. The compound of embodiment 89, where R_1 is methyl.

91. The compound of embodiment 87, wherein R_1 is unsubstituted benzyl.

92. The compound of embodiment 87, wherein P_1 is tetrahydrofuranyl (THP), benzyl, 2,4-dinitrobenzyl, methoxymethyl (MOM), tertiarybutyldimethylsilyl (TBDMS), tertiarybutyldiphenylsilyl (TBDPS) or triethylsilyl (TES).

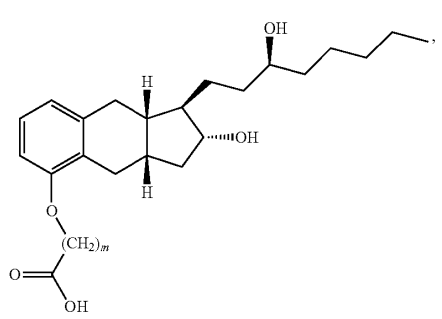
93. The compound of embodiment 92, wherein P_1 is THP.

Although the foregoing refers to particular preferred embodiments, it will be understood that the present invention is not so limited. It will occur to those of ordinary skill in the art that various modifications may be made to the disclosed embodiments and that such modifications are intended to be within the scope of the present invention.

All of the publications, patent applications and patents cited in this specification are incorporated herein by reference in their entirety.

What is claimed is:

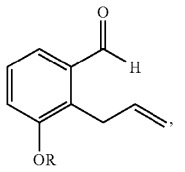
1. A method of preparing a compound represented by the following structural formula:



(IX)

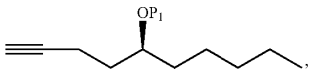
or a pharmaceutically acceptable salt thereof, comprising:

reacting a compound represented by structural formula (I):



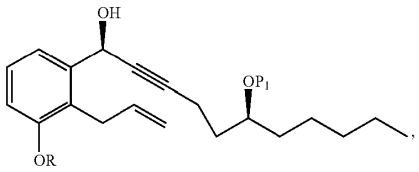
(I)

with a compound represented by structural formula (a):



(a)

to form a compound represented by structural formula (A):



(A)

wherein:

P_1 is an alcohol protecting group;

R is —$(CH_2)_mX$;

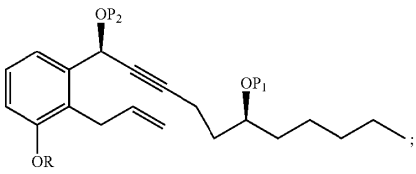
X is $COOR_1$;

R_1 is an alkyl group; and

m is 1, 2 or 3, wherein the process further comprises:

(a) reacting the compound of structural formula (A) with a second alcohol protecting group to form a compound represented by structural formula (4):

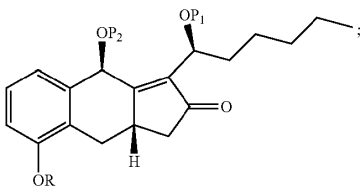
(4)



and

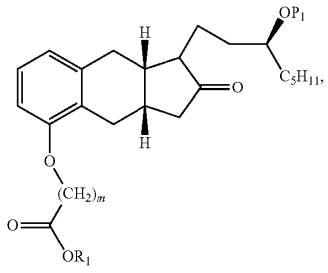
(b) converting the compound of structural formula (4) to a tricyclic compound represented by structural formula (5):

(5)



(c) hydrogenating the tricyclic compound of structural formula (5) to form a hydrogenated tricyclic compound represented by structural formula (6):

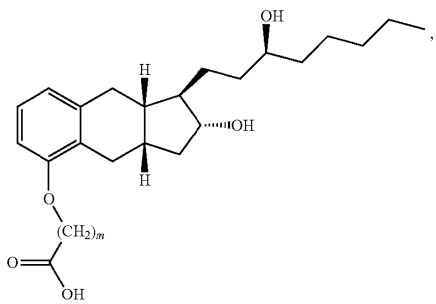
(6)



and

(d) converting the hydrogenated tricyclic compound represented by structural formula (6) to a compound represented by structural formula (IX):

(IX)



wherein said converting (d) accomplishes cleaving of the protective group P_1 and ester hydrolysis of R_1 in a single pot.

2. The method of claim **1**, wherein P2 is tert-butyldimethylsilyl (TBDMS), tertiarybutyldiphenylsilyl (TBDPS), triethylsilyl (TES) or triphenylmethyl (trityl group).

3. The method of claim **2**, wherein P2 is tert-butyldimethylsilyl (TBDMS).

4. The method of claim **1**, wherein P1 is tetrahydrofuranyl (THP), benzyl, 2,4-dinitrobenzyl, methoxymethyl (MOM), tertiarybutyldimethylsilyl (TBDMS), tertiarybutyldiphenylsilyl (TBDPS) or triethylsilyl (TES).

5. The method of claim **4**, wherein P1 is THP.

6. The method of claim **1**, wherein for the converting step (b), the compound of structural formula (4) is converted to the compound of structural formula (5) through a cobalt-mediated cyclization reaction.

7. The method of claim **6**, wherein the cobalt-mediated cyclization reaction is carried out in the presence of Co2(CO)8.

8. The method of claim **1**, wherein the hydrogenation reaction of step (c) is carried out in the presence of a base.

9. The method of claim **8**, wherein the base is K2CO3.

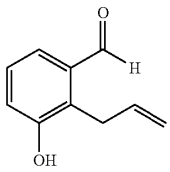
10. The method of claim **1**, wherein R1 is straight or branched C1-C5 alkyl.

11. The method of claim **10**, wherein R1 is methyl.

12. The method of claim **1**, further comprising

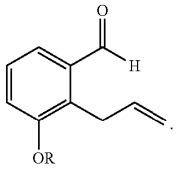
reacting the compound represented by formula (I):

(1)



to form the compound represented by the structural formula

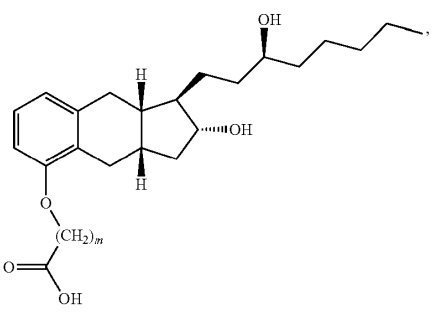
(I)



13. The method of claim **1**, wherein m=1.

14. A method of preparing a compound represented by the following structural formula:

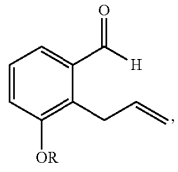
(IX)



or a pharmaceutically acceptable salt thereof, comprising:

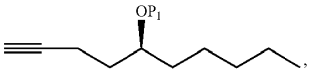
reacting a compound represented by structural formula (I):

(I)



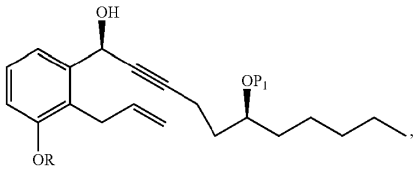
with a compound represented by structural formula (a):

(a)



to form a compound represented by structural formula (A):

(A)



wherein:

P_1 is an alcohol protecting group;

R is $—(CH_2)_mX$;

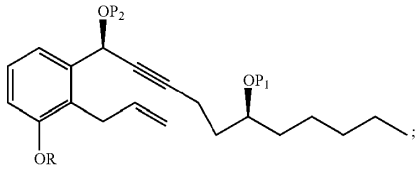
X is $COOR_1$;

R_1 is a substituted or unsubstituted benzyl group; and

m is 1, 2 or 3, wherein the process further comprises:

(a) reacting the compound of structural formula (A) with a second alcohol protecting group to form a compound represented by structural formula (4):

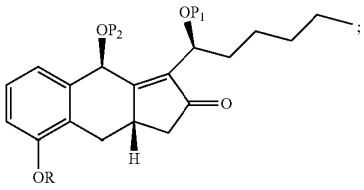
(4)



and

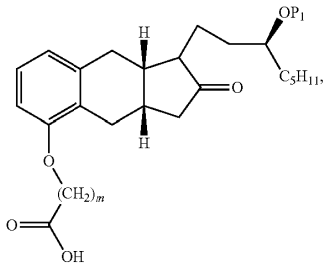
(b) converting the compound of structural formula (4) to a tricyclic compound represented by structural formula (5):

(5)



(c) hydrogenating the tricyclic compound of structural formula (5) to form a hydrogenated tricyclic compound represented by structural formula (6'):

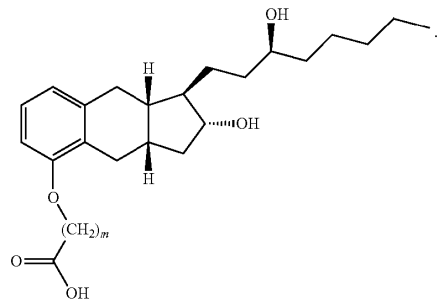
(6')



and

(d) converting the hydrogenated tricyclic compound represented by structural formula (6') to a compound represented by structural formula (IX):

(IX)



15. The method of claim **14**, wherein the hydrogenation reaction of step (c) is carried out in the presence of a base.

16. The method of claim **15**, wherein the base is K2CO3.

17. The method of claim **14**, wherein R1 is an unsubstituted benzyl group.

18. The method of claim **14**, wherein P2 is tert-butyldimethylsilyl (TBDMS), tertiarybutyldiphenylsilyl (TBDPS), triethylsilyl (TES) or triphenylmethyl (trityl group).

19. The method of claim **18**, wherein P2 is tert-butyldimethylsilyl (TBDMS).

20. The method of claim **14**, wherein P1 is tetrahydrofuranyl (THP), benzyl, 2,4-dinitrobenzyl, methoxymethyl (MOM), tertiarybutyldimethylsilyl (TBDMS), tertiarybutyldiphenylsilyl (TBDPS) or triethylsilyl (TES).

21. The method of claim **20**, wherein P1 is THP.

22. The method of claim **14**, wherein for the converting step (b), the compound of structural formula (4) is converted to the compound of structural formula (5) through a cobalt-mediated cyclization reaction.

23. The method of claim **22**, wherein the cobalt-mediated cyclization reaction is carried out in the presence of Co2(CO)8.

* * * * *

Electronic Patent Application Fee Transmittal

Application Number:	13910583
Filing Date:	05-Jun-2013
Title of Invention:	PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
First Named Inventor/Applicant Name:	Hitesh Batra
Filer:	Alexey V. Saprigin/Diana Meinecke
Attorney Docket Number:	080618-1255

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 1 month with $0 paid	70 1251	1	200	200

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Request for Continued Examination	1801	1	1200	1200
		Total in USD ($)		**1400**

Electronic Acknowledgement Receipt

EFS ID:	18493036
Application Number:	13910583
International Application Number:	
Confirmation Number:	7133
Title of Invention:	PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
First Named Inventor/Applicant Name:	Hitesh Batra
Customer Number:	22428
Filer:	Alexey V. Saprigin/Diana Meinecke
Filer Authorized By:	Alexey V. Saprigin
Attorney Docket Number:	080618-1255
Receipt Date:	17-MAR-2014
Filing Date:	05-JUN-2013
Time Stamp:	15:17:52
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$1400
RAM confirmation Number	1664
Deposit Account	
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

1	Request for Continued Examination (RCE)	RCETransmittal.pdf	92980 eebe3d02d6e126e105d32e63da374b485e51ea06	no	3
Warnings:					
This is not a USPTO supplied RCE SB30 form.					
Information:					
2		SubstantiveSubmission.pdf	334536 7475fe3a696deffd82a0c4da65cdc64ee69d9c5d	yes	9
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Amendment/Argument after Patent Board Decision		1	1	
	Claims		2	3	
	Applicant Arguments/Remarks Made in an Amendment		4	9	
Warnings:					
Information:					
3	Non Patent Literature	Aristoffetal.pdf	1388064 0185df773bda620f2829a7db79e2888b662fa285	no	10
Warnings:					
Information:					
4	Other Reference-Patent/App/Search documents	US8481782.pdf	1527377 5d8509313fcfd0595f2da3ee84c3a956bdf8796a	no	25
Warnings:					
Information:					
5	Fee Worksheet (SB06)	fee-info.pdf	32607 46e4e52f6f9a5e1164c5c83007081a12ba04c16e	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	3375564		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 13/910,583	Filing Date 06/05/2013	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	03/17/2014	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 14	Minus	** 20	= 0	X $80 =	0
	Independent (37 CFR 1.16(h))	* 1	Minus	***3	= 0	X $420 =	0
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	**0**

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

LIE
/PAUL STANBACK/

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/910,583	06/05/2013	Hitesh Batra	080618-1255	7133

22428 7590 01/17/2014
FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

EXAMINER	
VALENROD, YEVGENY	
ART UNIT	PAPER NUMBER
1672	
MAIL DATE	DELIVERY MODE
01/17/2014	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of Panel Decision from Pre-Appeal Brief Review	Application No. 13/910,583	Applicant(s) BATRA ET AL.
	Examiner BRANDON FETTEROLF	Art Unit 1672

This is in response to the Pre-Appeal Brief Request for Review filed 05 December, 2013.

1. ☐ **Improper Request** – The Request is improper and a conference will not be held for the following reason(s):

☐ The Notice of Appeal has not been filed concurrent with the Pre-Appeal Brief Request.
☐ The request does not include reasons why a review is appropriate.
☐ A proposed amendment is included with the Pre-Appeal Brief request.
☐ Other: .

The time period for filing a response continues to run from the receipt date of the Notice of Appeal or from the mail date of the last Office communication, if no Notice of Appeal has been received.

2. ☒ **Proceed to Board of Patent Appeals and Interferences** – A Pre-Appeal Brief conference has been held. The application remains under appeal because there is at least one actual issue for appeal. Applicant is required to submit an appeal brief in accordance with 37 CFR 41.37. The time period for filing an appeal brief will be reset to be one month from mailing this decision, or the balance of the two-month time period running from the receipt of the notice of appeal, whichever is greater. Further, the time period for filing of the appeal brief is extendible under 37 CFR 1.136 based upon the mail date of this decision or the receipt date of the notice of appeal, as applicable.

☒ The panel has determined the status of the claim(s) is as follows:
Claim(s) allowed: _____.
Claim(s) objected to: _____.
Claim(s) rejected: *1-14*.
Claim(s) withdrawn from consideration: _____.

3. ☐ **Allowable application** – A conference has been held. The rejection is withdrawn and a Notice of Allowance will be mailed. Prosecution on the merits remains closed. No further action is required by applicant at this time.

4. ☐ **Reopen Prosecution** – A conference has been held. The rejection is withdrawn and a new Office action will be mailed. No further action is required by applicant at this time.

All participants:

(1) *BRANDON FETTEROLF*.	(3)*Jeff Siew*.
(2) *Yevegeny Valenrod*.	(4)_____.

Brandon J Fetterolf SPE Art Unit: 1672		/BRANDON FETTEROLF/ Supervisory Patent Examiner, Art Unit 1672

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Hitesh Batra et al.
Title:	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
Appl. No.:	13/910,583
Filing Date:	June 5, 2013
Examiner:	Yevgeny Valenrod
Art Unit:	1621
Confirmation Number:	7133

PRE-APPEAL BRIEF REQUEST FOR REVIEW

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

According to the **Pre-Appeal Brief Conference Pilot Program**, announced July 11, 2005, Applicants file this Pre-Appeal Brief Request together with a Notice of Appeal.

REMARKS

Applicants request a pre-appeal brief review of the rejection under 35 U.S.C. § 103(a) over Phares *et al.* (US 2005/0085540) in view of Moriarty *et al.* (Journal of Organic Chemistry, 2004, 69, 1890-1902). In the present remarks, Applicants refer to pp. 3-6 of the reply filed Jul. 31, 2013 and pp. 3-10 of the reply filed Nov. 8, 2013. The PTO initially formulated the rejection on pp. 2-5 of the Final Office Action (FOA) dated Aug. 20, 2013. The PTO provided additional comments regarding the rejection on p. 2 of the Advisory Action (AA) dated Nov. 18, 2013.

There is no case of obviousness because the present claims recite a method of producing treprostinil with reduced impurities using a combination of steps not known in the art. Without knowing that a particular process of making a starting treprostinil batch contained impurities in the first place, one of ordinary skill in the art would not be motivated to change the process or combine additional process steps. Furthermore, the discovery by applicants that impurities can be reduced is itself an unexpected result that would rebut any possible case of obviousness. As shown previously, there are numerous different processes for making treprostinil suggested by Phares.

Phares provides the following disclosure of how to produce the diethanolamine salt of treprostinil:

> Synthesis of Tr[]eprostinil diethanolamine (UT-15C)
>
> ***Treprostinil*** acid [] is dissolved in a 1:1 molar ratio mixture of ethanol:water and diethanolamine is added and dissolved. The solution is heated and acetone is added as an antisolvent during cooling.

Phares further provides disclosure of at least two routes for obtaining treprostinil:

> "Compounds of the present invention can also be provided by modifying the compounds found in U.S. Pat. Nos. 4,306,075 and 5,153,222 in like manner."

U.S. Patent No. 4,306,075 ("the '075 patent") teaches that treprostinil is prepared without prior alkylation and hydrolysis (also, U.S. Patent No. 5,153,222 cites to the '075 patent for its disclosure of a process of making treprostinil). In particular, Example 32(H) of the '075 patent discloses treprostinil obtained from the methyl ester of treprostinil, where the methyl ester was "chromatographed on silica gel" (see Example 32(G)).

Still there are other schemes for producing treprostinil as depicted in Moriarty et al., J. Org. Chem., Vol. 69(6): 1890-1902 (copy of record), for detailed discussion see p. 4-5 of Jul 31st reply. Scheme 1 in Moriarty represents a summary of the '075 patent's process for making treprostinil, while Schemes 2 and 3 in Moriarty represent two additional processes for making treprostinil known at the time of publication of the Moriarty article in 2004.

As shown above, there are several different processes for preparing a starting batch of treprostinil, only one of which leads to treprostinil having one or more impurities resulting from prior alkylation and hydrolysis steps. Therefore, Phares does not inherently and necessarily result in a process in which the same kind or amount of impurities are present in the starting batch and in which the level of one or more such impurities resulting from prior alkylation and hydrolysis steps is reduced in the final product as required by claim 1. For this reason alone, Phares cannot anticipate the present claims based on inherency.

MPEP §2143 for obviousness provides the following guidelines for obviousness analysis based on the *KSR v Teleflex* Supreme Court decision: "The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. The Supreme Court in *KSR* noted that the analysis

supporting a rejection under 35 U.S.C. 103 should be made explicit." For discussion of *KSR* based legal standards for obviousness analysis see pp. 3-4 of Nov. 8th reply.

The PTO provides its summary of Phares in the 1st paragraph on p. 3 of FOA. The PTO explicitly acknowledges that Phares does not teach all the elements of claim 1 by stating that Phares "fails to teach impurities resulting from prior alkylation and hydrolysis being present in the said starting batch," see the 2nd paragraph on p. 3 of FOA. After providing its characterization of Moriarty in the last paragraph on p. 3 of FOA, the PTO attempts to rely on Moriarty to remedy the admitted deficiencies of Phares, see 1st full paragraph on p. 4 of FOA.

At least one deficiency of the PTO's obviousness analysis is the PTO's failure to provide the required reasoned explanation on why one of ordinary skill in the art would combine Phares with Moriarty to arrive at the claimed invention. Phares does not set any special requirements regarding which type of starting treprostinil batch should be used for making his treprostinil diethanolamine salt. At the same time, multiple treprostinil synthesis methods, other than Moriarty's method involving alkylation and hydrolysis steps, do exist, see e.g. discussion on pages 4-5 of Jul. 31st reply. In particular, besides Moriarty's method, treprostinil may be prepared using at least the following methods: a) the method of US patent 4,306,075 (Phares explicitly cites this method in paragraph 0052); b) the method based on Scheme 2 of Moriarty; c) the method based on Scheme 3 of Moriarty. None of the methods a)-c) involves alkylation and hydrolysis and therefore, none of these methods results in a treprostinil batch having one or more impurities resulting from prior alkylation and hydrolysis steps as claim 1 recites. Thus, at least one deficiency of the PTO's obviousness analysis is that the PTO failed to explain why one of ordinary skill in the art would select a treprostinil batch prepared by Moriarty's method as a starting batch for making Phares' treprostinil diethanolamine salt out of multiple other treprostinil batches.

The only reason for combining Moriarty and Phares that Applicants can grasp from the PTO's obviousness analysis on pp. 3-4 of FOA may be formulated as follows: Moriarty and Phares are combined because they can be combined since Phares refers to Moriarty as one of several different sources of treprostinil starting material. If this is the case, then Applicants submit that such reason for combining Moriarty and Phares is not sufficient for establishing a *prima facie* case of obviousness. One could just as easily choose another process as the source of treprostinil. Thus, there is no motivation supporting the particular combination of Phares and Moriarty.

Furthermore, the rejection has acknowledged that reduction of impurities is not expressly taught by the combination, but nevertheless maintains it is inherent. This misses the point – an inherent, unknown advantage is by definition an unexpected result that would rebut any possible case of prima facie obviousness. The reduction of impurities is not taught by Phares or Moriarty, and the rejection admits it was not a known result. Therefore, the unexpected result of impurity reduction rebuts any possible case of obviousness.

The PTO's comments on p. 4, ln. 5-7, of FOA that "[t]here is ample expectation of success because the process of Phares and that of Moriarty are expected to function in a manner described in the art" is misplaced. Reduction of impurites is an unexpected result NOT described in the art. Therefore, it rebuts any case of obviousness.

In the present rejection, the PTO ignores the "whereby" clause of claim 1 as well as the purity levels in claim 3 by relying on the inherency theory, see e.g. FOA, p. 4, lines 8-13 and also paragraph bridging p. 4-5.

The PTO cannot rely on inherency theory in articulating its required finding regarding predictability of the results of combination of Moriarty and Phares because the reduction of the impurity level was not known. The inherency of an advantage (reduction of impurity level in the present case) and its obviousness are entirely different questions:

"[T]**he inherency of an advantage and its obviousness are entirely different questions.** That which may be inherent is not necessarily known. **Obviousness cannot be predicated on what is unknown**." *In re Shetty*, 195 USPQ 753 (CCPA 1977), citing *In re Adams*, 148 USPQ 742 (1966). (Bold underlining added)

The present method claim is directed to a result that is recited in the preamble and the body of the claim, so this must be given weight as the purpose of the method claim (unlike other situations where inherency may be used if the claims are not methods). The PTO explicitly admits that the reduction of the impurity level was not known by stating in the paragraph bridging pp. 4-5 of FOA that "Phares does not teach reduction in impurities [due] to salt formation and crystallization." Thus, one of ordinary skill in the art would not have information in Moriarty and Phares based on which he or she could predict the reduction of impurities implied by claim 1.

The fact that Phares teaches a formation of a crystalline solid does not necessarily mean that such crystalline solid formation would necessarily result in reduction of impurities because a crystallization does not necessarily result in purification of the crystallized material, nor was there knowledge of which of several different starting processes for making

treprostinil would yield impurities that could be removed by such crystallization. For example, in some cases, impurities can incorporate into the lattice of the crystallized materials, hence, decreasing the level of purity of the crystal product, see e.g., Snell et al. Crystal Growth & Design 2001, vol. 1, 151-158 (provided with Nov. 8th reply), which provides documentary evidence of impurities incorporated into a lattice of a crystallized material.

Even if, for argument's sake only, relying on inherency theory was permissible in obviousness analysis, the PTO's reliance on inherency theory would still be improper because in the present rejection, the PTO attempts to establish inherency by relying on possibilities or probabilities when there is no explicit basis for selecting a particular starting batch of treprostinil in the first instance. According to guidelines from MPEP § 2112.IV for inherency based rejections: "**Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.**' " In re Robertson, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999)" (emphasis added) For additional discussion of legal standards for inherency based rejections, see pp. 9-10 of Nov. 8th reply.

In the present rejection, the PTO improperly tries to establish inherency theory based on possibilities or probabilities. This is particularly clear from the following sentence bridging pp. 4-5 of FOA: "if one is to produce treprostinil according to the process of [Moriarty] and [to] prepare a salt according to the process of Phares the reduction in impurities would be inherent." (underlining added) The above cited sentence contains the underlined conditional "if" clause, which, at least because there are processes for producing treprostinil other than the one of Moriarty (see discussion above and also pp. 4-5 of Jul 31st reply) provides evidence that the PTO improperly relies on probabilities or possibilities in its inherency based rejection.

Respectfully submitted,

Alexey Sagrigin

By _____

FOR Stephen B. Maebius
Attorney for Applicants
Registration No. 35,264

Reg #56,939

Date December 5, 2013

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Electronic Patent Application Fee Transmittal	
Application Number:	13910583
Filing Date:	05-Jun-2013
Title of Invention:	PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
First Named Inventor/Applicant Name:	Hitesh Batra
Filer:	Alexey V. Saprigin/Diana Meinecke
Attorney Docket Number:	080618-1255
Filed as Large Entity	

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Notice of Appeal	1401	1	800	800
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension - 1 month with $0 paid	1251	1	200	200
Miscellaneous:				
		Total in USD ($)		**1000**

Electronic Acknowledgement Receipt

EFS ID:	17576828
Application Number:	13910583
International Application Number:	
Confirmation Number:	7133
Title of Invention:	PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
First Named Inventor/Applicant Name:	Hitesh Batra
Customer Number:	22428
Filer:	Alexey V. Saprigin/Diana Meinecke
Filer Authorized By:	Alexey V. Saprigin
Attorney Docket Number:	080618-1255
Receipt Date:	05-DEC-2013
Filing Date:	05-JUN-2013
Time Stamp:	14:46:54
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$1000
RAM confirmation Number	1281
Deposit Account	
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

1	Notice of Appeal Filed	NoticeOfAppeal.pdf	63711 dc5d68f815453e1e94113a507d2edfb38e3f5041	no	2
Warnings:					
Information:					
2	Pre-Brief Conference request	PreAppealBrief.pdf	295323 064470145cce4e35b42ce945a5405050b0f6f9b1	no	5
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	32575 c1a61265a2a7d62891ac6a9e11e39eed7a3df72e	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	391609		

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New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor Name:	Hitesh BATRA
Title:	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
Appl. No.:	13/910,583
Filing Date:	06/05/2013
Examiner:	Yevgeny Valenrod
Art Unit:	1621
Confirmation Number:	7133

NOTICE OF APPEAL FROM THE EXAMINER TO THE PATENT TRIAL AND APPEAL BOARD

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

Applicants hereby appeal to the Patent Trial and Appeal Board from the decision of the Examiner in the Final Office Action dated August 20, 2013, and in the Advisory Action dated November 18, 2013, finally rejecting Claims 1-14.

[X] Applicants hereby petition for an extension of time under 37 C.F.R. §1.136(a) for the total number of months checked below:

[X] Notice of Appeal Fee

[X]To be paid as detailed below

The required fees are calculated below:

[X]	Notice of Appeal Fee	$800.00
[X]	Extension for response filed within the first month:	$200.00
[ ]	Extension:	$0.00
	TOTAL FEE:	$1000.00

The above-identified fees of $1000.00 are being paid by credit card via EFS-Web.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16, 1.17 and 41.20, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by the credit card payment instructions in EFS-Web being incorrect or absent, resulting in a rejected or incorrect credit card transaction, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741.

Please direct all correspondence to the undersigned attorney or agent at the address indicated below.

Respectfully submitted,

Date December 5, 2013

By _____

FOLEY & LARDNER LLP
Customer Number: 22428
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Facsimile: (415) 434-4507

Alexey V. Saprigin
Attorney for Applicants
Registration No. 56,439

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/910,583	06/05/2013	Hitesh Batra	080618-1255	7133

22428 7590 11/18/2013
FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

EXAMINER	
VALENROD, YEVGENY	
ART UNIT	PAPER NUMBER
1621	
MAIL DATE	DELIVERY MODE
11/18/2013	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 13/910,583	**Applicant(s)** BATRA ET AL.	
	Examiner YEVGENY VALENROD	**Art Unit** 1621	**AIA (First Inventor to File) Status** No

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED _____ FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

NO NOTICE OF APPEAL FILED

1. ☒ The reply was filed after a final rejection. No Notice of Appeal has been filed. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance;

(2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114 if this is a utility or plant application. Note that RCEs are not permitted in design applications. The reply must be filed within one of the following time periods:

a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action; or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

c) ☐ A prior Advisory Action was mailed more than 3 months after the mailing date of the final rejection in response to a first after-final reply filed within 2 months of the mailing date of the final rejection. The current period for reply expires months from the mailing date of *the prior Advisory Action* or SIX MONTHS from the mailing date of the final rejection, whichever is earlier.

Examiner Note: If box 1 is checked, check either box (a), (b) or (c). ONLY CHECK BOX (b) WHEN THIS ADVISORY ACTION IS THE FIRST RESPONSE TO APPLICANT'S FIRST AFTER-FINAL REPLY WHICH WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. ONLY CHECK BOX (c) IN THE LIMITED SITUATION SET FORTH UNDER BOX (c). See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) or (c) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendments filed after a final rejection, but prior to the date of filing a brief, will not be entered because

a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);

b) ☐ They raise the issue of new matter (see NOTE below);

c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).

5. ☐ Applicant's reply has overcome the following rejection(s): _____.

6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

7. ☐ For purposes of appeal, the proposed amendment(s): (a) ☐ will not be entered, or (b) ☐ will be entered, and an explanation of how the new or amended claims would be rejected is provided below or appended.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

9. ☐ The affidavit or other evidence filed after final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).

10. ☐ The affidavit or other evidence filed after the date of filing the Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing of good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).

11. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

12. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.

13. ☒ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____

14. ☐ Other: _____.

STATUS OF CLAIMS

15. The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: .
Claim(s) objected to: .
Claim(s) rejected: .
Claim(s) withdrawn from consideration: .

/YEVGENY VALENROD/
Primary Examiner, Art Unit 1621

Continuation of 11. does NOT place the application in condition for allowance because: The arguments presented by the applicants are not found convincing. Applicants have argued that a prima facie of obviousness has not been made at least in part because the office has failed to provide a reasoned explanation why one skilled in the art would select the method of Moriarty for preparation of treprostinil. This argument is not found persuasive because. As described in the office action one would select the method of Moriarty because said method produces treprostinil which is required for the method of Phares. Since Moriarty presents a functional methodology one would find it obvious to use the described methodology for its intended purpose. Applicants have alluded to why one would select the method of moriarty vs. numerous other methods where treprostinil is produced via alkylation and hydrolysis. Examiner has not uncovered other alkylation - hydrolysis methodologies for producing treprostinil where impurities from the synthetic steps are not present in the final product.
.

PTO/SB/08 (09-06)

Approved for use through 03/31/2007. OMB 0651-0031

U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Date Submitted: NOV 08 2013

(use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	13/910,583
Filing Date	6/5/2013
First Named Inventor	Hitesh BATRA
Art Unit	1621
Examiner Name	Yevgeny Valenrod
Attorney Docket Number	080618-1255

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number / Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Documents	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]
	B1	JP 56-122328 A	09/25/1981	Sumitomo Chem. Co.		✓
	B2	JP 59-044340 A	03/12/1984	Sankyo Co. Ltd.		✓

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]

Examiner Signature	/Yevgeny Valenrod/	Date Considered	11/15/2013

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. 1 Applicant's unique citation designation number (optional). 2 See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. 3 Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). 4 For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. 5 Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. 6 Applicant is to place a check mark here if English language Translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /YV/

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Hitesh BATRA et al.
Title:	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
Appl. No.:	13/910,583
Filing Date:	June 5, 2013
Examiner:	Yevgeny Valenrod
Art Unit:	1621
Confirmation Number:	7133

REPLY UNDER 37 C.F.R. § 1.116

Mailstop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

This paper responds to the Final Office Action mailed on August 20, 2013.

The listing of claims begins on page 2 of this document.

Remarks begin on page 3 of this document.

Listing of Claims:

1. (previously presented) In a process for producing a pharmaceutical composition comprising treprostinil, the improvement comprising forming a salt of treprostinil by combining a starting batch of treprostinil having one or more impurities resulting from prior alkylation and hydrolysis steps and a base, isolating the treprostinil salt, and preparing a pharmaceutical composition comprising treprostinil or a pharmaceutically acceptable salt thereof from the isolated treprostinil salt, whereby a level of one or more impurities found in the starting batch of treprostinil is lower in the pharmaceutical composition.

2. (original) The process of claim 1, wherein the salt is isolated in crystalline form.

3. (original) The process of claim 2, wherein the isolated salt is at least 99.8% pure.

4. (original) The process of claim 1, wherein the base is selected from the group consisting of sodium, ammonia, potassium, calcium, ethanolamine, diethanolamine, N-methylglucamine, and choline.

5. (original) The process of claim 4, wherein the base is diethanolamine.

6. (original) The process of claim 1, wherein the base is combined with treprostinil that has not been previously isolated.

7. (original) The process of claim 1, wherein the isolated salt is stored at ambient temperature.

8. (original) A pharmaceutical composition prepared by the process of claim 1.

9. (original) A pharmaceutical composition prepared by the process of claim 2.

10. (original) A pharmaceutical composition prepared by the process of claim 3.

11. (original) A pharmaceutical composition prepared by the process of claim 4.

12. (original) A pharmaceutical composition prepared by the process of claim 5.

13. (original) A pharmaceutical composition prepared by the process of claim 6.

14. (original) A pharmaceutical composition prepared by the process of claim 7.

REMARKS

Applicants respectfully request reconsideration and allowance of the present application.

CLAIMS STATUS

Claims 1-14 are pending.

CLAIM REJECTION UNDER 35 U.S.C. § 102(b)

Claims 1-14 stand rejected as obvious over Phares (US2005/0085540) in view of Moriarty et al. (Journal of Organic Chemistry, 2004, 69, 1890-1902). Applicants respectfully traverse.

The PTO failed to establish a *prima facie* case of obviousness at least because of the reasons discussed below.

"The Supreme Court in *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___, ___, 82 USPQ2d 1385, 1395-97 (2007) identified a number of rationales to support a conclusion of obviousness which are consistent with the proper "functional approach" to the determination of obviousness as laid down in *Graham*. **The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious**. **The Supreme Court in *KSR* noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit**. > In *Ball Aerosol v. Limited Brands*, 555 F.3d 984 (Fed. Cir. 2009), the Federal Circuit offered additional instruction as to the need for an explicit analysis. The Federal Circuit explained that the Supreme Court's requirement for an explicit analysis does not require record evidence of an explicit teaching of a motivation to combine in the prior art.

[T]he analysis that "should be made explicit" refers not to the teachings in the prior art of a motivation to combine, but **to the court's analysis**. . . . Under the flexible inquiry set forth by the Supreme Court, the district court therefore erred by failing to take account of "the

inferences and creative steps," or even routine steps, that an inventor would employ and by failing to find a motivation to combine related pieces from the prior art.

Ball Aerosol, 555 F.3d at 993. The Federal Circuit's directive in *Ball Aerosol* was addressed to a lower court, but **it applies to Office personnel as well.** When setting forth a rejection, Office personnel are to continue to make appropriate findings of fact as explained in MPEP § 2141 and § 2143, and **must provide a reasoned explanation as to why the invention as claimed would have been obvious to a person of ordinary skill in the art at the time of the invention**. This requirement for explanation remains even in situations in which Office personnel may properly rely on intangible realities such as common sense and ordinary ingenuity." (Bold underlining added)

The PTO failed to establish a *prima facie* case of obviousness because the PTO failed to make its obviousness analysis explicit or because, in other words, the PTO failed to provide the required reasoned explanation as to why the invention as claimed would have been obvious to a person of ordinary skill in the art at the time of the invention.

The PTO failed to provide the required reasoned explanation about why one of ordinary skill would **combine Moriarty and Phares**. In particular, the PTO failed to provide the required reasoned explanation of why one of ordinary skill in the art would select treprostinil having one or more impurities resulting from prior alkylation and hydrolysis produced by Moriarty's method out of various other treprostinil batches that could be produced by multiple other methods. The PTO also fails to supply the required reasoned explanation of why one of ordinary skill in the art would be able to predict that, should he or she select Phares' diethanolamine salt treprostinil method to apply to a treprostinil batch produced by Moriarty's method, the resulting salt would have a lower level of impurities compared to the initial treprostinil produced by Moriarty's method. Applicants provide additional discussion below.

The PTO provides its summary of Phares in the first paragraph on page 3 of the Office Action. The PTO explicitly acknowledges that Phares does not teach all the elements of claim 1 by stating that Phares "fails to teach impurities resulting from prior alkylation and

hydrolysis being present in the said starting batch," see the second paragraph on page 3 of the Office Action. After providing its characterization of Moriarty in the last paragraph on page 3 of the Office Action, the PTO attempts to rely on this Journal of Organic Chemistry reference in order to remedy the admitted deficiencies of Phares, see the first full paragraph on page 4 of the Office Action.

Applicants respectfully submit that at least one deficiency of the PTO's obviousness analysis is the PTO's failure to provide the required reasoned explanation on why one of ordinary skill in the art would combine Phares with Moriarty in order to arrive at the claimed invention. Phares does not set any special requirements around which type of starting treprostinil batch should be used for making his treprostinil diethanolamine salt. At the same time, as Applicants explained on pages 4-5 of their response filed July 31, 2013, multiple treprostinil synthesis methods, other than Moriarty's method involving alkylation and hydrolysis steps, do exist. These other synthesis methods result in treprostinil batches which are different from "the starting batch of treprostinil having one or more impurities resulting from prior alkylation" recited in claim 1. Thus, at least one deficiency of the PTO's obviousness analysis is that the PTO failed to explain why one of ordinary skill in the art would select a batch of treprostinil having one or more impurities resulting from prior alkylation as a starting batch for making Phares' treprostinil diethanolamine salt out of multiple other treprostinil batches.

The only reason for combining Moriarty and Phares that Applicants can grasp from the PTO's obviousness analysis on pages 3 and 4 of the Office Action may be formulated as follows: Moriarty and Phares are combined because they can be combined. If the PTO thinks that there are other reasons for combining Moriarty and Phares, then Applicants respectfully request that the PTO articulate these other reasons in the next Office Action. The PTO's reason for combining Moriarty and Phares stated in the first sentence of this paragraph is not sufficient for establishing a *prima facie* case of obviousness, see MPEP § 2143.01.III: "The mere fact that references can be combined or modified **does not render** the resultant combination obvious **unless** the results would have been **predictable** to one of ordinary skill in the art. *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___, ___, 82 USPQ2d 1385, 1396

(2007)" (Emphasis added) Applicants respectfully submit that in the present case, the results of combining Phares and Moriarty would not have been predictable to one of ordinary skill in the art at least because Phares does not teach anything with respect to reduction in impurities due to salt formation and crystallization (the PTO explicitly admits this fact in the paragraph bridging pages 4-5 of the Office Action). Applicants provide additional comments regarding the predictability issue below.

In order to illustrate what constitutes a properly explicit obviousness analysis, MPEP § 2143 provides a number of exemplary obviousness rationales based on the suggestions in the Supreme Court decision in *KSR v Teleflex*. Although it is not totally clear which particular rationale from MPEP § 2143 wanted to apply in the present rejection, Applicants believe that the obviousness rationale from MPEP § 2143.A "Combining Prior Art Elements According to Known Methods to Yield Predictable Results" is the closest to the PTO's logic in the rejection (If the PTO's intention was to use another obviousness rationale from MPEP § 2143, then Applicants respectfully that the PTO specifies a particular rationale for the present rejection in the next Office Action). MPEP § 2143.A states as follows:

> "To reject a claim based on this rationale, Office personnel must resolve the *Graham* factual inquiries. Then, Office personnel **must articulate** the following:
>
> - (1) a finding that the prior art included each element claimed, although not necessarily in a single prior art reference, with the only difference between the claimed invention and the prior art being the lack of actual combination of the elements in a single prior art reference;
> - (2) a finding that one of ordinary skill in the art could have combined the elements as claimed by known methods, and that in combination, each element merely performs the same function as it does separately;
> - (3) **a finding that one of ordinary skill in the art would have recognized that the results of the combination were predictable**; and

- (4) whatever additional findings based on the *Graham* factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness.

  The rationale to support a conclusion that the claim would have been obvious is that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art. *KSR*, 550 U.S. at ___, 82 USPQ2d at 1395; *Sakraida v. AG Pro, Inc.*, 425 U.S. 273, 282, 189 USPQ 449, 453 (1976); *Anderson's-Black Rock, Inc. v. Pavement Salvage Co.*, 396 U.S. 57, 62-63, 163 USPQ 673, 675 (1969); *Great Atlantic & P. Tea Co. v. Supermarket Equipment Corp.*, 340 U.S. 147, 152, 87 USPQ 303, 306 (1950). "[I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *KSR*, 550 U.S. at ___, 82 USPQ2d at 1396. **If any of these findings cannot be made, then this rationale cannot be used** to support a conclusion that the claim would have been obvious to one of ordinary skill in the art." (Bold underlining added)

Applicants respectfully submit that the PTO cannot rely on the rationale from MPEP § 2143.A in the present rejection at least because the PTO failed to articulate the required finding (3) "that one of ordinary skill in the art would have recognized that **the results of the combination were predictable**." Applicants appreciate that the PTO provides the following comments on page 4, lines 5-7, of the Office Action: "There is ample expectation of success because the process of Phares and that of Moriarty are expected to function in a manner described in the art." At the same time, Applicants submit that the above cited PTO's comments cannot serve as the required articulation of finding (3) in MPEP § 2143.A because these comments say nothing regarding the predictability or the reasonable expectation of success for the results of the combination. In the claimed invention, the results of the combination, which one of ordinary skill in the art could not predict based on Moriarty and Phares, are presented in the "whereby" clause, which can be reformulated as the reduction of the impurity level compared to the starting batch of treprostinil. In the present rejection, the

PTO ignores the "whereby" clause of claim 1 as well as the purity levels in claim 3 by relying on the inherency theory, see e.g. page 4, lines 8-13:

> "The purity limitations found in the instant claim [3 and 10] are inherently met by the combination of the two references. Regarding the limitations directed to increased purity of the pharmaceutical composition vs. starting batch of treprostinil. Phares described forming the pharmaceutical composition as a crystalline solid. The purity of the salt is inherently increased since the same steps directed to formation of the salt are followed in both instant claims and Phares."

See also, the paragraph bridging pages 4-5:

> "if one is to produce treprostinil according to the process of [Moriarty] and [to] prepare a salt according to the process of Phares the reduction in impurities would be inherent. The process of Phares inherently reduces impurities even through it was not the subject of [Phares'] invention."

In response, Applicants first bring the PTO's attention to the following legal standard, which explains the inherency of an advantage (reduction of impurity level in the present case) and its obviousness are entirely different questions:

"[T]**he inherency of an advantage and its obviousness are entirely different questions.** That which may be inherent is not necessarily known. **Obviousness cannot be predicated on what is unknown**." *In re Shetty*, 195 USPQ 753 (CCPA 1977), citing *In re Adams*, 148 USPQ 742 (1966). (Bold underlining added)

In view of the above legal standard, the PTO cannot rely on inherency theory in articulating its required finding regarding predictability of the results of combination of Moriarty and Phares because the reduction of impurities was not known. In the present claim, the method claim is directed to a result that is recited in the preamble and the body of the claim, so this must be given weight as the purpose of the method claim (unlike other situations where inherency may be used if the claims are not methods). The PTO explicitly admits this by stating in the paragraph bridging pages 4-5 of the Office Action that "Phares does not teach reduction in impurities [due] to salt formation and crystallization." Thus, one of ordinary skill in the art would not have information in Moriarty and Phares based on which he or she could predict the reduction of impurities implied by claim 1.

Applicants further submit that the fact that Phares teaches a formation of a crystalline solid does not necessarily mean that such crystalline solid formation would necessarily result in reduction of impurities because a crystallization does not necessarily result in purification of the crystallized material. For example, in some cases, impurities can incorporate into the lattice of the crystallized materials, hence, decreasing the level of purity of the crystal product, see e.g. the enclosed reference, Snell et al. Crystal Growth & Design 2001, vol. 1, 151-158, which provides documentary evidence of impurities incorporation into a lattice of a crystallized material.

In sum, the PTO failed to establish a *prima facie* case of obviousness because the PTO failed to articulate the required finding regarding predictability of the results of the combination of Moriarty and Phares. For the record, Applicants submit that although the above comments are based on the obviousness rationale from MPEP § 2143.A, each of the other obviousness rationales in MPEP § 2143 also requires for establishing a *prima facie* case of obviousness articulation of a finding regarding predictability and/or reasonable expectation of success for the proposed combination/modification of prior art. If such a finding cannot be made, then a particular rationale from MPEP § 2143 cannot be used to support a conclusion of obviousness.

Even if, for argument's sake only, relying on inherency theory was permissible in obviousness analysis, the PTO's reliance on inherency theory would still be improper because in the present rejection, the PTO attempts to establish inherency by relying on possibilities or probabilities when there is no explicit basis for selecting a particular starting batch of treprostinil in the first instance. Prior to providing further comments, Applicants bring the PTO's attention to the following guidelines from MPEP § 2112.IV for inherency based rejections:

> "IV. EXAMINER MUST PROVIDE RATIONALE OR EVIDENCE TENDING TO SHOW INHERENCY"
>
> "The fact that a certain result or characteristic **may occur or be present** in the prior art is **not sufficient to establish** the inherency of that result or characteristic. In re Rijckaert, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed

rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); In re Oelrich, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "To establish inherency, the extrinsic evidence '**must make clear** that the missing descriptive matter **is necessarily present** in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. **Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient**.' " In re Robertson, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (citations omitted)" (Bold underlining added)

"In relying upon the theory of inherency, the **examiner must provide a basis** in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic **necessarily** flows from the teachings of the applied prior art." Ex parte Levy, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original)" (Bold underlining added)

Applicants respectfully submit that in the present rejection, the PTO improperly tries to establish inherency theory based on possibilities or probabilities. This is particularly clear from the following sentence bridging pages 4-5: "if one is to produce treprostinil according to the process of [Moriarty] and [to] prepare a salt according to the process of Phares the reduction in impurities would be inherent." (underlining added) The above cited sentence contains the underlined conditional "if" clause, which, at least because there are processes for producing treprostinil other than the one of Moriarty (see discussion above and also pages 4-5 of their response filed July 31, 2013) provides evidence that the PTO improperly relies on probabilities or possibilities in its inherency based rejection.

CONCLUSION

Applicants believe that the present application is in condition for allowance. Favorable reconsideration of the application is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing or a credit card payment form being unsigned, providing incorrect information resulting in a rejected credit card transaction, or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date NOV 0 8 2013

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor Name:	Hitesh BATRA
Title:	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
Appl. No.:	13/910,583
Filing Date:	6/5/2013
Examiner:	Yevgeny Valenrod
Art Unit:	1621
Confirmation Number:	7133

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR §1.56

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

Applicants submit herewith documents for the Examiner's consideration in accordance with 37 CFR §§1.56, 1.97 and 1.98.

Applicants respectfully request that each listed document be considered by the Examiner and be made of record in the present application and that an initialed copy of Form PTO/SB/08 be returned in accordance with MPEP §609.

The submission of any document herewith is not an admission that such document constitutes prior art against the claims of the present application or that such document is considered material to patentability as defined in 37 CFR §1.56(b). Applicants do not waive any rights to take any action which would be appropriate to antedate or otherwise remove as a competent reference any document submitted herewith.

CONCISE EXPLANATION OF RELEVANCE

An English translation is provided for foreign language Documents B1 and B2.

Foreign language Documents B1 and B2 were cited during the prosecution of the corresponding Japanese application in an Office Action dated August 13, 2013. An English translation of the Japanese Office Action is submitted herewith and sets forth the portion of the document considered relevant by the examiner.

TIMING OF THE DISCLOSURE

The listed documents are being submitted in compliance with 37 CFR §1.97(d), before payment of the issue fee.

STATEMENT UNDER 37 CFR §1.97(e)

The undersigned hereby states in accordance with 37 CFR §1.97(e)(1) that each item of information contained in this information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three (3) months prior to filing of this Statement.

FEE

Fees in the amount of $180.00 to cover the fee associated with an information disclosure statement under 37 CFR §1.97(d) are being paid by credit card via EFS-Web.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this submission under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741.

Respectfully submitted,

Date NOV 0 8 2013

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PTO/SB/08 (09-06)
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Date Submitted: NOV 08 2013

(use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	13/910,583
Filing Date	6/5/2013
First Named Inventor	Hitesh BATRA
Art Unit	1621
Examiner Name	Yevgeny Valenrod
Attorney Docket Number	080618-1255

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number / Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Documents	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]
	B1	JP 56-122328 A	09/25/1981	Sumitomo Chem. Co.		✓
	B2	JP 59-044340 A	03/12/1984	Sankyo Co. Ltd.		✓

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. 1 Applicant's unique citation designation number (optional). 2 See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. 3 Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). 4 For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. 5 Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. 6 Applicant is to place a check mark here if English language Translation is attached. This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

Citation 3

PATENT ABSTRACTS OF JAPAN

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(43)Date of publication of application : 25 September 1981

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C07C 51/43
C07C 59/62
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C07C 177/00

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(21) Application number: 55-025726 (71)Applicant: SUMITOMO CHEM CO LTD
(22) Date of filing: 29 February 1980 (72) Inventor: KAWAKAMI HAJIME
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(54) CRYSTALLINE AMINE SALT OF METHANOPROSTACYCLIN, ITS PREPARATION AND REFINING METHOD

1. TITLE: CRYSTALLINE AMINE SALT OF METHANOPROSTACYCLIN, ITS PREPARATION AND REFINING METHOD

2. CLAIMS

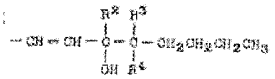
1. A dicyclohexyl amine salt of a methanoprostacyclin derivative represented by a general formula:

[wherein, R^1 is trithyloxymethyl group, 3-trithyloxy-trans-1-propenyl group and general formula:

(wherein, R^2, R^3, R^4 are each a hydrogen atom or a methyl group)].

2. A method for producing dicyclohexylamine salt of methanoprostacyclin derivative represented by a general formula:

[wherein, R^1 is trithyloxymethyl group, 3-trithyloxy-trans-1-propenyl group and general formula:



(wherein, R^2, R^3, R^4 are each a hydrogen atom or a methyl group)] comprising:
forming a crystalline salt of a mixture of methanoprostacyclin derivative represented by a general formula:

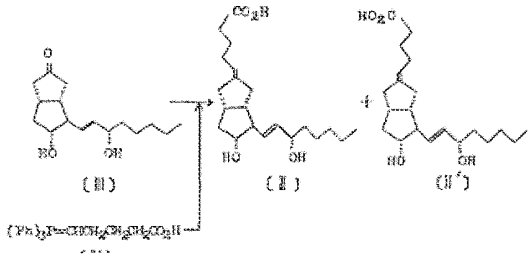
(wherein, R^1 is as described above) and a 7-Z isomer thereof using dicyclohexylamine; and further recrystallizing as necessary.

3. Detailed Description of the Invention

The present invention relates to a crystalline dicyclohexylamine salt of methanoprostacylcin derivative, its preparation and purifying method.

Methanoprostacylcin (II) was discovered as a stable derivative of prostacyclin (PGI_2), which is a natural bioactive substance having a strong thrombocyte aggregation suppression effect (Tetrahedron Letters 2607 (1979)), and it is much more chemically stable compared to prostacyclin, with the same level of strong thrombocyte aggregation suppression effect as PGI_2, and it is an extremely useful compound in the treatment of

arteriosclerosis, cardiac failure or thrombosis. Meanwhile, the total synthesis of methanoprostacylcin and a derivative thereof is reported by several groups aside from the present inventors, but all those methods use the Wittig reaction of ketone derivative (III) and ylide derivative (IV) as shown below.



The reaction has an excellent yield, but holds a severe fault of always generating an unnecessary side product, 7Z-isomer [II'] (the generation ratio is at [II]:[II']=7:2, Tetrahedron Letters 433 (1979)), and the physical property of the two forms are quite similar (the Rf value of 7E-isomer =0.14 and 7Z-isomer =0.17, Tetrahedron Letters 433 (1979)), so it is quite difficult to separate or refine the reaction product. Further, the melting point of the present compound is quite low (68-69°C Tetrahedron Letters 3743 (1978)), so crystallization can be largely inhibited by a minute amount of impurity that enters into the reaction product.

The physiological activity of 7Z isomer [II'] compared to methanoprostacyclin [II] is quite low. For example, a thrombocyte aggregation suppression effect of II' is about 1/100 that of II (Tetrahedron Letters 433 (1979)).

As such, it will be a definite requirement to establish an efficient and industrial separation method in the development of methanoprostacyclin derivative as a pharmacological product.

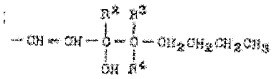
Hence, the present inventors have studied various separation and refining methods ever since their success in synthesizing methanoprostacyclin, and have now successfully developed an easy and industrial refining method. The present invention relates to the new refining method and a new dicyclohexylamine salt of methanoprostacyclin derivative [I] obtained by the method.

A methanoprostacyclin derivative represented by general formula [I], in which one of R^2, R^3, R^4 is a methyl group, has an excellent thrombocyte aggregation suppression effect similar to methanoprostacyclin (JP 54-119444 A), and a methanoprostacyclin derivative, in which R^1 is a trithyloxymethyl group or 3-trithyloxy-trans-1-propenyl group, is essential as an intermediate of a methanoprostacyclin synthesis.

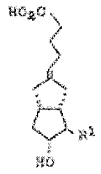
(JP 54-29233 A, JP 54-29236 A)

In the present invention, the dicyclohexylamine salt of methanoprostacyclin derivative represented by a general formula:

[wherein, R^1 is trithyloxymethyl group, 3-trithyloxy-trans-1-propenyl group and general formula:



(wherein, R^2, R^3, R^4 are each a hydrogen atom or a methyl group)] is obtained as described below. That is, the methanoprostacyclin derivative [I] or a methanoprostacyclin derivative [I] comprising a corresponding 7Z-isomer [I']:



(I')

(wherein, R^1 is as shown above)
is mixed with an appropriate amount of dicyclohexylamine (0.7 folds to 1.2 folds by mole) in an appropriate solvent, cooled as necessary, and the precipitated crystal is obtained by filtration.

The dicyclohexylamine salt of methanoprostacyclin derivative [I] obtained above generally has quite a high purity, and its purity can be increased by recrystallization using an appropriate solvent as necessary.

A suitable solvent to be used in the present invention includes alkanol (e.g. ethanol, n-propanol, 180-propanol) and alkanone (e.g. acetone, methylethyl ketone, diethyl ketone, methyl-180 buthyl ketone), and of these, acetone, methylethyl ketone and the like are particularly advantageous.

The dicyclohexylamine salt obtained in the present invention can be easily returned to a free methanoprostacyclin derivative [I] by a common method, and moreover, the obtained methanoprostacyclin derivative shows a good crystal quality compared to those that has not been subjected to refining by the present invention.

Dicyclohexylamine salt of the following exemplary compounds can be easily obtained by the present invention.

2-β-Trithyloxymethyl-3α-hydoxy-7E-(4'-carboxybutylidene)-bicyclo[3,3,0]octane

2-β-(3'-Trithyloxy-trans-1-propenyl)-3α-hydoxy-7E-(4'-carboxybutylidene)-bicyclo[3,3,0]octane

2-β-(3'α-Hydroxy-trans-1'-octenyl)-3α-hydoxy-7E-(4'-carboxybutylidene)-bicyclo[3,3,0]octane

2-β-(3'α-Hydroxy-4',4'-dimethyl-trans-1'-octenyl)-3α-hydoxy-7E-(4'-carboxybutylidene)-bicyclo[3,3,0]octane

2-β-(3'α-Hydroxy-3'β-methyl-trans-1'-octenyl)-3α-hydoxy-7E-(4'-carboxybutylidene)-bicyclo[3,3,0]octane

Next, Examples are given to explain the present invention in detail.

Example 1

The 7-E,Z mixture (0.8 g) of crude 2-β-trithyloxymethyl-3α-hydoxy-7-(4'-carboxybutylidene)-bicyclo[3,3,0]octane obtained by the Wittig reaction of 4-carboxybutylene triphenylphosphorane and 2-β-trithyloxymethyl-3α-hydoxy-bicyclo[3,3,0]octane-7-on was dissolved in acetone, and dicyclohexyl amine of an equivalent mole was introduced under agitation. The mixture was further agitated under room temperature, and the precipitated crystal was obtained by filtering and washed with little acetone to obtain a dicyclohexylamine salt of 2-β-trithyloxymethyl-3α-hydoxy-7E-(4'-carboxybutylidene)-bicyclo[3,3,0]octane.

Melting Point: 69-71°C

Example 2

A brown oil-like matter (0.39 g) of 2-β-(3'α-hydroxy-trans-1'-octenyl)-3α-hydoxy-7E-(4'-carboxybutylidene)-bicyclo[3,3,0]octane containing a 7-Z isomer was dissolved in acetone, and dicyclohexylamine of an equivalent mole was introduced under agitation. The mixture was agitated for 2 hours and left under room temperature, and the precipitated crystal was obtained by filtering to obtain a dicyclohexylamine salt of 2-β-(3'α-hydroxy-trans-1'-octenyl)-3α-hydoxy-7E-(4'-carboxybutylidene)-bicyclo[3,3,0]octane.

Melting Point: 105.5-106.5°C

The above dicyclohexylamine salt was neutralized by a $KHSO_4$ aqueous solution of 0.5 N, then extracted with ether, after which the ether layer was washed with water and dried, and the solvent was removed by distillation under reduced pressure to

obtain a crystal of 2-β-(3'α-hydroxy-trans-1'-octenyl)-3α-hydoxy-7E-(4'-carboxybutylidene)-bicyclo[3,3,0]octane.

Melting Point: 66.5-68°C

⑲ 日本国特許庁（JP）　　⑪ 特許出願公開

⑫ 公開特許公報（A）　　昭56—122328

⑤Int. Cl.³	識別記号	庁内整理番号	㊸公開　昭和56年(1981)9月25日
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59/62		7188—4C	審査請求　未請求
// A 61 K 31/557	AEL	6617—4C	
C 07 C 177/00		7430—4H	（全 4 頁）

⑭メタノプロスタサイクリン誘導体の結晶性アミン塩及びその製法及び精製法

⑳特　願　昭55—25726
㉒出　願　昭55(1980)2月29日
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㉔代　理　人　弁理士　木村勝哉

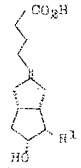
明　　細　　書

1．発明の名称

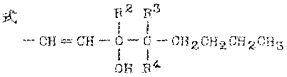
メタノプロスタサイクリン誘導体の結晶性アミン塩及びその製法及び精製法

2．特許請求の範囲

1）一般式



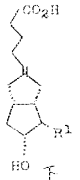
〔式中、R^1はトリチルオキシメチル基、3—トリチルオキシ—トランス—1—プロペニル基及び一般式



（式中、R^2、R^3、R^4は各々水素原子又はメチル基をあらわす。）をあらわす。〕

であらわされるメタノプロスタサイクリン誘導体のジシクロヘキシルアミン塩。

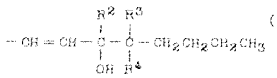
2）一般式



〔式中、R^1は前記のとおりである。〕

であらわされるメタノプロスタサイクリン誘導体及びその7—epi異性体の混合物をジシクロヘキシルアミンにより結晶性塩とし、更に必要に応じて再結晶を行なうことを特徴とする一般式

〔R^1はトリチルオキシ基、3—トリチルオキシ—トランス—1—プロペニル基及び一般式



（式中、R^2、

（1）　　（2）

R^3、R^4は各々水素原子又はメチル基をあらわす。）をあらわす。〕

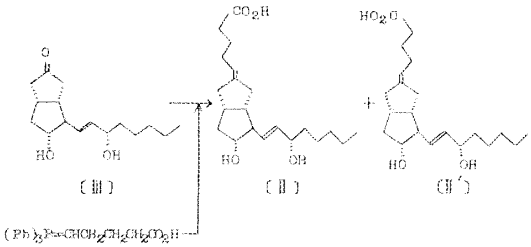
であらわされるメタノプロスタサイクリン誘導体のジシクロヘキシルアミン塩の製法。

3．発明の詳細を説明

本発明はメタノプロスタサイクリン誘導体の結晶性ジシクロヘキシルアミン塩及びその製法及びその精製法に関するものである。

メタノプロスタサイクリン〔Ⅱ〕は強力な血小板凝集抑制作用を有する天然生理活性物質であるプロスタサイクリン（PGI_2）の安定誘導体として見出されたものであり（テトラヘドロン・レターズ 2607（1979））、プロスタサイクリンに比べてはるかに化学的に安定であり、しかもPGI_2と同等の強い血小板凝集抑制作用を有しており、動脈硬化、心不全又は血栓症等の治療に極めて有用な化合物である。一方、このメタノプロスタサイクリン及びその誘導体の全合成は本発明者等の他にもいくつかのグループにより報告がなされているが、それらの方法はいず

れも下記の如くケトン誘導体〔Ⅲ〕とイリド誘導体〔Ⅳ〕とのヴィッティッヒ反応を用いるものである。



〔Ⅲ〕　〔Ⅱ〕　〔Ⅱ′〕

〔Ⅳ〕

本反応は収率的には優れているが、常に不要の7Z体〔Ⅱ′〕が副生するという重大な欠点を有しており（生成比は〔Ⅱ〕：〔Ⅱ′〕＝7：2、テトラヘドロン・レターズ 433（1979））、しかも両者の物性が極めて類似しているため（Rf値 7Z体＝0.14、7Z体＝0.17、テトラヘドロン・レターズ 433（1979））分離、精製が極めて困難である。又、本化合物の融点はかなり低く（68～69℃ テトラヘドロン・レターズ 3743

（1978））、そのため微量の不純物の混入により著しく結晶化が妨げられる。

一方、この7Z異性体〔Ⅱ′〕はメタノプロスタサイクリン〔Ⅱ〕に比べてその薬理活性が極めて低く、たとえばⅡ′の血小板凝集抑制作用はⅡのおよそ1/100である（テトラヘドロン・レターズ 433（1979））。

これらのことから、メタノプロスタサイクリン誘導体を医薬品として開発する場合、この異性体の効率的かつ工業的な分離法の確立が絶対的な要件となる訳である。

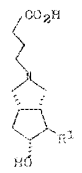
そこで本発明者等はメタノプロスタサイクリンの合成に成功して以来鋭々の分離、精製法について検討を行ない、この度極めて簡便でかつ工業的な精製法を開発することに成功した。本発明はこの新規な精製法及びそれによって得られるメタノプロスタサイクリン誘導体〔Ⅰ〕の新規なジシクロヘキシルアミン塩に関するものである。

一般式〔Ⅰ〕に於てR^2、R^3、R^4のいずれかがメ

チル基であらわされるメタノプロスタサイクリン誘導体と同様に優れた血小板凝集抑制作用を有するものであり（特開昭54－129429号公報）、又R^1がトリチルオキシメチル基あるいは3－トリチルオキシ－トランス－1－プロペニル基であらわされるメタノプロスタサイクリン誘導体はメタノプロスタサイクリン合成の中間体として重要なものである。

（特願昭54－29233、特願昭54－29236）

本発明によればメタノプロスタサイクリン誘導体〔Ⅰ〕



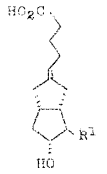
〔Ⅰ〕

〔式中、R^1はトリチルオキシメチル基、3－トリチルオキシ－トランス－1－プロペニル基及び一般式 $-CH=CH-\underset{OH}{\overset{R^2}{C}}-\underset{OH}{\overset{R^3}{C}}-CH_2CH_2CH_2CH_3$（式中

R^2、R^3、R^4は各々水素原子又はメチル基をあ

らわす。）をあらわす。〕

であらわされるメタノプロスタサイクリン誘導体のジシクロヘキシルアミン塩は以下のようにして得られる。すなわち、メタノプロスタサイクリン誘導体〔Ⅰ〕あるいは対応するアルファー異性体〔Ⅰ′〕



〔Ⅰ′〕

〔R^2は前記のとおりである。〕

を含有するメタノプロスタサイクリン誘導体〔Ⅰ〕を適当な溶媒中適当量（0.7倍～1.2倍モル）のジシクロヘキシルアミンと混合し、必要に応じて冷却し、析出した結晶を戸取することにより得られる。

このようにして得られたメタノプロスタサイクリン誘導体〔Ⅰ〕のジシクロヘキシルアミン塩は一般にかなり高純度であるが、必要に応じて更に適当な溶媒を用いて再結晶することにより純度を上げることができる。

本発明に於て用いられる適当な溶媒としてはアルカノール（例えばエタノール、n-プロパノール、iso-プロパノール）及びアルカノン（例えばアセトン、メチルエチルケトン、ジエチルケトン、メチル-iso-プチルケトン）が適しているが特にアセトン、メチルエチルケトン等が優れている。

本発明によって得られたジシクロヘキシルアミン塩は常法に従って容易に遊離のメタノプロスタサイクリン誘導体〔Ⅰ〕に戻すことができ、しかも得られたメタノプロスタサイクリン誘導体は本発明の精製を行なわないものに比べて優れた結晶性を示す。

本発明によって例えば次に掲げる化合物のジシクロヘキシルアミン塩が容易に得られる。

2-β-トリチルオキシメチル-3α-ヒドロキシ-7β-(ω′-カルボキシプチリデン)-ビシクロ〔3，3，0〕オクタン

（6）

（7）

2-β-(3′-トリチルオキシ-トランス-1′-プロペニル)-3α-ヒドロキシ-7β-(ω′-カルボキシプチリデン)-ビシクロ〔3，3，0〕オクタン

2-β-(3′α-ヒドロキシ-トランス-1′-オクテニル)-3α-ヒドロキシ-7β-(ω′-カルボキシプチリデン)ビシクロ〔3，3，0〕オクタン

2-β-(3′α-ヒドロキシ-ω′，ω′-ジメチル-トランス-1′-オクテニル)-3α-ヒドロキシ-7β-(ω′-カルボキシプチリデン)ビシクロ〔3，3，0〕オクタン

2-β-(3′α-ヒドロキシ-3′β-メチル-トランス-1′-オクテニル)-3α-ヒドロキシ-7β-(ω′-カルボキシプチリデン)ビシクロ〔3，3，0〕オクタン

次に実施例をあげて本発明を詳細に説明する。

実施例1

ω-カルボキシプチレントリフェニルホスホラン及び2-β-トリチルオキシメチル-3α-ヒドロキシ-ビシクロ〔3，3，0〕オクタン-7-オンのヴィッティヒ反応によって得た粗2-β-トリチルオキシメチル-3α-ヒドロキシ-7-(ω′-カルボキシプチリデン)-ビシクロ〔3，3，0〕オクタン-7β，Z混合物0.8gをアセトン1mlに溶解し、撹拌下等モルのジシクロヘキシルアミンを加注し、更に室温にて撹拌して後、析出した結晶を戸取し、少量のアセトンにて洗浄し2-β-トリチルオキシメチル-3α-ヒドロキシ-7β-(ω′-カルボキシプチリデン)-ビシクロ〔3，3，0〕オクタンのジシクロヘキシルアミン塩を得た。

融点　89～92℃

実施例2

7-Z異性体を含有する2-β-(3′α-ヒドロキシ-トランス-1′-オクテニル)-3α-ヒドロキシ-7β-(ω′-カルボキシプチリデン)-ビシクロ〔3，3，0〕-オクタンのカッ色油状物0.39gをアセトン1mlに溶解し、撹拌下等モルのジシクロヘキシルアミンを加注し、2時間撹拌後室温にて放置し、析出結晶を戸取することにより2-β-(3′α-ヒドロキシ-トランス-1′-オクテニル)-

（9）

（10）

3α－ヒドロキシ－7β－（4′－カルボキシブチリデン）ビシクロ〔3，3，0〕オクタンのジシクロヘキシルアミン塩を得た。

融点　105.5～106.5℃

上記ジシクロヘキシルアミン塩を0.5Nの$KHSO_4$水溶液で中和し、エーテルにて抽出して後、エーテル層を水洗、乾燥し、減圧下溶媒を留去することにより2β－（3′α－ヒドロキシ－トランス－1′－オクテニル）－3α－ヒドロキシ－7β－（4′－カルボキシブチリデン）ビシクロ〔3，3，0〕オクタンの結晶を得た。

融点　66.5～68℃

（ノ）（元）

Citation 2

PATENT ABSTRACTS OF JAPAN

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(43)Date of publication of application : 12 March 1984

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(51)Int.Cl. C07C 59/46
C07C 59/56
C07C 59/62
C07C 59/72
C07C 101/30
C07C 149/26
C07C 149/40
// C07C 91/18

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(21)Application number : 57-155205 (71)Applicant : SANKYO CO LTD
(22)Date of filing : 08 September 1982 (72)Inventor : AMAMIYA SHIGEO
KOJIMA KOICHI

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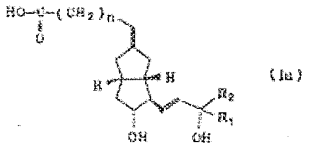
(54) OPTICAL ACTIVE CRYSTALLINE AMINE SALT OF METHANOPROSTACYCLIN DERIVATIVE AND ITS PREPARATION

TITLE: OPTICAL ACTIVE CRYSTALLINE AMINE SALT OF METHANOPROSTACYCLIN DERIVATIVE AND ITS PREPARATION

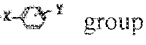
CLAIMS

1. A salt of methanoprostacyclin derivative having a general formula:



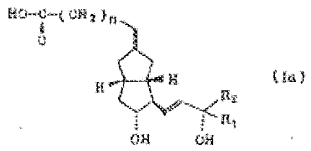
(Ia)

[wherein, R_1 is a hydrogen atom or a methyl group, R_2 is an alkyl group of 1 to 12 carbons, an alkenyl group of 2 to 12 carbons, a formula –A group (wherein, A is a cycloalkyl group of 3 to 8 carbons that can be substituted by a lower alkyl group), a

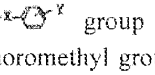
formula –X-A group (wherein, A is the same as shown above, and X is a methylene group, an ethylene group, a –NH- group, an oxygen atom or a sulfur atom) or a formula  group (wherein, X is the same as shown above, Y is a halogen atom or a trifluoromethyl group), and n is an integer of 1 to 5] and l-threo-2-amino-3-paranitrophenyl-1,3-propanediol (IIa).

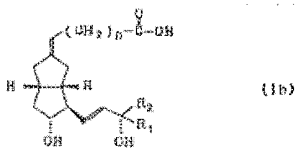
2. A method for preparing a salt of a compound (Ia) and a compound (IIa) comprising:

treating 4 types of mixtures, consisting of a mixture of methanoprostacyclin derivative having a general formula:



(Ia)

[wherein, R_1 is a hydrogen atom or a methyl group, R_2 is an alkyl group of 1 to 12 carbons, an alkenyl group of 2 to 12 carbons, a formula –A group (wherein, A is a cycloalkyl group of 3 to 8 carbons that can be substituted by a lower alkyl group), a formula –X-A group (wherein, A is the same as shown above, and X is a methylene group, an ethylene group, a –NH- group, an oxygen atom or a sulfur atom) or a formula  group (wherein, X is the same as shown above, Y is a halogen atom or a trifluoromethyl group), and n is an integer of 1 to 5] and an X-isotope of a compound (Ia) having a general formula:



(Ib)

(wherein, R_1, R_2 and n are the same as shown above),

a mixture of a compound (Ia) and an antipode compound (Ic) thereof, or

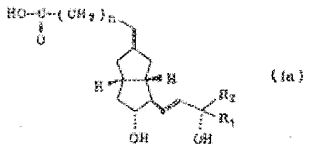
a mixture of a compound (Ia), a compound (Ib), a compound (Ic) and an antipode compound (Id) of compound (Ib),

with l-threo-2-amino-3-paranitrophenyl-1,3-propanediol (IIa) to produce a crystalline salt; then

recrystallizing as necessary.

3. Detailed Description of the Invention

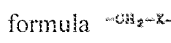
The present invention relates to a salt of a new methanoprostacyclin derivative having a general formula:



(IIa)

and

l-threo-2-amino-3-paranitrophenyl-1,3-propanediol (IIa), which is useful in the separation or refinement of an optical isomer and a stereoisomer, and a preparation method of the same.

In the above formula, R_1 is a hydrogen atom or a methyl group, R_2 is an alkyl group of 1 to 12 carbons, an alkenyl group of 2 to 12 carbons, a formula –A group (wherein, A is a cycloalkyl group of 3 to 8 carbons that can be substituted by a lower alkyl group), a formula –X-A group (wherein, A is the same as shown above, and X is a methylene group, an ethylene group, a –NH- group, an oxygen atom or a sulfur atom) or a formula  group (wherein, X is the same as shown above, Y is a halogen atom or a trifluoromethyl group), and n is an integer of 1 to 5.

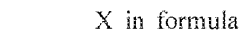
Examples of alkyl groups having 1 to 12 carbons of R_2 include methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, isobutyl group, n-pentyl group, isopentyl group, 1-methylpentyl group, 2-methylpentyl group, n-hexyl group, n-heptyl group, 1,1-dimethylpentyl group, 2-ethylpentyl group, n-octyl group, 2-methyloctyl group, n-nonyl group 2-methylnonyl group, 2-ethyloctyl group, n-decyl group, 2-methyldecyl group or 2-ethyldecyl group; and preferably, alkyl groups having 4 to 10 carbons, such as, n-butyl group, isobutyl group, n-pentyl group, isopentyl group, 1-methylpentyl group, 2-methylpentyl group, n-hexyl group, n-heptyl group, 1,1-dimethylpentyl group, 2-ethylpentyl group, n-octyl group, 2-methyloctyl group, or 2-ethyloctyl group; and more preferably, n-pentyl group, 1-methylpentyl group, n-hexyl group or 2-methylhexyl group.

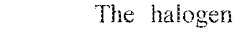
Examples of alkenyl groups having 2 to 12 carbons of R_2 include vinyl group, allyl group, 2-butenyl group, 2-pentenyl group, 3-pentenyl group, 2-methyl-3-pentenyl group, 4-methyl-3-pentenyl group, 1-methyl-4-pentenyl group, 4-hexenyl group, 5-hexenyl group, 1,4-dimethyl-3-pentenyl group, 5-heptenyl group, 6-methyl-5-heptenyl group, 2,6-dimethyl-5-heptenyl group, 1,1,6-trimethyl-5-heptenyl group, 6-methyl-5-octenyl group, 2,6-dimethyl-5-ocetenyl group, 6-ethyl-5-octenyl group, 2-methyl-6-ethyl-5-octenyl group or 2,6-diethyl-5-octenyl group; and preferably

alkenyl groups having 4 to 12 carbons, such as 2-butenyl group, 2-pentenyl group, 3-pentenyl group, 2-methyl-3-pentenyl group, 4-methyl-3-pentenyl group, 1-methyl-4-pentenyl group, 4-hexenyl group, 5-hexenyl group, 1,4-dimethyl-3-pentenyl group, 5-heptenyl group, 6-methyl-5-heptenyl group, 2,6-dimethyl-5-heptenyl group, 1,1,6-trimethyl-5-heptenyl group, 6-methyl-5-octenyl group, 2,6-dimethyl-5-octenyl group, 6-ethyl-5-octenyl group, 2-methyl-6-ethyl-5-octenyl group or 2,6-diethyl-5-octenyl group; and more preferably, 2-pentenyl group, 4-hexenyl group, 5-hexenyl group, 6-methyl-5-heptenyl group or 2,6-dimethyl-5-heptenyl group.

Examples of lower alkyls constituting substituents of formula –A group and formula –X-A group of R_2 include methyl group, ethyl group, n-propyl group, n-butyl group or isobutyl group, and preferably a methyl group or an ethyl group.

Examples of cycloalkyl groups having 3 to 8 carbons in formula –A group and formula –X-A group of R_2 include cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group, cycloheptyl group or cyclooctyl group; and preferably, cyclopentyl group or cyclohexyl group.

X in formula –X-A group or formula  group of R_2 is preferably methylene group, oxygen atom or sulfur atom.

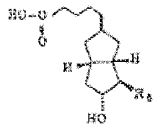
The halogen atom constituting Y in formula  group of R_2 is fluorine atom, chlorine atom, bromine atom, or iodine atom; and preferably, fluorine atom or chlorine atom. The letter n is preferably an integer of 3 to 5, and more preferably, the integer 3.

Or else, compound (Ia) can preferably be a compound constituted of R_1 being a hydrogen atom or a methyl group; R_2 being the above alkyl group having 4 to 10 carbons; the above alkenyl group having 4 to 12 carbons; a cyclopentyl group or cyclohexyl group that can be substituted with a methyl group or an ethyl group; a cyclopentyl methyl group, cyclohexyl methyl group, cyclopentyl amino group, cyclohexyl amino group, cyclopentyl oxy group, cyclohexyl oxy group, cyclopentyl thio group or cyclohexyl thio group that can be substituted with a methyl group or an ethyl group; a 2-phenylethyl group, anilinomethyl group, phenoxymethyl group or phenylthiomethyl group having a phenyl ring that can be substituted with a fluorine atom, chlorine atom or a trifluoromethyl group; and n being an integer of 3 to 5.

Compound (Ia) can more preferably be a compound constituted of R_1 being a hydrogen atom or a methyl group, R_2 being a n-pentyl group, 1-methylpentyl group, n-hexyl group, 2-methylhexyl group, 2-pentenyl group, 4-hexenyl group, 5-hexenyl group, 6-methyl-5-heptenyl group, 2,6-dimethyl-5-heptenyl group, cyclopentyl group, 3-ethylcyclopentyl group, cyclohexyl group, 3-methylcyclohexyl group,

cyclopentylmethyl group, 3-methylcyclopentylmethyl group, cyclohexylmethyl group, 3-ethylcyclohexylmethyl group, cyclopentyloxy group, 3-methylcyclopentyloxy group, cyclohexyloxy group, cyclopentyl thio group, cyclohexyl thio group, 3-methylcyclohexyl thio group, 2-phenylethyl group, 2-(m-fluorophenyl)ethyl group, 2-(p-fluorophenyl)ethyl group, 2-(o-chlorophenyl)ethyl group, 2-(p-chlorophenyl)ethyl group, 2-(m-trifluoromethylphenyl)ethyl group, 2-(p-trifluoromethylphenyl)ethyl, phenoxymethyl, m-fluorophenoxymethyl, p-chlorophenoxymethyl, p-trifluorophenoxymethyl, phenylthiomethyl, o-fluorophenylthiomethyl, m-chlorophenylthiomethyl or p-trifluoromethylphenylthio methyl group, and n being an integer 3.

Methanoprostacyclin derivative is a chemically stable prostacyclin derivative, and its development as an advantageous therapeutic agent of thrombosis, etc. is in progress. The compound includes many asymmetric carbons and double bonds, so it has various optical isomers and stereoisomers, and a target compound cannot be obtained by synthesis without the above isomer entering the product. For separation of isomers of methanoprostacyclin derivatives, the separation of compound (IIIa) using dicyclohexylamine from a mixture of a compound having a general formula:



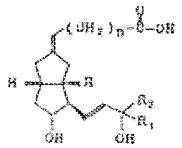
(IIIa)

(wherein, R_3 is trithyloxymethyl group, 3-trithyloxy-trans-1-propenyl group) and a 5Z-isomer (IIIb) of the same (JP 56-122328 A).

The present inventors conducted extensive studies for many years concerning the separation of isomers of the methanoprostacyclin derivatives, and found a new carbonic acid-amine salt that is useful for separating the E, Z-isomers based on double bonds more efficiently than known technology and also separate an optical isomer based on asymmetric carbon, and thus completed the invention.

The salt of a compound (Ia) and a compound (IIa) relating to the present invention is produced by the following method.

The salt can be obtained by treating 4 types of mixtures, consisting of a mixture of compound (Ia) and a Z-isotope of a compound (Ia) having a general formula:



(Ib)

(wherein, R_1, R_2 and n are the same as shown above),
a mixture of a compound (Ia) and an antipode compound (Ic) thereof, or
a mixture of a compound (Ia), a compound (Ib), a compound (Ic) and an antipode compound (Id) of compound (Ib), in an inert solvent to produce a crystalline salt, then recrystallizing as necessary.

Examples of the inert solvent to be used include water; aliphatic hydrocarbons, such as n-pentane, n-hexane, n-octane; and aromatic hydrocarbons, such as benzene, toluene, xylene; halogenated hydrocarbons, such as dichloromethane, chloroform, carbon tetrachloride; ethers, such as ether, tetrahydrofuran, dioxane; esters, such as methyl acetate, ethyl acetate; nitriles, such as acetonitrile, benzonitrile; ketones, such as acetone, methylethyl ketone; alcohols such as methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutanol, sec-butanol, t-butanol, n-amyl alcohol, sec-amyl alcohol, t-amyl alcohol, isoamyl alcohol, sec-isoamino alcohol, active amyl alcohol, or mixtures of such solvents; and preferably, esters or mixtures of esters with the above various solvents; and more preferably, esters or mixtures of alcohols and esters.

The amount of compound (IIIa) to be used is an equivalent of 0.7 to 1.5 against carbonic acid, and preferably an equivalent of 0.9 to 1.1 against carbonic acid.

The temperature to produce a salt of compounds (Ia), (Ib), (Ic) and (Id) with compound (IIa) is normally around room temperature and the recrystallization of the above salt is performed by preferably heating to 50°C to 100°C to produce a supersaturated solution, then precipitating crystals at -10°C to 50°C.

Further, a salt of compound (Ic) and d-threo-2-amino-3-paranitrophenyl-1,3-propanediol (IIb) can be produced by a similar method as the one mentioned above.

The salt of compound (Ia) and compound (IIa) or the salt of compound (Ic) and compound (IIb), produced by the above method, can be formed into compound (Ia) or compound (Ic), which have excellent pharmacological effects. An exemplary method of obtaining such compound (Ia) or compound (Ic) is to dissolve an appropriate salt in a little water, add a dilute alkali solution to the water to induce precipitation of an amine compound (IIa) or (IIb), filter out the amine compound, add a dilute acid to acidify the solution, and then extract the above compound with a water-immiscible solvent, removing the solvent from the liquid extract by distillation.

Compounds (Ia), (Ib), (Ic) and (Id), which are used as the starting material of the present method, can be readily produced according to a known method (JP 54-95552 A, JP 54-130543 A or JP 55-28945 A).

Next, the invention is described in more detail by the Examples.

Example 1

L-threo-2-amino-3-paranitrophenyl-1,3-propanediol salt of (8S,9R,11R,12R,15S,17R)-6,9-methylene-11,15-dihydroxy-17-methyl-20-isopropylideneprost-5(E),13(E)-dienoic acid

A mixture of (8S,9R,11R,12R,15S,17R)-6,9-methylene-11,15-dihydroxy-17-methyl-20-isopropylideneprost-5(E),13(E)-dienoic acid and its 5(Z)-isomer (at about 6.5:3.5) in an amount of 0.38 g and an equivalent amount of l-threo-2-amino-3-paranitrophenyl-1,3-propanediol was thermally dissolved in ethyl acetate containing isopropanol at 10%, and recrystallized at room temperature to obtain the desired salt of 5(E)-isomer in an amount of 0.26 g.

Melting point: 68-70°C

IR spectrum (Nujol) cm^{-1}:

1350, 1375, 1460, 1520, 3350

NMR spectrum (CD_3OD) δ ppm:

5.50 (2H, m, )

7.93 (4H, q, )

Example 2

L-threo-amino-3-paranitrophenyl-1,3-propanediol salt of (8S,9R,11R,12R,15S)-6,9-methylene-11,15-dihydroxyprost-5(E),13(E)-dienoic acid

a) Method using an E,Z-mixture

A mixture of (8S,9R,11R,12R,15S)-6,9-methylene-11,15-dihydroxyprost-5(E),13(E)-dienoic acid and its 5(Z)-isomer (at about 6.5:3.5) in an amount of 0.10 g and an equivalent amount of l-threo-2-amino-3-paranitrophenyl-1,3-propanediol was thermally dissolved in ethyl acetate containing ethanol, and recrystallized at room temperature to obtain the desired salt of 5(E)-isomer in an amount of 0.07 g.

Melting point: 55-65°C

IR spectrum (liquid film) cm^{-1}:

1040, 1350, 1405, 1530, 3250

NMR spectrum (CD_3OD) δ ppm:

0.88 (3H, t, )

5.50 (2H, m, )

7.93 (4H, q, )

b) Method using an antipode mixture

A mixture of (8S,9R,11R,12R,15S)-6,9α-methylene-11α,15α-dihydroxyprost-5(E),13(E)-dienoic acid and its antipode (at 1:1) in an amount of 63 mg and 38 mg of l-threo-2-amino-3-paranitrophenyl-1,3-propanediol was processed as in a) to obtain the desired salt in an amount of 40 mg.

Example 3

L-threo-2-amino-3-paranitrophenyl-1,3-propanediol salt of (8R,9R,11R,12R,15S)-6,9-methylene-11,15-dihydroxy-15-cyclopentyl-16,17,18,19,20-pentanolprost-5(E),13(E)-dienoic acid

A mixture of (8S,9R,11R,12R,15S)-6,9-methylene-11,15-dihydroxy-15-cyclopentyl-16,17,18,19,20-pentanolprost-5(E),13(E)-dienoic acid and its 5(Z)-isomer (at about 8:2) in an amount of 63 mg and an equivalent amount of l-threo-2-amino-3-paranitrophenol-1,3-propanediol was thermally dissolved in ethyl acetate containing isopropanol at 10%, and recrystallized at room temperature to obtain the desired salt of 5(E)-isomer.

Melting point: 90-92°C

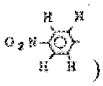
IR spectrum (Nujol) cm^{-1}:

1350, 1460, 1520, 2600, 2850, 3350

NMR spectrum (CD_3OD) δ ppm:

5.26 (1H, t, )

5.52 (2H, m, )

7.95 (4H, q, )

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発明の数　2
審査請求　未請求

（全 6 頁）

⑭メタノプロスタサイクリン誘導体の光学活性結晶性アミン塩およびその製法

⑳特　　願　昭57—155205
㉒出　　願　昭57(1982)9月8日

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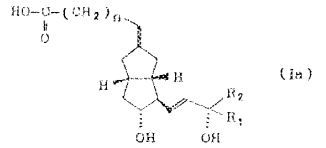
明　　細　　書

1. 発明の名称

メタノプロスタサイクリン誘導体の光学活性結晶性アミン塩およびその製法

2. 特許請求の範囲

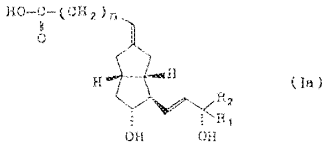
1)　一般式



（Ia）

〔式中、R_1は水素原子またはメチル基を示し、R_2は炭素数1乃至12個を有するアルキル基、炭素数2乃至12個を有するアルケニル基、式 -A 基（式中、Aは低級アルキル基によつて置換されてもよい炭素数3乃至8個のシクロアルキル基を示す。）、式 -X-A 基（式中、Aは前述したものと同意義を示し、Xはメチレン基、エチレン基、-NH- 基、酸素原子または硫黄原子を示す。）または式 $-CH_2-X-\langle\bigcirc\rangle-Y$ 基（式中、Xは前述したものと同意義を示し、Yはハロゲン原子またはトリフルオロメチル基を示す。）を示し、nは1乃至5の整数を示す。〕を有するメタノプロスタサイクリン誘導体とL-スレオ-2-アミノ-3-パラニトロフェニル-1,3-プロパンジオール（Ba）との塩。

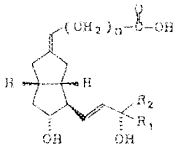
2)　一般式



（Ia）

〔式中、R_1は水素原子またはメチル基を示し、R_2は炭素数1乃至12個を有するアルキル基、炭素数2乃至12個を有するアルケニル基、式 -A 基（式中、Aは低級アルキル基によつて置換されてもよい炭素数3乃至8個のシクロアルキル基を示す。）、式 -X-A 基（式中、Aは前述したものと同意義を示し、Xはメチレン基、エチレン基、-NH- 基、酸素原子または硫黄原

子を示す。）または式 $-CH_2-X-$ 基（式中、Xは前述したものと同意義を示し、Yはハロゲン原子またはトリフルオロメチル基を示す。）を示し、nは1乃至5の整数を示す。］を有するメタノプロスタサイクリン誘導体と一般式



(Ib)

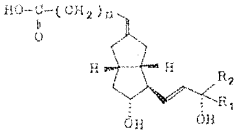
（式中、R_1，R_2およびnは前述したものと同意義を示す。）を有する化合物(Ia)のZ－異性体との混合物、

化合物(Ia)とその対掌体化合物(Ic)との混合物または

化合物(Ia)、化合物(Ib)、化合物(Ic)および化合物(Id)の対掌体化合物(Id)からなる4種類の混合物にL－スレオ－2－アミノ－3－パラニトロフェニル－1,3－プロパンジオール(IIa)を作用させて結晶性塩を製造し、次いで必要に応じて、再結晶をすることを特徴とする化合物(Ia)と化合物(IIa)との塩の製法。

3. 発明の詳細な説明

本発明は光学および立体異性体の分離、精製に有用でありかつ新規な一般式



(Ia)

を有するメタノプロスタサイクリン誘導体とL－スレオ－2－アミノ－3－パラニトロフェニル－1,3－プロパンジオール(IIa)との塩およびその製法に関する。

上記式中、R_1は水素原子またはメチル基を示し、R_2は炭素数1乃至12個を有するアルキル基、炭素数2乃至12個を有するアルケニル基、式－A 基（式中、Aは低級アルキル基によつて置換されてもよい炭素数3乃至8個のシクロアルキル基を示す。）、式 $-X-A$ 基（式中、Aは前述したものと同意義を示し、Xはメチレン基、エチレン基、$-NH-$ 基、酸素原子または硫黄原子を示す。）または式 $-CH_2-X-$ 基（式中、Xは前述したものと同意義を示し、Yはハロゲン原子またはトリフルオロメチル基を示す。）を示し、nは1乃至5の整数を示す。

R_2の炭素数1乃至12個を有するアルキル基としては例えばメチル、エチル、n－プロピル、イソプロピル、n－ブチル、イソブチル、n－ペンチル、イソペンチル、1－メチルペンチル、2－メチルペンチル、n－ヘキシル、n－ヘプチル、1,1－ジメチルペンチル、2－エチルペンチル、n－オクチル、2－メチルオクチル、n－ノニル、2－メチルノニル、2－エチルオクチル、n－デシル、2－メチルデシルまたは2－エチルデシル基をあげることができ、好適には炭素数4乃至10個を有するアルキル基、例えばn－ブチル、イソブチル、n－ペンチル、イソペンチル、1－メチルペンチル、2－メチルペンチル、n－ヘキシル、n－ヘプチル、1－ジメチルペンチル、2－エチルペンチル、n－オクチル、2－メチルオクチルまたは2－エチルオクチル基をあげることができ、さらに好適にはn－ペンチル、1－メチルペンチル、n－ヘキシルまたは2－メチルヘキシル基をあげることができる。

R_2の炭素数2乃至12個を有するアルケニル基としては例えばビニル、アリル、2－ブテニル、2－ペンテニル、3－ペンテニル、2－メチル－3－ペンテニル、4－メチル－3－ペンテニル、1－メチル－4－ペンテニル、4－ヘキセニル、5－ヘキセニル、1,4－ジメチル－3－ペンテニル、5－ヘプテニル、6－メチル－5－ヘプテニル、2,6－ジメチル－5－ヘプテニル、1,1,6－トリメチル－5－ヘプテニル、6－メチル－5－オクテニル、2,6－ジメチル－5－オクテニル、6－エチル－5－オクテニル、2－メチル－6－エチル－5－オクテニル または2,6－ジエチル－5－オクテニル基をあげることができ、好適には炭素数4乃至12個

を有するアルケニル基、例えば2-ブテニル、2-ペンテニル、3-ペンテニル、2-メチル-3-ペンテニル、4-メチル-3-ペンテニル、1-メチル-4-ペンテニル、4-ヘキセニル、5-ヘキセニル、1,4-ジメチル-3-ペンテニル、5-ヘプテニル、6-メチル-5-ヘプテニル、2,6-ジメチル-5-ヘプテニル、1,1,6-トリメチル-5-ヘプテニル、6-メチル-5-オクテニル、2,6-ジメチル-5-オクテニル、6-エチル-5-オクテニル、2-メチル-6-エチル-5-オクテニルまたは2,6-ジエチル-5-オクテニル基をあげることができ、さらに好適には2-ペンテニル、4-ヘキセニル、5-ヘキセニル、6-メチル-5-ヘプテニルまたは2,6-ジメチル-5-ヘプテニル基をあげることができる。

R_2 における式 $-A$ 基および式 $-X-A$ 基の置換分である低級アルキル基としては例えばメチル、エチル、n-プロピル、n-ブチルまたはイソブチル基をあげることができ、好適にはメチル

メチル若しくはエチル基で置換されてもよいシクロペンチル若しくはシクロヘキシル基；メチル若しくはエチル基で置換されてもよいシクロペンチルメチル、シクロヘキシルメチル、シクロペンチルアミノ、シクロヘキシルアミノ、シクロペンチルオキシ、シクロヘキシルオキシ、シクロペンチルチオ若しくはシクロヘキシルチオ基；フェニル環が弗素原子、塩素原子若しくはトリフルオロメチル基で置換されてもよい2-フェニルエチル、アニリノメチル、フェノキシメチル若しくはフェニルチオメチル基であり、nが3乃至5の整数である化合物をあげることができる。

化合物(Ia)において、さらに好適には R_1 が水素原子またはメチル基であり、R_2 がn-ペンチル、1-メチルペンチル、n-ヘキシル、2-メチルヘキシル、2-ペンテニル、4-ヘキセニル、5-ヘキセニル、6-メチル-5-ヘプテニル、2,6-ジメチル-5-ヘプテニル、シクロペンチル、3-エチルシクロペンチル、

またはエチル基である。

R_2 における式 $-A$ 基および式 $-X-A$ 基の炭素数3乃至8個を有するシクロアルキル基としては例えばシクロプロピル、シクロブチル、シクロペンチル、シクロヘキシル、シクロヘプチルまたはシクロオクチル基をあげることができ、好適にはシクロペンチルまたはシクロヘキシル基をあげることができる。

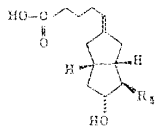
R_2 における式 $-X-A$ 基または式 $-CH_2-X-$ 基のXは好適にはメチレン基、酸素原子または硫黄原子である。

R_2 における式 $-CH_2-X-$ 基に含まれるYのハロゲン原子は弗素、塩素、臭素または沃素原子であり、好適には弗素または塩素原子である。nは好適には3乃至5の整数であり、さらに好適には3の整数である。

または化合物(Ia)において、好適には R_1 が水素原子またはメチル基であり、R_2 が前記の炭素数4乃至10個を有するアルキル基；前記の炭素数4乃至12個を有するアルケニル基；シクロヘキシル、3-メチルシクロヘキシル、シクロペンチルメチル、3-メチルシクロペンチルメチル、シクロヘキシルメチル、3-エチルシクロヘキシルメチル、シクロペンチルオキシ、3-メチルシクロペンチルオキシ、シクロヘキシルオキシ、シクロペンチルチオ、シクロヘキシルチオ、3-メチルシクロヘキシルチオ、2-フェニルエチル、2-(m-フルオロフェニル)エチル、2-(p-フルオロフェニル)エチル、2-(o-クロロフェニル)エチル、2-(p-クロロフェニル)エチル、2-(m-トリフルオロメチルフェニル)エチル、2-(p-トリフルオロメチルフェニル)エチル、フェノキシメチル、m-フルオロフェノキシメチル、p-クロロフェノキシメチル、p-トリフルオロフェノキシメチル、フェニルチオメチル、o-フルオロフェニルチオメチル、m-クロロ[redacted]フェニルチオメチルまたはp-トリフルオロメチルフェニルチオメチル基であり、nが3の整数である化合物をあげることができ

る。

メタノプロスタサイクリン誘導体は化学的に安定なプロスタサイクリン誘導体で血栓症等の優れた治療剤として開発が進められている。この化合物は数多くの不斉炭素および二重結合を有しているため、種々の光学異性体および立体異性体が存在し、合成によつて目的化合物を得るには上記異性体の混入は避けられない。メタノプロスタサイクリン誘導体の異性体の分離に関しては、一般式



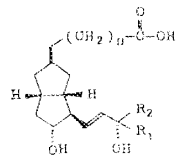
(IIIa)

(式中、R_5はトリチルオキシメチル基、3-トリチルオキシ-トランス-1-プロペニル基等を示す。)を有する化合物とその5Z-異性体(IIIb)との混合物からジシクロヘキシルアミンを用いて、化合物(IIIa)を分離できることが知られている(特開昭56-122328号公報)。

本発明者らはメタノプロスタサイクリン誘導体の異性体の分離について、最近に至り鋭意検討を行つた結果、二重結合に基づくE,Z-異性体を公知技術よりも効率よく分離し、しかも不斉炭素に基づく光学異性体をも分離するために有用な新規カルボン酸-アミン塩を見出して本発明を完成した。

本発明に係る化合物(Ia)と化合物(IIa)との塩は以下の方法に従つて製造される。

化合物(Ia)と一般式



(Ib)

(式中、R_1, R_2およびnは前述したものと同意義を示す。)を有する化合物(Ib)の2-異性体との混合物、

化合物(Ia)とその対掌体化合物(Ic)との混合物

または

化合物(Ia)、化合物(Ib)、化合物(Ic)および化合物(Id)の対掌体化合物(Id)からなる4種類の混合物に不活性溶剤中、化合物(IIa)を作用させ結晶性塩を製造し、次いで必要に応じて、再結晶することによつて得ることができる。

使用される不活性溶剤としては、水、例えばn-ペンタン、n-ヘキサン、n-オクタンのような脂肪族炭化水素類、ベンゼン、トルエン、キシレンのような芳香族炭化水素類、ジクロロメタン、クロロホルム、四塩化炭素のようなハロゲン化炭化水素類、エーテル、テトラヒドロフラン、ジオキサンのようなエーテル類、酢酸メチル、酢酸エチルのようなエステル類、アセトニトリル、ベンゾニトリルのようなニトリル類、アセトン、メチルエチルケトンのようなケトン類、メタノール、エタノール、n-プロパノール、イソプロパノール、n-ブタノール、イソブタノール、sec-ブタノール、t-ブタノール、n-アミルアルコール、sec-アミルアルコール、t-アミルアルコール、イソアミルアルコール、sec-イソアミノアルコール、活性アミルアルコールのようなアルコール類またはこれら溶剤の混合物をあげることができるが、好適にはエステル類またはエステル類と上記広範囲の溶剤との混合物であり、特に好適にはエステル類またはアルコール類とエステル類の混合物である。

使用される化合物(IIa)の量はカルボン酸に対して0.7乃至1.5当量であり、好適には0.9乃至1.1当量である。

化合物(Ia)、(Ib)、(Ic)および(Id)と化合物(IIa)との塩を製造する温度は通常室温付近であり、上記塩の再結晶は好適には50℃乃至100℃に加熱して、過飽和溶液とし、次いで-10℃乃至50℃で結晶を析出させることによつて行われる。

また、上述と同様な方法に従つて、化合物(Ic)とd-スレオ-2-アミノ-3-パラニトロフェニル-1,3-プロパンジオール(IIb)との塩も製造することができる。

以上のようにして製造された化合物(Ia)と化合物(IIa)との塩または化合物(Ic)と化合物(IIb)との塩は常法に従って、薬理作用のすぐれた化合物(Ia)または化合物(Ic)に導くことができる。例えば相当する塩を少量の水に溶解させ、希アルカリ水溶液を加え、析出したアミン化合物(IIa)または(IIb)を沪去した後、希酸を加えて溶液を酸性となし、水不混和性溶剤で抽出し、抽出液から溶剤を留去することによって得ることができる。

本方法に原料として用いられる化合物(Ia)，(Ib)，(Ic)および(Id)は公知の方法に従って容易に製造することができる(特開昭54-95552号，特開昭54-130543号または特開昭55-28945号公報)。

次に実施例をあげて、さらに発明を具体的に説明する。

実施例1

(8S，9R，11R，12R，15S，17R)-6,9-メチレン-11，15-ジヒドロキシ-17-メチル-20-イソプロピリデンプロスト-5(E)，13(E)-ジエン酸のL-スレオ-2-アミノ-3-パラニトロフェニル-1,3-プロパンジオール塩

(8S，9R，11R，12R，15S，17R)-6,9-メチレン-11，15-ジヒドロキシ-17-メチル-20-イソプロピリデンプロスト-5(E)，13(E)-ジエン酸とその5(Z)-異性体との混合物(約65対35) 0.36 gと当量のL-スレオ-2-アミノ-3-パラニトロフェニル-1,3-プロパンジオールを10 mlのイソプロパノールを含む酢酸エチルに加熱溶解して室温にて再結晶することにより目的の5(E)-異性体の塩0.26 gを得た。

融点 68 - 70 ℃

IRスペクトル(Nujol) cm^{-1} :

1350，1375，1460，1520，3350

NMRスペクトル(CD_3OD) δ ppm :

5.50 (2H，m， )

7.93 (4H，q， )

実施例2

(8S，9R，11R，12R，15S)-6,9-メチレン-11，15-ジヒドロキシプロスト-5(E)，13(E)-ジエン酸のL-スレオ-アミノ-3-パラニトロフェニル-1,3-プロパンジオール塩

ⓐ E，Z-混合物を用いる方法

(8S，9R，11R，12R，15S)-6,9-メチレン-11，15-ジヒドロキシプロスト-5(E)，13(E)-ジエン酸とその5(Z)-異性体との混合物(約6.5対3.5) 0.10 gと当量のL-スレオ-2-アミノ-3-パラニトロフェニル-1,3-プロパンジオールをエタノールを含む酢酸エチルに加熱溶解して室温にて再結晶することにより目的の5(E)-異性体の塩を0.07 g得た。

融点 55 - 65 ℃

IRスペクトル(液状フイルム) cm^{-1} :

1040，1350，1405，1530，3250

NMRスペクトル(CD_3OD) δ ppm :

0.88 (3H，t， )

5.50 (2H，m， )

7.93 (4H，q，)

ⓑ 対掌体混合物を用いる方法

(8S，9R，11R，12R，15S)-6,9α-メチレン-11α，15α-ジヒドロキシプロスト-5(E)，13(E)-ジエン酸とその対掌体との混合物(1対1) 63 mgと38 mgのL-スレオ-2-アミノ-3-パラニトロフェニル-1,3-プロパンジオールをⓐと同様に処理して目的の塩40 mgを得た。

実施例3

(8R，9R，11R，12R，15S)-6,9-メチレン-11，15-ジヒドロキシ-15-シクロペンチル-16，17，18，19，20-ペンタノルプロスト-5(E)，13(E)-ジエン酸のL-スレオ-2-アミノ-3-パラニトロフェニル

－1,3－プロパンジオール塩

（8S，9R，11R，12R，15S）－6,9－メチレン－11，15－ジヒドロキシ－15－シクロペンチル－16，17，18，19，20－ペンタノルプロスト－5(E)，13(E)－ジエン酸とその5(Z)－異性体との混合物（約8対2）63mgと当量のビス－2－アミノ－3－パラニトロフェノール－1,3－プロパンジオールを10容イソプロパノールを含む酢酸エチルに加熱溶解して室温にて再結晶することにより目的とする5(E)－異性体の塩を得た。

融点 90 ～ 92℃

IRスペクトル（Nujol）cm^{-1}：

1350，1460，1520，2500，2850，3330

NMRスペクトル（CD_3OD）δ ppm：

5.26（1H，t，  ）

5.52（2H，m，  ）

7.95（4H，q，  ）

特許出願人　三共株式会社

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Electronic Patent Application Fee Transmittal	
Application Number:	13910583
Filing Date:	05-Jun-2013
Title of Invention:	PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
First Named Inventor/Applicant Name:	Hitesh Batra
Filer:	Alexey V. Saprigin/Karen Walker
Attorney Docket Number:	080618-1255
Filed as Large Entity	

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**180**

Electronic Acknowledgement Receipt

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Application Number:	13910583
International Application Number:	
Confirmation Number:	7133
Title of Invention:	PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
First Named Inventor/Applicant Name:	Hitesh Batra
Customer Number:	22428
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Submitted with Payment	yes
Payment Type	Credit Card
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Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

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	Applicant Arguments/Remarks Made in an Amendment	3	11

Warnings:					
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5	Foreign Reference	JP59044340.pdf	11483009 0ceb2c76ce5863b398ee97a8b16382c7ef2a5375	no	14
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If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 13/910,583	Filing Date 06/05/2013	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☒ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	**280**
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	**280**

APPLICATION AS AMENDED – PART II

AMENDMENT	**11/08/2013**	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 14	Minus	** 20	= 0	X $80 =	0
	Independent (37 CFR 1.16(h))	* 1	Minus	***3	= 0	X $420 =	0
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	**0**

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

LIE
/GLORIA TRAMMELL/

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/910,583	06/05/2013	Hitesh Batra	080618-1255

CONFIRMATION NO. 7133

22428
FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

PUBLICATION NOTICE

OC000000064323931

Title:PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN?

Publication No.US-2013-0267734-A1
Publication Date:10/10/2013

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Office of Public Records. The Office of Public Records can be reached by telephone at (703) 308-9726 or (800) 972-6382, by facsimile at (703) 305-8759, by mail addressed to the United States Patent and Trademark Office, Office of Public Records, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently http://pair.uspto.gov/. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/910,583	06/05/2013	Hitesh Batra	080618-1255	7133

22428 7590 08/20/2013
FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

EXAMINER	
VALENROD, YEVGENY	
ART UNIT	PAPER NUMBER
1621	
MAIL DATE	DELIVERY MODE
08/20/2013	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 13/910,583	Applicant(s) BATRA ET AL.	
	Examiner YEVGENY VALENROD	Art Unit 1621	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 July 2013*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *1-14* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-14* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some * c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

DETAILED ACTION

Rejection of claims 1-14 under 35 USC 102(b) is withdrawn in view of applicants' amendments.

Claim Rejections - 35 USC § 103

The following is a quotation of pre-AIA 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under pre-AIA 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of pre-AIA 35 U.S.C. 103(c) and potential pre-AIA 35 U.S.C. 102(e), (f) or (g) prior art under pre-AIA 35 U.S.C. 103(a).

Claims 1-14 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Phares et al. (US 2005/0085540) in view of Moriarty et al. (*Journal Of Organic Chemistry*, **2004**, *69*, 1890-1902).

Scope of prior art

Phares teaches a method of producing a pharmaceutical composition comprising combining a starting batch of treprostinil which comprises treprostinil, ethanol and water with diethanolamine to produce treprostinil diethanolamine salt (page 9, paragraph [0105]). Phares describes the produced diethanolamine salt of treprostinil as a crystalline form A (page 38, paragraph [0330] – [0331]). On page 36, paragraphs [0311] – [0314] pharmaceutical compositions comprising treprostinil diethanolamine are described. Capsule and tablet forms are described in paragraph [0314]. Finally on page 38, paragraph [0039] Phares describes storing treprostinil diethanolamine salt at ambient temperature.

Ascertaining the difference

Although Phares teaches a starting batch comprising treprostinil, he fails to teach impurities resulting from prior alkylation and hydrolysis being present in the said starting batch.

Secondary reference

Moriarty teaches a method of preparing treprostinil acid wherein said method comprises an alkylation step and a hydrolysis step (page 1895, Scheme 4, compound **34** to compound **35,** and compound **35** to compound **7**).

Obviousness

One skilled in the art wishing to prepare a treprostinil diethanolamine salt according to the method of Phares would have found it obvious to prepare treprostinil using methods known in the art such as the methodology described my Moriarty. One would therefore find it obvious to prepare treprostinil according to Moriarty and subsequently prepare the diethanolamine salt according to Phares. There is ample expectation of success because both the process of Phares and that of Moriarty are expected to function in a manner described in the art. The purity limitations found in the instant claim 3and 10 are inherently met by the combination of the two references. Regarding the limitations directed to increased purity of the pharmaceutical composition vs. starting batch of treprostinil. Phares described forming the pharmaceutical composition as a crystalline solid. The purity of the salt is inherently increased since the same steps directed to formation of the salt are followed in both instant claims and Phares.

Reply to applicants' remarks and to the Declaration under 37 CFR 1.132

Examiner agrees with the applicant that the amended claims are not anticipated by Phares.

Examiner disagrees with the applicant that the amended claims are non-obvious over Phares and Moriarty. Phares does not teach reduction in impurities dues to salt formation and crystallization. However if one is to produce treprostinil according to the process of Moriatry and the prepare a salt according to the process of Phares the

reduction in impurities would be inherent. The process of Phares inherently reduces impurities even through it was not the subject of Phareses invention.

Conclusion

Claims 1-14 are pending

Claims 1-14 are rejected

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yevgeny Valenrod whose telephone number is 571-272-9049. The examiner can normally be reached on 8:30am-5:00pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/YEVGENY VALENROD/
Primary Examiner, Art Unit 1621

Notice of References Cited	Application/Control No. 13/910,583	Applicant(s)/Patent Under Reexamination BATRA ET AL.	
	Examiner YEVGENY VALENROD	Art Unit 1621	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-			
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Moriarty et al. Journal Of Organic Chemistry, 2004, 69, 1890-1902
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13910583	BATRA ET AL.
	Examiner	**Art Unit**
	YEVEGENY VALENROD	1621

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	07/17/2013	08/14/2013							
	1	✓	✓							
	2	✓	✓							
	3	✓	✓							
	4	✓	✓							
	5	✓	✓							
	6	✓	✓							
	7	✓	✓							
	8	✓	✓							
	9	✓	✓							
	10	✓	✓							
	11	✓	✓							
	12	✓	✓							
	13	✓	✓							
	14	✓	✓							

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13910583	BATRA ET AL.
	Examiner	Art Unit
	YEVEGENY VALENROD	1621

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
EAST search	8/14/2013	YV
Inventor search	8/14/2013	YV

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

	/YEVEGENY VALENROD/ Primary Examiner.Art Unit 1621

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	11	((HITESH) near2 (BATRA)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2013/08/14 15:52
L2	9	((SUDERSAN) near2 (TULADHAR)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2013/08/14 15:52
L3	21	((RAJU) near2 (PENMASTA)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2013/08/14 15:52
L4	208	((DAVID) near2 (WALSH)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2013/08/14 15:52
L5	207	L1 or L2 or L3 or L4	US-PGPUB; USPAT	OR	OFF	2013/08/14 15:52
L6	10	L5 and treprostinil	US-PGPUB; USPAT	OR	OFF	2013/08/14 15:52
L7	693	treprostinil	US-PGPUB; USPAT	OR	OFF	2013/08/14 15:52
L8	61	L7 same diethanolamine	US-PGPUB; USPAT	OR	OFF	2013/08/14 15:52
L9	0	L8 same (crystal or crystallized)	US-PGPUB; USPAT	OR	OFF	2013/08/14 15:52
L10	7	L8 same polymorph	US-PGPUB; USPAT	OR	OFF	2013/08/14 15:52
L11	814	(562/466).CCLS.	US-PGPUB; USPAT; USOCR	OR	OFF	2013/08/14 15:52
L12	14	L7 and L11	US-PGPUB; USPAT	OR	OFF	2013/08/14 15:52
L13	11	L12 and diethanolamine	US-PGPUB; USPAT	OR	OFF	2013/08/14 15:52

EAST Search History (Interference)

		<This search history is empty>				

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Hitesh BATRA et al.
Title:	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
Appl. No.:	13/910,583
Filing Date:	June 5, 2013
Examiner:	Yevgeny Valenrod
Art Unit:	1621
Confirmation Number:	7133

AMENDMENT AND REQUEST FOR RECONSIDERATION

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

This paper responds to the outstanding Office Action mailed on July 19, 2013.

The listing of claims begins on page 2 of this document.

Remarks begin on page 3 of this document.

Listing of Claims:

1. (currently amended) In a process for producing a pharmaceutical composition comprising treprostinil, the improvement comprising forming a salt of treprostinil by combining a starting batch of treprostinil having one or more impurities resulting from prior alkylation and hydrolysis steps and a base, isolating the treprostinil salt, and preparing a pharmaceutical composition comprising treprostinil or a pharmaceutically acceptable salt thereof from the isolated treprostinil salt, whereby a level of one or more impurities found in the starting batch of treprostinil is lower in the pharmaceutical composition.

2. (original) The process of claim 1, wherein the salt is isolated in crystalline form.

3. (original) The process of claim 2, wherein the isolated salt is at least 99.8% pure.

4. (original) The process of claim 1, wherein the base is selected from the group consisting of sodium, ammonia, potassium, calcium, ethanolamine, diethanolamine, N-methylglucamine, and choline.

5. (original) The process of claim 4, wherein the base is diethanolamine.

6. (original) The process of claim 1, wherein the base is combined with treprostinil that has not been previously isolated.

7. (original) The process of claim 1, wherein the isolated salt is stored at ambient temperature.

8. (original) A pharmaceutical composition prepared by the process of claim 1.

9. (original) A pharmaceutical composition prepared by the process of claim 2.

10. (original) A pharmaceutical composition prepared by the process of claim 3.

11. (original) A pharmaceutical composition prepared by the process of claim 4.

12. (original) A pharmaceutical composition prepared by the process of claim 5.

13. (original) A pharmaceutical composition prepared by the process of claim 6.

14. (original) A pharmaceutical composition prepared by the process of claim 7.

REMARKS

Applicants respectfully request reconsideration and allowance of the present application.

CLAIMS STATUS

Claims 1-14 are pending. Claim 1 is amended to clarify that the starting batch of treprostinil is one having one or more impurities resulting from prior alkylation and hydrolysis steps and to clarify that the end pharmaceutical composition may include a pharmaceutically acceptable salt of treprostinil. Support for these changes can be found at least in the abstract, paragraph 7, and paragraph 107. No new matter has been added.

35 U.S.C. 102

Claims 1-14 have been rejected under 35 U.S.C. 102(b) as anticipated by Phares. Reconsideration of the rejection is respectfully requested.

The rejection correctly points out that Phares teaches synthesis of the diethanolamine salt of treprostinil and oral pharmaceutical compositions comprising it. The rejection further asserts that the impurity level of the product recited in dependent claims 3 and 10 would inherently result from the example of Phares. Without acquiescing to the correctness of the rejection and solely to advance prosecution, applicants have amended claim 1 to recite that the starting batch of treprostinil has one or more impurities resulting from prior alkylation and hydrolysis steps. Phares neither anticipates nor renders obvious amended claim 1 or any claim depending from it because Phares discloses more than one process for providing a starting batch of treprostinil and because Phares does not provide evidence of whether salt formation can remove any impurities from a given type of treprostinil starting material.

Phares provides the following disclosure of how to produce the diethanolamine salt of treprostinil:

Synthesis of Tr[]eprostinil diethanolamine (UT-15C)

> ***Treprostinil*** acid [] is dissolved in a 1:1 molar ratio mixture of ethanol:water and diethanolamine is added and dissolved. The solution is heated and acetone is added as an antisolvent during cooling.

Phares further provides disclosure of at least two routes for obtaining treprostinil:

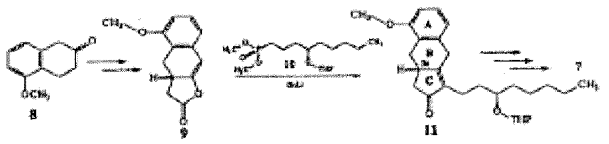
> "Compounds of the present invention can also be provided by modifying the compounds found in U.S. Pat. Nos. 4,306,075 and 5,153,222 in like manner."

U.S. Patent No. 4,306,075 ("the '075 patent") teaches that treprostinil is prepared without prior alkylation and hydrolysis (also, U.S. Patent No. 5,153,222 cites to the '075 patent for its disclosure of a process of making treprostinil). In particular, Example 32(H) of the '075 patent discloses treprostinil obtained from the methyl ester of treprostinil, where the methyl ester was "chromatographed on silica gel" (see Example 32(G)).

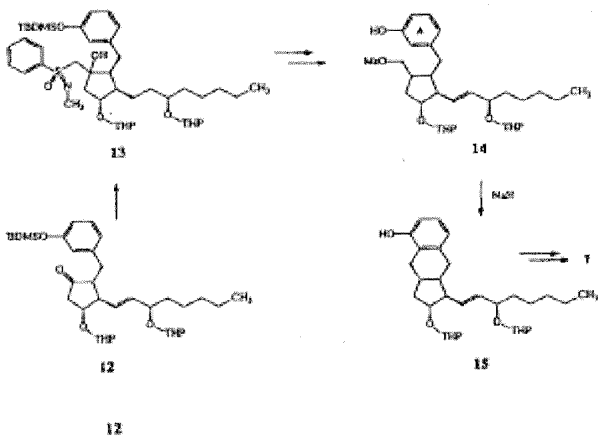
In another section, Phares discloses that treprostinil can be "synthesized using the stereoselective intramolecular Pauson Khand reaction as a key step and Mitsunobu inversion of the side-chain hydroxyl group" (col. 35, lines 39-42). This latter synthesis route for treprostinil does involve prior alkylation and hydrolysis.

Still other schemes for producing treprostinil are depicted Moriarty et al., J. Org. Chem., Vol. 69(6): 1890-1902 (copy of record):

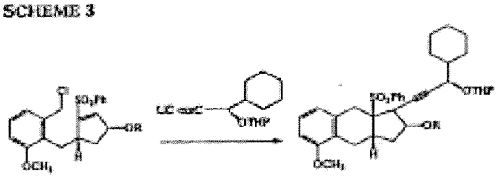
SCHEME 1



SCHEME 2



SCHEME 3



Scheme 1 above represents a summary of the '075 patent's process for making treprostinil, while Schemes 2 and 3 represent two additional processes for making treprostinil known at the time of publication of the Moriarty article in 2004.

As shown above, there are several different processes for preparing a starting batch of treprostinil, only one of which leads to treprostinil having one or more impurities resulting from prior alkylation and hydrolysis steps. Therefore, Phares does not inherently and necessarily result in a process in which the same kind or amount of impurities are present in the starting batch and in which the level of one or more such impurities resulting from prior alkylation and hydrolysis steps is reduced in the final product as required by claim 1. For this reason alone, Phares cannot anticipate the present claims based on inherency.

Applicants further point out that the present claims are unobvious over the prior art for reasons set forth in parent application Ser. No. 13/548,446 in the Declaration of David Walsh (copy enclosed). It would not have been obvious to a person of ordinary skill in the art that forming a salt of treprostinil with a base could provide a reduction in the level of one or more impurities present in the starting batch of treprostinil resulting from prior alkylation and hydrolysis steps. In the first place, Phares does not disclose that any impurities are present in a starting batch of treprostinil resulting from prior alkylation and hydrolysis steps. Furthermore, Phares does not disclose that the level of any of these impurities can be reduced from such a starting batch of treprostinil via salt formation. To the contrary, Phares is directed at finding salt and ester forms of treprostinil that have favorable characteristics for oral pharmaceutical formulations.

One of ordinary skill in the art would not have looked to Phares for guidance about reducing the level of an impurity in a starting batch of treprostinil, even if there had been a disclosure about the presence of impurities in a starting batch of treprostinil resulting from prior alkylation and hydrolysis steps. Thus, the present invention represents a solution to a problem unrecognized in the prior art. Moreover, reducing the level of one or more of the particular type of impurities resulting from prior alkylation and hydrolysis steps as detailed in the Walsh Declaration of the parent application represents an unexpected result.

Accordingly, withdrawal of the rejection under 35 U.S.C. 102 based on Phares is requested.

CONCLUSION

Applicants believe that the present application is in condition for allowance. Favorable reconsideration of the application is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a

check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing or a credit card payment form being unsigned, providing incorrect information resulting in a rejected credit card transaction, or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date July 31, 2013 By _____

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 672-5569
Facsimile: (202) 672-5399

Stephen B. Maebius
Attorney for Applicants
Registration No. 35,264

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Hitesh BATRA et al.
Title:	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
Appl. No.:	13/548,446
Filing Date:	7/13/2012
Examiner:	Yevgeny Valenrod
Art Unit:	1621
Confirmation Number:	2092

DECLARATION OF DAVID WALSH UNDER 37 C.F.R. 1.132

I, David A. Walsh, do hereby declare:

1. I am the Executive Vice President of Chemical Research and Development at the United Therapeutics Corporation.

2. I have extensive experience in the field of Pharmaceutical Chemistry as evidenced by my Ph.D. degree received in organic chemistry from the University of New Hampshire and over 39 years of professional experience. My Curriculum Vitae attached as Appendix A provides additional details on my qualifications and experience.

3. My employer, United Therapeutics Corporation, is the owner of the above identified application.

4. I am not receiving additional compensation for providing this Declaration beyond my normal compensation from my employer.

DAW 6/4/13

5. I am familiar with the Office Action dated May 15, 2013, as well as with Moriarty et al. (J. Org. Chem. 2004, 69(6), 1890-1902, "Moriarty") cited therein.

6. In my opinion, each of treprostinil as the free acid and treprostinil diethanolamine prepared according to the process specified in claim 1 or 10 of the present application is physically different from treprostinil prepared according to the process of "Moriarty." In particular, each of treprostinil as the free acid and treprostinil diethanolamine prepared according to the process specified in claim 1 or 10 differ from treprostinil prepared according to the process of "Moriarty" in their respective impurity profiles. In support, I provide the following data obtained from representative Certificates of Analysis with impurity profiles for treprostinil prepared according to the process of "Moriarty", treprostinil diethanolamine prepared according to the process specified in claim 1 or 10 of the present application, and treprostinil as the free acid prepared according to the process specified in claim 1 or 10 of the present application, respectively.

Treprostinil free acid prepared according to "Moriarty"

Chromatographic Purity (HPLC) NB 1, PDR 16	1AU90:	Not more than 0.4%	ND
	2AU90:	Not more than 0.1%	< 0.05%
	97W86 (Benzindene Trial):	Not more than 0.2%	0.07%
	3AU90:	Not more than 1.0%	0.3%
	Treprostinil Methyl Ester:	Not more than 0.2%	< 0.05%
	Treprostinil Ethyl Ester:	Not more than 0.5%	0.1%
	750W93:	Not more than 0.5%	0.1%
	751W93:	Not more than 0.3%	0.07%
	Unidentified at:	Not more than 0.1% AUC each	ND
Total Related Substances NB 1, PDR 16	Not more than 3.0%		0.6%

4852-8288-2836.1

6/14/13

Treprostinil diethanolamine prepared according to claims 1 or 10

	Com pound	Specifications	
Impurities (HPLC) [Known Impurities] (UTW-11-0327)	1AU90	Not more than 0.4 %	ND
	2AU90	Not more than 0.1 %	ND
	97W86	Not more than 0.2 %	ND
	3ALI9D	Not more than 0.5 %	< 0.05 % w/w
	Treprostinil Methyl Ester	Not more than 0.2 %	ND
	Treprostinil Ethyl Ester	Not more than 0.5 %	ND
	750W93	Not more than 0.5 %	ND
	751W93	Not more than 0.3 %	ND
Impurities (HPLC) [Unidentified Impurities] (UTW-11-0327)	Not more than 0.2 % AUC each		0.07 % AUC (RRT 0.26)
Impurities (HPLC) [Total Related Substances] (UTW-11-0327)	Not more than 1.5 %		0.1 % w/w

Treprostinil as the free acid prepared according to claims 1 or 10

	Compound	Specifications	
Impurities (HPLC)	1AU90	Not more than 0.40%	ND
	2AU90	Not more than 0.10%	ND
	3AU90	Not more than 1.00%	ND
	750W93	Not more than 0.50%	0.06 % w/w
	751W93	Not more than 0.30%	< 0.05 % w/w
	97W86 (Benzindene Triol)	Not more than 0.20%	ND
	Treprostinil Ethyl Ester	Not more than 0.50%	0.13 % w/w
	Treprostinil Methyl Ester	Not more than 0.20%	ND
Impurities (HPLC) [Unidentified Impurities]	Not more than 0.10% AUC each		ND
Impurities (HPLC) [Total Related Substances]	Not more than 3.00%		0.2 %

In each case, in the above tables, "ND" means not detected. The far right column represents the testing results for that product batch.

7. The impurity profiles shown above examine the following eight impurities: 1AU90, 2AU90 and 3AU90, each of which is a stereoisomer of treprostinil; triol; methyl ester of treprostinil and ethyl ester of treprostinil; 750W93 and 751W93, each of which is a dimer of treprostinil, in which the acid group of one treprostinil molecule esterifies with an alcohol group on another treprostinil molecule. According to the first profile above, treprostinil produced according to the process of "Moriarty" has 7 out of 8 impurities in detectable amounts. According to the second profile above, treprostinil diethanolamine prepared according to the process specified in claim 1 or 10 of the present application has only one impurity, treprostinil stereoisomer 3A90, in a detectable amount. According to the third profile above, treprostinil as

the free acid prepared according to the process specified in claim 1 or 10 of the present application has only three impurities, treprostinil ethyl ester, treprostinil dimers 750W93 and 751W93.

8. Based on the results shown above, I conclude that each of treprostinil as the free acid and treprostinil diethanolamine prepared according to the process specified in claim 1 or 10 of the present application is physically different from treprostinil prepared according to the process of "Moriarty" at least because neither of them contains a detectable amount of any of benzindene triol, treprostinil methyl ester, 1AU90 treprostinil stereoisomer and 2AU90 treprostinil stereoisomer, each of which were present in detectable amounts in treprostinil produced according to the process of "Moriarty".

9. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States.

Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed this 4th day of JUNE, 2013.

David A. Walsh

David A. Walsh

4852-8288-2836.1

Electronic Acknowledgement Receipt	
EFS ID:	16466959
Application Number:	13910583
International Application Number:	
Confirmation Number:	7133
Title of Invention:	PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
First Named Inventor/Applicant Name:	Hitesh Batra
Customer Number:	22428
Filer:	Stephen Bradford Maebius
Filer Authorized By:	
Attorney Docket Number:	080618-1255
Receipt Date:	31-JUL-2013
Filing Date:	05-JUN-2013
Time Stamp:	15:31:30
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		AmendmentReqforReconsideration.pdf	332085 5ce998885ddff58298d19e1a4d84fc7ccfb72d33	yes	7

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment Copy Claims/Response to Suggested Claims	1	1
	Claims	2	2
	Applicant Arguments/Remarks Made in an Amendment	3	7

Warnings:					
Information:					
2	Affidavit-traversing rejectns or objectns rule 132	WalshDec.pdf	262602 b4b00f0e2605f3a16e3f633aa9e87a16abf33861	no	5
Warnings:					
Information:					
		Total Files Size (in bytes):	594687		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 13/910,583	Filing Date 06/05/2013	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	07/31/2013	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 14	Minus	** 20	= 0	X $80 =	0
	Independent (37 CFR 1.16(h))	* 1	Minus	***3	= 0	X $420 =	0
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	**0**

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

LIE
/HENRIETT K. DENDY/

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/910,583	06/05/2013	Hitesh Batra	080618-1255	7133

22428 7590 07/19/2013
FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

EXAMINER	
VALENROD, YEVGENY	
ART UNIT	PAPER NUMBER
1621	
MAIL DATE	DELIVERY MODE
07/19/2013	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 13/910,583	Applicant(s) BATRA ET AL.	
	Examiner YEVGENY VALENROD	Art Unit 1621	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *5 June 2013*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *1-14* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-14* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some * c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/5/13*.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of pre-AIA 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-14 are rejected under pre-AIA 35 U.S.C. 102b as being anticipated by Phares et al. (US 2005/0085540).

Phares discloses a method of producing a pharmaceutical composition comprising combining a starting batch of treprostinil which comprises treprostinil, ethanol and water with diethanolamine to produce treprostinil diethanolamine salt (page 9, paragraph [0105]). Phares describes the produced diethanolamine salt of treprostinil as a crystalline form A (page 38, paragraph [0330] – [0331]). Since the process steps of claim 1 are the same as the process steps described by Phares et al, the purity of the Phares salt is inherently the same as the instantly claimed purity of claims 3 and 10. On page 36, paragraphs [0311] – [0314] pharmaceutical compositions comprising treprostinil diethanolamine are described. Capsule and tablet forms are described in paragraph [0314]. Finally on page 38, paragraph [0039] Phares describes storing treprostinil diethanolamine salt at ambient temperature.

Conclusion

Claims 1-14 are pending

Claims 1-14 are rejected

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yevgeny Valenrod whose telephone number is 571-272-9049. The examiner can normally be reached on 8:30am-5:00pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/YEVGENY VALENROD/

Primary Examiner, Art Unit 1621

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13910583	BATRA ET AL.
	Examiner	Art Unit
	YEVEGENY VALENROD	1621

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	07/17/2013								
	1	✓								
	2	✓								
	3	✓								
	4	✓								
	5	✓								
	6	✓								
	7	✓								
	8	✓								
	9	✓								
	10	✓								
	11	✓								
	12	✓								
	13	✓								
	14	✓								

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Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

BIB DATA SHEET

CONFIRMATION NO. 7133

SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
13/910,583	06/05/2013	~~562~~ 562/466	1621	080618-1255

APPLICANTS

United Therapeutics Corporation, Silver Spring, MD, Assignee (with 37 CFR 1.172 Interest);
Hitesh Batra, Herndon, VA;
Sudersan M. Tuladhar, Silver Spring, MD;
Raju Penmasta, Herndon, VA;
David A. Walsh, Palmyra, VA;

**** CONTINUING DATA ***************************

This application is a CON of 13/548,446 07/13/2012 PAT 8497393
which is a CON of 12/334,731 12/15/2008 PAT 8242305
which claims benefit of 61/014,232 12/17/2007

**** FOREIGN APPLICATIONS ***************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****

06/24/2013

Foreign Priority claimed ☐ Yes ☑ No 35 USC 119(a-d) conditions met ☑ Yes ☐ No Verified and Acknowledged /YEVEGENY VALENROD/ Examiner's Signature	☐ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		VA	0	14	1

ADDRESS

FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007
UNITED STATES

TITLE

PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®

FILING FEE RECEIVED		
1900	FEES: Authority has been given in Paper No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

BIB (Rev. 05/07).

PTO/SB/08 (09-06)

Approved for use through 03/31/2007. OMB 0651-0031

U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

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Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Date Submitted: June 5, 2013

(use as many sheets as necessary)

Sheet 1 of 4

Complete if Known	
Application Number	Unassigned
Filing Date	Herewith
First Named Inventor	Hitesh BATRA
Art Unit	Unassigned
Examiner Name	Unassigned
Attorney Docket Number	080618-1255

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	A1	2002/0173672 A1	11/21/2002	Moriarty et al.	
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Examiner Initials*	Cite No.[1]	Foreign Patent Document	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Documents	Pages, Columns, Lines, Where Relevant	T[6]

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This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Date Submitted: June 5, 2013

(use as many sheets as necessary)

Sheet 2 of 4

Complete if Known	
Application Number	Unassigned
Filing Date	Herewith
First Named Inventor	Hitesh BATRA
Art Unit	Unassigned
Examiner Name	Unassigned
Attorney Docket Number	080618-1255

		Country Code[3]-Number[4]-Kind Code[5] *(if known)*				
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	A36	CN 101891596 A	11/24/2010	Shanghai Techwell Biopharmaceutical Co. Ltd.		A ✓
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NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]
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Examiner Signature		Date Considered	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Date Submitted: June 5, 2013

(use as many sheets as necessary)

Sheet 3 of 4

Complete if Known	
Application Number	Unassigned
Filing Date	Herewith
First Named Inventor	Hitesh BATRA
Art Unit	Unassigned
Examiner Name	Unassigned
Attorney Docket Number	080618-1255

NON PATENT LITERATURE DOCUMENTS

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Examiner Signature		Date Considered	

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Substitute for form 1449/PTO				*Complete if Known*	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	Unassigned
				Filing Date	Herewith
Date Submitted: June 5, 2013				**First Named Inventor**	Hitesh BATRA
				Art Unit	Unassigned
(use as many sheets as necessary)				Examiner Name	Unassigned
Sheet	4	of	4	Attorney Docket Number	080618-1255

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]
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Examiner Signature	/Yevgeny Valenrod/	Date Considered	07/17/2013

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 ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /YV/

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	10	((HITESH) near2 (BATRA)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2013/07/17 15:50
L2	8	((SUDERSAN) near2 (TULADHAR)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2013/07/17 15:50
L3	20	((RAJU) near2 (PENMASTA)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2013/07/17 15:50
L4	203	((DAVID) near2 (WALSH)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2013/07/17 15:50
L5	202	L1 or L2 or L3 or L4	US-PGPUB; USPAT	OR	OFF	2013/07/17 15:50
L6	9	L5 and treprostinil	US-PGPUB; USPAT	OR	OFF	2013/07/17 15:50
L7	674	treprostinil	US-PGPUB; USPAT	OR	OFF	2013/07/17 15:50
L8	60	L7 same diethanolamine	US-PGPUB; USPAT	OR	OFF	2013/07/17 15:50
L9	0	L8 same (crystal or crystallized)	US-PGPUB; USPAT	OR	OFF	2013/07/17 15:50
L10	6	L8 same polymorph	US-PGPUB; USPAT	OR	OFF	2013/07/17 15:50
L11	812	(562/466).CCLS.	US-PGPUB; USPAT; USOCR	OR	OFF	2013/07/17 15:50
L12	13	L7 and L11	US-PGPUB; USPAT	OR	OFF	2013/07/17 15:50
L13	10	L12 and diethanolamine	US-PGPUB; USPAT	OR	OFF	2013/07/17 15:50
L14	1	("20050085540").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2013/07/17 15:50

EAST Search History (Interference)

		<This search history is empty>				

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13910583	BATRA ET AL.
	Examiner	Art Unit
	YEVEGENY VALENROD	1621

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
EAST search	7/17/2013	YV
Inventor search	7/17/2013	YV

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

	/YEVEGENY VALENROD/ Primary Examiner.Art Unit 1621

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FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
WASHINGTON DC 20007

MAILED
JUL 08 2013
OFFICE OF PETITIONS

Doc Code: TRACK1.GRANT

Decision Granting Request for Prioritized Examination (Track I or After RCE)	Application No.: 13/910,583

1. THE REQUEST FILED June 5, 2013 IS **GRANTED**.

The above-identified application has met the requirements for prioritized examination

A. ☒ for an original nonprovisional application (Track I).
B. ☐ for an application undergoing continued examination (RCE).

2. **The above-identified application will undergo prioritized examination.** The application will be accorded special status throughout its entire course of prosecution until one of the following occurs:

A. filing a **petition for extension of time** to extend the time period for filing a reply;
B. filing an **amendment to amend the application to contain more than four independent claims, more than thirty total claims**, or a multiple dependent claim;
C. filing a **request for continued examination**;
D. filing a notice of appeal;
E. filing a request for suspension of action;
F. mailing of a notice of allowance;
G. mailing of a final Office action;
H. completion of examination as defined in 37 CFR 41.102; or
I. abandonment of the application.

Telephone inquiries with regard to this decision should be directed to Irvin Dingle at (571)272-3210, Office of Petitions.

Irvin Dingle
/Irvin Dingle/
[*Signature*]

Petitions Examiner
(Title)

U.S. Patent and Trademark Office
PTO-2298 (Rev. 02-2012)

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
13/910,583	06/05/2013	1629	1900	080618-1255	14	1

CONFIRMATION NO. 7133

22428
FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

FILING RECEIPT

OC000000062167264

Date Mailed: 07/02/2013

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Hitesh Batra, Herndon, VA;
Sudersan M. Tuladhar, Silver Spring, MD;
Raju Penmasta, Herndon, VA;
David A. Walsh, Palmyra, VA;

Applicant(s)

United Therapeutics Corporation, Silver Spring, MD

Power of Attorney: The patent practitioners associated with Customer Number 22428

Domestic Priority data as claimed by applicant

This application is a CON of 13/548,446 07/13/2012
which is a CON of 12/334,731 12/15/2008 PAT 8242305
which claims benefit of 61/014,232 12/17/2007

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

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Projected Publication Date: 10/10/2013

Non-Publication Request: No

Early Publication Request: No

Title

PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®

Preliminary Class

514

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

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NOT GRANTED

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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 13/910,583

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	280
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	600
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	720
TOTAL CLAIMS (37 CFR 1.16(i))	14 minus 20 =	*			OR	x 80 =	0.00
INDEPENDENT CLAIMS (37 CFR 1.16(h))	1 minus 3 =	*				x 420 =	0.00
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						0.00
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	1600

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/910,583	06/05/2013	Hitesh Batra	080618-1255

CONFIRMATION NO. 7133

22428
FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

POA ACCEPTANCE LETTER

OC000000062167315

Date Mailed: 07/02/2013

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 06/05/2013.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

/gmihtsun/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor Name: Hitesh BATRA

Title: AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®

Prior Appl. No.: 13/548,446

Prior Appl. Filing Date: 7/13/2012

Examiner: Unassigned

Art Unit: Unassigned

CONTINUING PATENT APPLICATION TRANSMITTAL LETTER

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

Transmitted herewith for filing under 37 C.F.R. § 1.53(b) is a:

[**X**] Continuation [ ] Division [ ] Continuation-In-Part (CIP)

of the above-identified copending prior application in which no patenting, abandonment, or termination of proceedings has occurred. Priority to the above-identified prior application is hereby claimed under 35 U.S.C. § 120 for this continuing application. The entire disclosure of the above-identified prior application is considered as being part of the disclosure of the accompanying continuing application and is hereby incorporated by reference therein.

[ ] Applicant claims small entity status under 37 CFR 1.27.

Enclosed are:

[**X**] Description, Claims, and Abstract (23 pages).

[**X**] Executed Declaration (4 pages).

[**X**] Power of Attorney (1 page).

[**X**] Information Disclosure Statement, Form PTO-SB08.

[**X**] Application Data Sheet (37 CFR 1.76).

[**X**] PTO/SB/424 - Request for Prioritized Examination.

The adjustment to the number of sheets for EFS-Web filing follows:

Number of Sheets		**EFS-Web Adjustment**	**Number of Sheets for EFS-Web**
23	x	75%	18

The filing fee is calculated below at the large entity rate:

	Number Filed		**Included in Basic Fee**		**Extra**		Rate		Fee Totals
Basic Filing Fee							$280.00	=	$280.00
Search Fee							$600.00		$600.00
Examination Fee							$720.00		$720.00
Size Fee	18	-	100	= 0		x	$400.00		$0.00
Total Claims:	14	-	20	= 0		x	$80.00	=	$0.00
Independent:	1	-	3	= 0		x	$420.00	=	$0.00
If any Multiple Dependent Claim(s) present:						+	$780.00	=	$0.00
Surcharge under 37 CFR 1.16(e) for late filing of Executed Declaration or late payment of filing fee						+	$140.00	=	$0.00
Prioritized Examination fee (Track I) under 37 C.F.R. § 1.17 (c)									$4,000.00
Processing Fee (Track I) under 37 C.F.R. § 1.17 (i)									$130.00
TOTAL FILING FEE:								=	$5,730.00
Assignment Recordation Fee:						+	$40.00	=	$0.00
Processing Fee under 37 CFR 1.17(i) for Late Filing of English Translation of Application:						+	$140.00	=	$0.00
Publication Fee									$300.00
TOTAL FEE								=	$6,030.00

The above-identified fees of $6,030.00 are being paid by credit card via EFS-Web.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment,

to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by the credit card payment instructions in EFS-Web being incorrect or absent, resulting in a rejected or incorrect credit card transaction, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741.

Please direct all correspondence to the undersigned attorney or agent at the address indicated below.

Respectfully submitted,

Date JUN 05 2013 By

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 672-5569
Facsimile: (202) 672-5399

Stephen B. Maebius
Attorney for Applicant
Registration No. 35,264

AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a Continuation of U.S. Application No. 13/548,446, filed July 13, 2013, which is a Continuation of U.S. Application No. 12/334,731, filed December 15, 2008, which claims priority from U.S. Provisional Patent Application 61/014,232, filed December 17, 2007, the entire contents of which are incorporated herein by reference.

BACKGROUND

[0002] The present invention relates to a process for producing prostacyclin derivatives and novel intermediate compounds useful in the process.

[0003] Prostacyclin derivatives are useful pharmaceutical compounds possessing activities such as platelet aggregation inhibition, gastric secretion reduction, lesion inhibition, and bronchodilation.

[0004] Treprostinil, the active ingredient in Remodulin®, was first described in US patent 4,306,075. Treprostinil, and other prostacyclin derivatives have been prepared as described in Moriarty, et al in *J. Org. Chem.* 2004, 69, 1890-1902, *Drug of the Future*, 2001, 26(4), 364-374, U.S. Pat. Nos. 6,441,245, 6,528,688, 6,765,117 and 6,809,223. Their teachings are incorporated by reference to show how to practice the embodiments of the present invention.

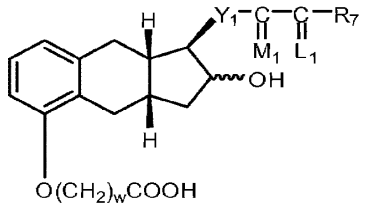
[0005] U.S. Patent No. 5,153,222 describes use of treprostinil for treatment of pulmonary hypertension. Treprostinil is approved for the intravenous as well as subcutaneous route, the latter avoiding septic events associated with continuous intravenous catheters. U.S. patents Nos. 6,521,212 and 6,756,033 describe administration of treprostinil by inhalation for treatment of pulmonary hypertension, peripheral vascular disease and other diseases and conditions. U.S. patent No. 6,803,386 discloses administration of treprostinil for treating cancer such as lung, liver, brain, pancreatic, kidney, prostate, breast, colon and head-neck cancer. U.S. patent application publication No. 2005/0165111 discloses treprostinil treatment of ischemic lesions. U.S. patent No. 7,199,157 discloses that treprostinil treatment improves kidney functions. U.S. patent application publication No. 2005/0282903 discloses treprostinil treatment of neuropathic foot ulcers. U.S. application No. 12/028,471 filed February 8, 2008,

discloses treprostinil treatment of pulmonary fibrosis. U.S. 6,054,486 discloses treatment of peripheral vascular disease with treprostinil. U.S. patent application 11/873,645 filed October 17, 2007 discloses combination therapies comprising treprostinil. U.S. publication No. 2008/0200449 discloses delivery of treprostinil using a metered dose inhaler. U.S. publication No. 2008/0280986 discloses treatment of interstitial lung disease with treprostinil. U.S. application No. 12/028,471 filed February 8, 2008 discloses treatment of asthma with treprostinil. U.S. 7,417,070, 7,384,978 and U.S. publication Nos. 2007/0078095, 2005/0282901, and 2008/0249167 describe oral formulations of treprostinil and other prostacyclin analogs.

[0006] Because Treprostinil, and other prostacyclin derivatives are of great importance from a medicinal point of view, a need exists for an efficient process to synthesize these compounds on a large scale suitable for commercial production.

SUMMARY

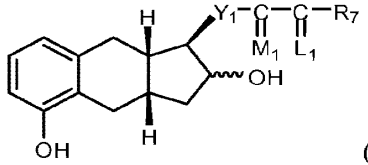
[0007] The present invention provides in one embodiment a process for the preparation of a compound of formula I, hydrate, solvate, prodrug, or pharmaceutically acceptable salt thereof.



(I)

[0008] The process comprises the following steps:

(a) alkylating a compound of structure II with an alkylating agent to produce a compound of formula III,



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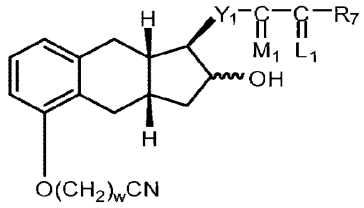


(III)

wherein

w= 1, 2, or 3;

Y_1 is trans-CH=CH-, cis-CH=CH-, $-CH_2(CH_2)_m-$, or -C≡C-; m is 1, 2, or 3;

R_7 is

(1) $-C_pH_{2p}-CH_3$, wherein p is an integer from 1 to 5, inclusive,

(2) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3) alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl, with the proviso that R_7 is phenoxy or substituted phenoxy, only when R_3 and R_4 are hydrogen or methyl, being the same or different,

(3) phenyl, benzyl, phenylethyl, or phenylpropyl optionally substituted on the aromatic ring by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3)alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl,

(4) cis-CH=CH-CH_2-CH_3,

(5) $-(CH_2)_2-CH(OH)-CH_3$, or

(6) $-(CH_2)_3-CH=C(CH_3)_2$;

wherein $-C(L_1)-R_7$ taken together is

(1) (C_4-C_7)cycloalkyl optionally substituted by 1 to 3 (C_1-C_5)alkyl;

(2) 2-(2-furyl)ethyl,

(3) 2-(3-thienyl)ethoxy, or

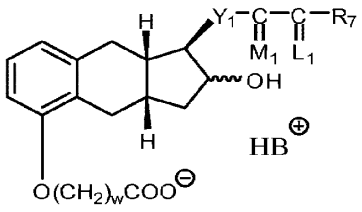
(4) 3-thienyloxymethyl;

M_1 is α-OH:β-R_5 or α-R_5:β-OH or α-OR_1:β-R_5 or α-R_5:β-OR_2, wherein R_5 is hydrogen or methyl, R_2 is an alcohol protecting group, and

L_1 is α-R_3:β-R_4, α-R_4:β-R_3, or a mixture of α-R_3:β-R_4 and α-R_4:β-R_3, wherein R_3 and R_4 are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R_3 and R_4 is fluoro only when the other is hydrogen or fluoro.

(b) hydrolyzing the product of step (a) with a base,

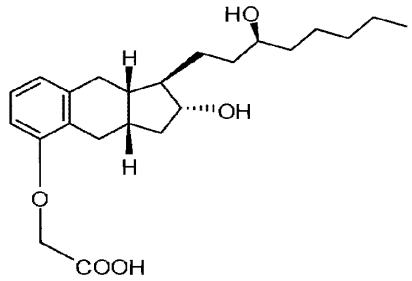
(c) contacting the product of step (b) with a base B to for a salt of formula I_s



(I_s)

(d) reacting the salt from step (c) with an acid to form the compound of formula I.

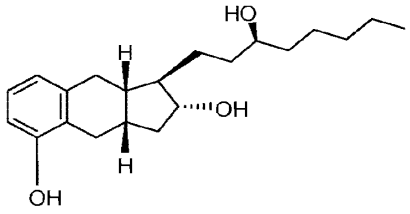
[0009] The present invention provides in another embodiment a process for the preparation of a compound of formula IV.



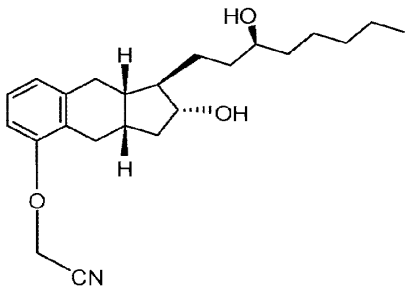
(IV)

[0010] The process comprises the following steps:

(a) alkylating a compound of structure V with an alkylating agent to produce a compound of formula VI,



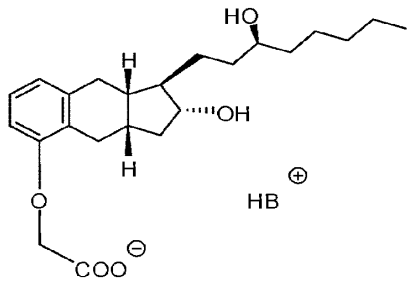
(V)



(VI)

(b) hydrolyzing the product of step (a) with a base,

(c) contacting the product of step (b) with a base B to for a salt of formula IV_s, and



(IV_s)

(d) reacting the salt from step (b) with an acid to form the compound of formula IV.

DETAILED DESCRIPTION

[0011] The various terms used, separately and in combinations, in the processes herein described are defined below.

[0012] The expression "comprising" means "including but not limited to." Thus, other non-mentioned substances, additives, carriers, or steps may be present. Unless otherwise specified, "a" or "an" means one or more.

[0013] C_{1-3}-alkyl is a straight or branched alkyl group containing 1-3 carbon atoms. Exemplary alkyl groups include methyl, ethyl, n-propyl, and isopropyl.

[0014] C_{1-3}-alkoxy is a straight or branched alkoxy group containing 1-3 carbon atoms. Exemplary alkoxy groups include methoxy, ethoxy, propoxy, and isopropoxy.

[0015] C_{4-7}-cycloalkyl is an optionally substituted monocyclic, bicyclic or tricyclic alkyl group containing between 4-7 carbon atoms. Exemplary cycloalkyl groups include but not limited to cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl.

[0016] Combinations of substituents and variables envisioned by this invention are only those that result in the formation of stable compounds. The term "stable", as used herein, refers to compounds which possess stability sufficient to allow manufacture and which maintains the integrity of the compound for a sufficient period of time to be useful for the purposes detailed herein.

[0017] As used herein, the term "prodrug" means a derivative of a compound that can hydrolyze, oxidize, or otherwise react under biological conditions (*in vitro* or *in vivo*) to provide an active compound. Examples of prodrugs include, but are not limited to,

derivatives of a compound that include biohydrolyzable groups such as biohydrolyzable amides, biohydrolyzable esters, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, and biohydrolyzable phosphate analogues (*e.g.*, monophosphate, diphosphate or triphosphate).

[0018] As used herein, "hydrate" is a form of a compound wherein water molecules are combined in a certain ratio as an integral part of the structure complex of the compound.

[0019] As used herein, "solvate" is a form of a compound where solvent molecules are combined in a certain ratio as an integral part of the structure complex of the compound.

[0020] "Pharmaceutically acceptable" means in the present description being useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes being useful for veterinary use as well as human pharmaceutical use.

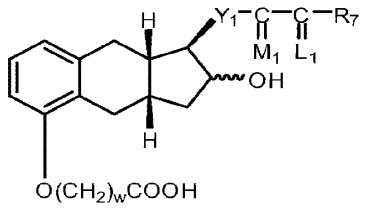
[0021] "Pharmaceutically acceptable salts" mean salts which are pharmaceutically acceptable, as defined above, and which possess the desired pharmacological activity. Such salts include acid addition salts formed with organic and inorganic acids, such as hydrogen chloride, hydrogen bromide, hydrogen iodide, sulfuric acid, phosphoric acid, acetic acid, glycolic acid, maleic acid, malonic acid, oxalic acid, methanesulfonic acid, trifluoroacetic acid, fumaric acid, succinic acid, tartaric acid, citric acid, benzoic acid, ascorbic acid and the like. Base addition salts may be formed with organic and inorganic bases, such as sodium, ammonia, potassium, calcium, ethanolamine, diethanolamine, N-methylglucamine, choline and the like. Included in the invention are pharmaceutically acceptable salts or compounds of any of the formulae herein.

[0022] Depending on its structure, the phrase "pharmaceutically acceptable salt," as used herein, refers to a pharmaceutically acceptable organic or inorganic acid or base salt of a compound. Representative pharmaceutically acceptable salts include, *e.g.*, alkali metal salts, alkali earth salts, ammonium salts, water-soluble and water-insoluble salts, such as the acetate, amsonate (4,4-diaminostilbene-2, 2 -disulfonate), benzenesulfonate, benzonate, bicarbonate, bisulfate, bitartrate, borate, bromide, butyrate, calcium, calcium edetate, camsylate, carbonate, chloride, citrate, clavulariate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexafluorophosphate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride,

hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, N-methylglucamine ammonium salt, 3-hydroxy-2-naphthoate, oleate, oxalate, palmitate, pamoate (1,1-methene-bis-2-hydroxy-3-naphthoate, einbonate), pantothenate, phosphate/diphosphate, picrate, polygalacturonate, propionate, p-toluenesulfonate, salicylate, stearate, subacetate, succinate, sulfate, sulfosalicylate, suramate, tannate, tartrate, teoclate, tosylate, triethiodide, and valerate salts.

[0023] The present invention provides for a process for producing treprostinil and other prostacyclin derivatives and novel intermediate compounds useful in the process. The process according to the present invention provides advantages on large-scale synthesis over the existing method. For example, the purification by column chromatography is eliminated, thus the required amount of flammable solvents and waste generated are greatly reduced. Furthermore, the salt formation is a much easier operation than column chromatography. Moreover, it was found that the product of the process according to the present invention has higher purity. Therefore the present invention provides for a process that is more economical, safer, faster, greener, easier to operate, and provides higher purity.

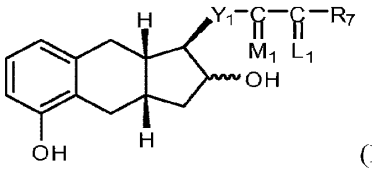
[0024] One embodiment of the present invention is a process for the preparation of a compound of formula I, or a hydrate, solvate, prodrug, or pharmaceutically acceptable salt thereof.



(I)

[0025] The process comprises the following steps:

(a) alkylating a compound of formula II with an alkylating agent to produce a compound of formula III,



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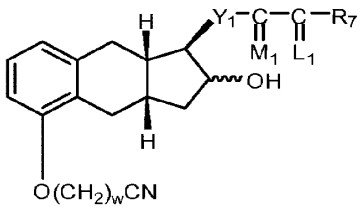


(III)

wherein

w= 1, 2, or 3;

Y_1 is trans-CH=CH-, cis-CH=CH-, $-CH_2(CH_2)_m-$, or -C≡C-; m is 1, 2, or 3;

R_7 is

(1) $-C_pH_{2p}-CH_3$, wherein p is an integer from 1 to 5, inclusive,

(2) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3) alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl, with the proviso that R_7 is phenoxy or substituted phenoxy, only when R_3 and R_4 are hydrogen or methyl, being the same or different,

(3) phenyl, benzyl, phenylethyl, or phenylpropyl optionally substituted on the aromatic ring by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3)alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl,

(4) cis-CH=CH-CH_2-CH_3,

(5) $-(CH_2)_2$-CH(OH)-CH_3, or

(6) $-(CH_2)_3$-CH=$C(CH_3)_2$;

wherein $-C(L_1)-R_7$ taken together is

(1) (C_4-C_7)cycloalkyl optionally substituted by 1 to 3 (C_1-C_5)alkyl;

(2) 2-(2-furyl)ethyl,

(3) 2-(3-thienyl)ethoxy, or

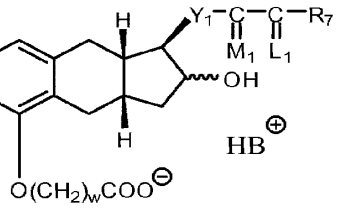
(4) 3-thienyloxymethyl;

M_1 is α-OH:β-R_5 or α-R_5:β-OH or α-OR_1:β-R_5 or α-R_5:β-OR_2, wherein R_5 is hydrogen or methyl, R_2 is an alcohol protecting group, and

L_1 is α-R_3:β-R_4, α-R_4:β-R_3, or a mixture of α-R_3:β-R_4 and α-R_4:β-R_3, wherein R_3 and R_4 are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R_3 and R_4 is fluoro only when the other is hydrogen or fluoro.

(b) hydrolyzing the product of step (a) with a base,

(c) contacting the product of step (b) with a base B to for a salt of formula I_s

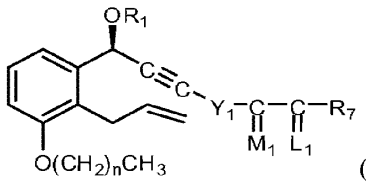


(I_s)

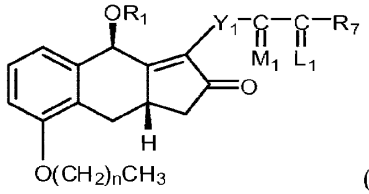
(d) reacting the salt from step (c) with an acid to form the compound of formula I.

[0026] In one embodiment, the compound of formula I is at least 90.0%, 95.0%, 99.0%.

[0027] The compound of formula II can be prepared from a compound of formula XI, which is a cyclization product of a compound of formula X as described in U.S. Pat. No. 6,441,245.



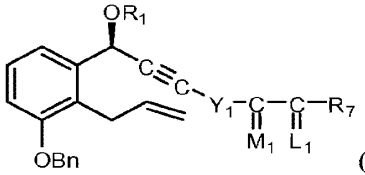
(X)



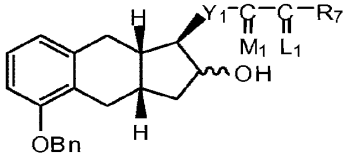
(XI)

Wherein n is 0, 1, 2, or 3.

[0028] The compound of formula II can be prepared alternatively from a compound of formula XIII, which is a cyclization product of a compound of formula XII as described in U.S. Pat. No. 6,700,025.

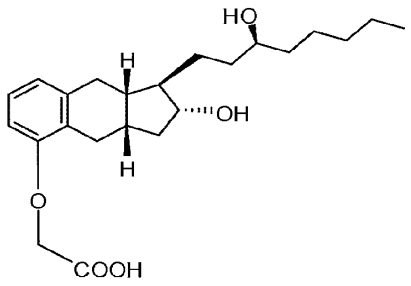


(XII)



(XIII)

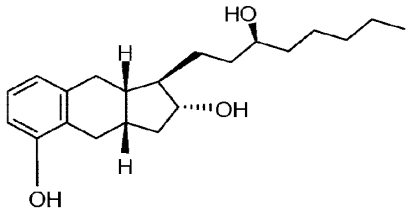
[0029] One embodiment of the present invention is a process for the preparation of a compound having formula IV, or a hydrate, solvate, or pharmaceutically acceptable salt thereof.



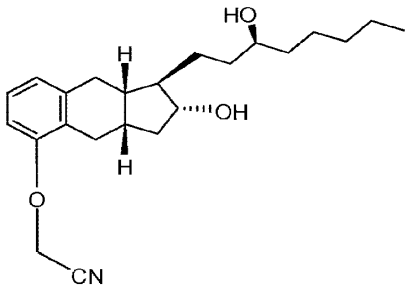
(IV)

[0030] The process comprises

(a) alkylating a compound of structure V with an alkylating agent such as $ClCH_2CN$ to produce a compound of formula VI,



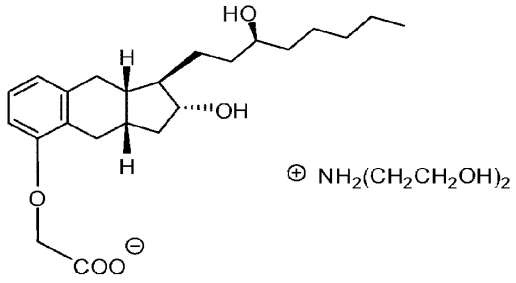
(V)



(VI)

(b) hydrolyzing the product of step (a) with a base such as KOH,

(c) contacting the product of step (b) with a base B such as diethanolamine to for a salt of the following structure, and



(d) reacting the salt from step (b) with an acid such as HCl to form the compound of formula IV.

[0031] In one embodiment, the purity of compound of formula IV is at least 90.0%, 95.0%, 99.0%, 99.5%.

[0032] In one embodiment, the process further comprises a step of isolating the salt of formula IV_s.

[0033] In one embodiment, the base B in step (c) may be ammonia, N-methylglucamine, procaine, tromethanine, magnesium, L-lysine, L-arginine, or triethanolamine.

[0034] The following abbreviations are used in the description and/or appended claims, and they have the following meanings:

"MW" means molecular weight.

"Eq." means equivalent.

"TLC" means thin layer chromatography.

"HPLC" means high performance liquid chromatography.

"PMA" means phosphomolybdic acid.

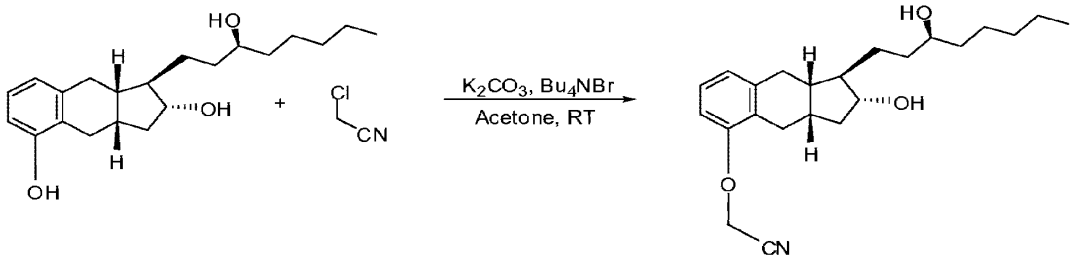
"AUC" means area under curve.

[0035] In view of the foregoing considerations, and specific examples below, those who are skilled in the art will appreciate that how to select necessary reagents and solvents in practicing the present invention.

[0036] The invention will now be described in reference to the following Examples. These examples are not to be regarded as limiting the scope of the present invention, but shall only serve in an illustrative manner.

EXAMPLES

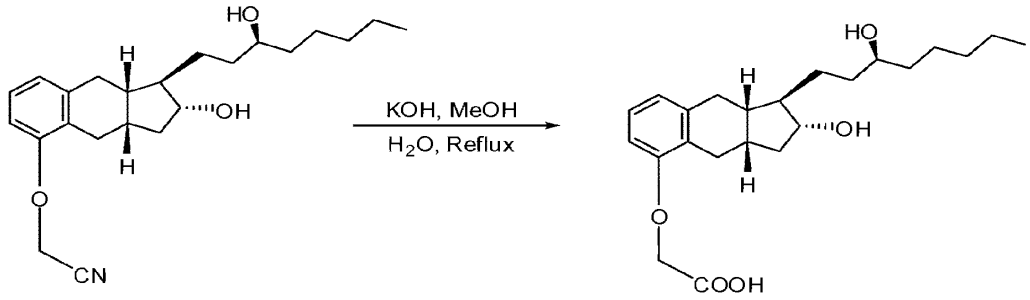
Example 1. Alkylation of Benzindene Triol



Name	MW	Amount	Mol.	Eq.
Benzindene Triol	332.48	1250 g	3.76	1.00
K_2CO_3 (powder)	138.20	1296 g	9.38	2.50
$ClCH_2CN$	75.50	567 g	7.51	2.0
Bu_4NBr	322.37	36 g	0.11	0.03
Acetone	--	29 L	--	--
Celite®545	--	115 g	--	--

[0037] A 50-L, three-neck, round-bottom flask equipped with a mechanical stirrer and a thermocouple was charged with benzindene triol (1250 g), acetone (19 L) and K_2CO_3 (powdered) (1296 g), chloroacetonitrile (567 g), tetrabutylammonium bromide (36 g). The reaction mixture was stirred vigorously at room temperature (23±2°C) for 16-72 h. The progress of the reaction was monitored by TLC. (methanol/CH_2Cl_2; 1:9 and developed by 10% ethanolic solution of PMA). After completion of reaction, the reaction mixture was filtered with/without Celite pad. The filter cake was washed with acetone (10L). The filtrate was concentrated *in vacuo* at 50-55°C to give a light-brown, viscous liquid benzindene nitrile. The crude benzindene nitrile was used as such in the next step without further purification.

Example 2. Hydrolysis of Benzindene Nitrile



Name	MW	Amount	Mol.	Eq.
Benzindene Nitrile	371.52	1397 g*	3.76	1.0
KOH	56.11	844 g	15.04	4.0
Methanol	--	12 L	--	--
Water	--	4.25 L	--	--

*Note: This weight is based on 100% yield from the previous step. This is not isolated yield.

[0038] A 50-L, cylindrical reactor equipped with a heating/cooling system, a mechanical stirrer, a condenser, and a thermocouple was charged with a solution of benzindene nitrile in methanol (12 L) and a solution of KOH (844 g of KOH dissolved in 4.25 L of water). The reaction mixture was stirred and heated to reflux (temperature 72.2°C). The progress of the reaction was monitored by TLC (for TLC purpose, 1-2 mL of reaction mixture was acidified with 3M HCl to pH 1-2 and extracted with ethyl acetate. The ethyl acetate extract was used for TLC; Eluent: methanol/CH_2Cl_2; 1:9, and developed by 10% ethanolic solution of PMA). After completion of the reaction (~5 h), the reaction mixture was cooled to -5 to 10°C and quenched with a solution of hydrochloric acid (3M, 3.1 L) while stirring. The reaction mixture was concentrated *in vacuo* at 50-55°C to obtain approximately 12-14 L of condensate. The condensate was discarded.

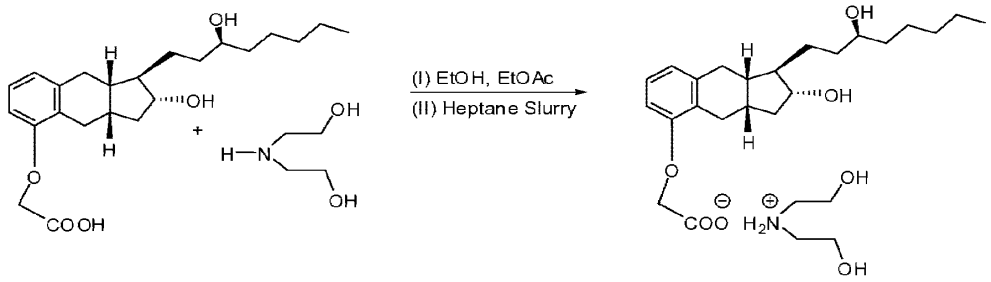
[0039] The aqueous layer was diluted with water (7-8 L) and extracted with ethyl acetate (2 × 6 L) to remove impurities soluble in ethyl acetate. To aqueous layer, ethyl acetate (22 L) was added and the pH of reaction mixture was adjusted to 1-2 by adding 3M HCl (1.7 L) with stirring. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 × 11 L). The combined organic layers were washed with water (3 × 10 L) and followed by washing with a solution of $NaHCO_3$ (30 g of $NaHCO_3$ dissolved in 12 L of water). The organic layer was further washed with saturated solution of NaCl (3372 g of NaCl dissolved in water (12 L)) and dried over anhydrous Na_2SO_4 (950-1000 g), once filtered.

[0040] The filtrate was transferred into a 72-L reactor equipped with mechanical stirrer, a condenser, and a thermocouple. To the solution of treprostinil in reactor was added activated carbon (110-130 g). The suspension was heated to reflux (temperature 68-70°C) for at least one hour. For filtration, a pad of Celite®545 (300-600 g) was prepared in sintered glass

funnel using ethyl acetate. The hot suspension was filtered through the pad of Celite®545. The Celite®545 was washed with ethyl acetate until no compound was seen on TLC of the washings.

[0041] The filtrate (pale-yellow) was reduced to volume of 35-40 L by evaporation *in vacuo* at 50-55°C for direct use in next step.

Example 3. Conversion of Treprostinil to Treprostinil Diethanolamine Salt (1:1)



Name	MW	Amount	Mol	Eq
Treprostinil	390.52	1464 g*	3.75	1.0
Diethanolamine	105.14	435 g	4.14	1.1
Ethanol	--	5.1 L	--	--
Ethyl acetate	--	35L**	--	--
Treprostinil Diethanolamine Salt (seed)	--	12 g	--	--

*Note: This weight is based on 100% yield from benzindene triol. It is not isolated yield. The treprostinil was carried from previous step in ethyl acetate solution and used as such for this step.

**Note: The total volume of ethyl acetate should be in range of 35-36 L (it should be 7 times the volume of ethanol used). Approximately 35 L of ethyl acetate was carried over from previous step and additional 1.0 L of ethyl acetate was used for rinsing the flask.

[0042] A 50-L, cylindrical reactor equipped with a heating/cooling system, a mechanical stirrer, a condenser, and a thermocouple was charged with a solution of treprostinil in ethyl acetate (35-40 L from the previous step), anhydrous ethanol (5.1 L) and diethanolamine (435 g). While stirring, the reaction mixture was heated to 60-75°C, for 0.5-1.0 h to obtain a clear solution. The clear solution was cooled to 55±5°C. At this temperature, the seed of

polymorph B of treprostinil diethanolamine salt (~12 g) was added to the clear solution. The suspension of polymorph B was stirred at this temperature for 1 h. The suspension was cooled to 20±2°C overnight (over a period of 16-24 h). The treprostinil diethanolamine salt was collected by filtration using Aurora filter equipped with filter cloth, and the solid was washed with ethyl acetate (2 × 8 L). The treprostinil diethanolamine salt was transferred to a HDPE/glass container for air-drying in hood, followed by drying in a vacuum oven at 50±5°C under high vacuum.

[0043] At this stage, if melting point of the treprostinil diethanolamine salt is more than 104°C, it was considered polymorph B. There is no need of recrystallization. If it is less than 104°C, it is recrystallized in EtOH-EtOAc to increase the melting point.

Data on Treprostinil Diethanolamine Salt (1:1)

Batch No.	Wt. of Benzindene Triol (g)	Wt. of Treprostinil Diethanolamine Salt (1:1) (g)	Yield (%)	Melting point (°C)
1	1250	1640	88.00	104.3-106.3
2	1250	1528	82.00*	105.5-107.2
3	1250	1499	80.42**	104.7-106.6
4	1236	1572	85.34	105-108

**Note*: In this batch, approximately 1200 mL of ethyl acetate solution of treprostinil before carbon treatment was removed for R&D carbon treatment experiments.

***Note*: This batch was recrystallized, for this reason yield was lower.

Example 4. Heptane Slurry of Treprostinil Diethanolamine Salt (1:1)

Name	Batch No.	Amount	Ratio
Treprostinil Diethanolamine Salt	1	3168 g	1
Heptane	--	37.5 L	12

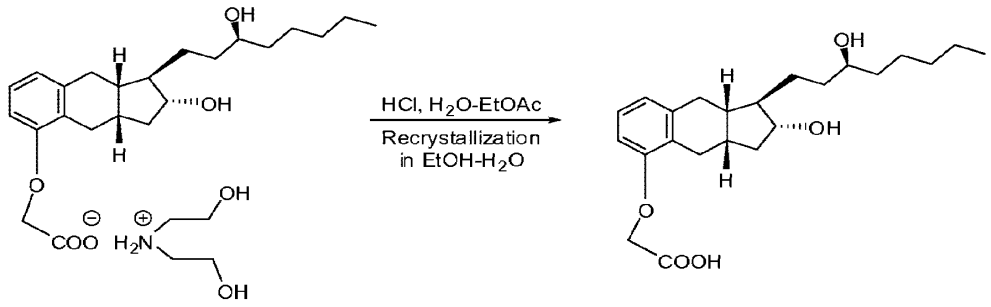
Name	Batch No.	Amount	Ratio
Treprostinil Diethanolamine Salt	2	3071 g	1
Heptane	--	36.0 L	12

[0044] A 50-L, cylindrical reactor equipped with a heating/cooling system, a mechanical stirrer, a condenser, and a thermocouple was charged with slurry of treprostinil diethanolamine salt in heptane (35-40 L). The suspension was heated to 70-80°C for 16-24 h. The suspension was cooled to 22±2°C over a period of 1-2 h. The salt was collected by filtration using Aurora filter. The cake was washed with heptane (15-30 L) and the material was dried in Aurora filter for 1 h. The salt was transferred to trays for air-drying overnight in hood until a constant weight of treprostinil diethanolamine salt was obtained. The material was dried in oven under high vacuum for 2-4 h at 50-55°C.

Analytical data on and Treprostinil Diethanolamine Salt (1:1)

Test	Batch 1	Batch 2
IR	Conforms	Conforms
Residue on Ignition (ROI)	<0.1% w/w	<0.1% w/w
Water content	0.1% w/w	0.0% w/w
Melting point	105.0-106.5°C	104.5-105.5°C
Specific rotation $[\alpha]^{25}_{589}$	+34.6°	+35°
Organic volatile impurities		
• Ethanol	• Not detected	• Not detected
• Ethyl acetate	• Not detected	• <0.05% w/w
• Heptane	• <0.05% w/w	• <0.05% w/w
HPLC (Assay)	100.4%	99.8%
Diethanolamine	Positive	Positive

Example 5. Conversion of Treprostinil Diethanolamine Salt (1:1) to Treprostinil



[0045] A 250-mL, round-bottom flask equipped with magnetic stirrer was charged with treprostinil diethanolamine salt (4 g) and water (40 mL). The mixture was stirred to obtain a clear solution. To the clear solution, ethyl acetate (100 mL) was added. While stirring, 3M HCl (3.2 mL) was added slowly until pH ~1 was attained. The mixture was stirred for 10 minutes and organic layer was separated. The aqueous layer was extracted with ethyl acetate (2 × 100 mL). The combined organic layers was washed with water (2 × 100 mL), brine (1 × 50 mL) and dried over anhydrous Na_2SO_4. The ethyl acetate solution of treprostinil was filtered and the filtrate was concentrated under vacuum at 50°C to give off-white solid. The crude treprostinil was recrystallized from 50% ethanol in water (70 mL). The pure treprostinil was collected in a Buchner funnel by filtration and cake was washed with cold 20% ethanolic solution in water. The cake of treprostinil was air-dried overnight and further dried in a vacuum oven at 50°C under high vacuum to afford 2.9 g of treprostinil (Yield 91.4%, purity (HPLC, AUC, 99.8%).

Analytical data on Treprostinil from Treprostinil Diethanolamine Salt (1:1) to Treprostinil

Batch No.	Yield	Purity (HPLC)
1	91.0%	99.8% (AUC)
2	92.0%	99.9% (AUC)
3	93.1%	99.7% (AUC)
4	93.3%	99.7% (AUC)
5	99.0 %	99.8% (AUC)
6	94.6%	99.8% (AUC)

Example 6. Comparison of the former process and a working example of the process according to the present invention

Step No.	Steps	Former Process (Batch size: 500g)	Working example of the Process according to the present invention (Batch size: 5 kg)
		Nitrile	
1	Triol weight	500 g	5,000 g
2	Acetone	20 L (1:40 wt/wt)	75 L (1:15 wt/wt)
3	Potassium carbonate	1,300 g (6.4 eq)	5,200 g (2.5 eq)
4	Chloroacetonitrile	470 g (4.2 eq)	2,270 g (2 eq)
5	Tetrabutylammonium bromide	42 g (0.08 eq)	145 g (0.03 eq)
6	Reactor size	72-Liter	50- gallon
7	Reflux time	8 hours	No heating, Room temperature (r.t.) 45 h
8	Hexanes addition before filtration	Yes (10 L)	No
9	Filter	Celite	Celite
10	Washing	Ethyl acetate (10 L)	Acetone (50 L)
11	Evaporation	Yes	Yes
12	Purification	Silica gel column Dichloromethane:0.5 L Ethyl acetate: 45 L Hexane: 60 L	No column
13	Evaporation after column	Yes	No
14	Yield of nitrite	109-112 %	Not checked
		Treprostinil (intermediate)	
15	Methanol	7.6 L (50-L reactor)	50 L (50-gal reactor)
16	Potassium hydroxide	650 g (8 eq)	3,375g (4 eq)
17	Water	2.2 L	17 L

18	% of KOH	30%	20%
19	Reflux time	3-3.5 h	4-5 h
20	Acid used	2.6 L (3 M)	12 L (3 M)
21	Removal of impurities	3 × 3 L Ethyl acetate	2 × 20 L Ethyl acetate
22	Acidification	0.7 L	6.5 L
23	Ethyl acetate extraction	5 × 17 L = 35 L	90+45+45 = 180 L
24	Water washing	2 × 8 L	3 × 40 L
25	Sodium bicarbonate washing	Not done	120 g in 30L water + 15 L brine
26	Brine washing	Not done	1 × 40 L
27	Sodium sulfate	1 kg	Not done
28	Sodium sulfate filtration	Before charcoal, 6 L ethyl acetate	N/A
29	Charcoal	170 g, reflux for 1.5 h, filter over Celite, 11 L ethyl acetate	Pass hot solution (75°C) through charcoal cartridge and clean filter, 70 L ethyl acetate
30	Evaporation	Yes, to get solid intermediate treprostinil	Yes, adjust to 150 L solution
Treprostinil Diethanolamine Salt			
31	Salt formation	Not done	1,744 g diethanolamine, 20 L ethanol at 60-75°C.
32	Cooling	N/A	To 20°C over weekend; add 40 L ethyl acetate; cooled to 10°C
33	Filtration	N/A	Wash with 70 L ethyl acetate
34	Drying	N/A	Air-dried to constant wt., 2 days
Treprostinil (from 1.5 kg Treprostinil diethanolamine salt)			
35	Hydrolysis	N/A	15 L water + 25 L ethyl acetate + HCl
36	Extraction	N/A	2 × 10 L ethyl acetate
37	Water wash	N/A	3 × 10 L

38	Brine wash	N/A	1 × 10 L
39	Sodium sulfate	N/A	1 kg, stir
40	Filter	N/A	Wash with 6 L ethyl acetate
41	Evaporation	N/A	To get solid, intermediate Treprostinil
42	Crude drying on tray	1 or 3 days	Same
43	Ethanol & water for cryst.	5.1 L + 5.1 L	10.2 L + 10.2 L (same %)
44	Crystallization in	20-L rotavap flask	50-L jacketed reactor
45	Temperature of crystallization	2 h r.t., fridge -0°C 24 h	50°C to 0°C ramp, 0°C overnight
46	Filtration	Buchner funnel	Aurora filter
47	Washing	20% (10 L) cooled ethanol-water	20% (20 L) cooled ethanol-water
48	Drying before oven	Buchner funnel (20 h) Tray (no)	Aurora filter (2.5 h) Tray (4 days)
49	Oven drying	15 hours, 55°C	6-15 hours, 55°C
50	Vacuum	<-0.095 mPA	< 5 Torr
51	UT-15 yield weight	~ 535 g	~ 1,100 g
52	% yield from triol)	~ 91%	~ 89%
53	Purity	~ 99.0%	99.9%

[0046] The quality of treprostinil produced according to this invention is excellent. The purification of benzindene nitrile by column chromatography is eliminated. The impurities carried over from intermediate steps (i.e. alkylation of triol and hydrolysis of benzindene nitrile) are removed during the carbon treatment and the salt formation step. Additional advantages of this process are: (a) crude treprostinil salts can be stored as raw material at ambient temperature and can be converted to treprostinil by simple acidification with diluted hydrochloric acid, and (b) the treprostinil salts can be synthesized from the solution of treprostinil without isolation. This process provides better quality of final product as well as saves significant amount of solvents and manpower in purification of intermediates.

[0047] Although the foregoing refers to particular preferred embodiments, it will be understood that the present invention is not so limited. It will occur to those of ordinary skill

in the art that various modifications may be made to the disclosed embodiments and that such modifications are intended to be within the scope of the present invention.

[0048] All of the publications, patent applications and patents cited in this specification are incorporated herein by reference in their entirety.

WHAT IS CLAIMED IS:

1. In a process for producing a pharmaceutical composition comprising treprostinil, the improvement comprising forming a salt of treprostinil by combining a starting batch of treprostinil and a base, isolating the treprostinil salt, and preparing a pharmaceutical composition comprising treprostinil from the isolated treprostinil salt, whereby a level of one or more impurities found in the starting batch of treprostinil is lower in the pharmaceutical composition.

2. The process of claim 1, wherein the salt is isolated in crystalline form.

3. The process of claim 2, wherein the isolated salt is at least 99.8% pure.

4. The process of claim 1, wherein the base is selected from the group consisting of sodium, ammonia, potassium, calcium, ethanolamine, diethanolamine, N-methylglucamine, and choline.

5. The process of claim 4, wherein the base is diethanolamine.

6. The process of claim 1, wherein the base is combined with treprostinil that has not been previously isolated.

7. The process of claim 1, wherein the isolated salt is stored at ambient temperature.

8. A pharmaceutical composition prepared by the process of claim 1.

9. A pharmaceutical composition prepared by the process of claim 2.

10. A pharmaceutical composition prepared by the process of claim 3.

11. A pharmaceutical composition prepared by the process of claim 4.

12. A pharmaceutical composition prepared by the process of claim 5.

13. A pharmaceutical composition prepared by the process of claim 6.

14. A pharmaceutical composition prepared by the process of claim 7.

ABSTRACT

This present invention relates to an improved process to prepare prostacyclin derivatives. One embodiment provides for an improved process to convert benzindene triol to treprostinil via salts of treprostinil and to purify treprostinil.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Hitesh BATRA et al.

Title: AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®

Appl. No.: Unassigned (CON of 13/548,446)

Filing Date: Herewith

Examiner: Unassigned

Art Unit: Unassigned

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR §1.56

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

Applicant submits herewith documents for the Examiner's consideration in accordance with 37 CFR §§1.56, 1.97 and 1.98.

Applicants respectfully request that each listed document be considered by the Examiner and be made of record in the present application and that an initialed copy of Form PTO/SB/08 be returned in accordance with MPEP §609.

Applicant requests that, in accordance with 37 CFR §1.98(d), the Examiner review all applications relied on for an earlier effective filing date under 35 U.S.C. 120, including application no. 12/334,731, filed 12/15/2008; application no. 13/548446, filed 7/13/2012, for copies of references of record therein that are not being provided here; although Applicant would be pleased to provide copies of any such documents at the Examiner's request.

The submission of any document herewith is not an admission that such document constitutes prior art against the claims of the present application or that such document is considered material to patentability as defined in 37 CFR §1.56(b). Applicants do not waive

any rights to take any action which would be appropriate to antedate or otherwise remove as a competent reference any document submitted herewith.

TIMING OF THE DISCLOSURE

The listed documents are being submitted in compliance with 37 CFR §1.97(b), within three (3) months of the filing date of the application.

Although Applicant believes that no fee is required, the Commissioner is hereby authorized to charge any additional fees which may be due to Deposit Account No. 19-0741.

Respectfully submitted,

Date JUN 05 2013 By _____

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Stephen B. Maebius
Attorney for Applicant
Registration No. 35,264

PTO/SB/08 (09-06)
Approved for use through 03/31/2007. OMB 0651-0031
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Date Submitted: June 5, 2013

(use as many sheets as necessary)

Sheet 1 of 4

Complete if Known	
Application Number	Unassigned
Filing Date	Herewith
First Named Inventor	Hitesh BATRA
Art Unit	Unassigned
Examiner Name	Unassigned
Attorney Docket Number	080618-1255

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	A1	2002/0173672 A1	11/21/2002	Moriarty et al.	
	A2	2004/0176645 A1	09/09/2004	Moriarty et al.	
	A3	2005/0085540 A1	04/21/2005	Phares et al.	
	A4	2005/0101608 A1	05/12/2005	Santel, Donald J.	
	A5	2005/0165111 A1	07/28/2005	Wade et al.	
	A6	2005/0282903 A1	12/22/2005	Wade et al.	
	A7	2005/0282901 A1	12/22/2005	Phares et al.	
	A8	2007/0078182 A1	04/05/2007	Phares et al.	
	A9	2007/0078095 A1	04/05/2007	Phares et al.	
	A10	2008/0200449 A1	08/21/2008	Olschewski et al.	
	A11	2008/0249167 A1	10/09/2008	Phares et al.	
	A12	2008/0280986 A1	11/13/2008	Wade et al.	
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	A15	4,306,075 A	12/15/1981	Aristoff, Paul A.	
	A16	4,424,376 A	01/03/1984	Moniot et al.	
	A17	4,463,183 A	07/31/1984	Haslanger, Martin F.	
	A18	4,486,598 A	12/04/1984	Aristoff, Paul A.	
	A19	4,544,764 A	10/01/1985	Aristoff, Paul A.	
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	A24	6,441,245 B1	08/27/2002	Moriarty et al.	
	A25	6,521,212 B1	02/18/2003	Cloutier et al.	
	A26	6,528,688 B2	03/04/2003	Moriarty et al.	
	A27	6,700,025 B2	03/02/2004	Moriarty et al.	
	A28	6,756,033 B2	06/29/2004	Cloutier et al.	
	A29	6,765,117 B2	07/20/2004	Moriarty et al.	
	A30	6,803,386 B2	10/12/2004	Shorr et al.	
	A31	6,809,223 B2	10/26/2004	Moriarty et al.	
	A32	7,199,157 B2	04/03/2007	Wade et al.	
	A33	7,384,978 B2	06/10/2008	Phares et al.	
	A34	7,417,070 B2	08/26/2008	Phares et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Documents	Pages, Columns, Lines, Where Relevant	T[6]

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. 1 Applicant's unique citation designation number (optional). 2 See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. 3 Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). 4 For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. 5 Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. 6 Applicant is to place a check mark here if English language Translation is attached.

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Date Submitted: June 5, 2013

(use as many sheets as necessary)

Sheet 2 of 4

Complete if Known	
Application Number	Unassigned
Filing Date	Herewith
First Named Inventor	Hitesh BATRA
Art Unit	Unassigned
Examiner Name	Unassigned
Attorney Docket Number	080618-1255

		Country Code[3]-Number[4]-Kind Code[5] *(if known)*				
	A35	CA 2 710 726 A1	01/22/2012	Alphora Research Inc., CA		
	A36	CN 101891596 A	11/24/2010	Shanghai Techwell Biopharmaceutical Co. Ltd.		A ✓
	A37	CN 101891715 A	11/24/2010	Shanghai Techwell Biopharmaceutical Co. Ltd.		A ✓
	A38	EP 0 004 335 A2	10/03/1979	Hoechst AG		A
	A39	EP 0 087 237 B1	05/14/1986	The Upjohn Company		
	A40	EP 0 159 784 B1	06/07/1989	The Upjohn Company		
	A41	EP 0 175 450 B1	03/22/1989	The Upjohn Company		
	A42	EP 0 496 548 A1	07/29/1992	Purdue Research Foundation		
	A43	WO 98/39337 A1	09/11/1998	Hoechst AG		A
	A44	WO 99/21830 A1	05/06/1999	United Therapeutics Corporation		
	A45	WO 03/070163 A2	08/28/2003	United Therapeutics Corporation		
	A46	WO 2005/007081 A2	01/27/2005	United Therapeutics Corporation		
	A47	WO 2007/134292 A2	11/22/2007	United Therapeutics Corporation		
	A48	WO 2008/100977 A2	08/21/2008	N.V. Organon		
	A49	WO 2009/117095 A1	09/24/2009	Arena Pharmaceuticals, Inc.		
	A50	WO 2012/009816 A1	01/26/2012	Alphora Research Inc.		

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]
	A51	ALEXANDER et al., "The Synthesis of Benzindene Prostacyclin Analogs as Potential Antiulcer Agents," Prostaglandins, 1986, 32(5):647-653.	
	A52	ARISTOFF et al., "Synthesis and Structure-Activity Relationship of Novel Stable Prostacyclin Analogs," Advances in Prostaglandin, Thromboxane, and Leukotriene Research, Samuelsson et al., .Eds., 1983, 11:267-274	
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	A54	ARISTOFF et al., "Total Synthesis of a Novel Antiulcer Agent via a Modification of the Intramolecular Wadsworth-Emons-Wittig Reaction," J. Am. Chem. Soc., 1985, 107:7967-7974.	
	A55	BATRA et al., "Crystallization Process Development for a Stable Polymorph of Treprostinil Diethanolamine (UT-15C) by Seeding," Organic Process Research & Development, 2009, 13:242-249.	

Examiner Signature		Date Considered	

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				Art Unit	Unassigned
(use as many sheets as necessary)				Examiner Name	Unassigned
Sheet	3	of	4	Attorney Docket Number	080618-1255

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]
	A56	BELCH et al., "Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of AS-013, a Prostaglandin E1 Prodrug, in Patients with Intermittent Claudication," Circulation, May 6, 1997, 95(9):2298-2302.	
	A57	CHEMBURKAR et al., "Dealing with the Impact of Ritonavir Polymorphs on the Late Stages of Bulk Drug Process Development," Organic Process Research & Development, 2000, 4:413-417.	
	A58	CHUNG et al., "Promoters for the (Alkyne)hexacarbonyldicobalt-Based Cyclopentenone Synthesis," Organometallics, 1993, 12:220-223.	
	A59	CLARK et al., "High-Performance Liquid Chromatographic Method for Determining the Enantiomeric Purity of a Benzindene Prostaglandin by a Diastereomeric Separation," Journal of Chromatography, 1987, 408:275-283.	
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	A61	HICKS et al., "A Practical Titanium-Catalyzed Synthesis of Bicyclic Cyclopentenones and Allylic Amines," J. Org. Chem., 1996, 61:2713-2718.	
	A62	JEONG et al., "Catalytic Version of the Intramolecular Pauson-Khand Reaction," J. Am. Chem. Soc., 1994, 116:3159-3160.	
	A63	KHAND et al., "Organocobalt Complexes. Part II. Reaction of Acetylenehexacarbonyl-dicobalt Complexes, $(R^1C_2R^2)Co_2(CO)_6$, with Norbornene and its Derivatives," J. Chem. Soc., J.C.S. Perkin I., 1973, 977-981.	
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	A66	MULZER et al., "Asymmetric Synthesis of Carbacyclin Precursors by Pauson-Khand Cyclization," Liebigs Ann. Chem., 1988, 891-897.	
	A67	NELSON, Norman A., "Prostaglandin Nomenclature," J. Med. Chem., September 1974, 17(9):911-918.	
	A68	PAGENKOPF et al., "Photochemical Promotion of the Intramolecular Pauson-Khand Reaction. A New Experimental Protocol for Cobalt-Catalyzed [2 + 2 + 1] Cycloadditions," J. Am. Chem. Soc., 1996, 118:2285-2286.	

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PTO/SB/08 (09-06)
Approved for use through 03/31/2007. OMB 0651-0031
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

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				Filing Date	Herewith
Date Submitted: June 5, 2013				**First Named Inventor**	Hitesh BATRA
				Art Unit	Unassigned
(use as many sheets as necessary)				Examiner Name	Unassigned
Sheet	4	of	4	Attorney Docket Number	080618-1255

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	A69	PAGENKOPF, Brian L., "Substrate and Reagent Control of Diastereoselectivity in Transition Metal-Mediated Process: Development of a Catalytic Photo Promoted Pauson-Khand Reaction," Diss. Abstr. Int., 57(12):7535, 1977, Abstract.	
	A70	PAULSON, Peter L., "The Khand Reaction," Tetrahedron, 1985, 41(24):5855-5860.	
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	A73	SNELL et al., "Investigating the Effect of Impurities on Macromolecule Crystal Growth in Microgravity," Crystal Growth & Design, 2001, 1(2):151-158.	
	A74	Sorbera et al. "UT-15. Treatment of Pulmonary Hypertension Treatment of Peripheral Vascular Disease," *Drug of the Future*, 2001, 26(4), 364-374.	
	A75	TAKANO et al., "Enantiodivergent Synthesis of Both Enantiomers of Sulcatol and Matsutake Alcohol from (R)-Epichlorohydrin," Chemistry Letters, 1987, 2017-2020.	
	A76	VIEDMA, Cristobal, "Selective Chiral Symmetry Breaking during Crystallization: Parity Violation of Cryptochiral Environment in Control?" Crystal Growth & Design, 2007, 7(3):553-556.	
	A77	ZHANG et al., "A Nickel(0)-Catalyzed Process for the Transformation of Enynes to Bicyclic Cyclopentenones," J. Org. Chem., 1996, 61:4498-4499.	

Examiner Signature		Date Considered	

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PTO/AIA/01 (modified)

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)	080618-1256

Title of Invention	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®

As the below named inventor, I hereby declare that:

This declaration is directed to:

☒ The attached application, or

☐ United States application or PCT international application number _____ filed on _____.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than (5) years, or both.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: Hitesh BATRA Date (Optional): June 4, 2013

Signature: _____

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

PTO/AIA/01 (modified)

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)	080618-1256

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LEGAL NAME OF INVENTOR

Inventor: Sudersan M. TULADHAR Date (Optional): Jan 4, 2013

Signature: _____

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

PTO/AIA/01 (modified)

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LEGAL NAME OF INVENTOR

Inventor: Raju PENMASTA Date (Optional): Jun 04 2013

Signature: Raju Penmasta

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

PTO/AIA/01 (modified)

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LEGAL NAME OF INVENTOR

Inventor: David A. WALSH Date (Optional): June 4, 2013

Signature: David A. Walsh

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

Doc Code: TRACK1.REQ
Document Description: TrackOne Request

PTO/SB/424 (12-11)

CERTIFICATION AND REQUEST FOR PRIORITIZED EXAMINATION UNDER 37 CFR 1.102(e) (Page 1 of 1)

First Named Inventor:	Hitesh BATRA	Nonprovisional Application Number (if known):	
Title of Invention:	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®		

APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS PRIORITIZED EXAMINATION FOR THE ABOVE-IDENTIFIED APPLICATION.

1. The processing fee set forth in 37 CFR 1.17(i), the prioritized examination fee set forth in 37 CFR 1.17(c), and if not already paid, the publication fee set forth in 37 CFR 1.18(d) have been filed with the request. The basic filing fee, search fee, examination fee, and any required excess claims and application size fees are filed with the request or have been already been paid.

2. The application contains or is amended to contain no more than four independent claims and no more than thirty total claims, and no multiple dependent claims.

3. The applicable box is checked below:

I. ☑ Original Application (Track One) - Prioritized Examination under § 1.102(e)(1)

i. (a) The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a). This certification and request is being filed with the utility application via EFS-Web.

---OR---

(b) The application is an original nonprovisional plant application filed under 35 U.S.C. 111(a). This certification and request is being filed with the plant application in paper.

ii. An executed oath or declaration under 37 CFR 1.63 is filed with the application.

II. ☐ Request for Continued Examination - Prioritized Examination under § 1.102(e)(2)

i. A request for continued examination has been filed with, or prior to, this form.
ii. If the application is a utility application, this certification and request is being filed via EFS-Web.
iii. The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a), or is a national stage entry under 35 U.S.C. 371.
iv. This certification and request is being filed prior to the mailing of a first Office action responsive to the request for continued examination.
v. No prior request for continued examination has been granted prioritized examination status under 37 CFR 1.102(e)(2).

Signature	Date JUN 05 2013
Name (Print/Typed) Stephen B. Maebius	Practitioner Registration Number 35,264

Note: *Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required in accordance with 37 CFR 1.33 and 11.18. Please see 37 CFR 1.4(d) for the form of the signature. If necessary, submit multiple forms for more than one signature, see below*.*

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PTO/AIA/80 (07-12)
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POWER OF ATTORNEY TO PROSECUTE APPLICATIONS BEFORE THE USPTO

I hereby revoke all previous powers of attorney given in the application identified in the attached statement under 37 CFR 3.73(c).

I hereby appoint:

☑ Practitioners associated with Customer Number: 22428

OR

☐ Practitioner(s) named below (if more than ten patent practitioners are to be named, then a customer number must be used):

Name	Registration Number	Name	Registration Number

As attorney(s) or agent(s) to represent the undersigned before the United States Patent and Trademark Office (USPTO) in connection with any and all patent applications a ssigned only to the undersigned according to the USPTO assignment records or assignments docu ments attached to this form in accordance with 37 CFR 3.73(c).

Please change the correspondence address for the application identified in the attached statement under 37 CFR 3.73(c) to:

☑ The address associated with Customer Number: 22428

OR

☐	Firm or Individual Name		
	Address		
	City		
	Country		
	Telephone		Email

Assignee Name and Address: United Therapeutics Corporation
1040 Spring Street
Silver Spring, Maryland 20910

A copy of this form, together with a statement under 37 CFR 3.73(c) (Form PTO/SB/96 or equivalent) is required to be Filed in each application in which this form is used. The statement under 37 CFR 3.73(c) may be completed by one of The practitioners appointed in this form, and must identify the application in which this Power of Attorney is to be filed.

SIGNATURE of Assignee of Record
The individual whose signature and title is supplied below is authorized to act on behalf of the assignee

Signature		Date	12/11/12
Name	Andrew J. Fisher	Telephone	202-742-1208
Title	Chief Strategic Officer & Deputy General Counsel		

This collection of information is required by 37 CFR 1.31, 1.32 and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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PTO/AIA/14 (03-13)
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	080618-1255
	Application Number	
Title of Invention	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Hitesh		BATRA	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Herndon	State/Province	VA	Country of Residence	US

Mailing Address of Inventor:

Address 1	2461 Leyland Ridge Road		
Address 2			
City	Herndon	State/Province	VA
Postal Code	20171	Country	US

Inventor 2 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Sudersan	M.	TULADHAR	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Silver Spring	State/Province	MD	Country of Residence	US

Mailing Address of Inventor:

Address 1	1501 Haddon Manor Court		
Address 2			
City	Silver Spring	State/Province	MD
Postal Code	20904	Country	US

Inventor 3 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Raju		PENMASTA	

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	080618-1255
	Application Number	
Title of Invention	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®	

City	Herndon	State/Province	VA	Country of Residence	US

Mailing Address of Inventor:

Address 1	12953 Centre Park Circle #115		
Address 2			
City	Herndon	State/Province	VA
Postal Code	20171	Country	US

Remove

Inventor 4

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	David	A.	WALSH	

Residence Information (Select One) (•) US Residency ( ) Non US Residency ( ) Active US Military Service

City	Palmyra	State/Province	VA	Country of Residence	US

Mailing Address of Inventor:

Address 1	56 Wildwood Drive		
Address 2			
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Correspondence Information:

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For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	22428		
Email Address	IPDocketing@foley.com	Add Email	Remove Email

Application Information:

Title of the Invention	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®		
Attorney Docket Number	080618-1255	Small Entity Status Claimed	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)		Suggested Figure for Publication (if any)	

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	080618-1255
	Application Number	
Title of Invention	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®	

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)
☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	◉ Customer Number	○ US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	22428		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, or 365(c) or indicate National Stage entry from a PCT application. Providing this information in the application data sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.

Prior Application Status			Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
This Application	Continuation of	13/548446	2012-07-13
Prior Application Status			Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
13/548446	Continuation of	12/334731	2008-12-15
Prior Application Status			Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
12/334731	An application claiming the benefit	61/014232	2007-12-17

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	080618-1255
	Application Number	
Title of Invention	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®	

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55(d). When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)[i] the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(h)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

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Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button.

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.

Authorization to Permit Access:

☒ Authorization to Permit Access to the Instant Application by the Participating Offices

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In accordance with 37 CFR 1.14(h)(3), access will be provided to a copy of the instant patent application with respect to: 1) the instant patent application-as-filed; 2) any foreign application to which the instant patent application claims priority under 35 U.S.C. 119(a)-(d) if a copy of the foreign application that satisfies the certified copy requirement of 37 CFR 1.55 has been filed in the instant patent application; and 3) any U.S. application-as-filed from which benefit is sought in the instant patent application.

In accordance with 37 CFR 1.14(c), access may be provided to information concerning the date o f filing this Authorization.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	080618-1255
	Application Number	
Title of Invention	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®	

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

◉ Assignee	○ Legal Representative under 35 U.S.C. 117	○ Joint Inventor
○ Person to whom the inventor is obligated to assign.	○ Person who shows sufficient proprietary interest	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor :

If the Applicant is an Organization check here. ☒

Organization Name	United Therapeutics Corporation		
Mailing Address Information For Applicant:			
Address 1	1040 Spring Street		
Address 2			
City	Silver Spring	**State/Province**	MD
Country	US	Postal Code	20910
Phone Number		Fax Number	
Email Address			

Additional Applicant Data may be generated within this form by selecting the Add button.

Non-Applicant Assignee Information:

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	080618-1255
	Application Number	
Title of Invention	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®	

Assignee 1

Complete this section only if non-applicant assignee information is desired to be included on the patent application publication in accordance with 37 CFR 1.215(b). Do not include in this section an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest), as the patent application publication will include the name of the applicant(s).

If the Assignee is an Organization check here. ☐

Prefix	**Given Name**	Middle Name	**Family Name**	Suffix

Mailing Address Information For Non-Applicant Assignee:

Address 1	
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City		**State/Province**	
Country i		Postal Code	
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Signature:

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Signature				Date (YYYY-MM-DD)	JUN 05 2013
First Name	Stephen B.	Last Name	Maebius	Registration Number	35264

Additional Signature may be generated within this form by selecting the Add button.

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Electronic Patent Application Fee Transmittal	
Application Number:	
Filing Date:	
Title of Invention:	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
First Named Inventor/Applicant Name:	Hitesh Batra
Filer:	Stephen Bradford Maebius/Karen Walker
Attorney Docket Number:	080618-1255
Filed as Large Entity	

Track I Prioritized Examination - Nonprovisional Application under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Utility application filing	1011	1	280	280
Utility Search Fee	1111	1	600	600
Utility Examination Fee	1311	1	720	720
Request for Prioritized Examination	1817	1	4000	4000
Pages:				
Claims:				
Miscellaneous-Filing:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Publ. Fee- Early, Voluntary, or Normal	1504	1	300	300
OTHER PUBLICATION PROCESSING FEE	1808	1	130	130
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**6030**

Electronic Acknowledgement Receipt

EFS ID:	15957568
Application Number:	13910583
International Application Number:	
Confirmation Number:	7133
Title of Invention:	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
First Named Inventor/Applicant Name:	Hitesh Batra
Customer Number:	22428
Filer:	Stephen Bradford Maebius/Karen Walker
Filer Authorized By:	Stephen Bradford Maebius
Attorney Docket Number:	080618-1255
Receipt Date:	05-JUN-2013
Filing Date:	
Time Stamp:	15:44:06
Application Type:	Utility under 35 USC 111(a)

Payment information:

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Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

1	TrackOne Request	Track1.pdf	81591 41450f49feb0aa0acae3cfd4b29e2652bfd2258d	no	1
Warnings:					
Information:					
2	Transmittal of New Application	Transmittal.pdf	101175 3da32eccfc741122a168ef660071f7755041476e	no	3
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3		Specification.pdf	221223 bdc2a6b1775c7b91d1b00e76dd8ec087954361c7	yes	23

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5	Oath or Declaration filed	Declaration.pdf	256633 c04cdce717353c4b076c9965f2df074359da1a16	no	4
Warnings:					
Information:					
6	Power of Attorney	POA.pdf	116513 77ebc675ac09a2143d9def4fd3e22d309202a0d0	no	1
Warnings:					

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7	Application Data Sheet	ADS.pdf	576789 99b6ba0b782f8805cd173084d7c31a771cfe7f8e	no	6
Warnings:					
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8	Fee Worksheet (SB06)	fee-info.pdf	40398 b26e6bb4fe0dff49f2f35d2d7fc5e71efd1d81a2	no	2
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If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

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If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

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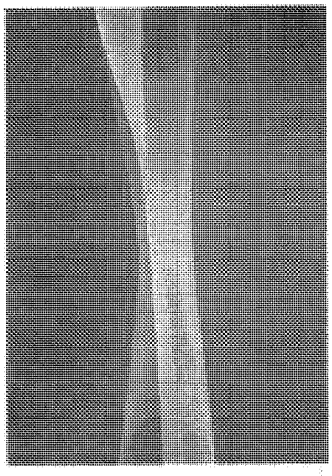
Steven S. Zumdahl
UNIVERSITY OF ILLINOIS

Chemistry



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To my parents and to Eunice, Whitney, and Leslie.

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GLOSSARY

Accuracy the agreement of a particular value with the true value. (1.3)

Acid a substance that produces hydrogen ions in solution; a proton donor. (4.2)

Acid-base indicator a substance that marks the end point of an acid-base titration by changing color. (15.4)

Acid rain a result of air pollution by sulfur dioxide. (5.9)

Acid dissociation constant (K_a) the equilibrium constant for a reaction in which a proton is removed from an acid by H_2O to form the conjugate base and H_3O^+. (14.1)

Acidic oxide a covalent oxide that dissolves in water to give an acidic solution. (14.10)

Actinide series a group of fourteen elements following actinium in the periodic table, in which the 5*f* orbitals are being filled. (7.11; 18.1)

Activated complex (transition state) the arrangement of atoms found at the top of the potential energy barrier as a reaction proceeds from reactants to products. (12.5)

Activation energy the threshold energy that must be overcome to produce a chemical reaction. (12.5)

Addition polymerization a type of polymerization in which the monomers simply add together to form the polymer, with no other products. (22.5)

Addition reaction a reaction in which atoms add to a carbon-carbon multiple bond. (22.2)

Adsorption the collection of one substance on the surface of another. (12.6)

Air pollution contamination of the atmosphere, mainly by the gaseous products of transportation and production of electricity. (5.9)

Alcohol an organic compound in which the hydroxyl group is a substituent on a hydrocarbon. (22.4)

Aldehyde an organic compound containing the carbonyl group bonded to at least one hydrogen atom. (22.4)

Alkali metal a Group 1A metal. (2.7; 18.2)

Alkaline earth metal a Group 2A metal. (2.7; 18.4)

Alkane a saturated hydrocarbon with the general formula C_nH_{2n+2}. (22.1)

Alkene an unsaturated hydrocarbon containing a carbon-carbon double bond. The general formula is C_nH_{2n}. (22.2)

Alkyne an unsaturated hydrocarbon containing a triple carbon-carbon bond. The general formula is C_nH_{2n-2}. (22.2)

Alloy a substance that contains a mixture of elements and has metallic properties. (10.4)

Alloy steel a form of steel containing carbon plus other metals such as chromium, cobalt, manganese, and molybdenum. (24.4)

Alpha (α) particle a helium nucleus. (21.1)

Alpha particle production a common mode of decay for radioactive nuclides in which the mass number changes. (21.1)

Amine an organic base derived from ammonia in which one or more of the hydrogen atoms are replaced by organic groups. (14.6; 22.4)

α-Amino acid an organic acid in which an amino group and an R group are attached to the carbon atom next to the carboxyl group. (23.1)

Amorphous solid a solid with considerable disorder in its structure. (10.3)

Ampere the unit of electrical current equal to one coulomb of charge per second. (17.7)

Amphoteric substance a substance that can behave either as an acid or as a base. (14.2)

Anion a negative ion. (2.6)

Anode the electrode in a galvanic cell at which oxidation occurs. (17.1)

Antibonding molecular orbital an orbital higher in energy than the atomic orbitals of which it is composed. (9.2)

Aromatic hydrocarbon one of a special class of cyclic unsaturated hydrocarbons, the simplest of which is benzene. (22.3)

Arrhenius concept a concept postulating that acids produce hydrogen ions in aqueous solution, while bases produce hydroxide ions. (14.1)

Arrhenius equation the equation representing the rate constant as $k = Ae^{-E_a/RT}$ where A represents the product of the collision frequency and the steric factor, and $e^{-E_a/RT}$ is the fraction of collisions with sufficient energy to produce a reaction. (12.5)

Aqueous solution a solution in which water is the dissolving medium or solvent. (4.0)

Atactic chain a polymer chain in which the substituent groups such as CH_3 are randomly distributed along the chain. (24.2)

Atmosphere the mixture of gases that surrounds the earth's surface. (5.9)

Atomic number the number of protons in the nucleus of an atom. (2.5; 21)

particle is formed having the same mass as an electron but opposite charge. The net effect is to change a proton to a neutron. (21.1)

Potential energy energy due to position or composition. (6.1)

Precipitation reaction a reaction in which an insoluble substance forms and separates from the solution. (4.5)

Precision the degree of agreement among several measurements of the same quantity; the reproducibility of a measurement. (1.3)

Primary structure (of a protein) the order (sequence) of amino acids in the protein chain. (23.1)

Principal quantum number the quantum number relating to the size and energy of an orbital; it can have any positive integer value. (7.6)

Probability distribution the square of the wave function indicating the probability of finding an electron at a particular point in space. (7.5)

Product a substance resulting from a chemical reaction. It is shown to the right of the arrow in a chemical equation. (3.6)

Protein a natural high-molecular-weight polymer formed by condensation reactions between amino acids. (23.1)

Proton a positively charged particle in an atomic nucleus. (2.5; 21)

Pure substance a substance with constant composition. (1.8)

Pyrometallurgy recovery of a metal from its ore by treatment at high temperatures. (24.4)

Qualitative analysis the separation and identification of individual ions from a mixture. (4.6)

Quantitative analysis a process in which the amounts of the components of a mixture are determined. (4.7)

Quantization the fact that energy can occur only in discrete units called quanta. (7.2)

Rad a unit of radiation dosage corresponding to 10^{-2} J of energy deposited per kilogram of tissue (from *r*adiation *a*bsorbed *d*ose). (21.7)

Radioactive decay (radioactivity) the spontaneous decomposition of a nucleus to form a different nucleus. (21.1)

Radiocarbon dating (carbon-14 dating) a method for dating ancient wood or cloth based on the rate of radioactive decay of the nuclide $^{14}_{6}C$. (21.4)

Radiotracer a radioactive nuclide, introduced into an organism for diagnostic purposes, whose pathway can be traced by monitoring its radioactivity. (21.4)

Random error an error that has an equal probability of being high or low. (1.3)

Raoult's law the vapor pressure of a solution is directly proportional to the mole fraction of solvent present. (11.4)

Rate constant the proportionality constant in the relationship between reaction rate and reactant concentrations. (12.2)

Rate of decay the change in the number of radioactive nuclides in a sample per unit time. (21.2)

Rate-determining step the slowest step in a reaction mechanism, the one determining the overall rate. (12.4)

Rate law an expression that shows how the rate of reaction depends on the concentration of reactants. (12.2)

Reactant a starting substance in a chemical reaction. It appears to the left of the arrow in a chemical equation. (3.6)

Reaction mechanism the series of elementary steps involved in a chemical reaction. (12.4)

Reaction quotient a quotient obtained by applying the law of mass action to initial concentrations rather than to equilibrium concentrations. (13.5)

Reaction rate the change in concentration of a reactant or product per unit time. (12.1)

Reactor core the part of a nuclear reactor where the fission reaction takes place. (21.6)

Reducing agent (electron donor) a reactant that donates electrons to another substance to reduce the oxidation state of one of its atoms. (4.9; 17.1)

Reduction a decrease in oxidation state (a gain of electrons). (4.9; 17.1)

Rem a unit of radiation dosage that accounts for both the energy of the dose and its effectiveness in causing biological damage (from *r*oentgen *e*quivalent for *m*an). The number of rems = (number of rads) × RBE, where RBE represents the relative effectiveness of the radiation in causing biological damage. (21.7)

Resonance a condition occurring when more than one valid Lewis structure can be written for a particular molecule. The actual electronic structure is not represented by any one of the Lewis structures but by the average of all of them. (8.12)

Reverse osmosis the process occurring when the external pressure on a solution causes a net flow of solvent through a semipermeable membrane from the solution to the solvent. (11.6)

Reversible process a cyclic process carried out by a hypothetical pathway, which leaves the universe exactly the same as it was before the process. No real process is reversible. (16.9)

Ribonucleic acid (RNA) a nucleotide polymer that transmits the genetic information stored in DNA to the ribosomes for protein synthesis. (23.3)

Roasting a process of converting sulfide minerals to oxides by heating in air at temperatures below their melting points. (24.4)

Root mean square velocity the square root of the average of the squares of the individual velocities of gas particles. (5.6)

Salt an ionic compound. (14.8)

Salt bridge a U-tube containing an electrolyte that connects the two compartments of a galvanic cell, allowing ion flow without extensive mixing of the different solutions. (17.1)

Chemistry

The Central Science

Ninth Edition

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becquerel The SI unit of radioactivity. It corresponds to one nuclear disintegration per second. (Section 21.4)

Beer's law The light absorbed by a substance (A) equals the product of its molar absorptivity constant (a), the path length through which the light passes (b), and the molar concentration of the substance (c): $A = abc$. (Section 14.2)

beta particles Energetic electrons emitted from the nucleus, symbol $^{0}_{-1}e$. (Section 21.1)

bidentate ligand A ligand in which two coordinating atoms are bound to a metal. (Section 24.2)

bimolecular reaction An elementary reaction that involves two molecules. (Section 14.6)

biochemistry The study of the chemistry of living systems. (Chapter 25: Introduction)

biocompatible Any substance or material that is compatible with living systems. (Section 12.3)

biodegradable Organic material that bacteria are able to oxidize. (Section 18.6)

biomaterial Any material that has a biomedical application. (Section 12.3)

biopolymer A polymeric molecule of high molecular weight found in living systems. The three major classes of biopolymer are proteins, carbohydrates, and nucleic acids. (Section 25.8)

body-centered cubic cell A cubic unit cell in which the lattice points occur at the corners and at the center. (Section 11.7)

bomb calorimeter A device for measuring the heat evolved in the combustion of a substance under constant-volume conditions. (Section 5.5)

bond angles The angles made by the lines joining the nuclei of the atoms in a molecule. (Section 9.1)

bond dipole The dipole moment due to the two atoms of a covalent bond. (Section 9.3)

bond enthalpy The enthalpy change, ΔH, required to break a particular bond when the substance is in the gas phase. (Section 8.8)

bonding atomic radius The radius of an atom as defined by the distances separating it from other atoms to which it is chemically bonded. (Section 7.3)

bonding molecular orbital A molecular orbital in which the electron density is concentrated in the internuclear region. The energy of a bonding molecular orbital is lower than the energy of the separate atomic orbitals from which it forms. (Section 9.7)

bonding pair In a Lewis structure a pair of electrons that is shared by two atoms. (Section 9.2)

bond length The distance between the centers of two bonded atoms. (Section 8.8)

bond order The number of bonding electron pairs shared between two atoms, less the number of antibonding electron pairs: bond order = (number of bonding electrons − number of antibonding electrons). (Section 9.7)

bond polarity A measure of how equally the electrons are shared between the two atoms in a chemical bond. (Section 8.4)

boranes Covalent hydrides of boron. (Section 22.11)

Born–Haber cycle A thermodynamic cycle based on Hess's law that relates the lattice energy of an ionic substance to its enthalpy of formation and to other measurable quantities. (Section 8.2)

Boyle's law A law stating that at constant temperature, the product of the volume and pressure of a given amount of gas is a constant. (Section 10.3)

Brønsted–Lowry acid A substance (molecule or ion) that acts as a proton donor. (Section 16.2)

Brønsted–Lowry base A substance (molecule or ion) that acts as a proton acceptor. (Section 16.2)

buffer capacity The amount of acid or base a buffer can neutralize before the pH begins to change appreciably. (Section 17.2)

buffered solution (buffer) A solution that undergoes a limited change in pH upon addition of a small amount of acid or base. (Section 17.2)

calcination The heating of an ore to bring about its decomposition and the elimination of a volatile product. For example, a carbonate ore might be calcined to drive off CO_2. (Section 23.2)

calorie A unit of energy, it is the amount of energy needed to raise the temperature of 1 g of water by 1°C, from 14.5°C to 15.5°C. A related unit is the joule: 1 cal = 4.184 J. (Section 5.1)

calorimeter An apparatus that measures the evolution of heat. (Section 5.5)

calorimetry The experimental measurement of heat produced in chemical and physical processes. (Section 5.5)

capillary action The process by which a liquid rises in a tube because of a combination of adhesion to the walls of the tube and cohesion between liquid particles. (Section 11.3)

carbide A binary compound of carbon with a metal or metalloid. (Section 22.9)

carbohydrates A class of substances formed from polyhydroxy aldehydes or ketones. (Section 25.10)

carbon black A microcrystalline form of carbon. (Section 22.9)

carbonyl group The C=O double bond, a characteristic feature of several organic functional groups, such as ketones and aldehydes. (Section 25.6)

carboxylic acid A compound that contains the —COOH functional group. (Sections 16.10 and 25.6)

catalyst A substance that changes the speed of a chemical reaction without itself undergoing a permanent chemical change in the process. (Section 14.7)

cathode An electrode at which reduction occurs. (Section 20.3)

cathode rays Streams of electrons that are produced when a high voltage is applied to electrodes in an evacuated tube. (Section 2.2)

cathodic protection A means of protecting a metal against corrosion by making it the cathode in a voltaic cell. This can be achieved by attaching a more easily oxidized metal, which serves as an anode, to the metal to be protected. (Section 20.8)

cation A positively charged ion. (Section 2.7)

cell potential A measure of the driving force, or "electrical pressure," for an electrochemical reaction; it is measured in volts: 1 V = 1 J/C. Also called electromotive force. (Section 20.4)

cellulose A polysaccharide of glucose; it is the major structural element in plant matter. (Section 25.10)

Celsius scale A temperature scale on which water freezes at 0° and boils at 100° at sea level. (Section 1.4)

ceramic A solid inorganic material, either crystalline (oxides, carbides, silicates) or amorphous (glasses). Most ceramics melt at high temperatures. (Section 12.4)

chain reaction A series of reactions in which one reaction initiates the next. (Section 21.7)

changes of state Transformations of matter from one state to a different one, for example, from a gas to a liquid. (Section 1.3)

charcoal A form of carbon produced when wood is heated strongly in a deficiency of air. (Section 22.9)

Charles's law A law stating that at constant pressure, the volume of a given quantity of gas is proportional to absolute temperature. (Section 10.3)

chelate effect The generally larger formation constants for polydentate ligands as compared with the corresponding monodentate ligands. (Section 24.2)

chelating agent A polydentate ligand that is capable of occupying two or more sites in the coordination sphere. (Section 24.2)

chemical bond A strong attractive force that exists between atoms in a molecule. (Section 8.1)

chemical changes Processes in which one or more substances are converted into other substances; also called **chemical reactions**. (Section 1.3)

chemical equation A representation of a chemical reaction using the chemical formulas of the reactants and products; a balanced chemical equation contains equal numbers of atoms of each element on both sides of the equation. (Section 3.1)

chemical equilibrium A state of dynamic balance in which the rate of formation of the products of a reaction from the reactants equals the rate of formation of the reactants from the products; at equilibrium the concentrations of the reactants and products remain constant. (Section 4.1; Chapter 15: Introduction.)

chemical formula A notation that uses chemical symbols with numerical subscripts to convey the relative proportions of atoms of the different elements in a substance. (Section 2.6)

product A substance produced in a chemical reaction; it appears to the right of the arrow in a chemical equation. (Section 3.1)

protein A biopolymer formed from amino acids. (Section 25.9)

protium The most common isotope of hydrogen. (Section 22.2)

proton A positively charged subatomic particle found in the nucleus of an atom. (Section 2.3)

pure substance Matter that has a fixed composition and distinct properties. (Section 1.2)

pyrometallurgy A process in which heat converts a mineral in an ore from one chemical form to another and eventually to the free metal. (Section 23.2)

qualitative analysis The determination of the presence or absence of a particular substance in a mixture. (Section 17.7)

quantitative analysis The determination of the amount of a given substance that is present in a sample. (Section 17.7)

quantum The smallest increment of radiant energy that may be absorbed or emitted; the magnitude of radiant energy is $h\nu$. (Section 6.2)

racemic mixture A mixture of equal amounts of the dextrorotatory and levorotatory forms of a chiral molecule. A racemic mixture will not rotate polarized light. (Section 24.4)

rad A measure of the energy absorbed from radiation by tissue or other biological material; 1 rad = transfer of 1×10^{-2} J of energy per kilogram of material. (Section 21.9)

radioactive series A series of nuclear reactions that begins with an unstable nucleus and terminates with a stable one. Also called **nuclear disintegration series**. (Section 21.2)

radioactivity The spontaneous disintegration of an unstable atomic nucleus with accompanying emission of radiation. (Section 2.2; Chapter 21: Introduction)

radioisotope An isotope that is radioactive; that is, it is undergoing nuclear changes with emission of radiation. (Section 21.1)

radionuclide A radioactive nuclide. (Section 21.1)

radiotracer A radioisotope that can be used to trace the path of an element. (Section 21.5)

Raoult's law A law stating that the partial pressure of a solvent over a solution, P_A, is given by the vapor pressure of the pure solvent, P_A°, times the mole fraction of a solvent in the solution, $X_A : P_A = X_A P_A^\circ$. (Section 13.5)

rate constant A constant of proportionality between the reaction rate and the concentrations of reactants that appear in the rate law. (Section 14.3)

rate-determining step The slowest elementary step in a reaction mechanism. (Section 14.6)

rate law An equation that relates the reaction rate to the concentrations of reactants (and sometimes of products also). (Section 14.3)

reactant A starting substance in a chemical reaction; it appears to the left of the arrow in a chemical equation. (Section 3.1)

reaction mechanism A detailed picture, or model, of how the reaction occurs; that is, the order in which bonds are broken and formed, and the changes in relative positions of the atoms as the reaction proceeds. (Section 14.6)

reaction order The power to which the concentration of a reactant is raised in a rate law. (Section 14.3)

reaction quotient (Q) The value that is obtained when concentrations of reactants and products are inserted into the equilibrium expression. If the concentrations are equilibrium concentrations, $Q = K$; otherwise, $Q \neq K$. (Section 15.5)

reaction rate The decrease in concentration of a reactant or the increase in concentration of a product with time. (Section 14.2)

redox (oxidation-reduction) reaction A reaction in which certain atoms undergo changes in oxidation states. The substance increasing in oxidation state is oxidized; the substance decreasing in oxidation state is reduced. (Chapter 20; Introduction)

reducing agent, or **reductant** The substance that is oxidized and thereby causes the reduction of some other substance in an oxidation-reduction reaction. (Section 20.1)

reduction A process in which a substance gains one or more electrons. (Section 4.4)

refining The process of converting an impure form of a metal into a more usable substance of well-defined composition. For example, crude pig iron from the blast furnace is refined in a converter to produce steels of desired compositions. (Section 23.2)

rem A measure of the biological damage caused by radiation; rems = rads × RBE. (Section 21.9)

renewable energy Energy such as solar energy, wind energy, and hydroelectric energy that is from essentially inexhaustible sources. (Section 5.8)

representative (main-group) element Element in which the s and p orbitals are partially occupied. (Section 6.9)

resonance structures (resonance forms) Individual Lewis structures in cases where two or more Lewis structures are equally good descriptions of a single molecule. The resonance structures in such an instance are "averaged" to give a correct description of the real molecule. (Section 8.6)

reverse osmosis The process by which water molecules move under high pressure through a semipermeable membrane from the more concentrated to the less concentrated solution. (Section 18.5)

reversible process A process that can go back and forth between states along exactly the same path; a system at equilibrium is reversible because it can be reversed by an infinitesimal modification of a variable such as temperature. (Section 19.1)

ribonucleic acid (RNA) A polynucleotide in which ribose is the sugar component. (Section 25.11)

roasting Thermal treatment of an ore to bring about chemical reactions involving the furnace atmosphere. For example, a sulfide ore might be roasted in air to form a metal oxide and SO_2. (Section 23.2)

root-mean-square (rms) speed (μ) The square root of the average of the squared speeds of the gas molecules in a gas sample. (Section 10.7)

rotational motion Movement of a molecule as though it is spinning like a top. (Section 19.3)

salinity A measure of the salt content of seawater, brine, or brackish water. It is equal to the mass in grams of dissolved salts present in 1 kg of seawater. (Section 18.5)

salt An ionic compound formed by replacing one or more H^+ of an acid by other cations. (Section 4.3)

saponification Hydrolysis of an ester in the presence of a base. (Section 25.6)

saturated solution A solution in which undissolved solute and dissolved solute are in equilibrium. (Section 13.2)

scientific law A concise verbal statement or a mathematical equation that summarizes a broad variety of observations and experiences. (Section 1.3)

scientific method The general process of advancing scientific knowledge by making experimental observations and by formulating laws, hypotheses, and theories. (Section 1.3)

scintillation counter An instrument that is used to detect and measure radiation by the fluorescence it produces in a fluorescing medium. (Section 21.5)

secondary structure The manner in which a protein is coiled or stretched. (Section 25.9)

second law of thermodynamics A statement of our experience that there is a direction to the way events occur in nature. When a process occurs spontaneously in one direction, it is nonspontaneous in the reverse direction. It is possible to state the second law in many different forms, but they all relate back to the same idea about spontaneity. One of the most common statements found in chemical contexts is that in any spontaneous process the entropy of the universe increases. (Section 19.2)

second-order reaction A reaction in which the overall reaction order (the sum of the concentration-term exponents) in the rate law is 2. (Section 14.4)

sigma (σ) bond A covalent bond in which electron density is concentrated along the internuclear axis. (Section 9.6)

sigma (σ) molecular orbital A molecular orbital that centers the electron density about an imaginary line passing through two nuclei. (Section 9.7)

significant figures The digits that indicate the precision with which a measurement is made; all digits of a measured quantity are significant, including the last digit, which is uncertain. (Section 1.5)

silicates Compounds containing silicon and oxygen, structurally based on SiO_4 tetrahedra. (Section 22.10)

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

UNITED THERAPEUTICS CORPORATION,

Vs.

SANDOZ, INC.,
DEFENDANT

CIVIL NO.
12-1617 (PGS)
13-316

MAY 1, 2014
CLARKSON S. FISHER COURTHOUSE
402 EAST STATE STREET
TRENTON, NEW JERSEY 08608

B E F O R E: THE HONORABLE PETER G. SHERIDAN
U.S. DISTRICT COURT JUDGE
DISTRICT OF NEW JERSEY

TRIAL DAY 1 - TUTORIAL

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by Title 28, U.S.C. Section 753
/S/ Francis J. Gable
FRANCIS J. GABLE, C.S.R., R.M.R.
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MR. JACKSON: Unless the Court has questions for Dr. Miller, that concludes the tutorial about the gram negative killing and the bactericidal effect. We thought it would be useful to go through the disease with Dr. White, the bacteria, and then the other patent, which is the actual synthesis of the molecule next. Unless the Court has questions for Dr. Miller.

THE COURT: No, I think I've got it. Thank you.

DR. MILLER: Thank you.

(Dr. Miller excused.)

MR. CARSTEN: So, your Honor, Dr. White started out with the whole body, the patient if you'll have it, the medical doctor talking about the disease and talking about the manner in treating that disease.

Dr. Miller just talked about smaller scale, the cells, the bugs as he called them, and the effect of the particular diluents or buffers on the growth or killing of those particular bugs.

Now, if we, you know, take off our microscope glasses and get down to sort of even smaller, you know, molecule level, we're going to be talking about some chemistry. And we brought with us here Professor Robert Williams, from Colorado State University, a synthetic organic chemist, who's going to talk to you about the '117 patent and the chemistry involved in that patent.

So, Professor Williams?

PROFESSOR WILLIAMS: Good afternoon, your Honor.

THE COURT: Good afternoon. How are you today?

PROFESSOR WILLIAMS: Good.

10:50 So, my name is Robert Williams from Colorado State University, I'm a professor there. And on behalf of plaintiff I've been asked to give a simple tutorial, a basic tutorial on some organic chemistry basics, we're going to hear a lot about organic chemistry in the coming days. And I'll tell you a 10:51 little bit about treprostinil and treprostinil sodium, and I'll also talk a little bit about the novel aspects of the '117 patent invention.

THE COURT: All right, thank you.

PROFESSOR WILLIAMS: So first on chemical bonding 10:51 and molecular structures we're going to see a lot of chemical structures with respect to the '117 patent. And treprostinil is an organic molecule, and most organism molecules are composed of the elements carbon, hydrogen, nitrogen and oxygen atoms, and organic compounds sometimes contain additional 10:51 elements, like sulphur, phosphorous, chlorine and so on. Treprostinil itself only contains carbon, hydrogen and oxygen.

And chemistry is a convention to draw three dimensional molecules on two dimensional surfaces, and so there's an example here. And because the skeletons of organic 10:51 molecules are composed of carbon, instead of drawing little Cs

all over the place we've adopted a convention where the intersection of lines represent carbon atoms. And then other elements like oxygen and so forth we would specifically label at their appropriate position.

10:52 And so the lines in these structures represent chemical bonds connecting the atoms in the molecular structure. So, a line like this, just one line is a single bond; between those two carbons, and sometimes carbon engages in more than one bond to another carbon so we draw two lines, 10:52 that would be a so-called double bond. Sometimes carbon atoms engage in three bonds between each other, so we draw three lines like shown here, that's a triple bond.

Organic molecules sometimes have linear portions like this chain here, and sometimes there's ring structures 10:53 like there aromatic ring.

THE COURT: Where's the aromatic ring?

PROFESSOR WILLIAMS: That's the six membered ring right here, and it's three double binds inside the ring. And so for example here I said other elements would be 10:53 specifically identified, so there's an oxygen atom, it's bonded with the hydrogen, that's called an hydroxyl group; and we also -- chemists have lots of acronyms unfortunately, but -- and we'll hear about some of those, so Me is an acronym for a methyl group or a CHe group. And we'll hear about this 10:53 acronym a little bit later in the litigation, THP, is a

so-called alcohol protecting group that's connected to an oxygen atom.

Now, also in this figure chemists have a convention where because molecules are three dimensional we want to represent their three dimensional structures on a two dimensional surface, we have a convention where straight lines indicate projection of that bond in the plane of the paper or surface; a darkened wedge would indicate projection away from the plane of that surface toward you; and a hashed line would indicate projection of that bond behind the screen or away from you.

Now, another term we're going to hear a lot about in the trial is the issue of stereoisomers, and what are stereoisomers. Well, stereoisomers are molecules, related molecules that have the same connectivity of atoms, but they're arranged in a different three dimensional configuration in space. Another term we're going to hear -- and I'll illustrate this for you in just a minute with a little movie clip, another term we're going to hear is a terms called enantiomers, and this is an term chemists have used to describe molecules that are non-superimposable mirror images of each other, just like our left hand is a non-superimposable mirror image of our right hand. You know, if you try to put your left hand into a right-handed glove, it just doesn't feel quite right, it doesn't fit in there.

And because of this property, particularly in organic chemistry, molecules can be produced in both enantiomeric forms, and chemists can measure the enantiomeric excess of one stereoisomer over the other, and we express that by the term enantiomeric excess or ee, which is a measure of -- one measure of purity.

So here to just drive home this concept of non-superimposable mirror images, here I have a carbon atom that I've just chosen four different colors, and carbon atoms that are bonded to four different groups, are called stereogenic centers or chiral centers. And so here's a carbon atom now bonded to four different groups or atoms, and just think of this as the right-handed version of that molecule.

Now, if that molecule went up to a mirror, the image it would see reflected in the mirror is what's shown on the right. Now, to prove that these two images are non-superimposable, what I'm now going to do is I'm going to rotate, spin the molecule on the left, and then I'm going to move it over and try to superimpose it into a ghost image of the molecule on the right. And so you can see that the white and the red groups line up or superimpose, but the green and purple ones are in opposite places in space. So this is by definition non-superimposable. So those molecules are enantiomers.

Just a little background on the treprostinil

molecule, which is not shown on this slide, I'll show it to you on the next one. It belongs to a family of very biologically active molecules, natural molecules that are derived from this 20 carbon molecule called -- called
00:57 arachidonic acid. And in all cells arachidonic acid is present, and depending on the state of the cell and the tissue, the environment, arachidonic acid can be oxydatively converted by enzymes into this complex structure, called prostaglandin H2, or PGH2, which is an important gateway
00:57 molecule for which a host of other very biologically important and active natural hormones can be produced.

So for example, PGH2 can be selectively converted into the prostaglandins like PGE2 and PGF2 which are important in birth. So for example, PGF2 induces labor, and PGE2
00:58 softens the cervix and induces uterine contraction.

The structurally related molecule that is also derived from the rearrangement of this precursor molecule PGH2, is prostacyclin, also known as PGI2. And the biological function of prostacyclin inhibits platelet aggregation and is
00:58 a potent vasodilator. So prostacyclin is what keeps our blood fluid, inhibits blood platelets from aggregating together.

Now another very important molecule has just the opposite effect of prostacyclin that's also derived from PGH2, is a molecule known as thromboxane A2. And what thromboxane
00:59 does is this is a very potent inducer of platelet aggregation,

and is a potent vasoconstrictor. So when we get cut, thromboxane A2 is rapidly produced, we get a blood clot so our blood doesn't all flow out of us when we get injured, and so you can see that small differences in chemical structure between this family of molecules, is manifest as vastly different types of biological activities.

THE COURT: Can you go back to that --

PROFESSOR WILLIAMS: Sure.

THE COURT: Can you just go through what the -- I can't say that word; arachidonic acid?

PROFESSOR WILLIAMS: Arachidonic acid.

THE COURT: So that goes into -- I can see on the bottom you regroup or -- I forget the word you used, but reformulate the PGH2, and you get these other PGF2 and PGE2, things of that nature --

PROFESSOR WILLIAMS: Correct.

THE COURT: But I don't get what the arachidonic acid does.

PROFESSOR WILLIAMS: This is the starting or the substrate molecule, the ubiquitous substrate molecule, that is ultimately derived from phospholipid bilayers, it's a fatty acid present in all cells; and it can be recruited when needed. And so this function right here, this carboxylic acid appears there and there and there, and there; and this CH3 group, the methyl group, so all of those same positions. As

we do some chemistry, forming bonds and adding oxygens to the center part that makes these different molecular structures.

THE COURT: All right. So, the arachidonic acid is somehow engulfed in PGH2; is that what --

01:01 PROFESSOR WILLIAMS: It's converted to PGH2.

THE COURT: Oh it's converted. How?

PROFESSOR WILLIAMS: How?

THE COURT: How is it converted?

PROFESSOR WILLIAMS: It's actually a very

01:01 fascinating and complicated reaction, it involves the addition of two molecules of oxygen; one is right there, the other one is derived from there. And there's going to be a bond formed across here that forms this five membered ring that we see present in these three structures.

01:01 THE COURT: So once you get the arachidonic acid converted to the PGH2, then you can reconvert to those other substances below.

PROFESSOR WILLIAMS: Correct. So depending on --

THE COURT: I said substances, that isn't the right

01:01 word --

PROFESSOR WILLIAMS: Certain enzymes will be recruited to convert PGH2 into the needed hormones, depending on what that cell or tissue or organ requires at that given time.

01:02 THE COURT: All right.

PROFESSOR WILLIAMS: Is that clear?

THE COURT: Well, I don't know about clear, but I understand somewhat.

PROFESSOR WILLIAMS: Okay. May I continue?

01:02 THE COURT: Yes, you may.

PROFESSOR WILLIAMS: Here now is the structure of treprostinil on the right, it has a very complex molecular structure like these hormones I just showed you. And treprostinil, which is the active ingredient in Remodulin, is

01:02 a structural analog of the natural hormone prostacyclin. So we can see some similar functionally; for example, up here is that carboxylic acid that we just talked about, and that's also present in treprostinil. And we had the same sort of side chain on the bottom with these oxygen atoms that you can

01:03 see; this five membered ring and a five membered ring there.

And one of the big differences that treprostinil being a synthetic molecule, totally synthetic molecular as you'll see, is called and you'll see this in the patent language as well, is a 9-Deoxy PGF1 type compound. So with

01:03 carbon 9, in the natural hormone there's an oxygen, whereas in treprostinil at that same carbon atom in that five membered ring, we don't have an oxygen but rather we have a carbon atom at that position.

May I proceed?

01:03 THE COURT: Yes, you may. Well, if you could go

back to that prior -- so we're doing the treprostinil now, but how is the treprostinil related to the chart before that one?

PROFESSOR WILLIAMS: So it's not derived from arachidonic acid, as we see it's synthesized from completely different types of molecules, but once it's assembled parts of the treprostinil molecule over-layer look like or resemble the natural hormone prostacyclin. So treprostinil is not made from arachidonic acid.

THE COURT: All right. So when you use the word analog, what does that mean?

PROFESSOR WILLIAMS: It means like it's a model, it looks very similar to.

THE COURT: Oh, okay.

PROFESSOR WILLIAMS: It resembles prostacyclin in many ways. It has structural features which are very similar, which imparts its biological activity.

THE COURT: All right, thank you.

PROFESSOR WILLIAMS: As we just talked about this concept of stereoisomerism, the treprostinil molecule actually contains five of these so-called stereogenic centers or chiral centers; in other words, carbon atoms that have four different groups bonded to each of those carbons, and I've highlighted those in red. And because each of those stereogenic centers or chiral centers can be either left-handed or right-handed, chemists use a nomenclature convention, we call those R or S.

And so since each of those stereogenic centers can be left or right-handed.

Within this connectivity of atoms represented by this structure, the total number of possible stereoisomers that that molecular structure can represent, is the product of all of the stereogenic centers. So two times two times two times two times two which is 32, possible centers that can have the same connectivity as we see here for treprostinil.

Now, to just show complicated this is, I've taken the trouble of drawing, even though the resolution of this is not all that easy to see, you might see it better on your screen here. But treprostinil is just one of those 32 possible stereoisomers, okay. And so all those other isomers will differ at their configuration at those stereogenic centers at one or more positions.

Now, the treprostinil compound is not and can never be one hundred percent pure in the real world. And so Remodulin as is depicted here which contains treprostinil as the active pharmaceutical ingredient, typically has with it small amounts of other stereoisomers based on that same molecular structure. And so these are boxed and have some code names; so treprostinil, the important active ingredient, also as a result of the chemical synthesis process, manufacturing process, also contains some of this other isomer 1AU90, 2AU90, and 3AU90.

And just typical average impurities in a typical clinically used sample of treprostinil, Remodulin would be mostly treprostinil, but contained in that vial also would be small amounts, .047 percent of 1AU90, .04 percent of 2AU90, and .25 percent of 3AU90. And those again are averages because these amounts vary from batch to batch.

THE COURT: And it's always those three?

PROFESSOR WILLIAMS: Those are always identified as trace impurities in the treprostinil product.

THE COURT: And they show up in the treprostinil why? Because --

PROFESSOR WILLIAMS: It's a result of the chemical synthesis process that inadvertently or unfortunately does produce some other small amounts of these stereoisomers.

THE COURT: Okay.

PROFESSOR WILLIAMS: I also want to introduce you to -- you're going to hear treprostinil is the acid in treprostinil sodium, and just so you know what these two substances are, treprostinil as the acid, this is the acid functional group right there; when you put it into water, depending on the pH, will rapidly dissociate in solution like water. And in the presence of a base like sodium hydroxide, the hydrogen atom on that acid right there, that hydrogen atom will get donated to the OH here in sodium hydroxide, making a water molecule, and then the sodium as a result of losing the

proton from here, get together to form treprostinil sodium.

And so these two species are always present in aqueous solution, and their relative ratio or proportion is a direct function of the pH, and Dr. Miller just told us a little bit about the pH scale. So depending on the pH, that will determine the relative ratio of these two species, but in any pH there will be some acid and some of the salt.

THE COURT: Okay.

PROFESSOR WILLIAMS: Can I proceed?

THE COURT: You may.

PROFESSOR WILLIAMS: Okay. So, just to introduce some aspects of the '117 patent, this was the first invention where stereoselectively produced treprostinil was made possible. The '117 patent also brought vastly improved yields as we'll see in a minute, that this is a synthetic compound and yields are very important, in the synthesis of the molecule. And a commercially viable and practical synthesis of any drug molecule including treprostinil when there are stereoisomers at issue, must make mostly one of those possible 32 stereoisomers.

THE COURT: That third point you just raised there, commercially viable and practical synthesis must make one of the possible 32 --

PROFESSOR WILLIAMS: Must make mostly one of those possible 32 stereoisomers --

THE COURT: Why is that important, Doctor?

PROFESSOR WILLIAMS: Because only the stereoisomer that has a configuration, a stereochemical configuration -- let me go back for a minute. Can you bring me back?

01:11 Here. Only the stereoisomer that has the same configuration at those centers, one, two, three, four, five, are the same one, two, three, four, five centers, those are the same as the natural hormone prostacyclin. And treprostinil bonds to the same biological receptor that the 01:11 natural hormone prostacyclin bonds to. So that three dimensional display of atoms is extremely important to the proper biological function of this drug.

Other stereoisomers may have no biological effect or a deleterious biological effect. So that's why it's extremely 01:12 important when there's other stereoisomers possible that the manufacturing process must make mostly one, the desire of biologically active isomer.

THE COURT: Okay, thank you.

PROFESSOR WILLIAMS: Okay?

01:12 Can we go back to the -- forward where to where I was?

So just -- we're going to be seeing the claims at issue in the '117 patent, so just some background on what these claims are going to look like, again we're going to be 01:12 seeing lots of these chemicals formulas, these molecular

structures. And representative claim 1 reads: A stereoselectively produced compound; okay, so this would be this more generic like structure represents treprostinil. Treprostinil fits into that first structure, so it's a
01:13 stereoselectively produced compound. And it's going to be made using as a starting material this novel starting enyne; that term enyne refers to the double bond down here, and the yne part of the triple bond. So novel starting enyne is going to have a structure just like this --

01:13 THE COURT: When you say the novel starting enyne, what do you mean by novel?

PROFESSOR WILLIAMS: That this hadn't been described elsewhere, and that this is a unique structural feature of the starting compound that's going to be used to manufacture the
01:13 final drug.

THE COURT: Okay. So when you have treprostinil, right, and I guess whatever it was known before you engaged in assembling this patent, does it have that novel starting enyne in it?

01:14 PROFESSOR WILLIAMS: No, so there was a prior synthesis of treprostinil that used a completely different chemical route, and did not use this type of novel enyne as a starting material.

THE COURT: All right.

01:14 PROFESSOR WILLIAMS: So the '117 patent brings forth

this novel starting material structure, that is then converted by a novel reaction that I'll describe in just a minute to make the next material --

THE COURT: So how did you get to the novel starting enyne? You had this stereoselectively produced compound; right?

PROFESSOR WILLIAMS: Right.

THE COURT: And then how do you get down to the novel starting enyne? Or is that just part of that --

PROFESSOR WILLIAMS: I'm going to show you that in just in a minute, I'll show you how we get there.

THE COURT: Oh, okay.

PROFESSOR WILLIAMS: It's a complex multi stage synthetic process to get there, but I'll show you in just a minute.

Okay. The next part of the claim is that that novel starting enyne is going to be converted by an intramolecular cyclization, I'll describe that reaction in just a minute, into this three ring or tricyclic cyclized intermediate. Down here and you can see that that has part of but not all of the structural features of the molecule up at the top, the final drug molecule, treprostinil.

So the claims at issue in the '117 patent, claims 1 through 4, all have these basic characteristic starting compounds and cyclized intermediate.

THE COURT: Okay. So when they used the intramolecular cyclization process, how does that occur?

PROFESSOR WILLIAMS: I'm going to show you that right now. So the '117 patent introduced a ground breaking stereoselect reaction that's known as the Pauson-Khand reaction, which is named after the two inventors of this process -- of this reaction rather, the cyclization type reaction. And what happens, since you asked about how the cyclization proceed, down at the bottom of the slide here's our novel starting enyne, right there, now with a little bit more structural detail shown; and the Pauson-Khand reaction uses a very special reagent, specific reagent that's called dicobalt octacarbonyl.

And what this reagent does is it makes this triply bonded carbon and that doubly bonded carbon form a new bond together right there by that dotted line; and then a carbon monoxide unit from this reagent shown right here, is going to be stitched in and we're going to form a new carbon carbon bond there and a new carbon carbon bond over here, to form now this novel tricyclic intermediate.

So that's how that cyclization process occurs. And the '117 patent is the very first industrial application -- I think that's still true today, of the Pauson-Khand reaction to be used on an industrial scale.

THE COURT: So when you say in your chart there, it

says that, regardless of the stereochemistry if any of the reactants; what does that mean?

PROFESSOR WILLIAMS: Sure. So, as called out in the patent claims, it says stereoselectively produced compound, if a compound is stereoselectively produced, it's going to produce predominantly one stereoisomer in the product regardless of whether or not there was any type of stereochemistry in the starting reactants or the starting --

THE COURT: I see.

PROFESSOR WILLIAMS: So in this particular case, here's our starting enyne, it actually has two existing stereogenic or chiral centers; and in the cyclization process we're going to form a new stereogenic center, right there, that's our new stereogenic center. So a stereoselectively produced product will be one that produces mostly or predominantly that one desired stereochemistry, the same as the natural hormone, prostacyclin; and by contrast a non-stereoselectively produced compound will be one where the product would be a mixture of the left-handed and the right-handed stereoisomers at that center.

THE COURT: I got you.

PROFESSOR WILLIAMS: Okay? So it's very important in manufacturing that would get a stereoselectively produced product because it's only that natural hormone stereochemistry that has the desired biological function.

Are we good?

THE COURT: I'm good.

PROFESSOR WILLIAMS: Okay. And so another thing that we're going to hear about in this litigation is the idea -- the concept of use of protecting groups in synthetic organic chemistry; chemists also call these masking groups or blocking groups.

So to help you understand the concept of what a protecting group is, very very much like what a painter uses when painting say a door, and you apply masking tape which is like a protecting group; for the trim around the door we only want to get the paint on the door not on the trim.

And so the first step when using a protecting group is you put it on, just like a painter would do; then we're going to do our chemical process step, in this analogy we're going to now paint the door red. Our protecting group is there, and so when we're done painting, we're then going to remove the protecting group and remove the masking tape and then we have our finished product.

So protecting groups are temporary, they do not -- they're not actually part of the final product. They're temporarily installed to protect another functional group from an undesired chemical reaction. We then do our desired chemical step, and then when we're done, we're done with the protecting group, we essentially remove it and then throw it

away, we're done -- it's done its job.

THE COURT: Okay. I'm sorry, Doctor, could you just go back to your prior -- there you go. So, the Pauson-Khand reaction --

01:21 PROFESSOR WILLIAMS: Yes.

THE COURT: Where does it show on that screen?

PROFESSOR WILLIAMS: Okay. Right there is the Pauson-Khand reaction. So, the Pauson-Khand reaction specifically uses this reagent, dicobalt octacarbonyl, and

01:21 what it does -- I'm just showing down here in a little bit more detail what's going on here, that the Pauson-Khand reaction, even though it doesn't show the cobalt, the net result is that one of those COs, this one right here, the carbon monoxide, gets added in to help form that new five

01:21 membered ring.

THE COURT: Okay. So the upper right then, so to speak, that's the final product?

PROFESSOR WILLIAMS: That's -- this is the tricyclic -- the novel tricyclic intermediate; this is then going to be

01:21 converted by more chemical steps as I'll show you in just a minute, into the final drug molecule treprostinil.

THE COURT: Okay, thank you. When they were doing the Pauson-Khand reaction, there was these two scientists hanging around the lab, and they just decided to -- what made

01:22 them do that? That's what the invention is?

PROFESSOR WILLIAMS: No. So the Pauson-Khand reaction was already known in the literature, it's just that the '117 patent is the first implementation of that chemical reaction to make stereoselectively produced treprostinil.

01:22 THE COURT: Thank you.

PROFESSOR WILLIAMS: So you asked about how -- now the whole picture fits together, so in the '117 patent in example 1, the entire synthesis of treprostinil is described. And as you can see it's a complex molecule which requires a

01:22 complex synthesis. And so organic synthesis is a lot like carpentry, you take building materials and you nail them together in a sequential fashion to finally build up the final structure.

And so in the case of treprostinil, the '117 patent

01:23 described what's called a convergent synthesis, where there's a four-step process to make this compound right here; so that would be made say in one set of reactors. And then separately there's another four-step process to make that fragment down there, and then those are going to be joined together

01:23 chemically. So just think of it as a carpenter nailing two boards together, we're going to join those two pieces to make now this molecule, which now you can see is starting to resemble our enyne, the novel enyne that's going to be used in the Pauson-Khand step, which is this portion right there.

01:24 THE COURT: I see.

PROFESSOR WILLIAMS: Okay? And the treprostinil, the final product down here, is ultimately going to be made after we've made that tricyclic intermediate. There's more chemical steps to --

01:24 THE COURT: When you say the tricyclic intermediate you're --

PROFESSOR WILLIAMS: That's this one.

THE COURT: That's right where the --

PROFESSOR WILLIAMS: That's the Pauson-Khand step

01:24 right here. So this is the PK, that's the Pauson-Khand step right there.

THE COURT: Okay, thanks.

PROFESSOR WILLIAMS: So you can see it's a complex molecule that requires a very complex synthesis. But it's a

01:24 stereoselective synthesis which is very important and was a vast improvement over what existed before.

THE COURT: Okay.

PROFESSOR WILLIAMS: So the '117 invention now, just to reiterate, is really this step right here, okay. Even

01:25 though the patent describes all this other stuff, the claims are really focused on this stereoselective reaction which allows the stereoselective synthesis of the final drug molecule.

And so to give you another way of thinking of this

01:25 complex synthetic situation scheme, I've made an analogy. We

can think of this as a bridge spanning a body of water like the Golden Gate Bridge connecting San Francisco to Sausalito.

So we have different starting materials maybe over here and different ways to get to our enyne, which is called out in the patent; and then once we get there there's one way to go across the bridge, which is this Pauson-Khand cyclization step, the cyclization step.

01:25

When we get to the end of the bridge we have now our tricyclic intermediate, but we had to go across the bridge to get there, in other words, the Pauson-Khand reaction. So this is -- this whole bit here, is that cyclization step, the invention of the '117 patent.

01:25

And then ultimately we want to get to stereoselectively produced treprostinil, and once we're at the tricyclic intermediate there are in fact several different ways you can go. Here I've called out the Moriarty Avenue or the Moriarty path that is described in the '117 patent, but there are other in fact ways to get from the tricyclic intermediate all the way to treprostinil.

01:26

01:26

THE COURT: Okay.

PROFESSOR WILLIAMS: Thank you for your attention.

THE COURT: Thank you.

(Professor Williams excused.)

MR. CARSTEN: A bit of a whirlwind, your Honor, shall we say, but we've started at the body, at the patient;

01:26

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

UNITED THERAPEUTICS CORPORATION,

Vs.

SANDOZ, INC.,
DEFENDANT

CIVIL NO.
12-1617 (PGS)
13-316

MAY 12, 2014
CLARKSON S. FISHER COURTHOUSE
402 EAST STATE STREET
TRENTON, NEW JERSEY 08608

B E F O R E: THE HONORABLE PETER G. SHERIDAN
U.S. DISTRICT COURT JUDGE
DISTRICT OF NEW JERSEY

TRIAL - DAY 6

Certified as true and correct as required
by Title 28, U.S.C. Section 753
/S/ Francis J. Gable
FRANCIS J. GABLE, C.S.R., R.M.R.
OFFICIAL U.S. REPORTER
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MR. CARSTEN: Perfect.

THE COURT: And so Friday we'll start at 11:00, and if we need to go to Monday we'll start at 11:00 also.

MR. CARSTEN: Thank you, your Honor. May I proceed?

01:16 THE COURT: You may proceed, yes.

MR. CARSTEN: Thank you. Your Honor, United Therapeutics calls as its next witness, Professor Robert Williams.

(ROBERT M. WILLIAMS, PH.D.), sworn.

01:16 THE DEPUTY CLERK: State your name for the record.

THE WITNESS: Robert Michael Williams.

MR. CARSTEN: Your Honor, I have some witness binders; may I approach please?

THE COURT: You may.

01:16 MR. CARSTEN: Thank you, your Honor.

(Handing to witness and to Court.)

(DIRECT EXAMINATION OF ROBERT WILLIAMS PH.D. BY MR. CARSTEN:)

Q. Good morning, Professor Williams.

A. Good morning, Mr. Carsten.

01:17 Q. Would you please introduce yourself to the Court?

A. Yes. My name is Robert M. Williams, I'm a professor of chemistry at Colorado State University, in Fort Collins, Colorado.

Q. Do you have a C.V.?

01:17 A. Yes, I do.

MR. CARSTEN: Could you show up PTX-139 on the screen, please?

Q. And what is this?

A. This is a copy of my C.V.

01:17 Q. You prepared it yourself?

A. Yes, I did.

Q. Is it true and accurate?

A. Yes, it is.

MR. CARSTEN: I'd like to admit into evidence

01:17 PTX-139, please.

THE COURT: Any objections?

MR. STEINDLER: No objection.

THE COURT: Okay. So PTX-139 is admitted.

(Plaintiff's Exhibit 139 was marked into evidence.)

01:17 BY MR. CARSTEN:

Q. Now, Professor Williams, would you please describe your educational background for the Court?

A. Certainly. So I obtained a Bachelor's Degree in Chemistry at Syracuse University in 1975 with highest

01:18 distinction; I did undergraduate research under a recent Nobel Laureate Professor Ei-ichi Negishi, and after I graduated from Syracuse 1975 I attended MIT, the Massachusetts Institute of Technology, and obtained a Ph.D. degree in 1975 under the direction of Professor Rastetter; and then after I graduated

01:18 from MIT I moved down the street to Harvard University and

became a post-doctoral fellow for one year, in the laboratories of the last Professor R.B. Woodward, a Nobel Laureate.

Q. I'm sorry; a Nobel --

01:18 A. Nobel Laureate.

Q. I may have misheard you, Professor Williams; did you say you took your Ph.D. degree in 1975 or 1979?

A. My Ph.D. was in 1979.

Q. Thank you. Where did you go to work after your post-doc

01:19 with the Nobel Laureate Dr. Woodward?

A. So in September of 1980 I joined the faculty of Colorado State University as assistant professor.

Q. Can you please describe your work experience. I think it's reflected on the next slide.

01:19 A. Yes. So I started on the faculty at Colorado State University in 1980, I was promoted with tenure to the rank of associate professor in 1985, I was then promoted to full professor in 1988, and then in 2002 I was named University Distinguished Professor in the chemistry department.

01:19 Q. What is a University Distinguished Professor?

A. So, this is the highest academic rank at our institution, and at any given time there's 12 university distinguished professors that represent roughly one percent of the 12 hundred full-time faculty of the university. It's a lifetime

01:20 appointment.

Q. Please continue.
A. So that was my progression through the ranks. And I also serve as the Director of the Colorado Center For Drug Discovery, it's C2D2, since 2012 to the present; I also serve as a co-director of the in infectious diseases subcluster of the university's infectious diseases supercluster; and I also serve as the co-director for the cancer supercluster developmental therapeutical subcluster at Colorado State University.
Q. You mentioned the C2D2; can you explain that a little bit to the Court?
A. Yes. This is a newly created entity by the State of Colorado to encourage translational research where faculty on campus are encouraged and enabled to get the discoveries inventions they make in the laboratory, translated into the private sector.
Q. Do you have a research group at Colorado State?
A. Yes, I do.
Q. Can you describe to me your research for the Court?
A. Yes. So my research is primarily been in the area of synthetic organic chemistry and chemical biology, and I've spent my entire career working on complex organic compounds, particularly natural products, these are compounds made in nature that have biological activity. We've also done quite a bit of work in developing synthetic methodology to make these

complex molecules; and we also study at the molecular level how these molecules work, how they exert their biological effects.

Q. Have you prepared a slide that shows some of the example compounds that you and your group have made?

A. Yes, I have a demonstrative on that. So, on this slide is shown a small collection that is representative of the types of molecules my laboratory's been interested in synthesizing over the years. My research group has completed multistep syntheses of over 80 complex natural products, this is just a sampling of some of those.

Q. Are these products synthesized in one step or multiple steps?

A. No. Most of these natural products have required quite a number of steps, in fact a few of them required over 50 steps.

Q. What do you mean by 50 steps?

A. 50 discreet chemical transformations. So there's a starting material a reaction, a product and then sometimes a purification step, and then another step, so sometimes 50 steps sequenced together.

Q. And can you just give an overview of the types of molecules that your research group has been interested in synthesizing?

A. Yes, so -- well, we've actually been interested in quite a number of different families of biologically active natural

products, and this includes amino acid and peptides, alkaloids, compounds that are called terpenes that are composed mostly of carbohydrate and oxygen; all the compounds shown here contain nitrogen, so the nitrogen containing compounds have been a very important focus of our laboratory's research, but not exclusively.

Q. Now, in terms of -- we've been hearing a little bit in terms of the tutorial that you presented about stereogenic centers; do these compounds have stereogenic centers?

A. Yes, all of them do, and all of them contain multiple stereogenic centers.

Q. So how many stereogenic centers are in some of the compounds that you and your group have successfully synthesized?

A. So on this slide there are a couple of molecules that have nine stereogenic centers, five stereogenic centers, six stereogenic centers.

Q. Do you have any experience with a reaction known as the Pauson-Khand reaction?

A. Yes.

Q. What's your experience with that?

A. So I directed the Ph.D. dissertation of a former graduate student who was working on the total synthesis of the alkaloid tuberostemoninol shown on the slide, and the key transformation that she investigated was in fact the

intramolecular Pauson-Khand cyclization reaction, which is shown in the box at the lower right of the slide.

Q. And do you have any experience with protecting groups?

A. Yes. I have extensive experience with protecting groups. And virtually every complex synthesis that we've done, every natural product that we've synthesized, almost without exception has mandated the use of protecting groups, and sometimes multiple protecting groups in these multistep transformations.

Q. Have you ever used methyl as a protecting group?

A. Many times.

Q. And have you ever used PMB or para-methoxy benzyl as a protecting group?

A. Yes, many many times?

Q. Have you ever done any work on prostaglandin type compounds?

A. Yes, so back in the mid 1980s I was the principle investigator on a Natural Institutes of Health research grant directed at making the molecule thromboxane A2, which we discussed in the tutorial, it's a member of the prostaglandin family of natural hormones.

Q. In connection with your work, in your academic career have you won any awards?

A. Yes, I'm happy to say the work in my laboratory has been recognized with some honors and awards, and those are listed

on my C.V. And early in my career I won the NIH, which is the National Institutes of Health Research Career Development Award; I was recognized with Eli Lilly Young Investigator Award in 1986; I was named a fellow of the Alfred P. Sloan
01:26 Foundation also in 1986. I don't have to go through all of them, maybe the most important ones were the Arthur C. Cope Scholar Award for the American Chemical Society in 2002; the Ernest Guenther Award in the Chemistry of Natural Products in 2011; and very recently I was awarded the Japanese Society For
01:26 The Promotion of Science Long-Term Fellowship Award.

Q. Do you have any publications?

A. Yes, I do.

Q. About how many?

A. Right around 300.

01:26 Q. Any patents?

A. Yes.

Q. About how many?

A. So I don't remember the exact number, but I think I have seven published patents, but about another 10 or so patent
01:27 applications that have also been published.

Q. Have you served on the editorial ordinary or as editor of any scientific journals or publications?

A. Yes, I briefly served as associate editor for the Journal of the American Chemical Society back in 1980/81; I was the
01:27 editor and chief of the Journal of Amino Acids for a couple of

years; I still serve on the editorial advisory board for the Journal of Chemistry and Biology; and I'm also on the editorial advisory board of Tetrahedron publications.

Q. Would you please explain how your educational background and your work experience has helped you in terms of the work and analysis you've done in this case?

A. Well, my extensive experience in complex molecule synthesis, synthetic organic chemistry, reaction methodology in particular Pauson-Khand reaction, as well as the prostacyclin family of molecules I think has given me a very very solid basis to understand and evaluate the technology relevant to the '117 patent, which is a complex synthesis of a complex molecule as we discussed in the tutorial last week of the treprostinil molecule.

Q. Have you ever served as an expert witness in patent cases before?

A. Yes.

Q. About how many times?

A. Many times. So I've worked on -- I think this is case number 17, and this is my fourth appearance in court at trial.

Q. Have you ever been excluded as an expert?

A. Never.

MR. CARSTEN: Your Honor, United Therapeutics would offer Professor Williams as an expert in organic chemistry, synthesis of complex organic molecules, including Pauson-Khand

reactions and protecting groups.

MR. STEINDLER: No objection.

THE COURT: So he's admitted as an expert as set forth by Mr. Carsten.

01:28 BY MR. CARSTEN:

Q. Now, Professor Williams, you understand that we're here in this part of the case to talk about infringement; correct?

A. Yes.

Q. Okay. Have you formed any opinions relating to

01:29 infringement in this case?

A. Yes.

Q. Have you prepared a slide to summarize those?

A. Yes.

Q. Would you please describe for the Court your summary of

01:29 your opinions.

A. Yes. So my opinion is that Sandoz's proposed ANDA product and related process, meets every limitation of claims 1 through 4 of the '117 patent; and the X limitation in claims 1 through 4 is present under the doctrine of equivalents.

01:29 Q. In reaching your conclusions in this case, what perspective did you apply to the claims?

A. I applied the perspective of the person of ordinary skill in the art.

Q. Did you reach an opinion on the level of ordinary skill

01:29 in the art that should be applied here for the '117 patent?

A. Yes I did and I put that in my expert report.
Q. I call your attention to the next slide, slide 8; what's depicted here?
A. So, this is an excerpt from my report where I defined what I thought to be an appropriate level of skill for a person of ordinary skill in the art as it relates to the technology in the '117 patent. And in 1997 I felt that someone should have held a Ph.D. in chemistry or a related field, or a Bachelor's or Master's Degree in chemistry or a related field, with at least three years of postgraduate experience in organic synthesis.
Q. Would you qualify as a person of ordinary skill in the art under that -- under that test?
A. Yes.
Q. Are you aware that Professor Buchwald, Sandoz's chemistry expert, has proffered his own view of what the requirements would be for a person of ordinary skill in the art?
A. Yes.
Q. Have you considered that?
A. Yes.
Q. Would you qualify under his definition as well?
A. Yes.
Q. Would your opinions change depending on which of the levels of ordinary skill in the art you applied?
A. Not at all.

Q. I'd like to turn to the '117 patent. Do you recognize the '117 patent?
A. I certainly do.
Q. And this is PTX-002. Is this the patent that you considered in connection with your work in this case?
A. Yes, it is.
MR. CARSTEN: Your Honor, United Therapeutics would move to admit PTX-002.
MR. STEINDLER: No objection. This is a demonstrative we're looking at, but no objection to the admission of PTX-2.
THE COURT: Okay, admitted. PTX-002 is admitted.
(Plaintiff's Exhibit 2 was marked into evidence.)
BY MR. CARSTEN:
Q. Now, Professor Williams, let's turn to the claims if we could. Did you consider the claims in connection with your work in this case?
A. Yes.
Q. And would you please summarize the claims for the Court, at least claim 1?
A. Yes. So representative claim 1 has four limitations, and it begins with a stereoselectively produced isomeric compound, and according to the first formula shown at the top that's highlighted in yellow. And the next limitation is that that is produced via a novel starting enyne, with a very specific

structure shown in the next box down in the middle. And third limitation is that that novel enyne will be transformed into a novel cyclized intermediate that we call the tricyclic intermediate, because it now has three rings. And that
01:32 transformation is done by an intramolecular cyclization process.

Q. Now, you highlighted only certain parts of the claim here and identified them in the boxes on the left as A, B, C and D; do you see that?

01:32 A. Yes.

Q. Did you consider just those boxes in your infringement analysis or did you consider the whole claim?

A. I considered the whole claim.

Q. You highlighted some things here on the left, but there's
01:33 nothing highlighted on the column on the right; why is that?

A. So the column on the right gives a menu or tool box of all the different substituent variables that can be plugged into the various structures shown in the left column.

Q. Now, in between the top A and the element that you've
01:33 identified here as B, it says that is a produced by a process for making 9-deoxy-PGF1 type compounds, the process comprising, et cetera, et cetera. Do you know what 9-deoxy-PGF1 type compounds are?

A. Yes. So as we showed in the -- as I showed in the
01:33 tutorial last week, this is based on the numbering system of

the prostacyclin molecule, and at carbon 9 where there is an oxygen present in the natural hormone, 9-deoxy-PGF1 type compounds would have a non-oxygen atom, for example, hydrogen, carbon or something non-oxygen at that position.

01:34 Q. Is treprostinil and treprostinil sodium, are those 9-deoxy-PGF1 type compounds?

A. Yes, they are.

Q. Now, there's been a little bit of discussion already today about the term that's in the first line of the claim,

01:34 stereoselectively produced isomeric compound; do you see that?

A. Yes.

Q. Did you consider that term in connection with your work in this case?

A. I certainly did.

01:34 Q. How can you tell if a compound or a product is stereoselectively produced?

A. One needs to look at -- to analyze the product compound, and one also needs to understand the starting material from which it was fashioned.

01:34 Q. And down at the bottom on the left-hand column, it says intramolecular cyclization at the enyne; do you see that?

A. Yes.

Q. What is an intramolecular cyclization of the enyne?

A. So the intramolecular cyclization means that we're going

01:35 to bring functional groups present in the enyne together,

we're going to form bonds within that molecular framework. And in this particular cyclization reaction we also are going to bring in one additional extraneous group, the CO group or the carbon monoxide group. So this reaction is called a carbonylative cyclization, intramolecular cyclization.

Q. Carbonylative?

A. That refers to the carbon monoxide that is added to the enyne.

Q. Now, let's turn back to the stereoselectively produced isomeric compound phrase. Do you think that a person of ordinary skill in the art would understand that phrase as written?

A. Yes.

Q. And what would a person of ordinary skill in the art understand about that phrase?

A. That stereoselectively produced refers to the compound.

Q. It doesn't refer to the process?

A. No.

Q. Why not?

A. Well, because the words I think are very simple and clear; produced tells us that it's the product of chemical reaction, process. And so it's -- so produced is the adjective modifying compound.

Q. Sandoz's recently taken a position that this stereoselectively produced isomeric compound talks about a

single molecule; do you understand that?
A. Yes.
Q. Is that correct?
A. I don't think that's correct.
01:36 Q. Why not?
A. Well, because the fact that it's a stereoselectively produced compound means that it's made from a real world chemical reaction. And so in that context we know that we're not talking about the single molecule, we're talking about
01:36 trillions of molecules that are produced in a real world reaction, and we get a real world compound, the product, that is produced in this case predominantly as one stereoisomer, but there are other impurities and other stereoisomers that are a signature of this manufacturing process.
01:37 Q. In your experience -- how long have you been a practicing chemist?
A. Let's say 39 years.
Q. In your 39 years have you ever produced a compound from a reaction that's been 100 percent pure?
01:37 A. No.
Q. Why not?
A. Because we never start with 100 percent pure starting material, there is no such thing exists, and it's also physically impossible to get a 100 percent pure product, no
01:37 matter how many times we purify it. We can purify and purify

and purify and approach 100 hundred percent purity, but can never actually get to 100.0 percent purity.

Q. So you've never held in your hand a vial that had a hundred percent pure compound in all the years you've been a chemist?

A. I never have and no one ever has.

Q. With respect to this claim 1, you said representative, how many claims are there in the '117 patent?

A. Four.

Q. Did you find anything in the specification that sort of represents or embodies claim 1 in the other claims in the patent?

A. Yes, there's a detailed example, example 1 in the '117 patent.

Q. Did you create a demonstrative that lays out the overarching approach identified and described in example 1?

A. Yes.

MR. STEINDLER: Let me just object briefly to this. This is an demonstrative that they gave us on Friday I think, with one -- maybe Thursday night; when they were planning to put them on. Now, they've changed it, they gave it to us 10 minutes before this witness was to go on, and they've changed what is in this demonstrative.

I would submit to you that the changes aren't significant, but we haven't had a chance to examine what these

changes are in detail, we haven't had a chance to talk about it with our experts. And we're now using a demonstrative that they changed.

They could have given it to us over the weekend for us to be able to take a look at it, but we got it just before this witness went on the stand. Now --

THE COURT: So what relief do you want?

MR. STEINDLER: I'm about to say it. I am willing to have the examination go forward because I don't think the changes that are made are actually going to be material to Dr. Williams' testimony, but the relief that I'm asking is that if we're going to get changed demonstratives, that we get them in advance so we can have a look at them.

THE COURT: Do you have any problem with that?

MR. CARSTEN: Your Honor, no, I don't have any problem with that.

THE COURT: All right. How far in advance?

MR. STEINDLER: Well, we have a -- we have an agreement with the parties that there's an exchange of demonstratives that are going to be used, at 5:00 p.m. or 6:00 p.m., I think it is, the day before the witness is going to -- just in the normal course that would be fine. I just don't want to get blind-sighted in court with some changed demonstratives.

THE COURT: So, I think you should just agree to the

agreement or to provide them in accordance with your present agreement.

MR. CARSTEN: We have identified this slide. The issue, your Honor, is that there was a typographical error. Or all the wedges and hashes and structures on this page, there was one wedge upon which was represented as a straight line not a wedge. And so that's the correction that we made to this slide.

MR. STEINDLER: But, Judge, it's a different compound when you change it that way, and that's why --

THE COURT: I'll let you cross-examine on it.

MR. STEINDLER: That's fine. As I say, I'm happy to have the examination proceed, I just don't want to have this happen again.

THE COURT: All right. So I think we've resolved it, Mr. Steindler.

MR. STEINDLER: Yes.

THE COURT: Okay. You may proceed, Mr. Carsten.

MR. CARSTEN: Thank you, your Honor.

BY MR. CARSTEN:

Q. Professor Williams, what are you showing here?

A. So this is all reactions steps that are described in example 1 of the '117 patent for the stereoselectively synthesis of treprostinil.

Q. Now, with respect to the claim we talked about a

intramolecular cyclization reaction; right?
A. Yes.
Q. Where is that shown on this demonstrative 11?
A. So that would be the third line down, sort of over toward
01:41 the middle right portion, that's the intramolecular
cyclization of the enyne, to the tricyclic intermediate.
Q. So it's the compound before and after the third arrow on
the third line?
A. Yes, that's correct.
01:41 Q. And it's that transformation?
A. Yes.
Q. What is that reaction called?
A. So that's an example of a carbonylative cyclization,
specifically named the Pauson-Khand reaction.
01:42 Q. Why is it called the Pauson-Khand reaction?
A. It's named after the two inventors of that particular
cobalt dicobalt octacarbonyl reagent that affects that
cyclization reaction.
Q. I'm sorry; dicobalt octacarbonyl, where is that?
01:42 A. That's on the top of the line between the enyne and the
tricyclic intermediate right there. CO2, paren, CO, close
paren, 8.
Q. Now, would you please walk the Court through that
reaction briefly, and what the importance of it is?
01:42 A. Yes. So this is really in a nutshell the invention, and

the enyne must have this OTBS group at that position in order for the Pauson-Khand reaction to proceed stereoselectively. And so the enyne of course must have this double bond down here, sort of at the -- it's at the 4 o'clock position coming off the six membered ring; and then coming off maybe the 2 o'clock position where that OTBS group is connected to that carbon, there's three lines that, indicates a triple bond, that's in chemistry we call the alkyne, so that's the enyne; and then we then add the react dicobalt octacarbonyl, that's the CO2(CO) 8; and a new six membered ring is formed between -- in the middle here, so adjacent to this six membered ring we're going to form another six membered ring, a hexagonal ring; and then with the addition on the carbon monoxide unit from the dicobalt octacarbonyl, that is going to be installed in the newly created five membered ring. So this cyclization creates two new rings, this new six membered ring and a new five membered ring.

Q. Does it create any stereogenic centers?

A. Yes. And so it creates one new stereogenic center, and -- that was pointed out in the tutorial; that's right there at that position, at the position at the junction between the newly created six and five membered rings, at the bottom.

Q. Is that important?

A. That's extremely important, that's really Dr. Moriarty's ingenious invention here, that putting the OTBS group, which

he calls a stereo directing group, over at this position up here, coming off the 2 o'clock position of the six membered ring; that -- that stereo directing group forces the molecule into the proper orientation to set the newly created
01:44 stereogenic center, to have the desired configuration that is present in the final treprostinil molecule.

Q. So, comparing the treprostinil -- the treprostinil structure down at the lower right-hand side, versus the starting enyne or the cyclized intermediate, I don't see that
01:45 OTBS or any substituent on that carbon; what happened to it?

A. That's correct. It gets removed. It's actually put in as a sacrificial stereo directing group. It does its job and then it's removed, because it does not appear in the final treprostinil molecule.

01:45 Q. Is that a fairly common approach?

A. It's done, sometimes in synthetic organic chemistry to put a stereo directing group on the starting material. I think this is a very ingenious and novel application of that in the context of the Pauson-Khand reaction. And it required
01:45 at least two steps to put that group -- to install it to do its job.

Q. Now, we're talking about -- we're going to be talking about infringement here. What materials did you consider in rendering your opinions in forming infringement opinions?

01:46 A. Oh, I looked at a lot of materials. I certainly had the

patent, and I had Sandoz's ANDA, Alphora's DMF; I also considered deposition testimony; other publications in the literature, patent applications; the prosecution history of the '117 patent; I don't know if this is all inclusive, but many many documents.

Q. I'd like to turn to a demonstrative that shows the cover page of PTX-250 in evidence. Is this one of the documents that you considered?

A. Yes.

Q. Why did you consider this document?

A. So this document is what the -- that Sandoz submitted to the FDA, it's their ANDA, which indicates that they plan to synthesize and sell treprostinil in the United States.

Q. And did you also look -- I believe you said you looked at Alphora DMF?

A. Yes.

Q. I'd like to turn to the next demonstrative. And what's depicted on the cover page of -- the page of this demonstrative?

A. So, this is a letter from Sandoz where on behalf of Alphora Research we are submitting the original drug master file, that's what DMF stands for, for treprostinil sodium.

Q. And this is the cover page in this demonstrative of PTX-333?

A. Yes.

Q. Did you consider PTX-333 in forming your opinions in this case?

A. Yes, I did.

MR. CARSTEN: Your Honor, United Therapeutics would move to admit PTX-333.

MR. STEINDLER: No objection.

THE COURT: So, PTX-333 is admitted.

(Plaintiff's Exhibit 333 was marked into evidence.)

BY MR. CARSTEN:

Q. Now, I believe I heard you say, Professor Williams, you understand that Sandoz's ANDA means they're going to synthesize and sell treprostinil; is it your understanding that Sandoz is going to be the one that synthesizes the treprostinil active ingredient?

A. No, Alphora is making the treprostinil for Sandoz.

Q. Okay. Now, turning to the infringement analysis that you conducted here, have you prepared a chart to help you explain your findings to the Court?

A. Yes, on the next demonstrative.

Q. Now, here I see on the left-hand side you've got the A, B, C, D that we talked about previously, but I want to be clear, you considered the whole claim, not just these A, B, C, D elements; is that right?

A. That's correct.

Q. Now, for the stereoselectively produced isomeric compound

limitation, would you explain your analysis to the Court?
A. Yes. So, as we just saw a few slides back when we were looking at claim 1, the formula directly following the phrase, a stereoselectively produced isomeric compound, according to
01:49 the following formula; so right next to that statement I reproduced the formula as it appears in the '117 patent claim 1.
Q. And did you prepare a demonstrative to walk through the analysis on that first A limitation?
01:49 A. Yes, I did.
Q. And would you please explain this to the Court.
A. Certainly. So, on the left in the box at the left, it says '117 patent, and that's the structural formula from claim 1 shown in the top left. It's also at the top left of claim
01:49 1.
And then I compared that formula to the final product of Sandoz's ANDA, which is treprostinil, which is shown -- the structure shown in the middle box, which came directly from their ANDA filing.
01:50 Q. And that's at PTX-250, page 279?
A. Yes. I'm sorry; my screen isn't on and it's a little hard for me to see the tiny numbers at the bottom.
Q. I'll do my best to read them in for you if you --
THE COURT: Do you want to read mine?
01:50 THE WITNESS: That's a little better.

BY MR. CARSTEN:
Q. So, Professor Williams, we will do our best and on whatever break is next we'll try to get that fixed for you.
A. Okay.
01:51 Q. Would you please continue describing your analysis in terms of this -- of this element -- or limitation A from claim 1?
A. Yes. So I compared the formula that's shown in claim 1 of the '117 patent, to the structure of the treprostinil
01:51 molecule that's shown in Sandoz's ANDA, that's in the middle box. And then on the right is also the molecular structure of the treprostinil molecule that comes -- that was reproduced directly from Alphora's drug master file.
Q. And the source of that is PTX-333, the last Bates number
01:52 -- last four digits of Bates number was 8441?
A. Yes.
Q. Thank you. Would you please continue.
A. Yes. So to compare those two structures on the right to the '117 patent claim formula, it was necessary to input all
01:52 of the substituent variables, which is the exercise I went through in the box in the middle at the bottom.
Q. Would you please walk through that box in the middle on the bottom and how it applies to that '117 patent formula structure in the upper left?
01:52 A. Yes. And I think it's also important that the two

structures on the right are rotated 90 degrees relative to how the structure on the left was drawn, and chemists do this, and I know it makes things confusing, but I think we have an animation that shows it. If you rotate that, the rings, line
01:53 up, to just get the prop orientation.

So, we'll just now leave the '117 patent -- we didn't change anything we just rotated it 90 degrees in the plane of the screen.

So, the Z substituent, which is -- oops; I'm sorry. I
01:53 inadvertently pushed the wrong button.

Q. Do you need a pointer?

A. Yes -- no, this is a pointer, I just pushed the wrong button on it.

So the Z substituent in the '117 patent formula, comes
01:53 off of the top six membered ring at the 9 o'clock position, so that's where the Z is. And that's oxygen, that's the O. And so in the two structures to the right, that oxygen is right there, at the exact same 9 o'clock position on that six membered ring.

01:54 The -- that group is Z(CH2)nX, so we just define Z; and CH2, that's a methylene group, a carbon with two hydrogens; and n is equal to 1, and as we discussed in the tutorial last week the intersection of lines in organic chemistry imply that's a carbon atom at that position; and then we saturate
01:54 the carbon with the requisite number of hydrogen atoms if

they're not drawn to get four net bonds. So that intersection of lines right there, coming off of the oxygen, pointing sort of northwest, is a CH2 group. So that's where (CH2)n is equal to 1, and we have the same exact feature of course in the structure on the right.

01:54

The next variable is the X variable. So, Z(CH2)nX, and that X is COOR9, where the R9 is equal to a hydrogen; so now again the intersection of these lines indicate that that's A carbon atom, so that's the C; and then O and then the O, and then the R9 is the H. So that functional group is called a carboxylic acid, but that Z(CH2)nX reads exactly on the structural element we have coming off of the 9 o'clock position on the top ring of the treprostinil molecule as drawn.

01:55

01:55

Q. Any doubt in your mind about that.

A. No.

Q. Would any chemist dispute that?

A. No.

Q. There are more variables down at the lower right-hand part hanging off of that five membered ring; did you consider those variables?

01:55

A. Yes, of course.

Q. Would you walk the Court through those, please?

A. Sure. Now, if we come down through the top six membered ring to the middle six membered ring to the five membered

01:56

ring, at 3 o'clock coming off of the five membered ring as its now shown, there is a Y substituent. And in claims that's Y equals CH2CH2, and that corresponds to the intersection of those two lines; so there's the CH2 coming off of that 3 o'clock position in the five membered ring, and then another intersection of lines coming from there is the second CH2, so these two intersections of line that zig-zag indicate a CH2CH2. So those exactly map on top of each other.

Q. And is that found within the scope of the claim?

A. Yes.

Q. Please continue.

A. Okay. And then the next carbon over in the '117 patent formula is a carbon that has two lines to an M1. So that would be now going past the two zig-zags in the middle structure, there's an intersection of two more lines, so that's a carbon; and then the two lines to the M1 would be -- oops; I'm really sorry. Can you get me back to the slide I was on? These buttons are very close together, I apologize.

So the two -- the two bonds coming off of the M1 are to an oxygen, that's the OH group, so that's the alpha OH; and then beta indicates an atom not drawn in, it's the hydrogen atom that chemists know are there, so that would be projecting toward the viewer. So that carbon, the third carbon over then, the third intersection of lines corresponds to the C double bond M1.

Okay. Moving to the next substituent variable, the C, another C, and then there's two lines to an L1; and so that would then be as defined here as alpha-R3 beta-R4, both of those are hydrogens, so that is another CH2 group, methylene group. And then R7, the final substituent on the '117 patent formula is a butyl group, that's four carbon so-called alkane group; so when we add the CH2 at this position, the C double bond L1, that's a CH2 to the butyl, you get C5H11.

So the combination of those three variables give you a C5H11, or a normal pentyl group, five carbon straight chain connection of carbons items.

Q. Any doubt in your mind about that section of the molecule?

A. Absolutely no doubt.

Q. And would any chemist agree with that analysis?

A. Yes.

Q. And is it your understanding that Dr. Buchwald has challenged any of that attribution of identities of Z and X, et cetera, in connection with claim 1 here?

A. He has not.

Q. Now -- so we've just walked through the formulas; did you look at the ANDA or the DMF to determine whether the product, the compound itself, was stereoselectively produced isomeric compound?

A. Yes.

Q. And what was your conclusion?
A. That the product is stereoselectively produced.
Q. In connection with your work in the case, did you look at the label of Sandoz's proposed label for Sandoz's product?
02:00 A. Yes, I did.
Q. And do you have a demonstrative of that?
A. Yes.
Q. And this is from the excerpt on the label is from PTX-250, last Bates number page is 54. And on the left we
02:00 have the '117 patent PTX-002; correct?
A. Yes.
Q. And did this inform your analysis in any way?
A. Yes. So, what's shown on this demonstrative, on the left again is the claim 1 -- the top claim 1 formula, the first one
02:00 at the top of the column under -- where claim 1 starts. And then on the right is the molecular structural drawing of the treprostinil molecule as it appeared in Sandoz's proposed label for their ANDA product.
Q. And you have a variety of boxes in the middle with a
02:01 variety of variables, Z, n, X, Y1, M1, L1 and R7; correct?
A. Yes.
Q. How do these relate to the variable assignments we just looked at in connection with the last demonstrative?
A. They're all identical.
02:01 Q. And so is it your opinion then -- or what is our opinion

with respect to the structural formula set forth in Sandoz's label in terms of being within the formula of claim 1 of the '117 patent?

A. Yes, that corresponds to the molecular structure of treprostinil.

Q. Are you familiar with the term free acid?

A. Yes.

Q. What is a free acid?

A. A free acid is -- in chemistry is a group that is so-called free to give up a hydrogen atom proton, hydrogen atom with no electrons on it, so it's just a proton; and it can -- it's free to donate that to a base -- a base molecule, or atom.

Q. Is this the compound or the structure shown on the right, would that qualify as a free acid?

A. Yes, that's a carboxylic acid that would be called a free acid in organic chemistry.

Q. Now, when that proton donation occurs, what -- is that anymore known as a free acid?

A. Excuse me; I didn't quite understand.

Q. After that proton donation occurs and that proton leaves, is it still known as a free acid?

A. No, once it donates its proton then chemists would call that the salt or the carboxylate or the anion of the acid, the conjugate anion.

Q. And did that affect your analysis at all in connection with this case for claim 1?
A. I guess I don't understand your question.
Q. In terms of the salt form, is the salt form also covered by claim 1?
A. Yes.
Q. Do you have a demonstrative of that?
A. Yes. Okay. So here, claim 1 also defines the X variable COOR9, where R9 equals a pharmacologically acceptable cation. And so pharmacologically accepting cations, there are many such known, sodium is perhaps the most common, like we have in table salt, sodium chloride.
Q. Now, with respect to everything but R9 in the box in the middle of the page, where Z equals zero, n equals 1, X equals COOR9, Y1 equals CH2CH2, M1 equals alpha-OH, beta-R5, R5 equals H, L1 equals alpha-R3, betaR4 where R3 and R4 equal hydrogen, and R7 equals butyl; are those variables the same as or different from what we talked about in connection with the earlier work that you had done on claim 1?
A. They're all the same with the exception of R9 is now a pharmacologically acceptable cation, and in the example shown that's sodium.
Q. And the structures that are shown in the center and the right-hand side of the graph, the one from the center comes from Sandoz's ANDA at PTX-250, page 279; correct?

A. Correct.
Q. And the one with Alphora's DMF, that's structure comes from PTX-333, the last four digits of the Bates number 8441; is that right?
02:04 A. That's correct.
Q. Now, what does this pharmacologically acceptable cation thing mean?
A. Well, this is a salt form of treprostinil, and it's very common in organic chemistry and medicinal chemistry to make
02:05 salt, because they're more water soluble than the free acid forms.
Q. Now, did the '117 patent teach anything about a pharmacologically acceptable cations?
A. Yes. So in the '117 patent there's -- here's an excerpt,
02:05 where it says pharmacologically acceptable salts of the novel prostaglandin analogs of this invention for the purposes describe are those with pharmacologically acceptable metal cations, especially preferred metal cations are those derived from the alkali metals, for example, lithium, sodium, and
02:05 potassium.
Q. And the use of sodium as we saw in the last demonstrative in those two formulae from the ANDA and the DMF, in your view is that within the scope of pharmacologically acceptable cations for the '117 patent?
02:06 A. Yes.

Q. Now, can you explain to the Court the transition between a free acid -- or the relationship between a free acid on one hand and the salt form on the other?

A. Yes. And I have a slide. This is very -- almost identical to what I presented in the tutorial last week. So, on the left is the molecular structure of treprostinil acid, or the free acid, and if you put treprostinil in water, in aqueous solution, it will immediately dissociate; so the acid can donate a proton to -- a proton acceptor, in this case I have sodium hydroxide shown as the acceptor group. So when the free acid donates that H plus, the hydrogen atom, to the OH, which is part of sodium hydroxide, Na plus, OH minus, the OH minus and the H plus get together and form a water molecule that's shown on the right.

And then the result of losing the proton from the acid leaves a negatively charged or the anion of the acid, and then that gets together with sodium, so we have net neutral species and that would be the sodium salt. And these are rapidly inter-converting with each other in solution.

Q. So, both the free acid and the salt form exist together?

A. Yes. And so, the relative proportions of the free acid and the sodium salt are a direct function of the pH of the water solution.

Q. Is there a way you can determine the particular pH where 50 percent is free acid and 50 percent is salt form?

A. Yes, there's a very well-known method in organic chemistry, where one can determine the so-called acid strength of any given proton donor or free acid; and in the case of treprostinil that acid strength is defined by a term called PKA, and it's a measure of how readily that particular acid can donate its proton to an acceptor molecule. So in the case of treprostinil, PKA I believe is about three and a half, 3.5.

Q. So what happens then if you have treprostinil free acid in a solution at a pH of 7.5, roughly neutral?

A. Yes. So at pH 7 you're going to have mostly the carboxylate or the salt form, and the pH scale like the PK scale are both logarithmic; so each time you go up one unit in pH, you're increasing by a factor of 10, the relative ratios of the two species that we're talking about.

Q. So what's the rough ratio of free acid to salt form at pH of 7.5?

A. 7.5 would be roughly 10,000 of the salt forms to one of the acid.

Q. Now, if you were to take the treprostinil and change the pH up to 10.5, what would the relative ratios be?

A. So it would be a 10 to the 7th difference.

Q. 10 million?

A. That's 10 million.

Q. 10 million salt form to one?

A. To one acid.

Q. Now, treprostinil and treprostinil sodium, are they both 9-deoxy-PGF1 type compounds?
A. Yes, they are.
Q. With respect to this first limitation we've been talking about the A limitation; with respect to treprostinil free acid and treprostinil sodium, what is your conclusion regarding the Sandoz ANDA product and whether it meets that limitation?
A. Well, my conclusion is that both the treprostinil free acid and treprostinil sodium meet that the -- that first claim limitation of claim 1.
Q. Any doubt in your mind about that?
A. No, doubt.
Q. Let's turn to the second limitation that you've identified or called out specifically from the claim, and that is the enyne limitation. Okay? And did you run through the similar analysis with respect to the enyne limitation?
A. Yes, I did.
Q. And would you please describe what you did here for the Court.
A. Certainly. So, similarly shown here this is now the next structure or formula down in claim 1 of the '117 patent, the starting enyne compound; and then drawn next to that in the middle box is the structure of the enyne molecule that is used in Sandoz's ANDA; and in the third box over to the right is molecular formula for the exact same structure. So the

structures are -- in the middle and on the right are exactly the same. And then --

Q. If I could for just a moment for the record, I'd just like to read where those structures come from. So the middle structure comes from the Sandoz ANDA PTX-250 at Bates page 278; correct?

A. Yes.

Q. And the Alphora DMF compound comes from the Alphora DMF PTX-333 at Bates number 8433; is that right?

A. That's correct.

Q. So please continue.

A. Yeah, so like the previous analysis, the molecular formula of the enyne has the same family of descriptors, the Z(CH2)nX, which now in the orientation drawn comes off of the 6 o'clock position of the six membered ring. And so I looked at that variable, and then -- or those variables, and so going through that, the Z again is the oxygen, and in the enyne used the Sandoz ANDA and Alphora DMF, that Z at 6 o'clock, is the oxygen in 6 o'clock in that same position in both structures.

And then CH2 is the next group, with n equal to 1, and so that's what's shown there, Z(CH2)n; and in the case of Sandoz's ANDA and Alphora's DMF, the acronym PMB is shown there, and chemists skilled in the art would know that is a para-methoxy benzyl group. And so the first atom coming off of the oxygen in the PMG group is a CH2 where n is equal to 1.

So that -- so both of these structures have the CH2 or n is equal to 1, even though it's written with the acronym PMB.

Q. A person skilled in the art would know that?

A. Yes.

02:13 Q. Please continue.

A. And then the X -- the X group substituent, is the equivalent of -- combined with the CH2, is the equivalent para-methoxy benzyl group, but the X itself after the CH2 is a par-methoxy phenol group.

02:14 Q. And do you have any opinions about whether that (CH2)n where n equals 1 and X taken together in the Alphora and the Sandoz product, are equivalent to the Z(CH2)nX group as claimed in the '117 patent?

A. Yes. My opinion and my analysis is that they -- the PM

02:14 group is functionally equivalent to that substituent called out in the '117 patent claims.

Q. We're going to talk about your equivalents analysis in some detail later, but I'd just like to continue running through each of the limitations of claim 1 first; is that

02:14 okay?

A. Okay.

Q. So please carry on.

A. Okay. So, now turning to the other variables, so from the six -- going back to the six membered ring on the '117

02:15 patent, coming off at the 2 o'clock position, there's a bond,

intersection of lines, then there's a wedge bond to OR1; and the R1 which is now defined at the bottom of the substituent variable box I have there, R1 is an alcohol protecting group, and TBS is one of the referred protecting groups that are specifically called out in the '117 patent. And in Sandoz and Alphora's enyne, there is the oxygen at that exact position coming off of the 2 o'clock position in the six membered ring, and TBS is the acronym for tert-butyl dimethyl silyl, which is an alcohol protecting group.

Q. We'll come back and talk a little bit about the TBS group on the next demonstrative that you prepared, but would you continue please walking through?

A. Sure. And so the next line over goes through a C in '117 patent formula, and then there's three lines to the next C, so that's the alkyne; and in the Sandoz ANDA, Alphora DMF structure, which are both the same, the carbon isn't written there, but a person of ordinary skill would understand that at that position is a C, carbon atom; and then there's three bonds, meaning three covalent bonds to the next carbon atom, which is shown in the '117 patent. So it's a C and C; the Cs aren't written in, but a chemist would understand again this is an intersection of lines and they're carbons atoms, so that is the exact same functional group, the alkyne, is what's depicted in the '117 patent formula.

And then the next substituent coming off of that second

C, on the triple bond is the Y1 substituent, and that is a CH2CH2. So just like we discussed in the previous formula, we have the zig-zag, that's intersections of two lines indicating a CH2 at that next position coming off, and then another CH2 connected to that. And so that set of zig-zags right there corresponds to CH2CH2.

Q. Which corresponds to Y1?

A. Yes, that's Y1.

Q. Please continue.

A. Yes. And then the next carbon or next substituent connected to Y1 is a C, another carbon atom; there's two lines to an M1; and here in the patent claims M1 is defined as alpha-OR1; so that's an oxygen with an alcohol protecting group on it as defined. And then beta-R5 where R5 is equal the hydrogen; so the alpha and beta are referring to the stereochemical projection of those bonds, alpha meaning that the oxygen goes behind the plane of the screen; the beta, meaning hydrogen, comes away during the plane of the screen.

So, that C, two lines to the M1 corresponds to the intersection of those lines, that's the carbon atom corresponding to that C; and then OBN, the oxygen, would be the oxygen, the alpha-OR oxygen; and then BN is an alcohol protecting group, the acronym used here is benzyl, or BN for benzyl.

Q. We'll come back and talk a little bit about benzyl, but

could you please carry on with respect to the L1 and R5 substituents?

A. Yes. So the next group over is C with two lines to an L1, and is defined that's alpha-R3 beta-R4, where both of those R3 and R4 are both equal to hydrogen; so again, that's a CH2 group, a methylene group. Then combining that with the R7, as we did previously, R7 is a four carbon straight chain of atoms; we combine a CH2, with the butyl and we get C5H11.

Q. So we'll talk a little bit about the particular protecting groups TBS and benzyl, but in your opinion are the claim 1 requirements relating to the enyne met by the Sandoz ANDA product and the product described in Alphora's DMF?

A. Yes, because the enyne in Sandoz's ANDA and Alphora's DMF as shown, have all of the structural and functional features importantly including the stereo-directing group, the OR1 group or the OTBS group.

Q. Does the patent teach anything about these protecting groups that you mentioned?

A. Yes.

Q. Can we go to PTX-2. At column 11, lines 1 through 5. Did you review this part of the '117 patent?

A. Yes, I did.

Q. And what does it teach here?

A. Well, the patent in the specification says, wherein R1 is in each case an independently selected alcohol protecting

group; and then it goes on to teach that preferred alcohol protecting groups are tertiary butyl dimethyl silyl; and in the patent they use the acronym TBDMS, which is the same group as the TBS acronym we just saw on the previous slide --

02:21 Q. Wait a minute; the TBDMS is the same as TBS?

A. Yes.

Q. Why is that?

A. Chemists have invented shorter and longer acronyms for thing, but any organic chemist would know that TBDMS and TBS

02:21 are the same, tert butyl dimethyl silyl.

And then the other preferred alcohol protecting group is the tetra hydro pyranyl, which is abbreviated with the acronym THP.

Q. In connection with your analysis on the last slide, you

02:21 pointed to something known as the benzyl and said that's a protecting group.

A. Yes.

Q. Is there some particular book or resource that chemists turn to for information about particular protecting groups?

02:21 A. Yes, there's actually many resources; the one that is probably far and above the most popular that both Dr. Buchwald and I cited in our reports is the book on protecting groups written by Green and Woods.

Q. I'd like to turn to the next demonstrative. This has a

02:22 couple of pages out of DTX-0409, specifically page 1163516; is

that right?
A. Yes.
Q. And what is -- what is this Green and Woods book?
A. The Green and Woods book is sort of the organic chemist's
02:22 bible and guide to protecting groups in synthetic organic
chemistry, and it's divided into various chapters that are
related to the various types of functional groups being
protected for organic chemistry reactions. And this page here
shows --
02:22 Q. Professor --
A. I'm sorry.
Q. Is this Green and Woods book something you relied upon in
connection with your analysis?
A. Yes, I cite it in my report.
02:22 MR. CARSTEN: Your Honor, UT would move to admit
DTX-409, Green and Woods chapter.
MR. STEINDLER: No objection.
THE COURT: So DTX-409 is admitted.
MR. CARSTEN: Thank you, your Honor.
02:23 (Defendant's Exhibit 409 was marked into evidence.)
BY MR. CARSTEN:
Q. So, Professor Williams, what's being shown here at this
excerpt from this page from the DTX-409?
A. So, this page comes out of the chapter on alcohol
02:23 protecting groups, and many are listed, and protecting group

number 42, is called the benzyl ether, BnOR, so that was the acronym that was used in Sandoz's and Alphora's molecular structure depiction. They used OBN, that acronym. And then what this book typically shows for protecting groups are literature cites for conditions to put on the protecting group, which is what's shown here, in one, two and three; so formation, this is putting the protecting group on the alcohol, which is an OH group. And then later pages will have cleavage or removal of that protecting group.

02:24 Q. Why is it important to have information about putting a protecting group on and then taking a protecting group off?

A. Well, this is what protecting groups do; they're temporary, so organic chemists need to know good reaction conditions with literature references, so that they can go to

02:24 the experimental details for reaction conditions to put that protecting group on in an effective way; and then also literature guidance on how to remove that protecting group when it's done its job later in the synthesis.

Q. So what is a protecting group's job?

02:24 A. It's to mask a functional group during an organic chemical reaction, such that it does not interfere, inhibit or get transformed because some functional groups are simply incompatible with certain reactions, organic reactions, and so we have to mask or protect that group from either doing damage

02:25 or in itself being converted into something undesirable.

Q. Now, does this page from the Green and Woods book at DTX-409, does this confirm or support your conclusion that benzyl is a protecting group?

A. Yes, benzyl is an extremely well-known protecting group in synthetic organic chemistry. I've used it enumerable times in my research.

Q. Did you also look at some deposition testimony from an Alphora witness confirming the benzyl is a protecting group?

A. Yes.

Q. So, this is deposition testimony from McGowan taken -- Dr. McGowan of Alphora, taken October 24th, 2013, and we're relying on pages 161 line 23, to page 162, line 9. Could you -- I know your monitor isn't working; can you read that into the record? You might be better off looking at this screen.

A. Okay. So let me read -- I can see better here.

Question: Looking back at B195, at the bottom, at the right, on that molecule is OBn group; do you see that?

Answer: I see that.

Question: Is that O-benzyl or does Bn represent benzyl?

Answer: It does, yes.

Question: Is that another protecting group?

Answer: Again, depending on the substrate it's on, it can be. It is frequently considered as a protecting group, yeah.

Q. And did that also support or confirm your opinion about

benzyl being a protecting group?
A. Yes.
Q. Now, getting back the claim 1 for a moment, is putting on and taking off a protecting group within the steps identified
02:27 in the claim of the '117 patent?
A. I didn't quite understand your question.
Q. So, is the transformations of putting a protecting group on and then taking a protecting group off, are they literally within the scope of what's claimed in the '117 patent?
02:27 A. It's not -- so the protocol of putting on a protecting group and taking off a protecting group is not specifically described, but a person of skill in the art knows that when alcohol protecting groups are identified as being part of the substrate, a person skilled in the art knows that it had to
02:27 get on somehow and has to come off at some later stage.
Q. Now, with respect to the enyne limitation, have you prepared a summary here of your conclusions regarding whether the enyne limitations are met in the Sandoz ANDA product and the Alphora DMF?
02:28 A. Yes, in my opinion the starting compound, the enyne, that is used in the Alphora DMF, the Sandoz ANDA, meets the second claim limitation.
Q. That's the enyne --
A. The enyne, yes.
02:28 Q. Now, let's turn to the cyclized intermediate aspect of

the claim if we could. Did you -- pardon me, Professor; did you analyze that aspect of the claim?

A. Yes, I did, and I have a demonstrative on that as well.

Q. Would you be so kind to walk the Court through this

02:28 demonstrative, please.

A. Yes. So, shown on in the upper left box is the third structure down in the '117 patent claims, the cyclized intermediate or the tricyclic intermediate. And once again, it is drawn 90 degrees counterclockwise from how the cyclized

02:29 intermediate is drawn in Sandoz's ANDA and Alphora's DMF, but we'll just leave the orientation as it is for now.

And again, the '117 patent formula has the 6 o'clock position in the most left-hand six membered ring is Z(CH2)nX. And so, I compared that variable to what's in the Sandoz and

02:29 Alphora molecular structures, and so the Z again is oxygen; so that's the first atom coming off at the 6 o'clock position in the six membered ring, so Z is oxygen or O. And then the next group over is (CH2)n, so those are CH2 groups where n is equal to 1. And X combining (CH2)n with the X is the equivalent

02:30 para-methoxy benzyl group.

Q. So is it the same analysis with respect to the Z(CH2)nX moiety taken as a whole here for the cyclized intermediate, as it was with respect for the enyne compound we talked about?

A. Yes. So it's the exact same functional group set up as

02:30 we had in the enyne, that is retained with fidelity in the

cyclized intermediate.

Q. Now, with respect to the Y1C2 bonds, M1C2 bonds, L1 and R7, is that the same analysis as it pertained to the previous limitation, that enyne limitation?

02:31 A. Yes. So we have exactly the same side chain that's defined by the Y1C2 lines to M1C2 lines to L1R7, and that exactly maps on the side chain that is specifically drawn in the Sandoz ANDA and Alphora's DMF molecular structures.

Q. Now, with respect to the center six membered ring coming

02:31 off at about the 12 o'clock position, there's that wedge up with the OR1; would you describe that for the Court?

A. Yes. So the patent uses the convention of a wedged line, which tells a person of skill in the art that that oxygen is projecting toward the viewer, out of the plane of the page;

02:31 and that same convection is shown in the Sandoz ANDA and Alphora DMF structure, so the wedge line is coming toward the viewer. And similarly the newly created stereogenic center which is at the junction between the six and five membered rings, also we have a wedged line to a hydrogen, that's also

02:32 drawn in both of the formulas from Sandoz's ANDA and Alphora's DMF.

Q. Now, with respect to this (CH2)nX coming off of the left-hand six membered ring at the 6 o'clock position, what's your opinion about the PMB and its relationship to that

02:32 (CH2)nX?

A. My opinion was that it's equivalent to what's literally claimed in the patent.

Q. And we'll talk in a moment once we completed going through the claim 1 about the equivalents analysis, but did you reach a conclusion about whether the Sandoz ANDA product and the Alphora DMF products identified on this demonstrative slide, met the cyclized intermediate limitation?

A. Yes.

MR. CARSTEN: And if we can just go back one slide, please, Mr. Merisier.

Q. Just for the record, the structure from Sandoz's ANDA comes from PTX-250, at page 278, and the structure for Alphora's DMF comes from PTX-333 at page 8433; is that correct?

A. That's correct.

MR. STEINDLER: Let me just object to the form of the last question, because it was a question that was directed to what's in Sandoz's ANDA product and Alphora's DMF product, and I'm not certain that that was the question that the counsel intended to ask. That is to say, we're now talking about intermediates, we're not talking about the finished product. And I want the record to be clear that the question here is with respect to intermediates that are used and not with respect to the final product.

THE COURT: But the cite that he referred to, that's

correct?

MR. STEINDLER: I'm not objecting to the citation. It was the immediately preceding question, which was directed to Sandoz's ANDA product as opposed to the intermediate.

02:34 THE COURT: All right.

MR. STEINDLER: So I just object to the form of that question and would respectfully suggest that it could be clarified so the record is clear.

THE COURT: All right. So why don't you clarify.

02:34 MR. CARSTEN: Sure, I'm happy to, your Honor.

BY MR. CARSTEN:

Q. The compound identified as found within the disclosure of Sandoz's ANDA at page 278, identified in the middle box on the upper part of the screen, in your opinion does that meet and

02:34 fulfill the claim requirements of the cyclized intermediate?

A. Yes.

Q. With respect to the Alphora DMF product identified with 8433 of PTX-333, would that claim be -- I'm sorry; would that compound be -- meet the limitations of the cyclized

02:35 intermediate limitation of claim 1?

A. Yes.

Q. Okay. Now, let's to turn -- have you prepared a summary slide here with your findings with respect to that C limitation, cyclized intermediate?

02:35 A. Yes.

Q. And what's your conclusion?
A. My conclusion is that that limitation is also met by Sandoz's ANDA and Alphora's DMF.
Q. Now, let's turn to the D limitation, by intramolecular
02:35 cyclization of the enyne, and says in parentheses, intramolecular cyclization process; do you see that?
A. Yes.
Q. Did you analyze any documents with respect to determining what that cyclized -- the intramolecular cyclization of the
02:35 enyne was found within the -- disclosed in the Sandoz ANDA or the Alphora DMF?
A. Yes.
Q. And what's being shown on here on this demonstrative, demonstrative 28?
02:36 A. So, on this demonstrative on the top, which comes from PTX-250, Bates page 278, is they have numbered the molecular formulas, B195 to correspond to the starting enyne compound; and there's an arrow which indicates to a chemist that's a chemical transformation or reaction; and B196 is the code
02:36 number or acronym they've assigned to the cyclized intermediate.

So, it's very clear that the enyne has undergone the carbonylative cyclization, the Pauson-Khand type reaction, to form that -- that new six membered and new five membered ring
02:37 with the creation of the new stereogenic center.

Q. And you just described for the Court the transformation on the upper portion of the screen, for PTX-250 at page 278. Could you also walk the Court through the transformation on the bottom of the screen at PTX-333, page 8433?

02:37 A. Yes. So this is the same transformation, so the structures of the B195 and the B196 are identical to those just above; the only difference between these two images is that in the Alphora DMF they wrote in plus CO2, paren CO, close paren, 8, which is the dicobalt octacarbonyl, the

02:37 classical reagent used in the classical Pauson-Khand cyclization reaction.

Q. So, did you reach a conclusion as to whether the disclosures in the Sandoz ANDA and Alphora's DMF demonstrate that the cyclized intermediate is prepared by a intramolecular

02:38 cyclization of the enyne.

A. Yes.

Q. And did you reach a conclusion as to whether that falls within the scope of claim 1?

A. Yes.

02:38 Q. What's your conclusion?

A. My conclusion is that that limitation is also met via the -- what's described in Alphora's DMF and Sandoz's ANDA.

Q. Now, to be clear, except for the PMB group which we'll talked about in a moment in terms of your equivalents

02:38 analysis, did you literally find each and every limitation of

claim 1 in the ANDA?
A. Yes.
Q. And the ANDA is PTX-250?
A. Yes.
02:38 Q. And did you literally find, except for the PMB equivalents, each and every limitation of claim 1 in the Alphora DMF, DTX-333?
A. Yes.
Q. Now, let's turn to the DOE, doctrine of equivalents,
02:39 analysis that you performed, if we could; okay? Did you prepare a summary slide?
A. Yes, I did.
Q. Would you please describe this for the Court.
A. Yes. So in my opinion the X limitation is met or present
02:39 under the doctrine of equivalents; and the summary of my opinion is that Sandoz's ANDA proposed ANDA product and related process uses a PMB group at the (CH2)nX position on the enyne and cyclized intermediate. And the PMB group performs the same function in the same way with the same
02:39 result as the X group or X groups identified in each claim. And there is an insubstantial difference between the PMB group and the X group identified in each claim.
Q. You mentioned function/way/result; what is that?
A. Yes. So I was given the legal standard by counsel to
02:40 perform a doctrine of equivalents analysis, and I've done this

before in previous cases, so I was familiar with the test and the standard I had to apply.

Q. And did you actually analyze the issue here using that function/way/result test?

02:40 A. Yes.

Q. Now, I'd like to point you to a portion of the specification of the '117 patent from example 1. So this is from PTX-002, it's the '117 patent in suit, at column 16, lines 53, through column 17, line 55. Which part of example 1

02:40 is this?

A. So, this is the intramolecular cyclization step of the Pauson-Khand step.

Q. And did you consider this example in connection with your function/way/result analysis?

02:41 A. Yes, I did.

Q. Why did you consider this step, this portion of example 1 in connection with that analysis?

A. Well, this step is the claimed invention.

Q. What do you mean by that?

02:41 A. Well, this is the way in which one can obtain stereoselectively produced treprostinil.

Q. Were you here in court for Mr. Steindler's opening statement?

A. Yes.

02:41 Q. And he criticized you for considering this example;

right?
A. Yes.
Q. Do you think that's a legitimate criticism?
A. No.
02:41 Q. Why not?
A. Because example 1 is an embodiment of the claims of claim 1, and Dr. Buchwald has acknowledged that and Sandoz has acknowledged that example 1 is an embodiment of claim 1.
Q. Is -- so what is the protecting group on that Z, the --
02:42 the analogous position of the Z(CH2)nX as shown here in example 1?
A. It's a methyl ether.
Q. Is methyl within the scope of (CH2)nX of the claims of the '117 patent?
02:42 A. Yes.
Q. Now, Dr. Buchwald you understand criticized you in his report for focusing on methyl as opposed to other things which may be within the scope of (CH2)nX; do you remember that?
A. Yes.
02:42 Q. And what did you do as a result of that criticism?
A. Yes, I responded in my reply report, to that criticism.
Q. And what -- how did you respond?
A. Well, I can -- I called out from the patent claims, two other exemplary protecting groups that are defined by the
02:42 patent claims.

Q. And did you consider those exemplary or additional protecting groups in connection with your analysis?
A. Yes.
Q. Now, you mentioned that example 1 is an embodiment of the claims; did you say that?
A. Yes.
Q. I'd like to show you a portion of the -- or an excerpt from the pretrial order in the stipulated facts section. Do you see stipulated fact 29 from the pretrial order?
A. Yes.
Q. Would you read that into the record please, Professor Williams?
A. Yes. It says 29, example 1 in the '117 patent is an embodiment of the claimed invention of the '117 patent. And that's what's highlighted.
Q. Now, this isn't something that was just admitted for summary judgment, your understanding is this is a stipulated fact by Sandoz in the pretrial order; correct?
A. That's my understanding.
Q. And does this confirm your view that example 1 is an embodiment of the claims?
A. Yes.
Q. Now -- all right. Let's turn to the function/way/result analysis that you actually performed. Let's start with function. You have a demonstrative, demonstrative 33; would

you please explain to the Court the function of PMB as reflected here?

A. Yes, the function of PMB is to serve as an alcohol protecting group, during the Pauson-Khand intramolecular cyclization reaction.

Q. Now, you said an alcohol protecting group; is the oxygen to which the PMB is attached, is that an alcohol?

A. It's a special type of alcohol that organic chemists call phenols, p-h-e-n-o-l. A phenol.

Q. How do they differ from a garden variety alcohol?

A. So, garden variety alcohols like the other two oxygens in the structure on the left, are distinct from phenol in that a phenol oxygen is directly connected to what's known as a aromatic ring, or in this case the six membered ring with the three additional bonds inside the ring. And by virtue of being directly connected to that special type of ring, phenols are more acidic than the other two types of alcohols shown, and they have different, distinct chemistry that is characteristic of phenol that is not -- doesn't completely overlap in chemistry of other types of alcohols.

Q. Now, you've shown here two compounds, B195 to B196, and these compounds were taken from PTX-250, the Sandoz ANDA at page 278; is that correct?

A. That's correct.

Q. Now, this may be a dumb question, I apologize, Professor,

but I see here it says OPMB, and here it says on the right-hand structure PMBO; is that different?

A. No, it's just the structures of the six membered ring was rotated, and so OPMB an organic chemist would understand is o-para-methoxy benzyl; and the structure on the right, just because it's been rotated to read that same substituent from left to right, we would then write PMBO. But those are the same, there's no difference between those two.

Q. So there is no transformation on the molecule at that -- at that position.

A. No.

Q. Okay. Now, so what is the function of PMB, what's it doing during this reaction?

A. It's not doing anything, it's a spectator, it's protecting the phenolic hydroxyl group.

Q. Well, comparing PMB with the (CH2)nX groups of claim 1, including methyl, what are those (CH2)nX groups in claim 1 doing during this reaction?

A. The same thing, they're protecting the phenolic hydroxyl group.

Q. So, if the PMB group is doing nothing in the reaction, how is it functioning equivalently to the (CH2)nX groups in the claim?

A. Well, both the methyl ether and para-methoxy benzyl ether are doing their job their job, they're a spectator; they're

not participating in the reaction, the cyclization reaction proceeds on both substrates to give a tricyclic intermediate, and neither the methyl ether or the para-methoxy benzyl ether are undergoing themselves any type of chemical transformation during that cyclization step.

Q. Did you find any evidence in the literature that these -- this phenolic oxygen, so the oxygen coming off of the six membered ring on the left-hand side of the structure at the 6 o'clock position, actually needs to be protected during a Pauson-Khand reaction?

A. Yes.

Q. I'd like to turn you to the next demonstrative, which is a page from PTX-1027.

MR. CARSTEN: Maybe, Mr. Merisier, would you be so kind actually to put up PTX-1027, please.

Q. Do you recognize this document?

A. Yes.

Q. What is it?

THE COURT: Do you need my chart to read it?

THE WITNESS: No, I read recognize it. This is a publication of from the Journal of the American Chemical Society, published in 1994, at page 3159.

BY MR. CARSTEN:

Q. Is this a document that you considered in connection with your analysis in this case?

A. Yes.

MR. CARSTEN: Your Honor, United Therapeutics would move PTX-1027 into evidence, please.

MR. STEINDLER: No objection.

02:48 THE COURT: Okay.

MR. CARSTEN: It's 1027, your Honor.

THE COURT: PTX-1027 -- can you give me the title of that again?

MR. CARSTEN: Certainly. The title of the Journal 02:48 of the American Chemical Society article is Catalytic Version of the Intramolecular Pauson-Khand Reaction.

THE COURT: It's admitted.

(Plaintiff's Exhibit 1027 was marked into evidence.)

MR. CARSTEN: Thank you, your Honor.

02:49 BY MR. CARSTEN:

Q. Now, this article was written -- the first author is a fellow by the name of Jeong; correct?

A. Yes.

Q. What did Jeong, et al, teach a person of ordinary skill 02:49 in the art regarding phenols and the Pauson-Khand reaction here?

A. Well, on the second page of the paper there's a table with their results, and in the text it's highlighted, Jeong says: In the case of propargyl allyl ether, compound 6, which 02:49 is shown directly above, 6A, the addition of potassium

carbonate, which is a base, to the reaction mixture turned out to be crucial for a reasonable yield, because of the traces of phenol during the reaction.

Q. So, what would a person of ordinary skill in the art understand from that disclosure?

A. That free phenol, which is relatively acidic compared to the garden variety alcohols we were talking about before, create a problem in this reaction. And so the addition of the potassium carbonate is to neutralize that phenol.

Q. Now, this Pauson-Khand reaction, we've been talking about it in terms of the dicobalt octacarbonyl reagent; correct?

A. Correct.

Q. Can you use other metals to perform a Pauson-Khand type reaction?

A. Yes.

Q. Which -- which other metals generally?

A. There's several, there's molybdenum, titanium, a few others.

Q. Did you find any evidence that phenols interfere with these Pauson-Khand type reactions in the literature?

A. Yes. So there was another paper I have on the next slide.

MR. CARSTEN: Mr. Merisier, could you please pull up PTX-1034?

BY MR. CARSTEN:

Q. Do you recognize this paper, Professor Williams?
A. Yes.
Q. And this is New promoters for molybdenum hexacarbonyl mediated Pauson-Khand reaction by Trindade, et al; correct?
02:51 A. Correct.
Q. Is this a paper that you analyzed and considered in connection with your work in this case?
A. Yes.
MR. CARSTEN: Your Honor, United Therapeutics would
02:51 move to admit PTX-1034 into evidence.
MR. STEINDLER: No objection.
THE COURT: All right, admitted.
(Plaintiff's Exhibit 1034 was marked into evidence.)
BY MR. CARSTEN:
02:51 Q. And what does -- Professor Williams, what does Trindade, et al, teach a person of ordinary skill in the art regarding phenols and Pauson-Khand type reactions?
A. Well, in this paper they were exploring different additives to examine their effect on that Pauson-Khand type
02:51 reaction, and they found that addition of phenol as an additive resulted in zero percent of the desired product.
Q. What does that mean, zero percent?
A. So none, no yield, no compound was formed.
Q. So, does that confirm your -- how does that impact your
02:52 analysis with respect to whether the phenol in that enyne

structure in claim 1 needs to be protected in order to have that Pauson-Khand type reaction occur?

A. Yes, this -- again, is another teaching that phenol -- phenols need to be protected in Pauson-Khand and Pauson-Khand type reactions.

Q. Did you see any Alphora patent materials that describe the PMB that's used in connection with the Alphora process or synthesis as a protecting group?

A. Yes.

Q. I'd like to show you PTX-1038. What is this, Mr. Professor Williams?

A. This is a PCT patent publication. WO 2012/009816 A1.

Q. And can you tell me who is the applicant for this PCT application?

A. It's Alphora Research.

Q. And can you identify for me what the filing date, the international filing date for this PCT?

A. 22 July, 2011.

Q. And can you also tell me what the priority date to which this publication claims priority is?

A. 22 July, 2010.

Q. Thank you. Is this PCT publication something you considered in connection with your work in this case?

A. Yes.

MR. CARSTEN: United Therapeutics would move to

admit PXT-1038 into evidence, please.

MR. STEINDLER: No objection.

THE COURT: All right, admitted.

(Plaintiff's Exhibit 1038 was marked into evidence.)

02:54 BY MR. CARSTEN:

Q. Now, you considered several paragraphs from this PCT, the Alphora PCT publication; correct?

A. Yes.

Q. And would you please describe for the Court what it is

02:54 you considered in connection with this PCT publication and how it affected your analysis.

A. Well, it just confirmed my understanding that the use of the para-methoxy benzyl group is indeed specifically a protecting group, the phenolic protecting group for use in the

02:54 Pauson-Khand cyclization. And the this document specifically says, and I'll just read: Treprostinil is prepared by a process which involves Pauson-Khand cyclization, the use of para-methoxy benzyl group as the phenolic protecting group. And then later down it says: Where PMB -- which is the

02:54 acronym for para-methoxy benzyl -- represents para-methoxy benzyl group.

Q. And this is from page with the last three digits of 509 from PTX-1038?

A. Yes.

02:55 Q. And that's the abstract it looks like; correct?

A. Yes.
Q. You have a second passage from that publication; would you please inform the Court how that affected your analysis?
A. Yes. So this is again a discussion that the chiral derivative compound number 16, the enyne is protected with the PMB, para-methoxy benzyl, at the phenol position.
Q. Is there any doubt in your mind that the PMB group in the Alphora method here, is being implemented to serve the function of a protecting group?
A. I have no doubt.
Q. And how does that relate to the (CH2)nX functionality claimed in claim 1 of the '117 patent?
A. Well, for the enyne it's serving as a protecting group. For the phenol.
Q. Is there any doubt in your mind that they're serving exactly the same function?
A. I have no doubt.
Q. Let's turn to the way analysis part of your test, or your analysis. Did you consider the way part of the function/way/result?
A. Yes.
Q. And what are we looking at on this demonstrative slide 37?
A. So, on this slide on the left is experimental details from example 1 from the '117 patent, which describes in detail

how the Pauson-Khand or intramolecular cyclization reaction was conducted in that example.

Q. So, that's PTX-002 at columns 17, lines 34 through 55?

A. Yes.

02:56 Q. And then what's over on the right-hand part of the screen?

A. Okay. And on the right this came from PTX-333, so this is a description from the Alphora DMF of the experimental details of how their B195 enyne is subjected to the

02:57 Pauson-Khand intramolecular cyclization reaction. So it's the experimental details of their transformation.

Q. So could you walk us through this please, Professor?

A. Certainly. So, in the upper left is a structure of the enyne in the '117 patent example, it's numbered compound 9;

02:57 and compound 9 specifically has the methyl ether protecting group on the phenol, the OTBDMS protecting group, at the position coming off of the 2 o'clock; and then the side chain as the OTHB protecting group. So, compound 9 is the starting material.

02:57 THE COURT: I'm sorry to interrupt you, Doctor.

But Mr. Steindler, you understand that in the pamphlet I have for the slides, that it's color-coded?

MR. STEINDLER: Yes, I do understand that. I'm expecting at some point we'll see the colored version of this,

02:58 and I'm sure Mr. Carsten will get there.

MR. CARSTEN: Yes. Yes, your Honor.
THE COURT: You may proceed.
MR. CARSTEN: Thank you.
BY MR. CARSTEN:
02:58 Q. So, would you please continue, Professor Williams?
A. Yes. So compound 9, is the substrate that is used, the starting enyne material that's used in the '117 patent example 1. And that is dissolved in C -- dry CH2CL2. And so on the left CH2CL2 is the shorthand acronym for the solvent
02:58 dichloromethane. And so on the right in the Alphora experimental description, instead of writing CH2CL2 they spelled out the solvent name, dichloromethane, but they're the same.
Q. So, here in sort of a reddish color you have CH2CL2 on
02:59 the last and dichloromethane on the right; is that the same thing?
A. Yes, it's the same solvent.
Q. And what's the next identity that you looked at here?
A. The next thing is the reagent that's used for the
02:59 cyclization, the dicobalt octacarbonyl; and so on the left the '117 patent example put the molecular formula, CO2, paren CO, close paren, 8, that's dicobalt octacarbonyl; and in the Alphora experimental description they spell out the name of that reactive, dicobalt octacarbonyl. So those are the same.
02:59 Q. So, the -- green chemical sort of formula, is the same as

dicobalt octacarbonyl in green on the right?
A. Yes.
Q. And what did you consider next?
A. And then next the ratios -- the actual ratio of the substrate molecule to the dicobalt octacarbonyl complex -- reagent, in the case of the example 1 it's 1.91 millimoles of the cobalt reagent to 1.59 millimoles of the substrate, and so --
Q. How many equivalents is that?
A. It's 1.2 to 1; so if you divide 1.9 one by 1.59, this means you have 1.2 equivalents of the dicobalt octacarbonyl per every one equivalent of the starting enyne.
Q. So what -- what level of equivalents did Alphora use in connection with their Pauson-Khand reaction?
A. That's exactly the same, 1.21.
Q. And that's shown in blue on --
A. That's shown in blue.
Q. Okay. What's the next thing you considered?
A. So after those materials are combined in dichloromethane, this is the so-called complex formation, this is where the cobalt is going to coordinate to the triple bond, the alkyne. And so they stir at room temperature as shown on the left in purple, and also that's exactly what's done in the Alphora process, stirred at room temperature.
Q. So they both got stirred at room temperature?

A. Yes.
Q. How long?
A. So in the case of the example on the left, which is a small scale reaction, .84 grams of the enyne, was stirred for 03:01 30 minutes; the example on the right is a much larger scale reaction that was stirred for four to six hours at room temperature.
Q. Well, 30 minutes and four to six hours, that's a big difference, isn't it?
03:01 A. Yes, but this is something a person of ordinary skill in the art would expect based on the huge difference in scale of these two reactions. That when you do larger scale reactions everything takes longer or takes longer to pour things together just because the volumes are larger. Often you have 03:02 to stir longer just because it takes longer to mix a larger volume than a smaller one.
Q. What's the difference in scale between the reaction on the left and the reaction on the right?
A. It's something like 2,000 times higher.
03:02 Q. So the Alphora DMF, PTX-333, on the right is more than 2,000 times bigger than the reaction described on the left?
A. Yes.
Q. And what's your next -- what's the next thing you compared with respect to the way analysis?
03:02 A. So, after the complex formation with both processes or

both examples do, there's a time highlighted; the methylene chloride was removed or distilled off. And so what's happening now is there's a solvent change, so we brought the enyne and the dicobalt octacarbonyl together in the solvent dichloromethane, methylene chloride CH2CL2, is the same as dichloromethane; sorry, I threw in another synonym for dichloromethane.

So, methyl chloride was distilled out, and an example on the right, the reaction mixture is vacuum distilled; this is doing the same thing, it's removing not all of, but a significant amount of the dichloromethane solvent.

Q. So what solvent is being used to replace the dichloromethane?

A. The solvent being used to replace is called acetonitrile on the left; again, the example 1 uses the formula CH3CN, and a person of skill in the art would immediately recognize that that's acetonitrile, which is spelled out with the full word in the example on the right, but that's the same solvent.

Q. Then what happens to the reaction mixture?

A. It's then heated, there's a heating step, and so this is when the actual bond formations occur during -- after you form the complex, we change the solvent, and then there's a warming step which then allows the actual chemical transformation to proceed.

Q. Then what happens next?

A. And so after the warming step, the typical procedure is that an organic chemist would go through to remove the solvent, isolate and purify the reaction products from those procedures.

03:04 Q. And how do they do it here, by distillation?

A. So, the -- in the case on the '117 patent example, the solvent was distilled out; the crude mass was dissolved in ether, passed quickly through a short column of neutral alumina, to yield a crude product, they give you a yield of 96

03:05 percent. And in the Alphora example on the right, the reaction mixture was vacuum distilled; again, this is to concentrate the solution to get rid of the solvents, and then they go on to do the isolation purification steps.

Q. So what's your conclusion with respect to the way prong

03:05 in terms of the way that the chemical transformation is accomplished in example 1 of the '117 patent, versus the disclosure in the PTX-333, Alphora DMF, are they the same?

A. They're identical.

Q. They're identical?

03:05 A. Identical.

Q. I just -- I think there may be a typographical error on the -- on the page number for the Alphora DMF.

MR. CARSTEN: Mr. Merisier, would you be so kind to pull up PTX-333. And could you go to the trailing page 8435,

03:06 please.

Q. Is the paragraphs -- the two central paragraphs on page 8435, are those the paragraphs that we just looked at with respect to the Alphora DMF process for the intramolecular cyclization transformation?

03:06 A. Yes. Yes, those look to be the same.

THE COURT: Mr. Carsten, can we stop here?

MR. CARSTEN: We certainly may, your Honor.

THE COURT: All right, thank you.

We'll reconvene tomorrow morning at 10:00 a.m.

03:06 MR. CARSTEN: Thank you, your Honor.

THE COURT: You may step down, Doctor.

THE WITNESS: Thank you, your Honor.

THE COURT: All right. Have a good day.

(Proceedings concluded for the day.)

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

UNITED THERAPEUTICS CORPORATION,

Vs.

SANDOZ, INC.,
DEFENDANT

CIVIL NO.
12-1617 (PGS)
13-316

MAY 13, 2014
CLARKSON S. FISHER COURTHOUSE
402 EAST STATE STREET
TRENTON, NEW JERSEY 08608

B E F O R E: THE HONORABLE PETER G. SHERIDAN
U.S. DISTRICT COURT JUDGE
DISTRICT OF NEW JERSEY

TRIAL - DAY 7

Certified as true and correct as required
by Title 28, U.S.C. Section 753
/S/ Francis J. Gable
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THE COURT: Good morning. Please be seated.
Any applications before we begin?
MR. CARSTEN: No, your Honor.
THE COURT: Mr. Steindler?
10:16 MR. STEINDLER: No, your Honor.
THE COURT: All right. So we'll continue the testimony of the doctor.
(ROBERT M. WILLIAMS, PH.D., previously sworn, resumes stand.)
10:16 THE COURT: So, Doctor, you're still under oath.
THE WITNESS: Yes, sir.
THE COURT: Mr. Carsten, you may continue.
MR. CARSTEN: Thank you, your Honor.
(DIRECT EXAMINATION OF ROBERT M. WILLIAMS, PH.D. CONTINUED BY
10:16 MR. CARSTEN:)
Q. Good morning, Dr. Williams.
A. Good morning.
Q. When we broke yesterday we had been through quite a bit of organic chemistry and a fair bit of heavy sledding. I
10:16 think we ended with the comparison that's presented on demonstrative 37; is that right?
A. That's right.
Q. Now, what was your conclusion after considering the steps of the '117 patent example, Pauson-Khand reaction, and the
10:17 details of the Alphora DMF Pauson-Khand reaction?

A. My conclusion was that the way in which that procedure is done is exactly the same.
Q. Would you agree it's substantially similar?
A. Yes.
Q. Now, just for orientation we're in the middle of the function/way/result analysis that you did with respect to the PMB group that's used by Alphora; correct?
A. Correct.
Q. Okay. In your tutorial you had a slide of a bridge; do you remember that?
A. Yes.
Q. Can -- let's put that up. Can you explain to the Court the Pauson-Khand reaction we've just walked through and walked through yesterday afternoon, how that fits into this demonstrative 38.
A. Yes. The enyne is the starting material for the slide we were just looking at, and the way is the carbonylative cyclization the Pauson-Khand reaction and the product is the cyclized intermediate, so that's the way in which that procedure is done.
Q. Now, do you have an opinion as to whether Alphora went over the same bridge?
A. Yes, they went over the same bridge.
Q. They didn't build another bridge?
A. No.

Q. Why not?
A. Well, because they used the enyne with the exact same structure with the exception of the X protecting group, they did the Pauson-Khand cyclization reaction, the same solvent, the same temperature, the same stoichiometry of the reagents, the same kind of systems, the heating procedure, the solvent change, and they ended up with a stereoselectively produced cyclized intermediate.
Q. You said stoichiometry; what does that mean?
A. I'm sorry; that's the ratio of the substrate to the Pauson-Khand, the dicobalt octacarbonyl reagent.
Q. So the number of equivalents?
A. Right 1.2 to 1 one is the same.
Q. And what's your conclusion with respect to the way prong of your analysis?
A. My conclusion is that Alphora, the way in which they're doing this step, is exactly the same way as the '117 patent claim.
Q. Now, let's turn to the result part of your analysis if we could. I put up demonstrative 39. Is this a demonstrative that summarizes your analysis on that -- on that portion of your analysis?
A. Yes.
Q. Would you please describe this for the Court.
A. So both the '117 patent claim and the Alphora reaction

that we were just looking at both result in a successful and scalable Pauson-Khand reaction that constructs stereoselectively the tricyclic intermediate, and both result in stereoselectively produced treprostinil and treprostinil sodium.

Q. Did the reaction -- was the reaction successful in both circumstances, the '117 patent route as well as the Alphora route?

A. Yes.

Q. And were the results equivalent the same?

A. They were substantially the same.

Q. Did you consider the yields of the Pauson-Khand reaction?

A. Yes.

Q. And what was your finding there?

A. That both procedures result in good yield, at least greater than 59 percent, on roughly comparable scales of about one and a half to two kilograms.

Q. And where did you find that information?

A. So the information for the two kilowatt scale came out of the Alphora DMF, and then the -- that range was obtained from batch records from UTC.

Q. Okay. And so we've got a reference down at the bottom of the slide to PTX-333, at page 8435. That's the Alphora DMF; correct?

A. Yes.

Q. And then we've got a reference to PTX-523 at page 26061; correct?
A. Yes.
Q. And that's the batch records?
A. I believe so, yes.
Q. And PTX-523 is one of the documents you were here in court when Dr. Zaccardelli admitted that document; correct?
A. Yes.
Q. So, what's your conclusion with respect to the results prong of the function/way/result test as applied here?
A. That the use of the PMB group is the -- is the functional equivalent, it meets -- it meets the functional result test.
Q. I may have misspoken; I may have said PTX-523 is a batch record, I think it's an NDA summary.
A. I'm sorry, that's right.
Q. Thank you. Now, we have been talking in part about -- and in the tutorial about a masking tape analogy; did you prepare a slide that sort of lays that out?
A. Yes.
Q. I've got demonstrative 40 on the screen. Would you please explain this to the Court?
A. Yes. So just the way we were talking about in the tutorial the function of protecting groups or masking groups, so I used a tutorial, the masking tape analogy as a protecting group to protect part of the door or the trim around the door

from being exposed to paint. I'm using that analogy here where the methyl group is put on as a protecting group and doesn't participate in the Pauson-Khand reaction. You get a successful stereoselectively Pauson-Khand reaction with the
10:22 methyl protecting group, and then after the tricyclic intermediate is formed it is later removed, to result in a stereoselectively synthesis of treprostinil. And similarly the PMB group is also functioning as a masking group, a protecting group, and is put on, it allows the stereoselective
10:23 Pauson-Khand reaction to proceed to give a stereoselectively produced tricyclic intermediate, which also allows for the synthesis of stereoselectively produced treprostinil and that PMB group is later removed.

Q. So, how do you attach a PMB or para-methoxy benzyl?

10:23 A. Excuse me; there's several ways to do it. The most common way is to use the para-methoxy benzyl chloride, which is an alkaline agent, it's a toxic lachrymator.

Q. What's a lachrymator?

A. It's a severe skin and eye irritant.

10:23 Q. Now, Mr. Steindler at his opening had a slide that showed a couple of test tubes, and one with a skull and cross bones on it; do you remember that?

A. I remember that.

Q. And he said that was a representation of the Moriarty
10:24 '117 process; right?

A. I think it was presented that way, yes.
Q. Now, do the claims require any particular way of removing protecting groups?
A. No.
10:24 Q. Now, this PMB chloride, the PMB chloride reagent that you just talked about, is that a safe chemical?
A. Hardly, no.
Q. Is that used in the Moriarty '117 route?
A. No.
10:24 Q. What route is it used in?
A. It's used in Alphora's route.
Q. Let's turn to the summary slide for claim 1 of the '117 patent in terms of your infringement opinions. Professor Williams what's your final conclusion regarding claim 1 and
10:24 the Sandoz ANDA product, in terms of infringement?
A. My conclusion is that every claim limitation is met, by the Sandoz ANDA product and process.
Q. And you've considered not just the A, B, C and D here, you actually considered the entire claim 1; correct?
10:25 A. Yes.
Q. Is there any doubt in your mind that the Sandoz ANDA product infringes claim 1?
A. I have no doubt.
Q. How many claims are there in the '117 patent?
10:25 A. There's four.

Q. Now, did you analyze the other remaining three claims as well?
A. Yes, I did.
Q. I'd like to put up claim 2 of the '117 patent in demonstrative 42. How does this differ from claim 1?
A. This differs -- it's a dependent claim and it -- the stereoselectively produced isomeric compound referring to claim 1 the substituents are all specified which gives specifically the molecular structure of treprostinil.
Q. Now, there's a variety of elements here, or limitations or variables which are specified, Z equals O, n equals 1, X equals COOH and so on, and this is all found in claim 2; right?
A. Yes.
Q. How did those Zs and ns and Xs and so forth match up with the analysis you did with respect to claim 1 for the stereoselectively produced isomeric compound?
A. So this is what we went through yesterday, and when you plug those substituent variables into the first structure under claim 1, that renders the molecular structure of treprostinil.
Q. Have you rendered an opinion in terms of claim 2 of the '117 patent and whether the Sandoz product infringes claim 2?
A. Yes.
Q. What's your opinion?

A. Yeah, I have the same opinion, that the Alphora process infringes claim 2.
Q. And does that opinion differ in any way from your opinion with respect to claim 1?
A. No.
Q. Now, let's turn to claim 3 of the '117 patent. Did you analyze claim 3?
A. Yes.
Q. How does claim 3 differ from claim 1?
A. Claim 3 begins with again the adjectival phrase, stereoselectively produced isomeric compound according to the following formula; and now a single formula is given with no variables, and that is a drawing of the molecular structure of the treprostinil molecule.
Q. We're talking about the first structure?
A. Yes.
Q. Depicted there, that's the final product compound?
A. Yes.
Q. And what is that?
A. That's treprostinil.
Q. Now, did you reach any conclusions with respect to the infringement of Sandoz's ANDA product with respect to claim 3 of the '117 patent?
A. Yes, my conclusion is that the Alphora product infringes claim 3.

Q. And what's the basis for that opinion, is it the same or different from claim 1?
A. It's the same analysis I did for claim 1.
Q. Let's turn to claim 4 of the '117 patent. How does this
00:28 claim differ from claim 3 to -- in your analysis?
A. So, claim 4 reads a stereoselectively produced isomeric compound in pharmacologically acceptable salt form, so again the molecular structure of the treprostinil molecule is shown as the first structure, but a person skilled in the art would
00:28 understand that the carboxylic acid is a pharmacologically acceptable salt form as we discussed yesterday.
Q. And what's your conclusion with respect to Sandoz's ANDA product and its infringement with respect to claim 4 of the '117 patent?
00:28 A. Yes, my conclusion is that the Alphora product also infringes claim 4 of the '117 patent.
Q. And what's the basis for that conclusion?
A. It's the same analysis that I did for claim 1.
Q. Now, you heard Mr. Steindler talk about narrow claiming
00:29 in connection with the arguments on one of the motions in limine last Friday; correct?
A. Yes, I was in court.
Q. And he represented to the Court that the variable X in claim 1 covered 15 to 20 compounds; do you remember that?
00:29 A. Yes.

Q. Did you -- do you agree with that first of --

A. No.

MR. STEINDLER: Objection, your Honor. There is nothing in this witness' expert report that addresses narrow claiming. Not in his expert report, not in his deposition.

THE COURT: Well, you brought it up last week; right?

MR. STEINDLER: I haven't waived my objection to this witness talking about it, it's -- you've already ruled that if it's not in his expert report and not in his deposition, then they can't talk about it.

MR. CARSTEN: Your Honor, yes, it is actually in his expert report, the fact that United Therapeutics did not narrowly claim at the Williams reply report at paragraphs 131 to 132.

MR. STEINDLER: In paragraphs 131 to 132 all that is there is the statement that it's not narrowly claiming. There is no analysis, there's no -- there's nothing in there that presages what's now about to be described and testified to by this witness in these slides. They just have that bald statement and that's it.

MR. CARSTEN: /TPHADZ your Honor, we never heard before that they believe that X contained 15 to 20 compounds. We're entitled to rebut that factual misrepresentation to the Court by counsel for Sandoz.

THE COURT: All right. Overruled.

You may answer the question, Doctor.

BY MR. CARSTEN:

Q. So, do you agree with that analysis that was presented to the Court as fact that X includes 15 to 20 compounds?

A. I do not agree.

Q. What did you do?

A. I made a demonstrative and I did a very conservative analysis of that issue.

Q. I'm presenting to you slide 45, a demonstrative 45. What is this?

A. So, this is a picture of the tricyclic intermediate from claim 1, and I've highlighted in red Z(CH2)nX, and I decided to do a very very conservative analysis of how many molecular entities would be covered by that descriptor; and I fixed Z as oxygen, even though the claims allow Z to be four different types of variables, oxygen, sulphur, CH2 or NR8, so I narrowed my analysis to just Z equals to oxygen.

And then the CH2 variable has a small n, which is equal to zero, one, two, or three, so that's four possibilities there. And then for the X limitation in the claim it's defined as hydrogen, CN which is a cyano or nitrile group, and COOR9, and the claim defines R9 further as hydrogen H, alkyl pharmacologically acceptable cation; THP, which is the acronym for the tetrahydro pyranol protecting group, or TBDMS, which

is the acronym for tert-butyl methyl silyl. So I restricted the alkyl variable there to just carbon C1 through C6, although alkyl covers larger groups than six carbons, but just to make it a very conservative analysis I restricted the alkyl groups to C1 through C6 which I also have demonstrative on.

Q. Let's go there, let me show that. What is shown on demonstrative 46?

A. Okay. So this is -- these are the alkyl groups, so-called straight chain alkyl groups of six carbons or less. And so there's actually 44 combinations of C1 through C6 carbons that do not include cyclo-alkyl type groups, so these are so-called straight chain alkyl groups, and a person of ordinary skill would understand that alkyl means these types of groups, alkyl groups.

Q. So let's go back to slide -- demonstrative 45, your analysis here. With that conservative estimate on alkyl, did you reach a conclusion as to roughly how many compounds were within the scope of the (CH2)nX moiety here within the scope of claim 1?

A. Yes. So taking that -- those 44 alkyl possibilities and the pharmacologically acceptable cations that are disclosed in the '117 patent, do the math and you come up with 436 distinct chemical entities.

Q. Now, you've included the variable ability of n there was being zero, one, two, or three, so that's four possibilities;

right?
A. That's right.
Q. Now, if we're superconservative and take out the n's variables, just select one of them, and just focus on the X with your conservative estimate, how many structures are within the scope of X?
A. A hundred and nine.
Q. A hundred and nine. Earlier you testified about the book, the Green and Woods book, which was the book on protecting groups which is in evidence; do you remember that?
A. Yes.
Q. Does that list alcohol protecting groups?
A. Yes.
Q. About how many alcohol protecting groups are in Green and Woods?
A. It varies from edition to edition, the one that I was using I think has somewhere around 200 hundred; a hundred 65; I don't remember the exact number.
Q. In your opinion did United Therapeutics narrowly claim the Z(CH2)nX portion of -- of the claim in claim 1?
A. No, not at all, no.
Q. Would a person of ordinary skill in the art think that that claim was written narrowly?
A. No.
Q. With respect to just the X prong, leaving aside Z,

leaving aside (CH2)nX, would a person of ordinary person of ordinary skill in the art believe that United Therapeutics had claimed the X part of claim 1 narrowly?

A. No.

10:35 Q. Why not?

A. Well, as you can see from the X variable, which is HCN or COOR9, the R9 has H alkyl pharmacologically acceptable cation THP or TBDMS, and this is -- leads to an explosion literally of the number of chemical entities that one could get.

10:36 Q. Let's turn to claims -- go back to summarizing your analysis with respect to claims 2 through 4. What is the slide I put up here, slide 47, in your demonstrative exhibits?

A. This is just summarizing my opinion that Sandoz's ANDA product and process infringes claims 2 through 4 of the '117

10:36 patent.

Q. Now, let's turn very briefly to your opinions -- well, before I do that is there any doubt in your mind about the infringement of 2, 3 and 4 by Sandoz's ANDA product?

A. I have no doubt.

10:36 Q. Now, let's turn very briefly to your opinions on induced infringement. What's your understanding in connection with your work in this case of the Alphora/Sandoz relationship?

A. My understanding is that Alphora, which is a company located in Canada, is the contract manufacturer that's doing

10:37 actual synthesis of the treprostinil and treprostinil sodium,

the API for Sandoz's proposed ANDA product.
Q. And did you see any submissions to the FDA regarding Alphora and Sandoz, and Sandoz's ability to incorporate by reference into their ANDA the Alphora material?
00:37 A. Yes.
Q. I'd like to put up here page 8371 from PTX-333 in evidence. Is this one of the documents that you considered in connection with evaluating that relationship?
A. Yes.
00:37 Q. And what is this?
A. This is a letter from Alphora to the Food and Drug Administration, where Alphora is authorizing Sandoz, Incorporated to incorporate by reference the drug master file for API, the active pharmaceutical ingredient, treprostinil
00:38 sodium, in the abbreviated new drug application, the ANDA, for treprostinil injection, and it gives a 200 mg per 20 mil, and 10 mg per mil dose forms in the letter.
Q. Now, the Sandoz's, Inc. there, that's not Sandoz Canada, is it?
00:38 A. I believe that's Sandoz United States.
Q. And in connection with your evaluation of Sandoz, Inc.'s abbreviated new drug application, did you see anything in there that referred to the Alphora DMF as being the applying supplier of the method and details of the method?
00:38 A. Yes.

Q. This is from PTX-250, the Sandoz ANDA at page 279; is this a document you considered in connection with your analysis?
A. Yes.
10:38 Q. And what does this say?
A. So this -- highlighted at the bottom it shows for more details about the manufacturing process and process controls; the figures just above show some of the transformations of the process, and here it says for more details about the
10:39 manufacturing process and process controls, please refer to Alphora's DMF for treprostinil sodium.
Q. Did you see any evidence submitted to the FDA about Alphora designating a particular entity to be its agent before the FDA with respect to the DMF?
10:39 A. Yes, I did.
Q. I'd like to show you a document from PTX-333, page 8373. What is this?
A. This is a letter from Alphora to the FDA, where they're confirming that Bernadette Attinger, director of regulatory
10:39 affairs for Sandoz, has been authorized as the official U.S. agent in matters pertaining to the above DMF on behalf of Alphora Research.
Q. And this is Sandoz U.S.; correct?
A. Yes.
10:39 Q. Now, you understand that Alphora's in Canada; right?

A. Yes.
Q. Does that affect your infringement analysis at all?
A. No.
Q. Why not?
10:40 A. Well, because even though the synthesis is being conducted in a foreign country, they're going to import the infringing product into the United States.
Q. Now, let's go to slide 51. And this is just intended to be a summary slide. Professor Williams, would you please
10:40 summarize for the Court your conclusions with respect to claims 1, 2, 3 and 4, and the infringement opinions you've got with respect to the Sandoz ANDA product?
A. So my opinion simply is that Sandoz's ANDA product and process infringes all four claims of the '117 patent.
10:40 Q. Now, a final couple of questions. During the course of our testimony we've used terms like compound and formula and structure, and the '117 patent uses the word compound, doesn't it?
A. Yes.
10:40 Q. When you're in your lab and you have your student in your office and you say hey, draw the structure or draw the compound treprostinil on the board, what do they do?
MR. STEINDLER: Objection to form.
MR. CARSTEN: I can rephrase, your Honor.
10:41 THE COURT: Okay, rephrase.

BY MR. CARSTEN:

Q. When you're in your office and you have a student and you ask the student to draw a compound on the board, what do they do?

10:41 A. They would draw the molecular structure with the relevant stereochemistry using the conventions that we talked about; the straight lines would be in the plane of the blackboard and darkened wedges would be projections toward me and hash lines would be projections behind the board, but they would draw a 10:41 single structure of that compound so that -- when that word compound is being used it's being used in a molecular structural context, and we use it in everyday conversation, a person skilled in the art uses the word compound in that molecular structural context.

10:41 Q. Now, what if you said instead to the student hey, bring me the compound treprostinil, what would the student do?

THE COURT: Why are we referring to a student?

MR. CARSTEN: Just I'm picking something that happens to Professor Williams every day. I can rephrase, your 10:42 Honor.

THE COURT: How about the POSITA, a person of ordinary skill in the art?

MR. CARSTEN: I'll rephrase to exactly address your concern, your Honor, thank you.

10:42 BY MR. CARSTEN:

Q. What if you were speaking to a colleague, one who qualified as a person of ordinary skill in the art, and you asked them to draw the compound treprostinil on the board, what would they do?

10:42 A. Well, exactly what I just said, and actually post-docs in my group qualify as persons skilled in the art, so I have this type of conversation on a daily basis with my post doctoral fellows.

THE COURT: Well don't some of them have to have two

10:42 years of experience or something of that nature, do they have that?

THE WITNESS: Oh, yes.

Q. And now with respect to this colleague, this hypothetical colleague who qualifies as a person of ordinary skill in the

10:42 art, if you said to them or asked them please bring me the compound treprostinil, what would they do?

A. Well, now we're talking about the real world compound that's made by the chemical reaction or some process, so I would expect him to bring me a bottle or a flask of real world

10:43 compound, and we would both understand that that flask or bottle does not -- is not constituted of one hundred percent only the molecular structure that we were just talking about, it would have impurities, stereoisomeric impurities in there.

Q. Have any of your colleagues, people who qualify as

10:43 ordinary skill in the art, has anyone brought to you a bottle

of a compound that was one hundred percent pure?
A. No, never, it's not possible.
Q. Have you ever made a compound that's a hundred percent pure in your 35, 40 years of chemistry experience?
10:43 A. I wish, but no, it's not possible.
Q. In which sense of compound is this term being -- this term compound being used in the '117 patent claims?
A. With respect to the claims the word compound is being used to describe the real world compound that's produced by
10:44 chemical reaction process, the '117 patent process. So we're talking about real material that you can see, weigh, formulate, put into a patient, it's a real chemical material.
Q. Any doubt in your mind about that?
A. No, doubt.
10:44 MR. CARSTEN: Pass the witness, your Honor.
THE COURT: All right, thank you.
Cross?
(CROSS-EXAMINATION OF ROBERT M. WILLIAMS PH.D. BY MR. STEINDLER:)
10:44 Q. Good morning, sir.
A. Good morning.
Q. The active pharmaceutical ingredient for Sandoz's ANDA product is made by Alphora outside the United States; right?
A. That's my understanding.
10:44 Q. You agree with me that we can refer to active

pharmaceutical ingredient by the phrase API; right?
A. Yes.
Q. And after Alphora makes the API it sends it to Sandoz Canada; right?
A. That's my understanding.
Q. Sandoz Canada then formulates the API into a final drug product; right?
A. Yes.
Q. And when Sandoz Canada formulates the API into the final drug product, it mixes the API with other ingredients; right?
A. Yes.
Q. And the API is heavily diluted in Sandoz's ANDA product; right?
A. Yes, it's ready-made for clinical administration.
Q. Right. And it's only that finished ANDA product that's going to be imported into the United States; right?
A. Yes, that's my understanding.
Q. Now, with respect to this last argument you made about induced infringement, who's inducing who under your theory?
A. Well, certainly Alphora is interested in selling their manufactured treprostinil and treprostinil sodium to Sandoz, and Sandoz has contracted Alphora to make that molecule for them, so it's a complimentary business relationship.
Q. Who's the inducer?
A. I would say Sandoz.

Q. Sandoz is inducing Alphora; is that your theory for induced infringement?
A. My theory; I'm not sure I understand your question.
Q. Well, you offered an opinion that there was induced infringement, and I'm just trying to understand who you contend is the inducer and who is the direct infringer.
A. Well, I mean -- so Alphora is using the '117 patent process to make the drug, they're going to sell it to Sandoz Canada which then is going to transfer that to Sandoz U.S., so Sandoz U.S. I guess ultimately is the inducer.
Q. So, it's your contention that Sandoz U.S. is inducing Alphora to infringe the '117 patent; is that your theory?
A. Well --
MR. CARSTEN: Your Honor, we're still talking about theories here; he's got opinions. I don't understand the question.
THE COURT: You don't understand the question? Could you rephrase then?
MR. STEINDLER: Sure.
BY MR. STEINDLER:
Q. Is it your opinion for induced infringement that Sandoz is inducing Alphora to infringe the '117 patent.
THE COURT: If you know.
A. Well, I'm not a legal expert or a lawyer on this, but my understanding is I think it's very simple that Sandoz U.S. is

going to pay ultimately Alphora for the API that they make. So -- and they know that it's being made by the '117 patent process. So, it seems reasonable to me that Sandoz U.S. is ultimately inducing -- is inducing infringement by Alphora.

10:48 Q. You understand that U.S. patents are territorial and that you can only infringe a U.S. patent by activity or conduct in the United States; correct?

MR. CARSTEN: Your Honor, this is a legal conclusion.

10:48 MR. STEINDLER: He's offered an opinion as to induced infringement, and I'm asking his understanding of the law.

THE COURT: Well, wait; Frank, can you repeat the question?

10:48 (Questioned read back.)

THE COURT: Do you understand that?

THE WITNESS: Yes, I understand the question. And my understanding --

THE COURT: Wait a second. So you're saying it

10:49 calls for a legal conclusion?

MR. CARSTEN: Exactly, your Honor.

THE COURT: And he's not a lawyer of any type; right, Mr. Steindler?

MR. STEINDLER: Sure.

10:49 THE COURT: So, but you were asking if he understood

that to be the law.

MR. STEINDLER: That's correct, because he's rendering an opinion about infringement. And I'm trying to understand the basis for his opinion about infringement.

10:49 THE COURT: I guess Mr. Steindler's question is do you understand that that could be a provision of the law; I don't know whether that's part of your interpretation or not.

THE WITNESS: Well, my understanding is that the activity is the importation of the product into the United

10:49 States. So, I guess I don't really understand --

THE COURT: All right. Next question. He doesn't understand.

BY MR. STEINDLER:

Q. You also understand, though, that Alphora will not import

10:50 its API into the United States; correct?

A. So your question was that Alphora will not import; yeah, that's my understanding, Sandoz Canada that will transfer the API to Sandoz U.S.

Q. So all of Alphora's conduct in this case takes place

10:50 outside the United States; correct?

A. Yes.

Q. So, if you were to assume that the law is that you cannot infringe a U.S. patent by conduct that's entirely outside the United States, Alphora cannot be infringing the '117 patent;

10:50 right?

A. No.
Q. So Alphora's API never is imported directly in the United States; right?
MR. CARSTEN: I object to the form of the question. That misrepresents the evidence in the case, your Honor.
THE COURT: Well, what was the evidence, because --
MR. CARSTEN: The evidence that was put on yesterday by Dr. Skoumboudis was that the Alphora API goes to Sandoz Canada, gets formulated and then would be imported into the United States. That's an absolute misrepresentation of the evidence. Your Honor.
THE COURT: All right, sustained.
MR. CARSTEN: Thank you.
BY MR. STEINDLER:
Q. Alphora never ships its API as API into the United States; right?
A. It's done -- no, that's right, it's done through Sandoz Canada, to Sandoz U.S.
Q. And the -- that API gets formulated into this finished product in highly diluted form; correct?
A. Correct.
Q. So Alphora itself doesn't engage in activity that comes into the United States directly; correct?
A. No.
Q. Why not?

A. Well, they synthesize the API, they sell it to Sandoz Canada and Sandoz Canada then imports it into the United States. So to be -- to be --

Q. Now, your infringement analysis --

10:52 THE COURT: Well, wait; he didn't finish his answer. Go ahead, Doctor.

THE WITNESS: So, to me it seem immaterial how many chains of ownership there are outside the U.S., once it's crosses the border, but I'm not a lawyer, so --

10:52 BY MR. STEINDLER:

Q. Now, your infringement analysis is directed to Sandoz's ANDA product that's imported into the United States; right?

A. So your question again please?

Q. The infringement analysis that we just heard from you, is

10:52 directed to the finished Sandoz ANDA product that will be imported into the United States; right?

A. Yes.

Q. And you contend that Sandoz's ANDA product infringes the '117 patent claims because it contains the treprostinil

10:53 compound made by a process that you say is equivalent to the process claimed in the '117 patent; right?

A. That was a long question; could you please --

THE COURT: He didn't understand it. Would you rephrase?

10:53 MR. STEINDLER: Sure, I'm happy to repeat it.

BY MR. STEINDLER:
Q. You contend that Sandoz's ANDA product infringes the '117 patent claims because it, the Sandoz ANDA product, contains the treprostinil compound, made by a process which you say is
10:53 equivalent to the process of the '117 patent; correct?
A. Correct.
Q. And you also contend that Sandoz's ANDA product infringes the '117 patent because it contains the acid form of treprostinil in very small amounts; right?
10:54 MR. CARSTEN: I object, your Honor; that's beyond the scope. We didn't talk about the intermediate product at all in terms of its presence in the final compound.
THE COURT: Well, if the doctor understands the question, I'll let him answer it.
10:54 THE WITNESS: Could you please ask me the question one more time please?
BY MR. STEINDLER:
Q. Sure, the question is a simple one. You recall in your testimony you talked about the acid form of treprostinil and
10:54 how it's in an equilibrium with the sodium form; correct?
MR. CARSTEN: Withdraw the objection. I apologize for --
Q. Let me ask the question again. You also contend that Sandoz's ANDA product, infringes the '117 patent because it
10:54 contains the acid form of treprostinil in very small amounts;

right?
A. Yes.
Q. Now, just to be clear, you agree with me that Sandoz's ANDA product does not literally infringe any of the claims of
10:55 the '117 patent; correct?
A. So my analysis uses the doctrine of equivalents and I did not -- I did not opine that it was literal infringement, that's correct.
Q. Can you go to slide 27. You recall with respect to bands
10:55 B and C -- strike that.
Your slide 27 sets out the four components of claim 1 that you address in your direct testimony; right?
A. Yes.
Q. Now, with respect to segments B and C, and D, you were
10:55 asked on direct whether Sandoz's ANDA product and process meets the claim limitation of each of these B, C and D; do you recall that?
A. Yes.
Q. And just so that we're clear, Sandoz's ANDA product
10:56 doesn't literally meet any of the B, C or D limitations; correct?
A. Not literally, but under the doctrine of equivalents it does.
Q. Now, with respect to your limitation A, limitation A
10:56 defines a stereoselectively produced isomeric compound

according to the following formula, and it sets out this specific chemical formula; correct?

A. Yes.

Q. And in your analogy that you used at the end of your testimony, that chemical formula here (indicating) refers to a particular compound; correct?

A. Could you please repeat the -- I'm not sure I understood your question.

Q. The chemical formula set out in claim 1, refers to a specific chemical compound; correct?

A. Well, no. So that formula is a more generic form that that has substituent variables, and that formula as written can correspond to not just one chemical compound, which I think is what you asked me, it can be used to describe other analogs of treprostinil.

Q. But it includes within the class claimed by this generic formula, the specific treprostinil compound; correct?

A. Yes. The molecular structure of treprostinil is embodied within that sort of general formula.

Q. And that would be the specific treprostinil compound; right?

A. Well, that would be the specific molecular structure, the molecular entity of treprostinil, yes.

Q. And according to the way in which you would ask your graduate student or your post-doc who is a person of ordinary

skill in the art to write the treprostinil compound, that's how they would write the treprostinil compound; right?
A. Well, no, I don't think they would draw that formula, they would draw the exact molecular structure of the
10:58 treprostinil molecule.
Q. And the exact molecular structure of the treprostinil molecule is what is depicted in claim 3 of the '117 patent; right?
A. Yes.
10:58 Q. Now, when you did your infringement analysis for limitation A, what you did was to compare the compound, depicted here in the '117 patent claim, with the compound depicted in Sandoz's ANDA, and Alphora's DMF; right?
A. That was an extremely long question; could you just maybe
10:59 parse it for me?
Q. Sure. Let's go to claim -- slide 15. Just start your infringement analysis. Are you with me?
A. Yes.
Q. So, your infringement analysis for limitation A, involved
10:59 comparing the compound, depicted in the '117 patent claim, with the compound depicted in Sandoz's ANDA, and Alphora's DMF; correct?
A. Yes. So the analysis here was to verify that the molecular structure of the treprostinil molecule, that's
11:00 reflected in Sandoz's ANDA and Alphora's DMF, read on the

general formula that is shown in claim 1 of the '117 patent. And my analysis showed that the structure shown in the two boxes on the upper right in fact do read on that generic formula on the left, when you plug in the substituent variables shown.

Q. And the compound depicted as Sandoz's ANDA is a specific chemical compound; correct?

A. Well, the product of Sandoz's ANDA is a real world compound with characteristic impurities, it's not constituted of just the molecular entity that you're pointing to in the box.

Q. Well, when you did your infringement analysis all you did was compare the structural formula of Sandoz's ANDA to the structural formula set out in the '117 patent claim; correct?

A. No, that's not correct, that's not all I did; that's one of the things I did.

Q. When you were identifying how limitation A in your analysis is met, what you did was compare the chemical formula set out in the '117 patent, to the exact chemical formula set out in the Sandoz's ANDA and Alphora's DMF; correct?

A. Yes, that's the API.

Q. Actually this is not the API, this is Sandoz's treprostinil compound that is included in the API; right?

A. Well, the sodium salt of treprostinil when it's administered to patients, even the sodium salt when it gets

into the bloodstream which is pH 7 is going to equilibrate with the acid, and my understanding is that these types of hormones actually bond the their receptor in the acid form. So in terms of the active pharmaceutical entity, the sodium
01:02 salt is rendered to make the compound water soluble, but in terms of biological activity it's actually the carboxylic acid that's important.

Q. When you did your infringement analysis for the limitation A, all you talked about was this specific chemical
01:03 molecule, the treprostinil compound; correct?

A. Well, as I just said, I verified that the -- what Sandoz has represented in their ANDA and Alphora represented in their DMF as the treprostinil, I just carefully showed that that molecular structure corresponds to the formula in the '117
01:03 patent with those substituent variables.

Q. And just to be clear, this molecular structure for the treprostinil compound in Sandoz's ANDA, (indicating) and this identical molecular structure for the treprostinil compound in Alphora's DMF, is just treprostinil it doesn't include the
01:03 impurities; correct?

A. No, so if we're talking about again the word compound in the molecular structural context, we'd only be talking about a single isomer of treprostinil, the one shown on the slide. But Sandoz's ANDA and Alphora's DMF are describing the
01:04 synthesis and formulation of a real compound made by a real

chemical process. So, characteristic impurities have to be there.

Q. But when you did your analysis for infringement purposes of limitation A, you didn't discuss impurities at all, you only focused on this single specific chemical molecule, the treprostinil compound depicted in Sandoz's ANDA and Alphora's DMF; correct?

A. Yes, the stereoselectively produced isomeric compound.

Q. Let's go to the next slide. Again, when you in your infringement analysis were identifying and proving a stereoselectively produced isomeric compound is disclosed in Sandoz's label, you simply referred to the exact molecular structure of the treprostinil compound; correct?

A. Your question one more time?

Q. Sure.

A. I think you're losing me here, I'm sorry.

Q. When you did your infringement proofs, for limitation A, to identify a stereoselectively produced isomeric compound, the proofs that you presented were the precise chemical structure of the treprostinil compound, in Sandoz's label; correct?

A. Well, I looked at the molecular structure of the compound that is shown here, I also looked at the starting material and the way it was made.

Q. But I -- I'm only talking about your proofs for

limitation A.

A. Okay.

Q. Okay? And when you got to your proofs for limitation A, for a stereoselectively produced isomeric compound, your proofs for infringement of that limitation were just the specific chemical molecule that is the treprostinil compound; correct?

A. I'm sorry, Mr. Steindler, I don't understand your question.

THE COURT: All right, next question.

Q. Let's go to slide 20. When you offered up your proofs as to why Sandoz's ANDA product and process met limitation A of a stereoselectively produced isomeric compound, those proofs were limited to showing that the specific chemical structure for treprostinil, was present in Sandoz's ANDA product; right?

A. Could you please repeat back that question?

THE COURT: Frank, can you repeat the question?

(Question read back.)

THE WITNESS: So again, the analysis I did was to just confirm that the major product of Sandoz's ANDA, Alphora's synthesis process, contains the molecular structure corresponding to what's shown in box A, when you plug into the appropriate substituent variables.

BY MR. STEINDLER:

Q. Let's go back to slide 15. Slide 15, your slide 15,

these are the proofs that you presented for why limitation A was met; right?

A. That was part of the analysis, yes.

Q. And the proofs that you're offering up for why limitation A is met is because this specific molecule (indicating) is present in Sandoz's ANDA product; right?

A. Well, like said what I did here was to unambiguously demonstrate that the structure shown in -- the molecular structure shown in the two boxes in the upper right, read directly on the more generic formula shown, the first formula shown in claim 1 of the '117 patent, when you plug in the variables shown in the box at the bottom, and I verified that they match.

Q. And the product depicted here for -- in Sandoz's ANDA and Alphora's DMF, is a single specific chemical compound, treprostinil; right?

A. No.

Q. It's your testimony that what's in Sandoz's ANDA and what's in Alphora depicted in these chemical structures is not a single compound?

A. So, my understanding is that Sandoz's ANDA product, the real world product, is constituted mostly of what's shown in the box, the molecular structure shown in the box, but it also contains characteristic impurities that are a signature of its manufacture which includes stereoisomeric impurities. So at

least the way I understood your question that was the way -- my best answer for it.

Q. This chemical structure that you used in your proofs is a single specific chemical molecule the treprostinil compound; correct?

A. That molecular structure as drawn certainly corresponds to the single molecular structure that has been assigned the name treprostinil, yes. So that's the molecular structural context that we're talking about.

Q. And the treprostinil that's depicted here is a single specific chemical molecule; correct?

A. I thought my answer was very clear, but that what's depicted in the box is a two dimensional representation that chemists use to describe the molecular structure of the molecule that has been assigned the name treprostinil.

Q. And that molecule that's been assigned the name treprostinil, is a single specific chemical molecule; correct?

A. Well, none of the other 32 stereoisomers that I showed in the tutorial are named treprostinil. If that's what you're asking me.

Q. No. I'm asking a very simple question. This treprostinil compound is a single specific chemical molecule; correct.

MR. CARSTEN: Your Honor, it's had been asked and answered I don't know how many times now.

THE COURT: All right. You may -- this is the last time, but you may answer it this time, Doctor. We have been through this a few times.

THE WITNESS: Could you please ask me your question one more time?

BY MR. STEINDLER:

Q. Sure. The treprostinil compound that's depicted here on the screen is a single specific chemical molecule; correct?

A. So again, if you're asking me about the molecular structural context the answer is yes. If you're asking me about treprostinil compound, real world compound made in the manufacturing facility, it is not constituted of one hundred percent the structure shown in the box, it's impossible.

Q. Now, you understand that treprostinil sodium is a very small percentage of Sandoz's ANDA; right?

A. Your question again was?

Q. You understand that the treprostinil sodium, is a very small percentage of Sandoz's ANDA product.

A. Well, it's one -- it's almost one hundred percent of the API.

Q. Your infringement proofs are directed to Sandoz's ANDA product; correct?

A. Yes.

Q. And you understand that treprostinil sodium is a very small percentage of Sandoz's ANDA product; correct?

A. So now you're talking about the diluted formulation? Is that --

Q. I'm talking --

THE COURT: You don't understand the question, Doctor?

THE WITNESS: I didn't understand the question.

THE COURT: All right. Next question.

BY MR. STEINDLER:

Q. Your infringement analysis is entirely directed to contending that Sandoz's finished ANDA product infringes the '117 patent claims; right?

A. Yes.

Q. And you understand that treprostinil sodium is a very small percentage of Sandoz's finished ANDA product; correct?

A. Well, as I just said it's percentage by weight in the formulation, which is mostly water, but it's almost one hundred percent of the active pharmaceutical ingredient.

Q. You don't contend that the active pharmaceutical ingredient infringes the '117 patent; right?

A. No, that is my contention.

Q. In claim -- in slide 15, your infringement proofs with respect to the infringement of the '117 patent relate to Sandoz's ANDA product and Alphora's DMF product; correct?

A. Yes.

Q. And so, again, your infringement opinions all are

directed to Sandoz's finished ANDA product; right?
A. Yes.
Q. And you understand that treprostinil sodium is a very small percentage of Sandoz's finished ANDA product; right?
01:14 A. So, the best way I can answer this is that, again, the small percentage is the API, and you can't disguise it or make it disappear by diluting it. I mean it's formulated ready for clinical use, so it's in a solution. But the API, the drug that's in that solution is the stereoselectively produced
01:15 isomeric compound that's made by the '117 patent process.
Q. But you understand that the API is a very small percentage of the finished Sandoz's ANDA product that you contend infringes the '117 patent claim; correct?
A. So you're asking me percentage by weight in --
01:15 THE COURT: You don't understand the question?
THE WITNESS: I don't understand the question; I'm sorry.
THE COURT: All right, next question.
BY MR. STEINDLER:
01:15 Q. All right. So, let's turn to DTX-28, please. Can you pull it up?
MR. STEINDLER: May I approach, your Honor?
THE COURT: You may.
(Handing to witness and Court.)
01:16 THE COURT: Thank you.

BY MR. STEINDLER:

Q. DTX-28 is an excerpt from Sandoz's ANDA. And it includes an amendment dated December 7, 2012; do you see that?

(Witness reviewing.)

01:16 A. Yes, I see the date.

Q. And you see that on the page Bate stamped 10688, there's this cover letter that's submitting this amendment to the FDA; correct?

A. Yes.

01:17 Q. Would you turn to the page Bate stamp 10811. Are you with me?

A. Yes.

Q. You see that on this page it sets out in table 1 the components and composition for Sandoz's treprostinil injection

01:17 products; correct?

A. Yes.

Q. And these products will be Sandoz's ANDA products; right?

A. Yes.

Q. And in this table 1 it sets out the percentages of

01:17 treprostinil sodium that are in Sandoz's ANDA product; right?

A. Yes.

Q. And you see that for the one milligram per milliliter dosage treprostinil sodium will only be present in 0.01 percent; right?

01:18 A. On a weight per volume basis, yes.

Q. You see that for the 2.5 milligram per milliliter dosage, treprostinil sodium will be present at 0.025 percent; right?
A. I see that.
Q. For the five milligram per milliliter dose, treprostinil sodium will only be present at 0.050 percent; correct?
A. I see that, yes.
Q. And for the 10 milligram dose, treprostinil will only be present at 0.10 percent; right?
A. Yes.
Q. So, for the highest percentage that treprostinil sodium will be present in any of Sandoz's ANDA products, is .1 percent; correct?
A. Yes, but as I said before it's virtually one hundred percent of the active ingredient.
Q. You understand that the API is never imported directly alone into the United States; right?
A. Directly alone; what do you mean -- I don't understand that question.
Q. You don't understand that. Alphora doesn't take its API and send the API by itself into the United States ever; right?
A. Do you mean like as a solid?
THE COURT: He doesn't understand the question. Next question.
Q. Your infringement analysis which you've said is based on Sandoz's ANDA product, is directed to less than .1 percent of

the treprostinil sodium being present in the Sandoz product; right?

A. No, my infringement analysis is directed to what the drug is. I mean the water isn't the drug, the drug is the active pharmaceutical ingredient, it's the molecule that gives its therapeutic effect, and so diluting it does not change my analysis or opinion.

Q. So, it's your opinion that Sandoz's ANDA product meets the product limitations of the '117 patent, even though it's less than .1 percent treprostinil sodium in Sandoz's ANDA product; right?

A. The question one more time, please?

Q. Sure. For purposes of infringement, it's your opinion that Sandoz's ANDA product meets the product limitations of the '117 patent, even though treprostinil sodium is present in Sandoz's ANDA product at less than .1 percent; correct?

A. Well, yes, but it's because it's -- the API is all the treprostinil sodium -- or it's mostly the treprostinil sodium.

Q. And treprostinil sodium is not in a pure form in Sandoz's ANDA product; correct?

A. Well, it's certainly dissolved in water and I know there are other excipients in there, so it's -- that formulation is not one pure molecular entity. It's a mixture of things.

Q. Now, I believe you testified that the acid form of treprostinil that's present in Sandoz's ANDA product, also

infringes the product limitations of the '117 patent; right?
A. Yes.
Q. And I believe you testified that the acid form in treprostinil is -- is contained in trace amounts, 1/10,000ths
01:22 of the amount of treprostinil sodium; right?
A. Yes, they're in a equilibrium.
Q. And so in Sandoz's ANDA product that you contend infringes the '117 patent claim, the acid form is contained in 1/10,000ths of .1 percent of the product; correct?
01:22 A. That would be correct, they're in equilibrium.
Q. So, for purposes of infringement, it's your contention that the Sandoz's ANDA product will infringe the '117 patent claims by having even trace amounts of the acid form of treprostinil; correct?
01:23 A. Yes, but they're in equilibrium, so all of the molecules are rapidly inter-converting, the acid and the salt form are rapidly inter-converting, and making the salt is not an irreversible reaction. You can change the pH and now have a substantial amount of the acid if you go to lower pH.
01:23 Q. So for purposes of infringement, it's your contention that a product meets the claims of the '117 -- strike that.
For purposes of infringement, it's your opinion that Sandoz's ANDA product meets the product limitations of the '117 patent, even where it has just trace amounts of
01:24 treprostinil acid in the product; correct?

A. That's correct.

THE COURT: Mr. Steindler, can we take a break here?

MR. STEINDLER: Absolutely.

THE COURT: All right. So we'll break for 10 minutes and we'll be back out.

You may step down, Doctor.

(Recess.)

THE COURT: Please be seated.

Doctor, you may take the stand. You're still under oath, Doctor.

THE COURT: You may continue, Mr. Steindler.

MR. STEINDLER: Thank you. I move in evidence DTX-28.

MR. CARSTEN: Your Honor, I believe this is part of the Alphora DMF, so it's already in evidence, but I have no objection to this document coming in if you want the duplicate.

THE COURT: So, it's admitted -- it's only a portion --

MR. CARSTEN: That's correct, your Honor.

THE COURT: So DTX-28 is admitted.

(Defendant's Exhibit 28 was marked into evidence.)

MR. STEINDLER: Thank you.

BY MR. STEINDLER:

Q. A person of ordinary skill in the art, would understand

that a compound refers to a single specific chemical molecule; correct?

A. No, it depends on the context, how the word compound's being used.

01:58 MR. STEINDLER: Can we go to the patent, please. PTX-2. Go to claim 3. Let's just blow up the structure of claim 3.

Q. In claim 3, the word compound is being used to describe a compound according to a specific formula that's set out in

01:58 claim 3; correct?

A. That's what's shown, but compound is a stereoselectively produced isomeric compound, so a person of skill in the art would understand that when one produces or tries to make predominantly that structure, there are going to be impurities

01:59 including stereoisomeric impurities.

Q. And this structural formula that is set out in claim 3 is a single specific chemical molecule; correct?

A. That image depicts the molecular structure of a single substance which has the name treprostinil, correct.

01:59 Q. And treprostinil is a single specific chemical compound; correct?

A. Again, if we're talking about the context of treprostinil the real world compound, it cannot be composed of a single molecular entity.

01:59 MR. STEINDLER: Could you please put up UTC slide

number 12 or admission number 12, please.
Q. Now, at summary judgment UTC admitted the following statement: Treprostinil is a single specific chemical compound, which is a single stereoisomer. That's a true
02:00 statement; correct?
A. Yes. With respect to the molecular structure of the molecular entity treprostinil, yes.
Q. And with respect to chemical compounds, if you change even just one atom you can have a completely different
02:00 compound; right?
A. So your question is -- ask me your question again? I didn't quite --
THE COURT: All right.
Q. With respect to chemical compounds, if you change just
02:00 one atom, you can have a completely different chemical compound; right?
A. So, is your question with respect to molecular structure, that's true, yes.
Q. Water is H2O; right?
02:00 A. Yes.
Q. And if you change just one atom and you make H2O2, you have hydrogen peroxide; right?
A. Yes.
Q. Hydrogen peroxide is a lot different than water; right?
02:01 A. Yes.

Q. If you drink hydrogen peroxide, it's not good for you; right?
A. Correct.
Q. And hydrogen peroxide is a different chemical compound than H2O; correct?
A. Yes.
Q. And in these complex organic molecules that we're talking about in this case, I believe you testified in your tutorial that tiny changes even in the stereochemistry can result in different compounds with different impurities, and different chemical properties; right? Strike that. Strike that.
A. I'm sorry; I didn't quite follow the question.
Q. Strike that.
With respect to the complex organic molecules that we're talking about in this case, you've testified that even small changes can create different molecules that have different properties; right?
A. That's correct.
Q. And all of the isomers that you've described as impurities are not the treprostinil compound; right?
A. Well, those isomers do not correspond to -- they all have their own unique molecular structure and they do not correspond to the molecular structure of treprostinil, but those other isomers can be part of the real world treprostinil compound that's made by a chemical synthesis process.

Q. Now, you were asked on direct your opinion as to what a person of ordinary skill in the art would understand by the phrase, stereoselectively produced isomeric compound; right?
A. Can you ask again? There was a loud noise.
02:02 THE COURT: I'm sorry; that was me. You may repeat the question, Mr. Steindler.
MR. STEINDLER: Sure.
BY MR. STEINDLER:
Q. You were asked in your direct examination, your opinion
02:03 as to what a person of ordinary skill in the art would understand by the phrase, stereoselectively produced isomeric compound; right?
A. Yes.
Q. What is your opinion as to what the phrase,
02:03 stereoselectively produced isomeric compound, means to a person of ordinary skill in the art as that phrase is used in the '117 patent claims?
A. Well, my understanding is that stereoselectively produced tells a person skilled in the art that we're talking about
02:03 synthesis or produced, means that we're going to make this compound by chemical reactions or chemical means. And that the compound, the real world compound which is going to be made from a real world starting material, which in it of itself cannot be one hundred percent chemically pure, will
02:04 result in a product that will also not be one hundred percent

chemically pure. Constituted of a single molecular entity.
Q. So stereoselectively produced refers to how the compound is produced; right?
A. Yes, but I need to look at the product and the starting material from which it was made.
Q. But to be clear, stereoselectively produced refers to how the product is made, not what it is; right?
A. No, it refers to what the product is, but we -- the how part is how the product was made. In the context of the '117 patent we need to have the enyne with a very defined structure in stereochemistry that is then converted to the tricyclic intermediate.
Q. And that enyne and the conversion is all part of the process by which the product's made; correct?
A. Yes, the enyne, and the carbonylative cyclization resulting in the tricyclic intermediate, that's all an integral part of the process, yes.
Q. Let's just go to a demonstrative slide that we prepared with respect to the specification of the '117 patent. You see this slide here?
A. Yes.
Q. Now, you've of course reviewed the '117 patent specification and the prosecution history in forming your opinions; right?
A. Yes.

Q. Now, the specification says: That the present invention relates to the process for preparing these type of compounds by a process that is stereoselective. Right?
A. I see those words.
02:06 Q. And that confirms your view that stereoselectivity refers to the process by which the product is made; right?
A. No, no, so -- we were just talking about the claim language stereoselectively produced isomeric compound, refers to the compound, the product.
02:06 Q. Let's turn to the next demonstrative slide. These are other portions of the specification where, again, the patent is repeatedly saying that the method is stereoselective; do you see these?
A. Yes.
02:06 Q. And they all stand for the proposition that the stereoselectivity refers to the method or process by which the product is made; right?
A. Yes, but the method is the enyne that has a stereo-directing group as we discussed, very recently, and
02:07 it's the -- what I'm saying is that the Pauson-Khand reaction in it of itself is not stereoselective, it's only stereoselective in the context of that very special enyne that has a stereo-directing group. If you take off the stereo-directing group the process itself is no longer
02:07 stereoselective. So the method requires the enyne.

Q. I'd like to turn to your equivalents opinion that you've testified to on direct; okay?
A. Okay.
Q. Now, your opinion is that the process used to make Sandoz's ANDA product is equivalent to the process claimed in the '117 patent because the PMB group that Alphora uses performs the same function as the methyl group in the cyclization step; right?
A. Well, I applied the function/way/result analysis under the doctrine of equivalents, yes. So it's not just function, it's function/way/result.
Q. And you are in agreement with me that there are other steps besides the cyclization steps that are necessary in order to make the treprostinil compound according to the '117 patent; right?
A. Yes.
Q. And your analysis is limited to the function that the PMB group performed in the cyclization step along with the way and the result of the cyclization step; right?
A. No.
Q. Now, you say that the PMB group and the methyl group both act as protecting groups in the cyclization step; right?
A. Yes.
Q. But you didn't actually present any -- strike that.
You didn't present any actual experimental evidence to

prove that the PMB group is actually acting as a protecting group in the cyclization step; right?
A. So your question is I didn't present experimental -- I'm sorry; your question again?
02:10 Q. You didn't present any experimental evidence to prove that the PMB group is actually acting as a protecting group in this cyclization step; right?
A. Well, there is -- first of all, the para-methoxy benzyl group is not part of the final treprostinil molecule. It's
02:10 well-known in organic chemistry that it's a protecting group. And Alphora's scientists admitted that it's being used specifically in the Pauson-Khand as a protecting group.
Q. My question, sir, is this. You didn't present any experimental evidence to prove that PMB group is actually
02:10 acting as a protecting group in the cyclization step; correct?
A. No, I don't need to because the enyne is converted successfully into the tricyclic intermediate, just as described in the '117 patent process, and the PMB group does not interfere.
02:11 Q. Now, Sandoz produced physical samples of the intermediates that Alphora uses in its manufacturing process; right? You're aware of that?
A. Your question again? I didn't quite --
Q. You're aware that Sandoz produced physical samples of the
02:11 intermediates that Alphora used in its manufacturing process

during this litigation.
A. So your question was that Sandoz produced samples of the intermediates. That Alphora made is that -- I'm just really just trying to follow your question.
02:11 Q. Yes. The question is this. You understand that Sandoz produced to UTC, samples of the intermediates that Alphora uses in its manufacturing process; right?
A. Okay. I don't specifically remember that, but I'll accept your -- your premise.
02:12 Q. You could have done experiments to determine whether in fact the PMB group was acting as a protecting group in the cyclization step; right?
A. You mean me personally in the laboratory?
Q. Either you or someone under your direction could have
02:12 done experiments to prove your case of infringement under the doctrine of equivalents; correct?
A. No, that seems completely unnecessary to me.
Q. Well, while you say it was unnecessary, you could have done experiments to prove your case, but you didn't do them;
02:12 right?
A. Well, I won't do anything that I would consider to be superfluous or -- I think what you're talking about to me is almost ridiculous.
MR. STEINDLER: Well, let's go to the '117 patent
02:12 DTX-2, please. And let's go to claim 1. And -- well, go

ahead and blow up -- not there. Let's go down here and identify the X substituent.

Q. Now, your infringement proofs for doctrine of equivalents is all directed to this (CH2)nX substituent; right?

02:13 A. Yes, that's correct.

Q. And X is defined with a set of possible functional groups that can be at that X position; right?

A. Yes.

MR. STEINDLER: Go out of this and go to the

02:13 definition of X. Which you'll find at the bottom of the page there.

Q. Do you see the definition that you've now discussed at some considerable length during your direct testimony; right?

A. Yes.

02:14 Q. Now, you would agree with me that some of the set that is defined for X, are not protecting groups; right?

A. Let me think about that for just a second; I haven't been posed with that question before.

The (CH2)n, so are you -- could you maybe give me more

02:14 specific question? Are we -- you're just talking about X, but there's also Z (CH2) and n.

Q. If n is zero and X is H, that's not a protecting group; right?

A. If n is zero -- and what's Z?

02:15 Q. Set Z aside for the time being. If n is zero and X is H,

that's not a protecting group; right?
A. So -- well, I guess I need to know what Z is.
Q. Let's say that -- let me just back up for a second.
THE COURT: This is a new question?
02:15 MR. STEINDLER: Yes, let me start with a new question.
THE WITNESS: Okay.
BY MR. STEINDLER:
Q. Are you not able to tell me by looking at these
02:15 definitions of whether X would include groups that are not protecting groups?
A. Well, if you ask me one at a time I can give you an answer.
Q. You can't just look at this and tell me whether X
02:15 includes groups that aren't protecting groups in the '117 patent?
A. Again, I need to have the entire definition of Z(CH2)n and then X. If you can give me an example I'll be happy to answer your question.
02:16 Q. All right. But you can't work this out on your own?
A. Of course I can.
Q. So work out for me on your own, if there are any combinations here with X where X is not a protecting group.
A. Okay. So you're asking me to define the substituents
02:16 where X -- when you put Z(CH2)nX together where that is not a

protecting group; is that what you're asking me?
Q. Correct.
A. Okay. So if Z is oxygen, and n is zero, so there's no CH2 groups, and X is H, that would be the free phenol that would be unprotected.
Q. So, in that scenario which is set out here in the '117 patent claim, X in that combination would not be a protecting group; right?
A. That's right.
Q. So, the patent is teaching that the cyclization reaction can't be performed without a protecting group; right?
A. It could.
Q. Let's go to PTX-2 in the patent at column 6, lines 5 through 22.
Now, this is describing the Pauson-Khand cyclization step; right? In the specification of the patent?
A. Yes.
Q. And you see in this step it's got X, which is this defined term and -- as part of the molecule; right?
A. Yes.
Q. And in the specification when it's describing the Pauson-Khand cyclization step, the patent is teaching that that step can be performed without a protecting group at that location; correct?
A. Yes, well, the patent claims are silent on the specific

type of reagent that is used to effect the carbonylative cyclization, the Pauson-Khand being one of many specific reagents that can be used to carry out that cyclization. And it's entirely conceivable that a chemist may discover a new carbonylation reagent that would work on unprotected phenols. But to my knowledge Pauson-Khand cyclization reactions have never been reported on unprotected phenols.

Q. But the patent is teaching that the Pauson-Khand step can be conducted without a protecting group here because there are substituents defined for X that are not protecting groups; right?

A. Yes.

Q. And let's go to slide -- your slide 40, please. And you were talking about this masking tape analogy, that there has to be a protecting group there. Do you remember that testimony?

A. I don't think I ever said that there has to be a protecting group there.

Q. So, isn't the patent teaching in fact there might be no masking tape in the cyclization step?

A. Well, the patent certainly accommodates that possibility, but the example in the '117 patent uses a methyl protecting group, and Alphora uses a para-methoxy benzyl protecting group, so I was comparing those two protecting groups side by side.

Q. So, let's go to your slide 42. And in claim 2, X is given a specific definition of COOH; right?
A. Yes.
Q. And the COOH, that would be at that X position, is never taken off the molecule all the way through to the treprostinil compound; right?
A. No. So there the claim 2 is defining the final compound treprostinil, where X is COOH.
Q. And is it -- and X is defined as COOH throughout the process here; correct?
A. No.
Q. So it's your opinion that when claim 2 defines X, it's defining X for one purpose in one part of the claim, but X could be something different in other parts of the claim; is that your testimony?
A. Yes.

MR. STEINDLER: Pass the witness.

THE COURT: All right.

(REDIRECT EXAMINATION OF ROBERT M. WILLIAMS PH.D. BY MR. CARSTEN:)

Q. Good afternoon, Professor Williams.
A. Good afternoon Mr. Carsten.

MR. CARSTEN: May I proceed, your Honor?

THE COURT: You may.

MR. CARSTEN: Thank you, your Honor.

Now, can we please have slide 15.
BY MR. CARSTEN:
Q. Just a couple of questions, Professor Williams. Now, Mr. Steindler was suggesting your infringement analysis was limited to molecular formulas or structure here. Is that what your analysis was for infringement?
A. No.
Q. Could you please just summarize very very briefly the things you did in terms of analyzing and conducting your -- and developing your opinions for infringement.
A. Well, I first carried out this step of confirming that the molecular formula that's represented in Sandoz's ANDA and Alphora's DMF read on the specific structure shown in the '117 patent. So I went through the exercise of making sure that the variables when they're plugged in render those molecular structures and that box got checked, that works.
But I also looked at Sandoz's ANDA product that it stereoselectively produced by the enyne going through the Pauson-Khand reaction to the tricyclic intermediate. So I also looked at the manufacturing process, I looked at their drug master file, I looked at this -- the example, the two kilowatt reaction, so forth, to verify that the real world compound is in fact made by the '117 patent process.
Q. And did you reach a conclusion that the active pharmaceutical ingredient that Sandoz is going to use to make

its product infringes claims 1 through 4 of the '117 patent?
A. Yes, that was my conclusion.
Q. Now, what -- what is the API that's going to be used in Sandoz's finished ANDA product?
02:23 A. They're making the treprostinil sodium.
Q. And where does that come from?
A. That comes from the carboxylic acid, the treprostinil free acid.
Q. And who's providing that to Sandoz?
02:23 A. Alphora.
Q. And that's the material that you considered in connection with your infringement analysis; is that fair?
A. Yes.
Q. Now, did you analyze anything in the Sandoz's ANDA
02:23 document in connection with your infringement analysis?
A. Yes, there was a flow chart showing the steps in the process and then they reference the details in Alphora's DMF, which has all the experimental details.
Q. Now, did you also find the Sandoz proposed label?
02:24 A. Yes.
Q. Can we go to slide 16, please. What is this?
A. So this was the proposed label disclosed in their -- in Sandoz's ANDA for the treprostinil product.
Q. And this is PTX-250 at page 54?
02:24 A. Yes.

Q. And what is the proposed label telling the world is the chemical compound and active ingredient moiety in Sandoz's finished ANDA product?
A. The treprostinil acid, free acid.
02:24 Q. Not the sodium?
A. That's not -- that is not is what is depicted in that molecular formula.
Q. Do you believe that Sandoz's proposed label is reliable?
A. Well, I assume they put careful thought into rendering
02:25 this.
Q. Now, let's turn to slide 19 if we could. Can you describe for the Court the relationship between the free acid on one hand and the salt on the other?
A. Yes. So if one say starts with the free acid, or
02:25 conversely one can start with the sodium salt treprostinil sodium, and put either of those substances, those compounds in water, they would rapidly establish an equilibrium between the two forms. So if you started with a hundred percent or nearly a hundred percent sodium salt, put it in water, it would
02:25 establish an equilibrium that would be a function -- the ratio would be a function of the pH of the solution that you put it in.
Q. Now, Mr. Steindler asked you some questions -- well, before I go on to that, would a person of ordinary skill in
02:25 the art understand that the acid and sodium are -- the free

acid and the sodium are existing simultaneously?
A. Yes.
Q. At what pHs?
A. All pHs.
02:26 Q. Mr. Steindler asked you some questions about water on one hand and hydrogen peroxide on the other; do you remember that?
A. Yes.
Q. Hydrogen peroxide -- can you buy hydrogen peroxide in a bottle that's a hundred percent pure?
02:26 A. No.
Q. Why not?
A. Well, first of all hydrogen peroxide is very hydroscopic, it's very -- absorbs water, so there's always going to be water in hydrogen peroxide and other things. So like any
02:26 chemical it will have whatever percent grade, reagent grade is being sold, will have water and other things in there, other impurities.
Q. Now, he also compared the hydrogen peroxide with water; right? Is there such a thing as a hundred percent pure water?
02:27 A. No.
Q. Why not?
A. Again in the real world, we can try and purify water, but there's going to be trace metals, there's going to be bacteria, dust particles, real world things.
02:27 Q. Mr. Steindler asked you some questions about

stereoselectivity and he said stereoselectivity refers to the process; do you remember him asking you that?

A. Yes.

Q. I'd like to show you PTX-480. Do you recognize PTX-480?

02:27 A. Yes. This is the inside page of the Eliel books, Stereochemistry of Organic Compounds, the large organic chemist's bible in stereochemistry.

Q. Now, in your said testimony you said no, no, no, stereoselective refers to the compound; right?

02:27 A. Yes.

Q. Is there a definition of stereoselective in the Eliel book?

A. Yes.

MR. STEINDLER: Judge, this is the beyond the scope

02:28 of my direct. I didn't examine the witness on this book.

MR. CARSTEN: He asked the witness, your Honor, whether stereoselective refers to a process. I'm entitled to support that opinion.

THE COURT: Sustained.

02:28 MR. CARSTEN: Thank you, your Honor.

BY MR. CARSTEN:

Q. Turning to -- there was some questions about the variability about the substituents; do you remember that?

A. Yes.

02:28 Q. Would a person of ordinary skill understand that the

substituents would be variable for the enyne and cyclized intermediate as opposed to final product reflected in the claims?

A. Yes. I put in my report that a person skilled in the art would understand that those variables are a tool box that can be -- that can be interchanged, between the enyne tricyclic intermediate and the final product.

Q. Now, finally, did Sandoz's expert ever present any evidence of a PMB protected phenol in the literature?

MR. STEINDLER: Judge, Sandoz's expert hasn't testified yet.

THE COURT: Can you rephrase the question?

MR. CARSTEN: Sure.

BY MR. CARSTEN:

Q. Mr. Steindler was asking you some questions about PMB as a protecting group; do you remember that?

A. Yes.

Q. Let me ask you this way. Have you ever seen a PMB protected phenol used in a Pauson-Khand reaction aside from your work in this case?

A. No.

MR. CARSTEN: Nothing further, your Honor.

THE COURT: All right, thank you.

You may step down, Doctor. Thank you for coming.

(Witness excused.)

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

UNITED THERAPEUTICS CORPORATION,

Vs.

SANDOZ, INC.,
DEFENDANT

CIVIL NO.
12-1617 (PGS)
13-316

MAY 16, 2014
CLARKSON S. FISHER COURTHOUSE
402 EAST STATE STREET
TRENTON, NEW JERSEY 08608

B E F O R E: THE HONORABLE PETER G. SHERIDAN
U.S. DISTRICT COURT JUDGE
DISTRICT OF NEW JERSEY

TRIAL - DAY 10

Certified as true and correct as required
by Title 28, U.S.C. Section 753
/S/ Francis J. Gable
FRANCIS J. GABLE, C.S.R., R.M.R.
OFFICIAL U.S. REPORTER
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know why we wouldn't just do it. The disease is a fatal disease, the patients are tenuous; Remodulin itself, even Sandoz's generic treprostinil, are very expensive drugs. The incremental cost for using SDF in my mind is trivial. And I agree with your Honor that SDF is the appropriate prescription.

THE COURT: Okay, thank you. You may step down.

THE WITNESS: Thank you, your Honor. Have a good weekend.

THE COURT: Yes, you too.

(Witness excused.)

MR. CARSTEN: Good afternoon, your Honor.

THE COURT: Good afternoon, Mr. Carsten. So we are prepared to call our next witness, however it's chemistry, so it's going to be -- direct last time we checked was just over an hour. It is now after 3 o'clock; I'm not sure if your Honor wants to open this up now.

THE COURT: Let's go.

MR. CARSTEN: Okay. United Therapeutics calls Dr. Paul Aristoff to the stand.

(PAUL ARISTOFF, PH.D.), sworn.

THE COURT: Doctor, can you just spell your last name, please?

THE WITNESS: Yes, it's spelled -- last name is spelled A-r-i-s-t-o-f-f.

THE COURT: Thank you.

MR. CARSTEN: Your Honor, we prepared some binders; may we approach?

THE COURT: Yes, you may.

04:19 (Handing to witness and Court.)

(DIRECT EXAMINATION OF PAUL ARISTOFF BY MR. CARSTEN:)

Q. Good afternoon, Dr. Aristoff.

A. Good afternoon.

Q. Would you please introduce yourself to the Court?

04:19 A. Yes, yes. Your Honor, my name is Paul Adrian Aristoff. I'm a medicinal chemistry consultant, and I recently moved to Fort Collins, Colorado.

THE COURT: Okay, thank you.

Q. What types of companies do you consult for?

04:20 A. I primarily consult for pharmaceutical companies, as well as some academic groups.

Q. Have you prepared a curriculum vitae?

A. Yes, I have.

Q. Can we turn to PTX-102, please. What is this, Dr. 04:20 Aristoff?

A. This is the cover page of my C.V.

Q. And this is a demonstrative reflected in the reflecting the cover page?

A. Yes.

04:20 Q. Is your C.V. true and accurate?

A. Yes, it is.

MR. CARSTEN: Your Honor, we'd move to admit PTX-102.

MR. STEINDLER: No objection.

04:20 THE COURT: All right, admitted.

(Plaintiff's Exhibit 102 was marked into evidence.)

BY MR. CARSTEN:

Q. Dr. Aristoff, have you prepared a slide describing or giving an overview of your educational background?

04:21 A. Yes, I have. It's taken from my C.V.

Q. Would you please explain to the Court the highlights of your educational background?

A. Yes, I received both my Bachelor's and Master's degree in chemistry from Northwestern University in 1973. I then

04:21 received a National Science Foundation fellowship to attend the California Institute of Technology, and I received my Ph.D. from Caltech then in 1977. I had a National Science Foundation post doctoral fellowship which I used to work at the Swiss Federal Institute of technology in Zurich,

04:21 Switzerland from 1977 to 1978.

Q. What was the subject of your Ph.D. thesis?

A. It was the total synthesis -- an approach to the total synthesis of aphidicolin.

Q. How complicated was it to synthesize aphidicolin?

04:22 A. Well, aphidicolin is a complex natural product diterpene,

it has 20 carbons and 12 chiral centers; I developed a synthesize of an intermediate on the way to the final product. It had 18 of the 20 carbon atoms, and had -- excuse me; yes, 18 of the 2 carbon atoms, and six out of the seven chiral centers.

Q. Over the course of your career have you routinely worked with molecules containing chiral centers?

A. Yes.

Q. Have you ever taught any chemistry classes?

A. Yes, since 2012 I've been adjunct professor in the Department Medicinal Chemistry at the University of Michigan, and I teach part of a medicinal chemistry course to graduate students there.

Q. Now, have you prepared a slide with respect -- summarizing your employment background?

A. Yes, I have.

Q. And could you please summarize your work experience for the Court.

A. Yes. Following my post doctoral studies I joined the Upjohn Company in 1978, where I was a scientist in a experimental chemistry research group; in 1984 I was promoted to associate director with overall responsibility for the cancer and viral diseases chemistry group; in 1991 I was promoted again to director of medicinal chemistry with responsibility for overall head of the medicinal chemistry

department at Upjohn; in 1995 Upjohn merged with a company called Pharmacia, and I was made director of medicinal chemistry in Kalamazoo for the new company called Pharmacia and Upjohn; in 1999, Pharmacia and Upjohn merged with yet another company called Searle Monsanto, I was named senior director of chemistry then for the new company, which was named Pharmacia, senior director of chemistry in Kalamazoo; in 2003 Pfizer bought Pharmacia and I moved to Ann Arbor, Michigan, where I was senior director of chemistry and head of the antibacterial chemistry group for Pfizer in Ann Arbor, Michigan; and in 2008 I retired from Pfizer and started my own medicinal chemistry consulting company, I was also then -- became a visiting research scientist at the University of Michigan.

Q. How long was your career at Upjohn and the related companies?

A. About 30 years.

Q. Are you a member of any professional organizations?

A. Yes, I am. I'm a member of the American Chemical Society, the American Association For the Advancement of Science, the American Association of Cancer Research, and the American Society For Microbiology.

Q. Do you have any scientific publications?

A. Yes, I have over 60 publications, including book chapters and reviews, about a dozen of these publications relate to

prostacyclin analogs including two reviews that I wrote.
Q. Have you served any editorial advisory positions for peer review journals?
A. Yes, I was on the editorial advisory board for the Journal of Organic Chemistry; I was also on the editorial advisory board for a journal called Chemical Biology and Drug Design. I also served as a member of a committee that was -- monitored the Journal of the American Chemical Society.
Q. You are you listed as an inventor or named as an inventor as any U.S. patents?
A. Yes, I'm the inventor or co-inventor on about 30 issued U.S. patents. These patents include 12 drug development candidates that went into clinical trials, and this includes three compounds that were actually approved by the Food and Drug Administration and entered the marketplace, one of those drugs being treprostinil. I'm also the inventor of two antiviral agents used to treat AIDS patients.
Q. So you're the named inventor of the patent covering treprostinil.
A. Yes, I'm the sole inventor on the original patent for the treprostinil.
Q. Now, over the course of your career, how many pharmaceutical molecules did you synthesize?
A. So, I personally synthesized over a hundred molecules, the majority of them being prostacyclin analogs. In terms of

chemists that have reported to me through the years, they've prepared many thousands of molecules, including over 30 development candidates that were in clinical trials, and three of these actually were approved by the FDA and entered the marketplace.

Q. Has your professional experience helped in your work in this case?

A. Most certainly. I was -- from the period of 1978 to 1984, I was a scientist in experimental chemistry research at Upjohn, and the primary focus of our work was actually the design and synthesis of prostacyclin analogs, and I was the one that came up with the class of prostacyclin analogs known as benzidine prostaglandins, benzidine prostacyclins including the compound treprostinil.

Q. Since you invented treprostinil, have you followed the developments in the area relating to treprostinil?

A. Yes, particularly chemistry work.

MR. CARSTEN: Your Honor, we'd offer Dr. Aristoff as an expert in the field of organic and medicinal chemistry, synthesis of prostacyclin analogs, and the subject matter of the '117 patent.

MR. STEINDLER: Just a quick voir dire?

THE COURT: Okay. You may.

MR. STEINDLER: Very quick.

(VOIR DIRE ON QUALIFICATIONS BY MR. STEINDLER:)

Q. You're not an expert in the Pauson-Khand reaction; correct?
A. No, I'm not.
MR. STEINDLER: All right. Subject to that I have no objection.
THE COURT: All right. So, he's an expert subject to Mr. Steindler's objection on the Pauson-Khand reaction.
MR. CARSTEN: Thank you, your Honor.
BY MR. CARSTEN:
Q. In connection with following the literature in your capacities of your work experience, do you become aware of the Pauson-Khand reaction?
A. Yes, I did. I certainly followed it in the literature.
Q. Were you aware of the Pauson-Khand reaction in the 1980s?
A. Yes, I was.
Q. Were you aware of it in the 1990s?
A. Yes.
Q. Are you aware of it today?
A. Yes.
Q. Have you studied the Pauson-Khand reaction in connection with your work in this case?
A. Yes, I've never carried out a Pauson-Khand reaction myself.
Q. But you've reviewed the literature; correct?
A. Yes.

Q. Now, have you ever testified as an expert before?
A. No, I have not.
Q. Are you nervous?
A. Yes, I've never done this before.
04:28 Q. Have you formed any opinions in the case, Doctor?
A. Yes, I have.
Q. Have you prepared a slide to describe one of the opinions that you formed as a person of ordinary skill in the art?
A. Yes. This is a definition I was using, it's actually not
04:29 very different from Dr. Buchwald's definition. The -- my opinion, a person of ordinary skill in the art at the time of the invention, would have held a Ph.D. in chemistry or a related field, or a Bachelor's or Master's degree in chemistry or a related field, with at least three years of experience in
04:29 -- postgraduate experience in organic synthesis.
Q. Did you meet this -- these criteria as of the priority date?
A. Yes.
Q. And the priority date we're talking about here is 1997;
04:29 correct?
A. That is correct.
Q. Now, you mentioned Dr. Buchwald's level of ordinary skill; did you consider that?
A. Yes, I don't think it's very different than mine.
04:29 Q. Would you qualify under his?

A. Yes.
Q. And would your opinions differ depending on if you applied his versus if you applied your level of ordinary skill?
04:29 A. No, not at all.
Q. What specifically were you asked to do in this case?
A. So, I was asked to review the claims of -- in the patent, the '117 patent, and consider their validity in light of the prior art referenced by Sandoz.
04:30 Q. Now, let's start with the '117 patent, which is PTX-002. You analyzed the '117 patent in connection with your work in this case; right?
A. Yes.
Q. And who's the first named inventor on the '117 patent?
04:30 A. Dr. Moriarty.
Q. Are you familiar with Dr. Moriarty's work regarding treprostinil?
A. Yes.
Q. When did you become aware of that work?
04:30 A. Well, I first became aware of his work in 2004 when his article in the Journal of Organic Chemistry was published that described his stereoselective synthesis of treprostinil.
MR. CARSTEN: Can I call up DTX-171 in evidence, please?
04:30 Q. Do you recognize this document?

A. Yes, I do.
Q. What is this?
A. This is that Journal of Organic Chemistry article from 2004 by Dr. Moriarty.
04:30 Q. Now, the chemistry presented in the JOC article, is this the same chemistry as reflected in the '117 patent?
A. Yes.
Q. Were there any key chemical transformations that you observed in this JOC article?
04:31 A. Yes, he used the key -- his key reaction in the synthesis was the Pauson-Khand reaction.
Q. Now, you were aware of the Pauson-Khand back in the '80s; correct?
A. Yes.
04:31 Q. When you were developing approaches to synthesizing treprostinil, the compound you invented, did you consider using the Pauson-Khand reaction?
A. No, I did not.
Q. Why not?
04:31 A. Well, I didn't see any way to use this particular reaction to make the molecule stereoselectively. I also didn't think it was a reaction that you could do on commercial scale?
Q. Is it a commonly used reaction this Pauson-Khand reaction
04:31 in the pharmaceutical context?

A. No, not at all. I'm actually not aware of any other commercial use of the Pauson-Khand reaction.
Q. What did you think of Dr. Moriarty's published synthesis of treprostinil?
04:32 A. Well, I was actually pretty -- very impressed. In a relatively few number of steps he was able to prepare all five chiral centers in the molecule stereoselectively, and have quite a good yield.
Q. Did you think that the Moriarty synthesis was a better
04:32 approach than the ones you had developed at Upjohn?
A. Well yes, because the chemistry that I had optimized was not stereoselective. I was able to control the stereochemistry in four out of the five chiral steps in treprostinil, but not the fifth, there was one I was not able
04:32 to and I ended up with a one-to-one mixture of compounds from the synthesis.
Q. Why is a -- and those compounds would be diastereomers?
A. Yes, that's correct.
Q. Can you just explain to the Court just very briefly, what
04:32 do you mean by diastereomers.
A. So, diastereomer will be a compound that at least has -- at least at one of the other chiral centers has a different orientation than the molecule you're interested in.
Q. And what's wrong with having a mixture of diastereomers?
04:33 A. Well, especially when you have a one-to-one mixture you

know you're going to have a lower yield, you know you're going to have a lot of material that you have to get rid of, particularly when you carry it all the way to the end of the synthesis you're going to have more impurities because of that.

Q. Now, when you say a one-to-one mixture, what exactly do you mean?

A. So, in the reaction -- and the key reaction in my synthesis, I actually ended up primarily with 50 percent of the desired compound I wanted for that reaction, plus 50 percent for an undesired diastereoisomer in that reaction. There were other impurities in there as well, but primarily those two. And I had to carry all that type of mixture through the subsequent seven steps of synthesis, all the way to the end of the synthesis. So it's just at the final step I still had this one-to-one mixture of now treprostinil, and an unwanted diastereomer of treprostinil.

Q. So leaving aside the other stuff that was in that reaction mix, half -- roughly half and half were these two diastereoisomers; is that right?

A. Well, half was treprostinil, half was this unwanted material.

Q. Now did you analyze the claims of the '117 patent in connection with your work in the --

A. Yes, I did.

Q. Let's turn to a portion of claim 1. How does claim 1 start?
A. So it starts talking about a stereoselectively produced isomeric compound according to the following formula, and then it gives kind of a generic chemical formula.
Q. And what does stereoselectively produced isomeric compound mean?
A. Well, I think it's very clear that stereoselectively produced modifies the word compound. That tells me we're talking about a product, a compound in the real world, a compound that's going to have primarily this generic chemical formula. But there'll be other substances in there as well, other impurities will be part of that, because of the way the compound is produced.
Q. And do you think that would have been apparent to a person of ordinary skill in the art --
A. Yes, I think --
Q. As of 1997?
A. Yes, I certainly think so, in terms of the way you read the claims, a stereoselectively produced compound.
Q. Now, your view is different than Dr. Buchwald's; right?
A. Yes, it is.
Q. You were here and you heard Dr. Buchwald testify; correct?
A. Yes.

Q. In which view, yours or Dr. Buchwald's, do you think is more natural for a person of ordinary skill in the art reading the claim?

A. Well, I think again a person of ordinary skill in the art in 1997 reading this claim, would know that stereoselectively produced modifies compound. You're talking about the real world, you can't have a hundred percent pure compound, so you have to be thinking, okay, what else is in that compound, what is there. So you're talking about maybe it's primarily this formula or treprostinil, but there's other impurities as well.

Q. Now, Dr. Aristoff, you've used the word compound at various times to refer to a single molecule or to a molecular structure; right?

A. Certainly.

Q. Under what circumstances?

A. Well, again, if you're asked to draw the structure of a compound, you will draw one -- one molecular structure. You will draw one -- the chemical structure of that molecule, realizing that no compound is a hundred percent pure, but it will be primarily that molecule.

Q. Now, do you have an understanding that the claims -- how many claims are there in the --

A. There's four claims in the '117 patent.

Q. Do you know what kinds of claims these are?

A. Yes, they're product-by-process claims.

Q. And do you have an understanding of the legal standards applicable to product-by-process claims?
A. Yes, I believe I do on the next slide.
Q. Would you please describe this slide for the Court.
04:37 A. So, again, it's my understanding in a product-by-process claim, that the focus of the anticipation analysis is the product produced by the claim, by the claimed process. And in a -- if the process -- if the process by which the product is made actually imparts structural functional differences, those
04:37 can be relevant to the anticipation analysis. And in fact, only structural differences are needed to distinguish the prior art.
Q. Now, let's talk about the word stereoselective for a moment if we could. Is there a book that's commonly used or
04:37 referred to by people of ordinary skill in the art that relates to stereochemistry?
A. Yes, we've heard this before, this is the textbook by Professor Eliel on stereochemistry.
Q. And do you have a call-out of the Eliel book?
04:38 A. Yes.
MR. CARSTEN: Your Honor, this is PTX-480 which is in evidence.
Q. How does -- would you please describe for the Court what excerpt from Eliel you put on the slide?
04:38 A. Yes. So again, what I've taken from the standard

chemistry textbook, the definition of the term stereoselective, and I took it right out of this particular page of his book. And the term -- it states: The term stereoselective is used to describe the stereochemical outcome
04:38 of a reaction when it's possible for more than one stereoisomer to be formed, but one is formed in excess, although its use should desirably be restricted to situations where the proportion of the major stereoisomer is substantially greater than that of the minor one.
04:38 Q. Does this definition support your view on stereoselectively produced isomeric compound?
A. Yes.
Q. How does that -- how does it support that opinion?
A. Well, it's clear from -- that the '117 patent is a
04:39 stereoselectively produced product, the end product and the chemical transform to make it are stereoselective.
Q. And does the Eliel definition refer to stereoselective in connection with the process or with the stereochemistry outcome of the reaction?
04:39 A. Well, in this particular definition it's referring to a particular reaction.
Q. Now, you analyzed the claims of the '117 patent; right?
A. Yes.
Q. Let's take a look at one representative claim, claim 3.
04:39 Can you please just walk the Court through this slide briefly?

A. So, claim 3 starts with a stereoselectively produced isomeric compound according to the following formula, and then in the yellow box, is the -- actually the chemical formula for treprostinil. And then it's produced from the starting enyne compound, which is this sort of pink colored box, that's the enyne used in the '117 patent.

And that's cyclized -- that's converted to this cyclized intermediate compound in orange in the claim, and that's by this intramolecular cyclization process in yellow at the very bottom of the slide.

Q. Now, when you were at Upjohn inventing the treprostinil structure, how many different syntheses roughly did you develop for treprostinil?

A. Well, I tried a lot of chemistry, but I developed basically two syntheses.

Q. Now, outside of the -- so have you prepared a slide that sort of groups these two synthetic approaches?

A. Yes.

Q. And would you please describe for the Court what's depicted on this slide?

A. So, my first Upjohn synthesis relates to what's described in the '075 patent. My second Upjohn synthesis relates to what was in the '814 patent.

MR. CARSTEN: Your Honor, we've put the DTX numbers which are the numbers that these are admitted under, next to

the PTX number. But the '075 patent's been admitted as DTX-53, and the '814 patent has been admitted as DTX-55.

THE COURT: Thank you.

BY MR. CARSTEN:

04:41 Q. Now, outside of the context of your work in this case, I presume you have some passing familiarity with these references?

A. Yes, I'm the co-inventor on both -- I'm actually the sole inventor, excuse me, on both these patents. This is based on

04:41 work that I did at the Upjohn Company.

Q. Now, in connection with your work in this case did you have opportunity to go back and re-review these patents?

A. Yes.

Q. Now, let me just ask you, is the treprostinil prepared by

04:42 the Moriarty synthesis the same or different than the treprostinil you prepared in your first and second syntheses?

A. The products of these two patents are clearly different than the product of the '117 patent.

Q. Now, with respect to the '075 patent, DTX-53, you heard

04:42 Dr. Buchwald testify about that; right?

A. Yes.

Q. Now, did you hear him say that I believed that the '075 patent anticipated the claims of the '117 patent?

A. I actually didn't hear that, no.

04:42 Q. Okay. Now, Dr. Buchwald mentioned that he hadn't

considered the synthesis of the '075 in some time; do you recall that?

A. Yes.

Q. What's your view on the '075 synthesis, is it a practical synthesis?

A. So, the -- I developed the '075 synthesis really to make a variety of prostacyclin analogs, not just the benzidine analogs, it was a synthesis really only meant for small scale. It was a very long synthesis, that means it was many many steps, very low yield, and in fact some steps in that synthesis couldn't be done on larger scale. They were either irreproducible or were too hazardous to conduct on a larger scale.

Q. In your opinion would a person of ordinary skill in the art believe '075 anticipates the claims of the '117 patent?

A. No, not at all.

Q. Since Dr. Buchwald didn't spend much time of it, just very briefly would you just summarize very quickly the reasons why you think that?

A. Well, again a number of reasons, the process in the '075 patent really led to a mixture of diastereoisomers, very low yields; certainly different impurity profile than the product of the '117 patent. And again, it had steps that you just couldn't do on any significant scales.

Q. Let me go to the next slide. This is DTX-53, the cover

page of the '075 patent; right?
A. That's correct.
Q. And who's the named inventor of the '075?
A. That would be me.
04:44 Q. Now, can you just tell us very very briefly, how the work that led to the '075 patent came about.
A. Again, for the '075 patent, it's my job at the Upjohn Company to design novel prostacyclin analogs. And one class I developed was the benzidine prostacyclin analogs, and this is
04:44 -- again this patent represents the -- those compounds in the process, the original process to prepare this.
Q. Now, I'd like to turn to the cover page of the '117 patent, PTX-002. Do you see in the references cited the '075 patent?
04:44 A. Yes.
Q. Now, that's the '075 patent we just discussed; right?
A. That's correct.
Q. That discloses treprostinil?
A. Yes.
04:45 Q. There was some suggestion yesterday by Mr. Steindler when he was examining Dr. Buchwald on redirect, that a person of ordinary skill in the art would have some difficulty determining the structure of treprostinil from the fact of the '075 patent; do you remember that?
04:45 A. Yes.

Q. Do you agree with that?
A. Well, it's clearly named in there, there was a publication by Dr. Nelson that explains how you name prostaglandin analogs. And I think that would make it apparent what that particular compound is.
Q. Now, the second document that's identify there is this 5,153,222 patent; are you familiar with that patent?
A. Yes.
Q. And what is that patent about?
A. So that's actually a method of treatment patent, describing how you could use treprostinil to treat pulmonary arterial hypertension.
Q. So both these patents disclose treprostinil?
A. Yes, yes, they do.
Q. So in your opinion, did the patent office have your patent and another patent both disclosing treprostinil in front of it when it decided to allow the '117 patent?
A. Yes, it's clearly cited on that cover page of the patent.
Q. Now, you mentioned that you had these two syntheses of treprostinil, the first one which is the '075; now let's turn to the second synthesis. Can we do that?
A. Yes.
Q. And what's being shown on slide 14 here, demonstrative 14?
A. So, this is the cover page of the '814 patent.

Q. And who's the inventor of the '814 patent?
A. That's me.
Q. Now, what does the '814 patent disclose?
A. So this discloses the improved synthesis I did to make
04:46 benzidine prostacyclin analogs, including the treprostinil
compound, I think that's example 3. Again, I developed a
synthesis that would allow me to at least make gram scale
quantities of material.
Q. Now, does the '814 patent in your opinion anticipate any
04:47 claim of the '117 patent?
A. No.
Q. Why not?
A. Well, again, you have a different product that's formed
here, this is with a different impurity profile. This '814
04:47 patent actually was a non-stereoselective synthesis
unfortunately, it also gave lower yields than the product of
the '117 patent.
Q. Does the '814 patent disclose stereoselectively produced
isomeric compound of treprostinil?
04:47 A. No, not at all.
Q. Would a person of ordinary skill in the art be well aware
of that?
A. Yes, as soon as you look at the patent you realize I'm
preparing a one-to-one mixture of compound at the final step,
04:47 not stereoselective.

Q. Does the '814 patent contain any disclosure of that enyne structure that we saw in connection with the claims of the '117 patent?
A. No, no, the enyne is not present in this patent at all.
04:47 Q. Does the '814 patent, which is DTX-055, disclose the claimed cyclized intermediate compound from the claims of the '117 patent we've seen?
A. No, no, that particular cyclized intermediate is not part of this patent.
04:48 Q. Is there a Pauson-Khand reaction in the '814 patent?
A. No, no.
Q. Now, on Wednesday -- were you here in court on Wednesday for Dr. Buchwald's direct examination?
A. Yes.
04:48 Q. He put up a slide that had a passage from your deposition; do you remember that?
A. That's correct.
Q. I'd like to show that to you. Now, this is the testimony of yours from your deposition that Dr. Buchwald referred to?
04:48 A. Yes.
Q. Now, Dr. Buchwald -- I'm sort of paraphrasing now, but he referred to your testimony as suggesting or admitting that treprostinil is treprostinil regardless of the source; right?
A. Yes.
04:48 MR. STEINDLER: Can I just pause here just for one

second? That slide deck that you gave me doesn't go past slide 33.

MR. CARSTEN: This is slide 36.

(Counsel conferring.)

04:49 MR. STEINDLER: Thank you.

BY MR. CARSTEN:

Q. Dr. Aristoff, I'm sorry; did you respond to my last question?

A. Could you repeat the last question?

04:49 Q. Dr. Aristoff, Dr. Buchwald, I'm paraphrasing now, referred to this testimony as suggesting or admitting that treprostinil is treprostinil regardless of the way it's made or the source; right?

A. Yes, that's what he said.

04:49 Q. And do you agree with that?

A. Well, the formula for treprostinil is the same. The chemical formula that you would draw if you were asked to draw the formula for the compound treprostinil. You only have one molecular formula, that would be the same.

04:50 Q. But is that what you said in your deposition?

A. Yeah, we were discussing it as I recall in this part of my testimony, we were looking at structures on the patent page. And again the chemical formula for treprostinil is indeed the chemical formula for treprostinil. You only --

04:50 that's a signature of the treprostinil.

Q. And what passages here make clear that you were talking about the molecular formula or the molecule, not the compound as it's made?

MR. STEINDLER: Objection; leading.

04:50 THE COURT: Overruled.

A. Well, there's several questions here, and each one -- so, I'll start with -- okay. So in this particular question, I was asked about the intramolecular cyclization, I say, it's the same compound, the same single molecular formula of either

04:51 process, the molecular formula doesn't change.

Again, in answer to the last question I was saying, this is the same molecule, the molecule treprostinil has a single molecular formula.

Q. But up above you say the word compound, it's the same

04:51 compound.

A. Yes, again, what I'm -- what I'm talking about here in the context, we've already heard the context of the word compound is important. In the context if you're asked to draw the structure of the compound treprostinil, you will draw a

04:51 single molecule. If you're asked to make the compound treprostinil, you'll recognize well, it's not going to be a hundred percent treprostinil, you're going to make some substance which has -- contains primarily treprostinil molecules -- molecular form of treprostinil, but that compound

04:51 will also have impurities.

Q. Now, would you -- have you printed out a slide to summarize the reasons why you think the treprostinil from the second Upjohn synthesis is different from the treprostinil from the '117 patent synthesis?

04:52 A. Yes.

Q. Would you please walk the Court through these points? And we're going to expound on each one going forward.

A. So I already mentioned that the product of the '814 patent was not stereoselective, was non-stereoselective, I

04:52 produced a one-to-one mixture of compounds, unlike the stereoselectively produced product of the '117 patent.

I also still unfortunately had a relatively low yield for the second route, '814 process relative to '117, and I have a different impurity profile in the product between --

04:52 the product of the '117 patent and the '814 patent.

Q. Now, I'd like the sort of unpack that a little bit. Let's turn to the non-stereoselective point.

MR. CARSTEN: Can I pull up DTX-56, please.

Q. Do you recognize this document, Dr. Aristoff?

04:53 A. Yes.

Q. What is this?

A. This is the technical report that I wrote describing my work on a -- this new synthesis of treprostinil, which is U62840.

04:53 Q. And could I turn to page 1096100, please. What does that

show?
A. So this is a rather complicated chemical scheme, that shows part of that synthesis starting from where I formed the -- do the intramolecular cyclization in my chemistry, and then going to the final product.
THE COURT: I'm sorry; where did this page come from? Is that attached to the tech report?
MR. CARSTEN: Yes, this is from the summary report that was DTX-56, and the Bates page number there, your Honor, is 1096100.
THE COURT: Can you give that again?
MR. CARSTEN: 1096100.
THE COURT: Okay, thank you.
BY MR. CARSTEN:
Q. Now, Dr. Aristoff, on this slide with your -- with your pointer, could you explain to the Court where it is that you obtained a mixture of diastereoisomers here?
A. Yes. Again, I apologize for how complicated this is, but at the top of the slide the first reaction that I show in this particular slide is actually the problematic one where I created a one-to-one mixture. If you were a chemist you would recognize that this squiggly line here refers to the fact that you have 50 percent of the molecules with that squiggly line being rather dashed below the plane, and 50 percent of the molecules being bolded line, which is the one -- that was the

isomer I wanted, it was the hydrogen with the wedged line.
Q. So relatively speaking, how much of stuff with the hydrogen under the plane, versus how much of the stuff outside of the plane were you getting in that step?
04:55 A. So in the particular reaction, I get a one-to-one mixture. So of the desired material from this reaction, and 50 percent of the undesired product from this reaction.
Q. And now going through this --
THE COURT: I'm sorry; when you say undesired
04:55 mixture --
THE WITNESS: Yes, so I'm --
THE COURT: Is that the impurities that we're talking about?
THE WITNESS: Yes, at this step I'm creating an
04:55 impurity, 50 percent of an impurity.
THE COURT: Okay.
THE WITNESS: That unfortunately is carried through the rest of the synthesis.
THE COURT: Okay, thank you.
04:55 BY MR. CARSTEN:
Q. Now, all throughout the synthesis, you have this parentheses 1:1 close parentheses, what does that refer to?
A. So again, at each stage of this chemistry I'm carrying along an unwanted diastereomer of the compound that I wanted.
04:56 So I just abbreviated chemically at each stages, either the

tri-epi isomer at this particular stage, as I did for further chemistry on the way to the treprostinil final product. I was changing the structure of the impurities, but it was still present, it was just now a different impurity. So I end up at each stage of this as I said fairly complicated route, I end up even at the final step with material I want, and then an equal amount of the material I don't want, another diastereomer.

At the very last step I don't show the unwanted diastereomer after purification, I have mostly 62840, but I suffered a very low yield in that final step to get rid of that unwanted diastereomer.

THE COURT: When you talk about you had a very low yield, is that where you say 30 to 40 percent?

THE WITNESS: Yes, that last step I lose two-thirds of my material, because I have to remove this unwanted diastereomer.

THE COURT: Thank you.

BY MR. CARSTEN:

Q. Now, that 30 to 40 percent yield, is that the yield that starts way way up here, and goes at the upper left part of the page and goes all the way down, or is that just the yield from this step at the bottom of the page?

A. No, that's just the last step. That unfortunately was my most lowest yielding step at the very final step of the

synthesis, but I had low yield at some of the other steps as well.

Q. Now, would a person of ordinary skill in the art have been able to divine this synthetic scheme during the '814 patent?

A. Yes, it's the same one as in the '814 patent.

Q. And would a person of ordinary skill in the art have concluded that this synthesis was stereoselective or non-stereoselective?

A. No, a person ordinary skill would recognize immediately that this is a non-stereoselective synthesis.

MR. CARSTEN: I'd like to pull up DTX-58 if I could please, Mr. Merisier?

Q. And this is a portion of the IND; correct?

A. Yes.

Q. And Dr. Buchwald talked about this?

A. Yes.

Q. I'd like to pull up page 101581. And I believe Dr. Buchwald referred to a passage from the bottom of the page that said lot WA, the enantiomeric purity was 99.1 percent weight to weight. Do you remember him talking about that?

A. Yes.

Q. What does that mean?

A. So that's talking about a specific diastereomer, if you recall from Dr. Williams -- Professor Williams' testimony

there's actually 32 possible diastereoisomers, one of them being treprostinil. This is another one, this was not one I was concerned, there's only a very small amount of this particular diastereomer.

04:59 Q. But doesn't this mean that the whole synthesis is stereoselective?

A. No, no, that's just referring to one compound of the many diastereoisomers you can have.

Q. Is there another passage on this page which demonstrates

04:59 that -- that the synthesis is not stereoselective?

A. Yes, I have that on my next overhead.

Q. And this is from the upper part of the page?

A. Yes, that's early on in the same page.

Q. And what does this say?

04:59 A. So this is just what I was describing in that complex synthetic scheme; the condensation of 2 with the racemic enol-lactone 1 results in a one-to-one mixture of diastereoisomers at the 3a carbon which are present throughout the rest of the synthesis.

04:59 Q. And we see that one-to-one mixture again; what does that tell a person of ordinary skill in the art?

A. That tells you you have a non-stereoselective synthesis, a non-stereoselectively produced product.

Q. Any doubt or question in your mind that the '814 patent

05:00 does not produce stereoselectively produced isomeric compound

of treprostinil?
A. There's no doubt, I have never considered this a stereoselectively produced product.
Q. Now, let's go back to your summary slide if we could.
05:00 The second point you made was low yield; what do you mean by low yield?
A. So the yield -- when I'm discussing here was the yield actually for the entire process starting from commercially available starting material to the final purified product.
05:00 Q. How do you calculate the yield?
A. So, you have to take the yield of each step along the way, each reaction just basically multiply the yield of each step.
Q. Did you do that for the '814 patent and for the '117
05:00 patent?
A. Yes, I did.
Q. And do you have a slide that presents the results?
A. Yes, I do.
Q. What's the conclusion?
05:00 A. So, here -- the conclusion here is that the yield from the -- of the product in the '117 patent is about 10 fold higher than the yield of the product in the '814 patent. So about 3 percent from the '117 patent, at .3 percent from '814 patent.
05:01 Q. Those are both pretty low; right?

A. Low, but one is significant lower than the other.
Q. Is that 10 fold difference significant at all?
A. Yes.
Q. Why?
05:01 A. Well, the purpose of a synthesis is so that you're able to make enough material at the end of the synthesis so you can do something with it; in this case administer patients. If you don't make enough material if your yield is low, don't make enough material, there's nothing to treat the patient,
05:01 you have no drug to sell.
Q. Are you familiar with the term theoretical yield?
A. Yes.
Q. Have you considered the '814 patent synthesis against the '117 patent synthesis in perspective of a theoretical yield?
05:01 A. Yes, I have, I have a slide for that as well.
Q. Could you describe for the Court exactly what a theoretical yield is?
A. So, for a particular reaction a theoretical yield would be the amount of product that be would formed if the reaction
05:02 worked perfectly. For a process a theoretical yield would be if every reaction worked perfectly in that process.
Q. In the real world do reactions work perfectly?
A. They never work perfectly.
Q. I see a 50 percent '814 yield, and a one hundred percent
05:02 '117 yield; is that right?

A. That is correct.
Q. Well, if every reaction is working perfectly in the '814 situation, why is it that the theoretical yield is only 50 percent?
05:02 A. Well, it's because of the way I designed the synthesis. I knew at that key cyclization step I would have to get -- I could get at best 50 percent of the compound I wanted. I would necessarily because of that reaction get 50 percent of an unwanted diastereoisomer.
05:02 Q. So what would you have to do?
A. That would mean I -- at the end of the -- some time during the process I would have to get rid of 50 percent of my material. The best I could ever hope to get would be a 50 percent yield of the desired product.
05:03 Q. So in a perfect world you're maxed out at 50 percent?
A. Yes.
Q. In considering the yield issue, did you review any contentions by Sandoz in the case that support your opinion?
A. Could you ask that again?
05:03 Q. Sure. In considering the yield issue, did you review any contentions asserted by Sandoz in this litigation?
A. Oh, yes, their -- they had an invalidity analysis, a portion of that which I found relevant to this particular discussion.
05:03 Q. And I'm putting up --

THE COURT: Can we go back to that prior slide?
MR. CARSTEN: Sure.
THE COURT: I just have a question. So you were talking about real world --
05:03 THE WITNESS: Yes.
THE COURT: As opposed on theoretical?
THE WITNESS: Yes.
THE COURT: So why on the '117 patent do you have that marked as hundred percent.
05:03 THE WITNESS: So again we're talking theoretically if everything worked, because the '117 patent is a stereoselectively produced product, they could actually get a hundred percent of material. The reality is they got less than that, I got much less of that in the '814 patent.
05:04 THE COURT: I see. Because it's stereoselective you can yield -- you may be able to yield a hundred percent --
THE WITNESS: Yes, you have the possibility of that happening.
THE COURT: Okay, thank you.
05:04 BY MR. CARSTEN:
Q. Now, turning back to PTX-082, the Sandoz invalidity contentions, was there any particular passage that you found instructive or helpful with respect to your analysis on the yield issue?
05:04 A. Yes. So this is a page -- looks like it's page 42 if I

can read the number, but it's an excerpt from a particular page in the Sandoz invalidity contention.

Q. And would you please read that into the record? And just for the record I believe it's from page 47 of Sandoz's invalidity contention.

A. Yes. So they're talking about my earlier syntheses of treprostinil, it says: Early preparations of treprostinil resulted in complex mixtures of diastereoisomers requiring separation and low yield; other early efforts by Upjohn in optimizing the preparation of treprostinil focused on closure strategies for the center ring, which also suffered from lack of sufficient stereo control, and/or low yields due to lengthy synthetic sequences.

Q. Now, when they're talking about other early efforts by Upjohn, what are they referring to?

A. They're referring to my work I believe.

Q. And since this is your work, is this a correct and accurate description of your work?

A. Yes, it is.

MR. CARSTEN: Your Honor, I'd move PTX-82 into evidence.

MR. STEINDLER: Judge, it's -- contentions don't come into evidence.

MR. CARSTEN: Your Honor, it's an admission of a party opponent, as well as it's not being offered for the

truth of the matter asserted. It confirms -- it's confirmatory evidence that the expert relied on and considered in connection with his opinions in this case.

MR. STEINDLER: What lawyers write in their contentions is never evidence and it doesn't come into evidence.

THE COURT: So, you're saying it's an admission, so it's an adverse admission?

MR. CARSTEN: Yes, your Honor.

THE COURT: All right. So I don't even understand that.

MR. CARSTEN: This is -- so early on in the case we had to exchange documents --

THE COURT: I understand that part.

MR. CARSTEN: Right. This is what -- this is how Sandoz characterized the very articles that they now say are anticipatory and somehow anticipate the '117 patent. They admit freely they're low yields, they're mixture of diastereoisomers requiring separation, and the syntheses lack -- or suffer from lack of sufficient stereo-control.

These are all exactly the points, your Honor, that we're submitting suggest and require in our view a finding that these references do not anticipate. This is an admission that goes right to the heart of the case.

MR. STEINDLER: Statements of counsel are not

evidence. These are -- these are papers, invalidity contentions prepared by counsel, they're not evidence and contentions never come into evidence in cases.

THE COURT: So whose admission is it?

05:07 MR. CARSTEN: It's the -- it's an invalidity contention offered on behalf of Sandoz, the party.

THE COURT: The party itself? Sustained. Go to your next point. I understand your point.

MR. CARSTEN: Thank you, your Honor. And we've read

05:07 the passage -- the particular passage into the record.

THE COURT: Exactly.

BY MR. CARSTEN:

Q. In addition to these contentions, Dr. Aristoff, did you review any references from Dr. Moriarty which looked back at

05:07 the work that you had done on treprostinil?

A. Yes, I did. I looked at what he had written in the 2004 Journal of Organic Chemistry article.

Q. And have you prepared a column of slides with call-outs from the Moriarty JOC article?

05:07 A. Yes, I do.

Q. And this is DTX-171, which I believe is in evidence. Would you please explain to the Court what's being shown on slide 22, and how it affects your analysis Dr. Aristoff?

A. Yes. This is from the discussion section of that

05:08 particular paper, and he's referring to my earlier syntheses,

of the -- as shown in the '814 patent. He says: Benzidine prostacyclin UT-15 -- which is treprostinil -- has been synthesized previously by Upjohn chemists with no stereochemical control in the creation of the C38 chiral center in 11. And that's what I've been talking about, that I got a one-to-one mixture at that particular step.

He goes on to say: Unfortunately, this low level of control of stereochemistry in this route led to significant separation problems in obtaining the final product, and could not be used to fulfill our scale-up needs for development of UT-15.

Q. And --

THE COURT: So you agree with that?

THE WITNESS: Yes, I definitely agree with that.

Q. Is that an accurate description in your view of the difficulties with the synthesis that you had developed at Upjohn?

A. Yes, it is.

Q. Was there anything else -- now, let me just back up for a second. Dr. Moriarty, Robert Moriarty, the author of this paper, he's the one who is the named -- a named inventor on the '117 patent; right?

A. That's correct.

Q. Now, did you find any other passages in the Dr. Moriarty JOC article that you found instructive or helpful?

A. Yes, there's several more, I have an additional one on the next page.

MR. CARSTEN: And before we move on, your Honor, for the record, the passage that we just quoted was from page 5997, from DTX-171.

THE COURT: Got it.

MR. CARSTEN: Thank you, your Honor.

BY MR. CARSTEN:

Q. Dr. Aristoff, would you please describe for the Court these passages from the Moriarty article that you found helpful and how they affected your analysis?

A. Yes. So again, he's -- in the top bullet point he's talking about referring to my earlier process, that the routes, although they're interesting were inadequate to producing kilogram quantities of UT-15; and they wanted to develop a better route, a novel route that was improved, and they wanted to provide a route that was -- provided an enantiopure intermediate. Basically he's talking about he wants to provide a stereoselective synthesis, that's basically what he's referring to here.

Then at the bottom of the slide, it talks about two points are noteworthy in connection with the Pauson-Khand cyclization; so now he's talking about the '117 patent process. The first is the high chemical yield, 89 percent, and the high degree of chiral induction of almost one hundred

percent. So now he has a very highly stereoselective reaction in that Pauson-Khand reaction.

MR. CARSTEN: Your Honor, for the record, the passages from DTX-171 that are referred to there are 5998 through 9, and 6001.

THE COURT: 5998?

MR. CARSTEN: To 5999, and then a second passage at page 6001.

THE COURT: Okay, thank you.

BY MR. CARSTEN:

Q. And does this comport with your understanding of the benefits of the Pauson-Khand reaction as it's described and claimed in the '117 patent?

A. Yes, it does.

Q. Now, we've talked about the stereoselectivity issue, we talked about the low yield, you also mentioned impurity profile; do the claims talk about impurities?

A. No, they do not specifically mention impurities.

Q. So why did you bother to consider the impurity profile?

A. So again, it's my understanding in a product-by-process claim, that any structural or functional differences are relevant, even if they're not specifically claimed. And I would consider impurity profile to be part of a structural difference.

Q. Now, in connection with your impurity profile analysis

that we're about to walk through, were you responding to something that Dr. Buchwald had did in his expert reports?

A. Yes. Both in his expert report and then his testimony the other day, he talked about comparing the impurity profile in the two Upjohn development lots, with some of the lots that UTC had prepared.

Q. And so, what did you do?

A. So, I just did more a complete analysis. He only picked in his expert report four lots, actually he showed the other day seven lots, I actually was able -- I see information on about 57 lots, development lots, from UTC, up through I think it was about April of 2004, that were made by the '117 process. So I used all the lots, not just the selective lots.

Q. I'd like to show you a slide that was used by Dr. Buchwald in his direct examination conducted by Mr. Steindler the other day. Is this showing the seven lots that you talked about?

A. Yes, it shows first the two Upjohn lots, and then the seven UTC lots from the '117 process.

Q. Now, did you perform exactly the same analysis as Dr. Buchwald did?

A. No, again, I used all the lots up through -- all the commercial and development lots from UTC through May of -- excuse me; through April of 2004.

Q. Now, I'd like you to turn in your binder to PTX-100A. Do

you recognize this document?
A. Yes.
Q. Now, what was your source material generally speaking for the information presented on 100A?
05:13 A. So that there were a lot of documents; this was taken from a lot of information in the NDA and IND amendment, also a certificate of analysis, so there's a lot of numbers here. They made a lot of lots.
Q. Was that data voluminous?
05:14 A. Yes.
MR. CARSTEN: And your Honor, I'd offer 100A as an exhibit under Rule 1006, as a chart that compiles voluminous data. And for the record, I'd identify the source as PTX-521, 742, 753, 894, and 905, which have all been admitted into
05:14 evidence when Dr. Zaccardelli was here. And Mr. Steindler reserved an objection because those documents had not been used at that time.
THE COURT: Any objection?
MR. STEINDLER: No objection.
05:14 THE COURT: All right, admitted.
(Plaintiff's Exhibit 100A was marked into evidence.)
MR. CARSTEN: Thank you, your Honor.
THE COURT: As a summary.
BY MR. CARSTEN:
05:14 Q. Dr. Aristoff, how do you know that all the UTC lots on

Exhibit 100A were made using the '117 patent process?
A. Well, this is information I got from UTC documents, the NDA, the amendments, certificate of analysis. I didn't see any other process that UTC was using in the NDA, so these
05:15 presumably were only made using this process.
Q. Now, with respect to the analysis that you did, what were the results?
A. So I've actually tried to summarize this mountain of data in a slide here. What I'm showing up on the -- what I'm
05:15 showing on the very bottom of the slide in blue, is the average of the impurities from the two Upjohn lots; so this is the same lots that Dr. Buchwald had used in his analysis. And then in orange, it's the average of the material that UTC provided following the '117 patent.
05:16 So I looked at the same impurities for this particular slide that Dr. Buchwald did, as well as the total related substances, which he also did.
Q. What was your conclusion?
A. So again I see significant differences in the impurity
05:16 profile on average between the material -- the product of the '814 patent versus the product of the '117 patent.
Q. Did you find any impurities in one of the sets or lots that were not in the other?
A. Yes, it's not shown on this slide, but there actually
05:16 were some impurities that were only present in the '117 patent

lots that UTC had prepared that would actually not in the two Upjohn lots.

Q. And just so the record is clear, let's just walk through them. In terms of the 2AU90 impurity, what was the '117 patent average versus the '814 patent average impurity?

A. Yes. So for this 2AU90, which the structure of that particular -- chemical structure of that particular compound is shown in the upper left, this particular diastereoisomer, there's actually about 20 fold more of this in the material prepared by the '814 patent, versus the product of the '117 patent.

Q. And what are the numbers that you came up with on the average?

A. So, on average -- so for the material from the '814 patent, there's about .8 percent, versus .04 percent in the '117 patent.

Q. And with respect to the 750W93 impurity, what was your -- what was the result there?

A. So here in this case there's about 10 fold higher levels of this particular impurity, going from .163 to 1.5, so 10 fold more of this impurity in the product of the '814 patent versus the product of the '117 patent.

Q. And with respect to the 751W93 impurity, what's your result there?

A. So again, that's similar, there's about 10 fold more of

that particular impurity in the '814 product versus the '117 product.

Q. And finally with respect to total related substances, what is total related substances first, and then what's the result there?

A. So the total related substances are the impurities that are related to the structure of the chemical formula known as treprostinil. And the total -- you just basically add those up, and then you get a sense, okay, what's the purity of the final treprostinil compound, the substance, the final product of the patent.

In this particular case, the '814 product is about four percent, has about four percent impurities, related impurities; the '117 product has just slightly under one percent impurities. So it's about four fold higher level of impurities in the '814 product relative to the '117 product.

Q. Did you consider in connection with your work in this case a memorandum by John Bettis relating to impurities of various lots?

A. Yes, I show that on the next slide.

Q. And this is PTX-753. What is this?

A. So I believe this is -- this is certainly a communication that he had recommending using tighter drug standards. He had noticed that in many -- all the recent -- actually I saw the same thing in my analysis; the last 30 or so lots that they

prepared at UTC -- and this is -- I think this memo was around 2004; the last 30 lots were very high purity. And you realize that they could actually have tighter specifications, they could put a requirement in okay, we'll only pass material if it's very highly pure, at least 99 percent pure, with less than this amount of impurities and he refers to specific impurities and numbers.

And he noticed that actually that under those proposed limits, the two Upjohn lots Dr. Buchwald used and that I had used, would actually not meet that specification. The impurity levels in those two Upjohn lots were too high.

Q. I recognize it's difficult to see --

MR. CARSTEN: But perhaps we can turn to PTX-753 and pull out the date down at the lower corner?

Q. When was that?

A. So this is March of 2004.

Q. Have you prepared a set of slides to try to help explain the differences between the products of the '814 patent on one hand and the '117 patent on the other to the Court?

A. Yes. There's a lot of numbers here, so it gets kind of difficult. So I try to put some visuals to make this a little more clear.

Q. Would you describe demonstrative 28 to the Court, please.

A. So, in this particular slide, I'm showing the product of the '117 patent compared to the '814 patent, the '814 patent

product is on the left. At the last step prior to purification, I'm showing that it's primarily a one-to-one mixture of treprostinil and its diastereoisomers in the '814 patent, and primarily the stereoselectively produced treprostinil in the '117 patent. There are small amounts of other isomers as well, but primarily the product at this stage is -- for the '814 patent is a one-to-one mixture of treprostinil and a diastereomer, whereas with the '117 patent it's nearly all treprostinil, the desired treprostinil.

Q. And now the next demonstrative 29, what are you showing here?

A. So I'm trying to go now sort of the next level of detail, when you actually do the final purification of the product of the '814 patent versus the product of the '117 patent, on average based on the analysis that I just described there's about four percent more -- excuse me; four fold more impurities in the '814 product versus the '117 product. And furthermore, there's actually some different impurities that are present only in the '117 product, but not in the '814 product.

Q. Now, with respect to demonstrative 33, what is this showing to the Court?

A. So again, this is to remind us that there's at least a 10 fold difference in yields from the -- of the '814 product versus the '117 product.

Q. Now, with respect to all four claims of the '117 patent, what's your opinion about whether the '814 patent anticipates the '117 patent?

A. So, I do not believe that the '814 patent invalidates the claims of the '117 patent. The claims of the '117 patent are valid despite the '814 patent.

Q. As the inventor of treprostinil, how confident are you that there are structural and functional differences between the '117 patent and the '814 patent?

A. Well, I have no doubt of that.

Q. Now, Dr. Buchwald also suggested that -- or indicated or testified that he believed the patent -- the '117 patent claims were obvious over the '814 patent; did you hear that?

A. Yes, I believe he testified to that.

Q. Are you familiar with Sandoz's position on obviousness as to the '117 patent?

A. Yes, I believe they state that even if the prior art had not anticipated, the claims of the '117 patent, that you would just simply purify the product of the '814 patent to have the same product as the '117 patent.

Q. Do you agree with that position?

A. No.

Q. Why not?

A. Well, for a number of reasons, I think I have some of this on the next slide.

THE COURT: Before you change slides, you talk about yield there, Doctor, on slide --

THE WITNESS: Yes.

THE COURT: So how do you define yield?

05:24 THE WITNESS: So the yield is for the entire process. I mean if you defined it for the last step -- my yield is terrible; the last step of the '117 patent it's actually quite good.

THE COURT: Okay. Let's say you're doing this

05:25 experiment, right, in the beginning you're going the synthesize, you would start out with the same amount of material; right?

THE WITNESS: Well, if you wanted to make the same amount of material at the end, you would have to start up with

05:25 a lot more starting material in the '814 patent.

THE COURT: But I'm trying to get how got the yield there.

THE WITNESS: Again, again, these particular yields are calculated from the examples in the patents, or actually

05:25 in one case I used the NDA process and yield and the '117 product was actually much higher.

THE COURT: So when you go through each step, you take out some of the impurities --

THE WITNESS: Well, you will do purification at many

05:25 of the steps, which sometimes remove some impurities.

Unfortunately in the '814 process I was not able to remove the major impurity. At the very end I'm still left with a one-to-one mixture, and that's with even the last step of my synthesis of low yield as well.

05:25 THE COURT: Okay. All right, thank you.

BY MR. CARSTEN:

Q. Now, for each individual step along the way, are you experiencing one hundred percent chemical transformations, so all the starting material goes all the way over and behaves

05:26 nicely and gets you product?

A. No, that never happens.

Q. So what kind of range of yields are you looking at in terms of each of the steps roughly?

A. So I can't recall all of -- each and every step. I

05:26 recall I had several low-yielding steps in the '814 patent, particularly the last step was the worse, but also when I did the intramolecular cyclization that was an unsatisfactory yield.

Q. Now, when you're sort of lining up various chemicals

05:26 transformations, how do you -- if you have a 30 percent yield and then another 30 percent yielding step, what's the over -- what's the net result in terms of the yield of those two steps taken together?

A. So those would be two poor yielding steps, after -- after

05:26 those two steps only a nine percent yield. So you're just

multiplying the yield of each of the steps to get the final yield.

THE COURT: I understand, thank you.

Q. And what's being shown on this slide?

05:27 A. So here we're talking about what -- wouldn't you just continue to purify the '814 product to get to the '117 product. Of course with the '117 product that's really not necessary, because you already have a stereoselective process, that you have at the crude stage a product that's actually

05:27 still relatively pure. The '814 process you have to get rid of a lot of material. There's no guarantee even by these purification techniques you would get to the same product as the '117 patent.

But furthermore, in a practical sense, when you try to

05:27 purify the '814 product, you lose so much material, the yields go down. And my last step with one recrystallization I lost nearly two-thirds of the material, I certainly lost over half of the material. And this is unacceptable. You continue to do this you will just end up with not enough material at end

05:28 of the synthesis.

Q. Now, we saw an example -- Dr. Buchwald talked about this reference standard lot, which was 99 and change percent pure, and that was from the Upjohn synthesis; right?

A. That is correct.

05:28 Q. Why doesn't that show that it's obvious to just try and

purify up material?
A. Well, first you have to remember that reference standard actually came from one of the lots I analyzed, which already had five to 10 recrystallizations to get to that point and a
05:28 lower yield. You would do recrystallization you'd have even less material. But I noticed in the analysis of that reference standard they still had 10 times as much of this 2AAU90 impurity that I talked about in earlier slide, as in the average of the '117 product, from the '117 patent.
05:29 Q. Now, you mentioned five to 10 recrystallizations; is that routine to a person of ordinary skill in the art to do that kind of level of purification?
A. No, even Dr. Buchwald agreed in his testimony that yield -- that's undesirable, you don't usually do that.
05:29 Q. Now, I'd like to call your attention to PTX-493. And this is an optimization memo at UTC. Did you consider this document in connection with your work in the case?
A. Yes, I did.
Q. And how did -- you have some portions of PTX-493, pages
05:29 176 through 177 here. How did these affect your analysis, or will you explain these to the Court, please?
A. Yes. So again they were considering using my particular synthesis of the '814 process, but they quickly recognized -- recognized that the '814 process would not be effective on
05:30 large scale because of the separation problems, particularly

the end of the synthesis because I have this non-stereoselective product. I've got isomers throughout this synthesis, and again at the very end I have to remove a large amount of the -- of the undesired isomer.

05:30 Q. And you're specifically referring to the bottom part of the lower quotation, extensive separation problems?

A. Yes, that's what I'm talking about.

Q. Any other portions of PTX-493 in evidence that you considered?

05:30 A. Yes, I have another slide which gives some more detail. Again, they're talking about the '814 process at the top box that was used -- actually used to prepare some lots of -- for development purposes. But they noticed that after crystallizations they had to do -- they did an initial

05:31 crystallization and then it says starting over here on this slide, it says five to 10 recrystallizations were necessary to yield a product that was purified by chromatography on silica gel to give a product that was recrystallized again to give 167 grams. And then they note the yield here in that step is

05:31 only 12 percent which is even worse than I got.

And in the bottom box they summarize all this, talking about the '814 type process: This prior work did not offer much guidance for our purification of the final product of UT-15 -- that's treprostinil -- because they had a mixture of

05:31 stereoisomers at this stage; the unacceptably lower recovery

of the product was not relevant because in contrast to the Upjohn work, we have a pure stereomer at the stage of trial 66 and 1. And they're are talking about the '117 process.

Q. With respect to the top passage -- and these passages are from PTX-493, at pages 176 through 177, and page 216. With respect to the top call-out here, is it customary to use five to 10 recrystallizations and then a chromatography column and then another recrystallization?

A. No, this is not what you want to be doing, this is not formerly done.

Q. And with respect to the lower portion of the UTC optimization memo, did you find that UTC actually considered the '814 purification methods in an amendment to try to purify material?

A. They considered using that process, yes.

Q. And what did they find?

A. And again they found that their judgment was that this just was not going to be practical, they needed a different process.

Q. In your view, your opinion, Dr. Aristoff, are the claims of the '117 patent obvious over the '814 patent?

A. No.

Q. And as the inventor of treprostinil, is there any doubt in your mind?

A. I have no doubt.

MR. CARSTEN: Pass the witness, your Honor.

THE COURT: Before cross, Doctor, you indicated that when you were undertaking your work with regard to treprostinil, that you never thought of doing a stereoselective type of procedure?

05:33

THE WITNESS: No, I wanted to do a stereoselective procedure, I just couldn't come up with one.

THE COURT: Oh, you couldn't come up with one. Even though you tried.

05:33

THE WITNESS: Yes.

THE COURT: Okay, thank you.

MR. STEINDLER: Judge, it's 4:30.

THE COURT: Oh, it is?

MR. STEINDLER: Yes. I respectfully request that we

05:33

begin the cross-examination on Monday.

THE COURT: Do you object to that?

MR. CARSTEN: No, your Honor.

THE COURT: Doctor, you can come back on Monday?

THE WITNESS: Yes.

05:33

THE COURT: All right. So we'll break for the day and I'll see you on Monday. We're starting on 11:00.

MR. STEINDLER: Two quick comments. One is, notwithstanding your previous objection, just before the examination of this expert, I got a slide deck that was

05:34

different than I got last night. It was renumbered and

reordered, and that was the source of my confusion before.

I'm going to ask again, that for the instruction to be given that I get the evening before the slide deck that they're going to use with the witness. It's very difficult to do a cross if you've got suddenly a reordered number of the slides that are being used.

MR. CARSTEN: Your Honor, may I just briefly address this? I don't think this is something you need to deal with. Dr. Buchwald testified yesterday, and he did not focus on a number of the issues we expected him to focus on. We presented that slide deck two nights ago. In light of Dr. Buchwald's testimony, we took slides out, and we included instead of the PTX number in addition the DTX number which were the documents which were admitted.

THE COURT: You know, I never usually give strict orders as to what everyone has to do, but generally as best as te attorneys can cooperate with each other, I think you should continue to do that. If you have changes in your presentation I think you should make your adversary know as soon as possible. And if you wouldn't mind, that's all we're requesting for you to do here.

MR. CARSTEN: Very well, your Honor, and in fact I did hand Mr. Steindler the revised presentation this morning and identified the changes.

MR. STEINDLER: No, that's not true. That is an

untrue statement. He did not identify that he had reordered and renumbered his the slides, I got them when he gave that to me in the middle of this examination.

THE COURT: All right. Well, you'll have all

05:35 weekend to --

MR. STEINDLER: I realize that, I understand that, I do have a weekend to revise that for my cross, but it is challenging. And I would ask in the future that that not take place.

05:36 THE COURT: All right. We've noted it on the record, so thank you.

MR. STEINDLER: And then lastly, you asked for a brief on claim construction; I'm going to hand up hard copies to your law clerk.

05:36 THE COURT: You gave a copy the your adversary? It must be filed --

MR. STEINDLER: Sorry; there's one in here, I have to take my courtesy copy to -- and we are filing it also, of course.

05:36 THE COURT: So, Doctor, you can step down.

THE WITNESS: Thank you, your Honor.

THE COURT: I'll see you on Monday. We are starting at 11:00 on Monday.

MR. STEINDLER: Thank you, your Honor.

05:36 MR. CARSTEN: And your Honor, we have filed our

claim construction position paper, whatever you want to call it.

THE COURT: So we're starting on 11:00 on Monday, because I have that criminal matter first which I forgot about, so you have to clean out that side if you don't mind.

05:36

Do you want to go through the documents that we had for this afternoon that have gone into evidence?

MR. CARSTEN: We're ready to proceed, your Honor.

THE COURT: I have PTX-102; PTX-100A; that's all I have.

05:37

MR. CARSTEN: That's all I have as well.

THE COURT: Okay, thank you. So I'll see you Monday.

(Counsel say thank you.)

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

UNITED THERAPEUTICS CORPORATION,

Vs.

SANDOZ, INC.,
DEFENDANT

CIVIL NO.
12-1617 (PGS)
13-316

MAY 19, 2014
CLARKSON S. FISHER COURTHOUSE
402 EAST STATE STREET
TRENTON, NEW JERSEY 08608

B E F O R E: THE HONORABLE PETER G. SHERIDAN
U.S. DISTRICT COURT JUDGE
DISTRICT OF NEW JERSEY

TRIAL - DAY 10

Certified as true and correct as required
by Title 28, U.S.C. Section 753
/S/ Francis J. Gable
FRANCIS J. GABLE, C.S.R., R.M.R
OFFICIAL U.S. REPORTER
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MR. CARSTEN: I understand, I just want to preserve the objection on the record, your Honor.

(PAUL ARISTOFF, PH.D., previously sworn, resumes stand.)

10:24 THE COURT: So, Dr. Aristoff, you're still under oath.

THE WITNESS: Yes, your Honor.

(CROSS-EXAMINATION OF PAUL ARISTOFF, PH.D., BY MR. STEINDLER:)

Q. Did good afternoon, Dr. Aristoff.

10:24 A. Good afternoon.

MR. STEINDLER: May I approach, your Honor?

THE COURT: Oh, yes, you may.

(Handing to witness and Court.)

BY MR. STEINDLER:

10:24 Q. Now, you see I have in this first slide just set out the basic law with respect to anticipation; do you see that, sir?

A. Yes.

Q. And the first step in an anticipation analysis involves construction of the claims of the patent; right?

10:25 A. Yes, it says that.

Q. And you did that in your invalidity analysis that you presented on your direct testimony; correct?

A. I certainly looked at what the claims said, yes.

Q. And in fact you were asked specifically questions by Mr.

10:25 Carsten as to the meaning of the claims; correct?

A. Yes.
Q. And the second step, of an anticipation analysis involves comparing the claims to the prior art, do you see that?
A. Yes.
Q. And you did that in your -- strike that.
You did that in your invalidity analysis that you discussed in your direct testimony; correct?
A. Yes.
MR. STEINDLER: And can we go to PTX-2, please.
Q. You'll recognize this as the '117 patent; correct?
A. Yes.
MR. STEINDLER: Can we go to claim 3.
Q. You're familiar with claim 3; right?
A. Yes.
Q. And claim 3 the '117 patent recites a stereoselectively produced isomeric compound, according to this specific chemical formula; right?
A. Yes.
Q. The compound according to this specific chemical formula set out in claim 3 is the treprostinil compound; correct?
A. Well, that's the molecular formula of treprostinil.
Q. It's your testimony that that's not -- strike that.
It's your testimony that that molecular formula does not refer to the treprostinil compound?
A. In the -- in the context of the you draw the compound

treprostinil, you have to draw -- you'd draw a single molecular formula in the context you may draw treprostinil you understand it's not hundred percent that molecular formula it contains that formula plus impurities.

00:26 Q. This patent is drawing the molecular structure of treprostinil compound; correct?

A. Yes, that's the molecular formula for treprostinil.

Q. Now, you invented the treprostinil compound 35 years ago; right?

00:27 A. Yes.

Q. And the compound depicted in claim 3 is the treprostinil compound you invented 35 years ago; correct?

A. That's the molecular formula for treprostinil.

Q. Treprostinil is a single specific chemical compound;

00:27 correct?

A. When you draw it as a structure when you make it it's -- it's a mixture with impurities.

MR. STEINDLER: Can we go to Dr. Aristoff's deposition transcript, page 27 lines 10 to 13.

00:27 Q. Now, you recall you were deposed in this case?

A. Yes.

Q. You were asked to the following question: Is treprostinil a single specific compound. And you answered: The chemical treprostinil the chemical structure is a single

00:27 chemical compound.

MR. CARSTEN: Your Honor, I object. This is improper impeachment. That's entirely consistent with what the man just said.

THE COURT: Overruled.

10:27 THE WITNESS: Yes, again in the context of talking about the molecular structure for a compound, when you're asked to draw a structure it's going to be a single molecular structure, but a chemist would recognize when you make treprostinil you make the compound it's primarily that

10:28 stereoisomer, it will contain other materials.

MR. STEINDLER: Can you pull up the admissions that UTC made at summary judgment.

Q. You recall that UTC admitted that treprostinil is a single specific compound -- strike that.

10:28 You recall that UTC admitted that treprostinil is a single specific chemical compound with is a single stereoisomer; correct?

A. Yes.

Q. Now, that admission was made in February 28, 2014; do you

10:28 recall that?

A. I don't recall the exact date, but I believe that, yes.

Q. And there's nothing about the physical world that has changed in the last three months that would cause that to be an untrue statement; correct?

10:29 A. No.

Q. There's nothing about the naming conventions in the chemical arts that has changed in the last three months that would make that statement untrue?
A. No.
Q. Now, a person of ordinary skill in the art would understand that the compound depicted by the chemical formula set out in claim 3 is a single specific chemical molecule; correct?
A. They would understand, yes, when you're talking about -- when you draw a structure of a compound you draw one structure.
MR. STEINDLER: Could you go back to the patent please and go to claim 3?
Q. A person of ordinary skill in the art would understand that when you draw a specific chemical formula as in claim 3, that this refers to a single specific chemical compound; correct?
A. Yes, but when I see stereoselectively produced compound, I'm talking about making a compound that would primarily be that single molecular structure.
Q. Now, in chemistry a compound refers to a single specific molecule; correct?
A. Yes, in the context when you're drawing a structure or giving a name, yes, that's correct.
MR. STEINDLER: Can we turn to the transcript of his

deposition to page 27, starting at line 21, and going to page 28, at lines 22. And just blow that up, please. 21 there, to 28-22.

Q. And you're asked: What do you understand compound to mean. And you say: I distinguish a compound as a specific molecule, but that's different from a process.

And then you go on to say: Of a chemical process which is the -- a mixture of molecules.

Right?

A. So, that's actually not correct. Can we start -- can you go back to the bottom of the previous page?

MR. STEINDLER: Go ahead.

A. So it says: So I distinguish a compound as a specific molecule, but that's different from a product. Because again I'm in the context of when you draw a structure you draw a single compound.

MR. STEINDLER: Can you then blow up here on page 28, from line 5 to the bottom.

Q. And you say: With respect to a particular structural formula is that a compound, and then you say under my definition that I just said where it's a specific molecule, yes.

And you want to distinguish that between what's in a reaction flask; correct?

A. Yes, when you make a compound versus when you draw a

structure of a compound.
Q. And when you draw the structure of a compound that refers to a specific molecule; right?
A. That's correct.
10:31 Q. And you are asked compound and molecule are synonymous; is that correct. And you say: I'm defining for my purposes compound to be a molecule, right.
A. That's correct. I'm trying to distinguish that between the product of a reaction or the product of a process. Which
10:32 is primarily that compound.
Q. And a compound is a specific molecule as opposed to a mixture of molecules; correct?
A. Yes, when you're asked to draw a compound it will be one single structure.
10:32 MR. STEINDLER: Can we go again in this deposition to page 29, lines 4 to 10.
Q. You're asked: It's commonly understood in the chemical arts that a compound is a specific molecule. And you say: Typically a compound is a specific molecule as opposed to a
10:32 mixture of molecules.
Right?
A. Yes, again in the context of drawing a molecule not in the context of making the molecule -- making the compound of the -- when you draw the structure of a compound you'll draw a
10:32 single molecule and when you make a compound it would be

understood it's not a hundred percent that molecule.
Q. Now, in the chemical arts a mixture of molecules is called a mixture; right?
A. Yes, it's called a mixture of them, yes. Particularly when it's like a one-to-one mixture like my '814 process.
THE COURT: I didn't hear the end of your answer.
THE WITNESS: Yes, particularly in my case where it was the '814 product, was a mixture because it was a one-to-one, it wasn't mostly one molecule.
BY MR. STEINDLER:
Q. So a person of ordinary skill in the art would understand that the term compound refers to a single specific molecule, while the term mixture refers to a mixture of different molecules; correct?
A. Yes.
Q. Now, you've talked a lot about the real world in your direct testimony; right?
A. Yes.
Q. And in the real world every man-made compound is produced with impurities; correct?
A. Yes.
Q. No man-made compound is a hundred percent pure; right?
A. Certainly not in my experience of working in the laboratory it has never been.
Q. Now, the many composition of matter patents are drawn to

a specific chemical compound depicted by a chemical formula; correct?

MR. CARSTEN: Your Honor, I object; relevance.

THE COURT: Relevance? You may answer the question.

10:34 THE WITNESS: Could you repeat the question?

BY MR. STEINDLER:

Q. Many composition of matter patents are drawn to a specific chemical compound depicted by a particular chemical formula; right?

10:34 A. Yes, that's correct.

Q. And is it your opinion that all of these types of compound claims to man-made compounds are actually claims to a mixture because the compounds are never a hundred percent pure in the real world?

10:34 A. So I'm -- I don't understand the legal definition we're getting at here.

THE COURT: You don't have the answer the question. Rephrase.

Q. Let me ask you this. Is it your opinion that all

10:35 product-by-process claims to a chemical compound made by some process, are actually claims to a mixture because the compounds are never a hundred percent pure in the real world?

MR. CARSTEN: Your Honor, I object. This man is not a lawyer. This is an incomplete hypothetical, it's nearly

10:35 impossible to answer.

THE COURT: It does seem like it's a hypothetical question, Mr. Steindler.

MR. STEINDLER: Well, I'm allowed to ask an expert a hypothetical because it bears directly on his interpretation of these claims.

THE COURT: Well, I think you have to rephrase it somehow. Because I couldn't understand it.

MR. STEINDLER: All right.

BY MR. STEINDLER:

Q. You say that the claims of the '117 patent are to a mixture of compounds; right?

A. They're to a product which is predominantly the molecular -- contains the molecular formula of treprostinil, but there's impurities with it.

Q. And the product that you say is the product of the '117 patent claims is a mixture of compounds; correct?

A. Yes, it could be defined as a mixture of compounds.

Q. And in fact, you're defining it as a mixture of compounds; right?

A. I'm defining it as a product -- a product as a the treprostinil molecule in there as the primary component plus impurities. That could be a compound -- I don't like the lab slang analogy, that's what we talk about in chemistry. But the impurities are also to be considered compounds as well because they have specific molecular structures.

Q. So you're interpreting the product of the '117 patent claims to be a mixture of compounds; correct?
A. Yes, in one sense.
Q. Now, you say that the claims of the '117 patent are
10:36 actually to this mixture of compounds because the claims include the process for making treprostinil; right?
A. That's a really long question; could you do that one again?
Q. Sure. Your contention is that the product of the '117
10:37 patent is to a mixture, because the patent claims include the process for making treprostinil; right?
A. I'm not sure -- I'm saying the product tells me that it's a -- stereoselectively produced compound tells me I'm talking real world, real compound, that is not a hundred percent pure
10:37 and has primarily the treprostinil molecular structure, but there other compounds in there.
Q. So in the '117 patent claims, you say the product is a mixture because the process for making that product gives you a mixture of compounds; right?
10:37 A. Again, could you say that again? I'm having a hard time following you.
Q. Sure. You're contending that the product of the '117 patent is a mixture; correct?
A. I'm saying yes, it's a mixture that primarily contains
10:38 treprostinil.

Q. And it's a mixture because the claims include process limitations -- strike that.

You say that the claim is to a mixture because the '117 patent includes a process for making that product; right?

10:38 A. Yes, if it's made it has to come from somewhere, that's the real world.

Q. In your opinion, is every product-by-process claim to a compound made by some process, actually a claim to the mixture of compounds that you get when you make that compound?

10:38 THE COURT: Don't answer yet, there's an objection.

MR. CARSTEN: I object to the question, your Honor; incomplete hypothetical and calls for a legal conclusion.

THE COURT: Okay. I think all these questions have been asked and answered already, so I don't see why we're

10:39 still harping on this subject. I think we should move on to a new topic. So the objection is sustained.

MR. CARSTEN: Thank you, your Honor.

MR. STEINDLER: Let's go to Dr. Aristoff's slide number 8, please.

10:39 I'll withdraw that -- no, let's go back to this slide.

BY MR. STEINDLER:

Q. This is a slide you put up in your direct testimony; right?

10:39 A. That's correct.

Q. And under the law of anticipation for a product-by-process claim, the focus is on the product that's produced by the claimed process; right?
A. Yes.
Q. And if you use a different process you're always going to get a different impurity profile for the final product; right?
A. That's possible. It depends how different the process is.
Q. Assuming the process is substantively different under the theory that you're applying in this case, you can get a patent to an old compound by developing a new process for making it; correct?
A. It's possible.
Q. Now, let's go back to claim 3 please of the '117 patent. You'll agree with me that the claims recite just the specific treprostinil compound with a specific chemical formula; right?
A. Well, the whole claim talks about it was produced by a process, there's more to that.
Q. The claim doesn't recite any impurities; correct?
A. No.
Q. If impurities were set out in the claim, they'd have to be drawn with a different chemical structure than the one we see here; right?
A. If you specifically mention impurities, you would put them in, you would draw their chemical structure.

Q. Now, the claim could have identified a particular impurity profile by setting out an actual impurity profile in the claims; right?

THE COURT: There's an objection.

10:41 MR. CARSTEN: Objection, your Honor; calls for speculation.

THE COURT: This is hypothetical and I don't know its relevance. So sustained.

MR. STEINDLER: May I be heard, your Honor?

10:41 THE COURT: You may.

MR. STEINDLER: The relevance of it is that the construction that he's adopting is reading in unrecited limitations into these claims.

THE COURT: All right. So you may proceed then.

10:42 You can reask the question.

MR. STEINDLER: Sure.

BY MR. STEINDLER:

Q. The claims of the '117 patent could have identified a particular impurity profile by setting out an impurity profile

10:42 in the claims; right?

A. I don't know, I've never seen anything like that so I don't know if you can do that.

MR. STEINDLER: Can we turn to DTX-60, which is a portion of UTC's new drug application --

10:42 THE COURT: When you say you've never seen anything

like --

THE WITNESS: Yeah, I don't --

THE COURT: Can you explain what --

THE WITNESS: I don't really understand -- you couldn't draw every impurity, that wouldn't be normally what you would do.

BY MR. STEINDLER:

Q. Have you seen UTC's NDA?

A. Yes, I have.

MR. STEINDLER: Can we turn to the page Bates marked 21940.

THE COURT: Mr. Steindler, just tell me what the exhibit number is again? I know we --

MR. STEINDLER: It's DTX-60, your Honor. I'm going to hand -- may I approach?

THE COURT: You may.

(Handing to witness and Court.)

THE COURT: Thank you.

BY MR. STEINDLER:

Q. You see this is UTC's specification for its drug substance; right?

A. Yes.

Q. And let's go to the following page, 21941. You see at the top of the page this is the specification for the treprostinil compound; right?

A. Yes.

MR. STEINDLER: Would you go to the following page, 21942. And blow up the bottom portion of the chromatographic purity. Actually that and what's underneath it as well. Let's just stay here for the time being.

Q. All right. Are you with me?

A. Yes.

Q. You see UTC's specification sets out particular limits for particular impurities; right?

A. Yes.

Q. And it says that: The total level of impurities can't be more than five percent. Right?

A. Yes.

Q. And put another way, treprostinil compound has to be not less than 95 percent of the final drug substance; right?

A. Yes.

Q. And so treprostinil drug substance meets this FDA approved specification if it's 95 percent pure; right?

A. Yes.

Q. Now, if UTC wanted to claim the treprostinil drug substance with this specific impurities profile, it could easily have done that by including that profile in its claims; right?

A. Could you ask that again? I'm not sure what you're asking.

Q. If UTC wanted to claim the treprostinil drug substance with this specific impurity profile, it could have done so by setting out this specific impurity profile in the claims; correct?

10:45 A. I suppose so. Again, I'm not used to seeing anything like this, but I suppose they could.

Q. And UTC didn't do that; right?

A. No.

Q. Now, the claims don't recite that they're to a mixture

10:46 that includes the treprostinil compound; right?

A. They don't read that way, no. They don't -- they're not written that way.

Q. And the claims don't -- strike that.

The claims use the word compound, not the word mixture;

10:46 correct?

A. That's correct.

Q. The claims do not recite that they're to treprostinil in substantially pure form; correct?

A. That's correct.

10:46 Q. And there are no impurities identified in the claims.

A. That's correct.

Q. And there's no composition of impurities or concentration of the purities set out in the claims; correct?

A. That's correct.

10:46 Q. Do you have an opinion as to whether there's a minimum

level of purity that's required by the '117 patent claims?
A. I don't know if you can state a number, it's a stereoselectively produced product, so that would imply predominantly one stereoisomer.
10:47 MR. CARSTEN: Your Honor, I'm not sure if the witness has water up there --
THE WITNESS: Thank you.
BY MR. STEINDLER:
Q. Is there a specific minimum level of purity required by
10:47 the claims?
A. I don't see one.
Q. Do you believe -- strike that.
Is it your opinion that there are no unrecited purity limitations of any kind that should be read into the claims?
10:47 A. Could you ask that again, please?
Q. Is it your opinion that there are no unrecited purity limitations of any kind that should be read into the claims?
A. I'm trying to understand the question.
THE COURT: If you don't understand it -- you have
10:47 to rephrase it, Mr. Steindler.
Q. Is it your opinion that there are any purity limitations required in the '117 patent claims?
A. No, but it does call for a stereoselectively produced product, so to me that's telling me it's predominantly one
10:48 stereoisomer, it doesn't tell me the number of the other

impurity, percent of the other impurities.
Q. Is it your opinion that in order to meet the claims of the '117 patent, whatever the mixture is has to be at least 51 percent treprostinil compound; is that right?
00:48 MR. CARSTEN: Your Honor, I object to the question. Meet the limitations sounds a lot like infringement, and this witness has not been retained or testified about infringement of the '117 claims whatsoever. Mr. Steindler's now trying to back door infringement testimony under the guise of
00:48 invalidity.
THE COURT: Overruled. Can you answer the question, Doctor?
THE WITNESS: Yes. Could you please ask that again?
THE COURT: Frank, can you repeat the question?
00:49 (Question read back by the reporter.)
THE WITNESS: No, again, I read stereoselectively produced as to meaning predominantly treprostinil.
BY MR. CARSTEN:
Q. What predominantly treprostinil mean?
00:49 A. So again there's no definition, it just means predominantly one isomer over the other, it wouldn't be 51 percent versus 49 percent.
Q. What does predominantly mean?
A. There is no specific definition of predominant.
00:49 Q. So, you can't give me the metes and bounds of your

understanding of what predominantly one stereoisomer means?
A. So as a chemist reading the patent I would assume for my purposes making pharmaceutical molecules, it would have to be at least 90 percent, I would prefer higher, 95 percent would be better.
Q. So in order to -- strike that.
In order for a mixture to meet the '117 patent claims, it is your opinion that that mixture must include 90 percent or higher of the treprostinil compound; is that correct?
A. So again, I can't give a specific number, there's no number in chemistry that says when you have stereoselectivity it's got to be 85, 90 -- it depends on the situation.
Q. You would agree with me that a mixture that contains just 50 percent of the treprostinil compound wouldn't meet the claims of the '117 patent; is that correct?
A. If it was 50/50 treprostinil and the diastereoisomer no, that would not meet the claims.
Q. Now, in your opinion the '117 patent claims require a solid as a product; correct?
A. The claims require a solid? No.
MR. STEINDLER: Could you pull up his deposition transcript at page 139, lines 7 to 15 please.
Q. You were asked the question at your deposition: Do you understand that the '117 patent claims require a solid as a product. And you answer: It's a stereoselectively produced

product, which I take to mean at the end of the day you have treprostinil as a solid.

And then you go on to say: So to me if it's the major component it's not in solution.

00:51 Correct?

A. That is correct.

Q. So in your opinion, the '117 patent claims require a solid as the product and it can't be a solution; correct?

A. We were actually talking -- I was talking about the claim 00:51 1 which contains not just treprostinil, but a lot of other compounds. And prostaglandins are sometimes solids when they're purified, and sometimes they're oils. So they're not always solids. Treprostinil is a solid when it's purified, other prostaglandins are not.

00:52 Q. Is it your opinion that for a mixture that includes treprostinil, to meet the '117 patent claims, it has to be a solid?

A. Yes, I would say so.

Q. And in fact the '117 patent claims don't cover products 00:52 that are solutions; correct?

MR. CARSTEN: Again, your Honor, we're into infringement land.

THE COURT: I'll allow that question.

THE WITNESS: So could you please ask that again?

00:52 BY MR. STEINDLER:

Q. The '117 patent claims don't cover products that are solutions; correct?
A. I guess as I read claim 1 again it could be a solid or an oil, I don't know the answer to your question to be honest.
Q. The '117 patent claim doesn't cover treprostinil products that are solutions; correct?
A. I don't know.
MR. STEINDLER: Can we turn to the deposition at transcript page 138, lines 21, to 139, line 6.
Q. You're asked the question, does the '117 patent claim cover -- strike that.
You're asked the question does the '117 patent claims cover products that are solutions. And you say: The example -- the example came out of solids, if it's a solution it has solvent so it's not the same material anymore. Now the solution has other components, the majority of which is no longer treprostinil, the majority is whatever solvents you used.
Right?
A. Yes, that's correct.
MR. STEINDLER: Let's go to the '117 patent and just go to claim 1.
Q. The claim 1 -- strike that.
Claim 1 is directed to a stereoselectively produced isomeric compound according to a particular formula; right?

A. Yes.
Q. The formula depicted in claim 1 includes treprostinil; correct?
A. Yes.
10:54 Q. Let's go to claim 2. Claim 2 is directed to the specific treprostinil compound; correct?
A. That's correct.
Q. Go to claim 3. Claim 3 is directed to the specific treprostinil compound; correct?
10:54 A. Yes, in terms of -- you're showing in the previous slide and the previous blowup, the name for them -- the compound treprostinil you're showing the structure, you show a single molecular formula.
Q. In claim 4 the formula depicted is also the treprostinil
10:55 compound; correct?
A. Yes.
Q. Now, claim 4 is directed to pharmacologically acceptable salt forms of treprostinil; right?
A. That's correct.
10:55 Q. That includes treprostinil sodium; correct?
A. That is correct.
Q. Let's go back to claim 3. Now, in your opinion what would a person of ordinary skill in the art understand the term, a stereoselectively produced isomeric compound, to mean
10:55 as that term is used in the '117 patent claims?

A. So again, as soon as I see stereoselectively produced I'm -- I realize I'm talking about the real world, I'm talking about a product, that primarily has a molecular structure here shown for treprostinil, but also includes whatever impurities which are a function of the way the compound was made.

Q. Now, the term stereoselectively produced modifies the word compound; right?

A. That is correct.

Q. And it refers to how the compound is produced; correct?

A. So, it's -- it does refer to that as well, yes.

Q. I didn't understand your answer. What do you --

A. So it's stereoselectively produced compound, so that's modifying compound, yes.

Q. And stereoselectively produced refers to how the compound is made; right?

A. I think they're certainly related.

Q. Now, in your direct testimony on the meaning of stereoselectively produced you referred to a reference by a Eliel; right?

A. Excuse me, I don't recall that.

MR. STEINDLER: Can we go to slide 9. Perhaps I mispronounced his name, but can we go --

A. Oh, Eliel. Right.

Q. Now, you understand in patent speak that's considered extrinsic evidence; right?

A. No, not really.
Q. All right. Well, let's take a look at the intrinsic evidence.
Can we go to D-Dem-624, please.
10:57 Q. You reviewed the intrinsic record in this case when coming up with your definition of stereoselectively produced isomeric compound that you used in your direct testimony; correct?
A. I don't know the meaning of the word intrinsic record.
10:57 Q. You looked at the patent; right?
A. Yes.
Q. And you see the patent says: In summarizing the invention that the present invention relates to a process for preparing these type of compounds by a process that is
10:57 stereoselective. Correct?
A. Yes.
Q. So, the specification is teaching that it's the process that's stereoselective; correct?
A. Well, it's a stereoselectively produced compound, but
10:57 it's also by a process that is stereoselective.
Q. Can we go to the next slide. This in several other places in the specification it describes the method for making the compound as being stereoselective; right?
A. That is correct.
10:58 Q. Now, I'd like to turn to DTX-5, please. The prosecution

history for the '117 patent.

MR. STEINDLER: May I approach?

THE COURT: Yes, you may.

(Handing to Court and witness.)

10:58 MR. STEINDLER: I move DTX-5 into evidence.

MR. CARSTEN: No objection, your Honor.

THE COURT: No objection? Okay. DTX-5 is admitted.

(Defendant's Exhibit 5 was marked into evidence.)

MR. STEINDLER: So, can we turn to the page Bates

10:59 marked 2865, please.

THE COURT: Before you do that, Mr. Steindler, can you just give me a description of what this document is?

MR. STEINDLER: This is the prosecution history, for the '117 patent.

10:59 THE COURT: Thank you.

BY MR. STEINDLER:

Q. All right. Dr. Aristoff, can you come with me to page 2865.

A. Yes.

10:59 Q. The product-by-process claims of the '117 patent started out as separate claims; right?

A. I didn't study the prosecution history.

Q. Well, let's take a look at it. You see that this is a an amendment submitted by UTC during the prosecution of this

10:59 patent; right?

A. That's what it says, yes.
Q. And if you go to --
MR. STEINDLER: Now, blow up the bottom portion of it.
01:00 Q. This is original claim 1; right?
A. Yes, that's what it says.
Q. And you see the original claim 1 is a process claim; right? A process for making these kinds of compounds; right?
A. Yes.
01:00 THE COURT: So Mr. Steindler, I'm sorry, I can't find the page.
MR. STEINDLER: I'm sorry, we are at page 2865.
THE COURT: Okay, thank you.
Q. And if you go to the next page, 2866, you see that this
01:00 claim continues and it also continues on to the following page, 2867. Do you see that?
A. Yes.
Q. And you see that the process limitations in this claim are the process limitations that end up in the '117 patent
01:01 claims; right?
A. Could you go through that again? I assume that's correct, I don't --
Q. The process limitations of original claim 1, end up as the process limitations of the issued claims of the '117
01:01 patent; right?

A. Yes, it looks like that.
Q. And if you then go to page 2867, you see the product claim that is original claim 15; right?
A. What's the rest of that? That's the first part of it certainly.
Q. It is. And we'll get to the rest of it, it's important. But it starts on page 2867; right?
A. Okay. Yes.
Q. Are you with me?
A. Yes.
Q. And these are what you see recited here on page 2867, is the product limitation that ends up in the issued '117 patent claims; right?
A. Yes, I guess I'm starting to lose it a little on the legal technology in the product limitation.
THE COURT: If you don't understand it, you don't to have answer the question.
THE WITNESS: I don't really understand it.
THE COURT: Next question.
BY MR. STEINDLER:
Q. This language here a stereoselectively produced compound according to the following formula, and the formula that's set out end up in the issued '117 patent claims; right?
A. Yes.
MR. STEINDLER: Let's then go to the next page,

2868. And blow up the top portion.
Q. You see here the rest of that original claim 15 in the top two lines of the page Bates marked 2868; right?
A. Yes.
01:03 Q. And it says: Said compound is produced according to the stereoselective synthesis of claim 1. Right?
A. Yes.
Q. So the prosecution history here makes clear that the word, stereoselective synthesis, refers to the process
01:03 limitations that we saw earlier in original claim 1; right?
A. So could you ask that again? I'm trying to understand what this says.
Q. The prosecution history here is referring to -- well, strike that.
01:03 We saw just a moment ago that original claim 1 set out the process limitations that are now in the issued claims of the '117 patent; right?
A. Yes, I believe so.
Q. And in original claim 15, the applicants are describing
01:03 that synthesis of claim 1 to be the stereoselective synthesis; correct?
A. Yes.
Q. So the prosecution history is teaching that stereoselective synthesis refers to the process limitations
01:04 that ended up in the '117 patent claims; correct?

A. Yeah, I'm not entirely sure I understand that, I guess I'm --

THE COURT: All right, next question.

MR. STEINDLER: Can we go to the next slide, which is UTC's claim construction, that we got on Friday May 16, 2014 in this case.

Q. Did you -- strike that.

UTC gave a proposed construction last Friday; are you aware of that?

A. Yes.

Q. Did you use this proposed construction in your analysis in your direct testimony in this case?

A. I didn't state these words, but I would agree this is accurate.

Q. But let me ask again. Is this UTC's proposed construction what you used and applied during your direct testimony in this case?

A. Yes. This is the one I referred to as stereoselectively produced isomeric compound, this is what I would use.

Q. Now, that construction isn't set out in any of your expert reports in this case; right?

A. No, I didn't use those words. I used the product to mean just -- not just treprostinil, but also the impurities that it contained.

Q. Can we go to your expert report, rebuttal report, to

paragraphs 81 and 82.

Now, you did provide an understanding of the claims in your expert report; right?

A. Yes.

01:06 Q. And -- but what you did is you simply repeated the words that are set out in the claims when you gave your definition; right?

A. At this point I'm just reading this point, that's what it says.

01:06 Q. Now, did you discuss UTC's current claim construction at any point with UTC's lawyers?

A. I didn't discuss those words, I discussed what a product means. I didn't -- again, I didn't use those word, I don't remember using those exact words. I discussed the product as

01:07 again mainly treprostinil, but also containing impurities.

Q. Did you ever have a discussion with UTC's lawyers about what the claims of the '117 patent meant?

A. Yes, as part of my expert report.

Q. But you didn't set out the construction that they're now

01:07 advancing in anywhere in your expert report; right?

A. No, that -- those words aren't in my expert report, that's correct.

Q. Did there come a time when you realized that you were construing the '117 patent claims differently than Sandoz?

01:07 A. Well, yes, I think -- isn't that what this is saying?

Q. When did you realize that you were construing the '117 patent claims differently than Sandoz?
A. I guess I don't remember the exact date, so I can't -- I can't tell you the date.
01:08 Q. Was it before you wrote your expert report?
A. It was during the -- it was before, yes, it was before the expert report was written, yes.
Q. And during what timeframe did it take place?
A. It was in the past year.
01:08 Q. Was it in connection with working on the invalidity contentions for UTC?
A. Yes.
Q. And you never suggested to UTC that hey, there's a dispute about the meaning of these terms and we ought to deal
01:08 with this?
A. I guess again I'm -- I'm confused by the question.
THE COURT: All right. You have to restate.
MR. STEINDLER: Sure.
BY MR. STEINDLER:
01:08 Q. Did you ever say the UTC's lawyers hey, we've got a claim construction dispute as to the meaning of the '117 patent claims, we ought get this resolved?
A. I certainly don't remember saying anything like that, no.
Q. Did you tell UTC's lawyers, I think we're interpreting
01:09 the claims of the '117 patent differently than Sandoz is?

A. No, I was interpreting the claims as I read them.
Q. So you realized that there was a dispute between you and Sandoz as to how to interpret the claims of the '117 patent but didn't say anything about it?
01:09 A. No, no, I mean Dr. Buchwald interpreted the claims differently than I did and this is what this talks about.
Q. Let's go back to the slide with this construction, a chemical -- strike that.
UTC's proposed construction is that the words,
01:09 stereoselectively produced isomeric compound, mean a chemical substance formed predominantly as one stereoisomer; right?
A. Yes.
Q. Now, in this construction the words, chemical substance, refers to a mixture; correct?
01:10 A. Well, it refers to the product of the reaction, but yes, it would be a mixture, it's predominantly --
THE COURT: Mr. Steindler, I think before you ask these questions, you need to do some foundation as to whether Dr. Aristoff came up with this proposed construction and how
01:10 it came about or something. But right now it just seems like you're -- I don't know whether he has the capability of answering your questions.
MR. STEINDLER: Well, Dr. Aristoff did testify that he used this construction in his direct testimony and in the
01:10 analysis that he set out. So now I'm asking about this

construction, but I'm happy to ask him foundational questions.

THE COURT: All right.

MR. CARSTEN: Your Honor, I've had the standing objection to this entire line of questioning, which is inconsistent with the claim construction. We have now spent, I don't know, 40 minutes talking about claim construction which is not at issue in the case.

THE COURT: You know, we spent some time on direct on it, so I was giving Mr. Steindler an opportunity to, you know, undermine the doctor's credibility, or make further arguments on the construction if he needs to use them on appeal.

MR. CARSTEN: It sounds like we're just re-treading ground we covered 20 minutes ago, your Honor.

THE COURT: I got you.

So, Mr. Steindler, you may continue. But I do think Mr. Carsten's right, we've been at this a long time. So it seems like we should move to new subjects.

MR. STEINDLER: I think you will see, your Honor, that it's not clear what even this means. But I'll get to that.

THE COURT: I don't even know why I have to get to that issue, I never ruled that a chemical substance forms predominantly one stereoisomer. I never adopted that.

MR. STEINDLER: All right. Let me just ask some

clarifying questions.
BY MR. STEINDLER:
Q. With respect to the words, formed predominantly as one stereoisomer, the word formed refers to the process by which the chemical substance is made; correct?
A. Yes.
Q. Now, would you agree that the word formed as used in this definition has the same meaning as the word produced?
A. Yes.
Q. Let's turn to another subject and maybe come back to this. Now, you invented the treprostinil compound 35 years ago; right?
A. Roughly, yes.
Q. You patented the treprostinil compound in the '075 patent; right?
A. Yes.
Q. The '075 patent issued in 1981; correct?
A. Yes.
Q. The '075 patent sets out a process for making treprostinil; correct?
A. Yes.
Q. And you later developed an improved process for making treprostinil; right?
A. That's correct.
Q. Now, that process was disclosed in the '814 patent;

right?
A. Correct.
Q. And indeed the process that was disclosed in the '814 patent was an improvement over your earlier process for making treprostinil; right?
A. That's correct.
Q. And after that Dr. Moriarty and his team developed another improved process for making treprostinil; correct?
A. Yes.
Q. And that's the process that's disclosed and claimed in the '117 patent; correct?
A. Yes.
Q. The '117 patent is a new process for making an old compound; right?
A. Well, it claims a stereoselectively produced product -- compound, but that compound is by -- made by through a new process, yes.
Q. So just to be clear, the '117 patent is a new process for making an old compound; correct?
A. The '117 patent includes experimental details of a process that's improved over the earlier processes.
Q. I'm not sure that's responsive to my question. The '117 patent is a new process for making an old compound; right?
A. So could you rephrase the question? Because I'm not -- are you saying the patent -- that's all the patent claims?

What are you -- I'm not sure what you're asking.

THE COURT: He doesn't understand the question. You have to --

Q. The '117 patent claims are to a new process for making an old compound; right?

A. I thought the claims were to a stereoselectively produced isomeric compound.

Q. Now, the '117 patent -- strike that.

Now, the treprostinil compound made in the '814 patent is the same treprostinil compound that's made using the '117 patent process; correct?

A. The molecular structure of the main compound of the product is the same between the '814 process and the -- the '117 patent and the '814 patent, is the same molecular formula in both compounds -- in both -- excuse me; I'm real getting tongue-tied. It is the same molecular formula that's the primary component of the product of either patent.

MR. STEINDLER: Can you go to D-Dem-639?

That's not the right one.

Q. You recall that you put this slide up in your direct testimony; right?

A. Yes.

Q. And it's not just that it's the same molecular formula, actually the same molecule is produced in the '814 patent that you make with this '117 patent; correct?

A. Yes, the product -- the major component of the product in either patents are molecules primarily of treprostinil.
Q. So, the treprostinil molecule is exactly the same whether you make it by the '814 patent process or you make it by the '117 patent process; correct?
A. That's correct.
Q. Now, let's go to DTX-53; we've seen this before. This is your '075 patent; right?
A. Yes.
Q. And this is the first patent that claimed treprostinil; right?
A. Yes.
Q. You invented treprostinil while you were working at Upjohn; right?
A. That's correct.
Q. And the '075 patent was based on your work at Upjohn; correct?
A. Yes.
MR. STEINDLER: Let's go to column 97, line 46, and look at claim 5, please. Just blow that up.
Q. Are you with me?
A. Yes.
Q. Claim 5 of the '075 patent claims the treprostinil compound; correct?
A. Or its methyl ester.

Q. Claim 5 of the '007 patent refers to treprostinil as a compound; correct?
A. It gives the name of the compound for -- it gives the name as you would name a molecular formula of treprostinil, that's correct.
Q. It also uses the word compound to describe the treprostinil; correct?
A. Yes. Yes.
Q. So, the '075 patent discloses the treprostinil compound; correct?
A. Yes, in the context of when you name a compound you give it a single name. You realize in the real world a compound must contain primarily that and other impurities.
Q. Is it your contention that claim 5 of the '075 patent is to the mixture that includes a compound of treprostinil?
A. Not when it's named like that, no.
Q. So, if you've got a specific name in a patent that's just referring to a compound; is that your view?
A. When -- yes, when you get -- when you ask to name a compound you give just the name of the primary compound of the product, which would be in this case treprostinil.
Q. And that same would be true that if -- strike that.
The same thing would be true, if the '075 patent had depicted the treprostinil compound by a structural formula; correct?

A. Yes.
Q. Let's turn to DTX-55. You'll see this is the '814 patent that you testified about; right?
A. Yes.
01:19 Q. Now, the '075 patent was based on work you did at Upjohn; correct?
A. Yes.
Q. The '814 patent was also based on work you did at Upjohn; correct?
01:19 A. Yes.
MR. STEINDLER: Let's go to column 29, starting at line 11. And blow up example 3.
Q. Now, example 3 describes a process for making treprostinil; correct?
01:20 A. Yes.
Q. And it discloses the treprostinil compound by the name in column 29, starting around line 11; correct?
A. Yes.
Q. Now, example 3 of the '814 patent describes this improved
01:20 process that you had for making treprostinil; correct?
A. Yes.
Q. And it also -- strike that.
The '814 patent also discloses pharmacologically acceptable salt forms of treprostinil; right?
01:20 A. Yes.

Q. And that would include treprostinil sodium; correct?
A. Yes.
Q. Now, a person of ordinary skill in the art would have been able to make treprostinil based on the disclosure in the '814 patent; correct?
A. Yes, he would make a product that contains primarily the molecular structure of treprostinil, that's correct.
MR. STEINDLER: Let's turn to column 32, and blow up the bottom starting around lines 58 or so.
Q. Are you with me?
A. Yes.
Q. Now, at the end of example 3, the '814 patent reports that the result is 1.20 grams of the treprostinil compound; right?
A. Yes.
Q. And that 1.20 grams of treprostinil is about 95 or 96 percent pure; correct?
A. I don't know if it's specified in the patent, it's my understanding, yes.
Q. I'm sorry, I didn't understand your --
A. I don't know if it's stated in the patent, but that's my recollection, it was around 95 percent pure.
Q. So, that 1.20 grams of treprostinil is a chemical substance as you're using that term; correct?
A. Could you ask that again?

Q. That 1.20 grams of treprostinil produced in example 3 of the '814 patent is a chemical substance as you're using that term; correct?
A. Yes, yes.
01:22 Q. And that 1.20 grams of chemical substance in example 3 of the '814 patent is predominantly one stereoisomer; correct?
A. That's correct.
Q. That one -- strike that.
Now, and that 1.20 grams of treprostinil is a chemical
01:23 substance that's formed predominantly as one stereoisomer; correct?
A. Yes, it wasn't stereoselectively produced, but it was 1.2 grams of the substance.
Q. So now let's turn to your slide 28. You recall that you
01:23 discussed this slide in your direct testimony; correct?
A. That is correct.
Q. Now, when you're looking at what you describe as the product of the '814 patent, you're actually looking at the unpurified crude product to -- for purposes of this slide;
01:24 right?
A. Yes, on this slide we're talking about the crude product, yes.
Q. But for the '117 patent you're actually looking at the purified product to define the product of the '117 patent;
01:24 right?

A. No, I was comparing both at the crude stage. These are approximately -- in the case of the '814 patent it's roughly -- there's other stuff in there, but primarily you have a one-to-one mixture of treprostinil and the diastereoisomer, and the '117 patent at the crude stage you primarily have treprostinil.

Q. At the crude stage in the '117 patent, the example is purified in order to get the final product; isn't that right?

A. Yes, that's on my next slide.

Q. Let's go to the next slide. You have to -- strike that.

The example of the '117 patent, has a purification step at the end; correct?

A. Yes.

Q. And you don't -- strike that.

The '117 patent doesn't report the purity level of the crude product prior to purification, does it?

A. No, but it -- the yield of the reaction is high enough that you would be able to tell that it's primarily treprostinil, otherwise you couldn't get a high yield.

Q. But you don't know what the purity level is of the '117 patent example before you purify it; correct?

A. No, but you know it's certainly at least 80 percent of -- or better of treprostinil.

Q. You're not showing 80 percent here in your comparison, are you?

A. No, on this slide we're showing after purification, the previous slide was before. And again that was just a visual to explain the one-to-one versus the other one is primarily treprostinil. There's other impurities in both those steps before the final purification.

Q. Let's turn to -- strike that.

You testified on your direct that the process of the '814 patent was not stereoselective; right?

A. Yes, '814 patent is not a stereoselectively produced product, that's correct.

Q. And it's your opinion that it's not stereoselectively produced because a stereoselectively produced -- strike that.

In your opinion, stereoselectively produced as that term is used in the '117 patent, requires that each of the five chiral centers have to be set using a stereoselective step; right?

A. Well, somewhere along the process you have to have chemical transformations that create predominantly one stereoisomer at each state, the problem configuration in each chiral center.

Q. But wasn't your testimony that you could set four of the five chiral centers stereoselectively in the '814 patent process?

A. Yes, for the overall process, that's correct.

Q. And so it's your opinion that in order to be

stereoselective, the process requires you to stereoselectively set each of the five chiral centers; is that right?

A. Yes, you have to have all them set correctly via chemical transformations.

01:27 Q. So, let's go to the '117 patent, claim 3. Now -- are you with me?

A. Yes.

Q. The '117 patent just describes a single process step; right?

01:27 A. That's correct.

Q. It's the cyclization step; correct?

A. Yes.

Q. And the '117 patent says that the process with that one step is stereoselective; correct?

01:28 A. That's correct.

Q. So, the double -- strike that.

So the '117 patent is teaching that as long as you have a single process step that is stereoselective, the process is stereoselective; correct?

01:28 A. I would say for this one since that one single center is then used to set all the subsequent centers, that's correct.

Q. But all those subsequent centers aren't set in the Pauson-Khand --

A. No, they're not set in that step, they're a result of

01:28 that step, but they're not set in that step.

Q. So th '117 patent is teaching that as long as you have one step that's stereoselective, the process is stereoselective; right?
A. Yes, it claims a stereoselectively produced isomeric
01:28 compound, but it only shows the Pauson-Khand step, that's correct.
Q. I'm not sure I understand your --
THE COURT: You can ask another question.
MR. STEINDLER: All right.
01:28 Q. According to the '117 patent, as long as a single step is stereoselective, the process is stereoselective; right?
A. Yes, if you do the appropriate reactions.
Q. Now, you would agree with me that the treprostinil compound depicted by the chemical formula set out in the '117
01:29 patent claims was disclosed in the '814 patent; right?
A. Yes.
Q. And you would agree with me that the treprostinil compound depicted by the chemical formula set out in the '117 patent claims, was also disclosed in the '075 patent; correct?
01:29 A. Yes.
Q. You would also agree that the treprostinil compound depicted by the chemical formula set out in the '117 patent claims, was further disclosed in numerous other prior art references?
01:30 A. I don't think numerous, but it was disclosed in at least

one other prior publication.

MR. STEINDLER: Can we go to the next slide, please.

Q. Do you recall that at summary judgment UTC admitted that numerous other prior art references disclosed treprostinil and the processes for making treprostinil, including U.S. Patent Number 513 -- let me start over again.

At summary judgment, UTC admitted that numerous other prior art references disclosed treprostinil and processes for making treprostinil?

A. Yes, I agree. I don't know what numerous means, though.

Q. There was a specific list of other prior art references that include U.S. Patent Number 5,153,222, U.S. Patent Number 4,306,075, and Aristoff, et al, Synthesis and Structure Activity Relationship of Novel Stable Prostacyclin Analogs published in 1983; correct?

A. Yes, that's all accurate.

Q. Now, if the Court were to find that the product of the '117 patent claims is the treprostinil compound, depicted by the specific chemical formula set out in the claims, then all of the claims of the '117 patent are anticipated by the disclosures of the treprostinil compound in the prior art; correct?

MR. CARSTEN: Objection, your Honor. That's a legal conclusion.

THE COURT: Sustained. Next question.

BY MR. STEINDLER:
Q. Now, your opinion is that the -- strike that.
MR. STEINDLER: Judge, it's about 1:30. I have a while to go; shall we break for lunch or shall I continue?
01:32 THE COURT: I think you should continue. We have only been at it for about an hour.
MR. STEINDLER: Understood.
BY MR. STEINDLER:
Q. Your opinion is that the product, made by the '814 patent
01:32 process, is different from the product made by the '117 patent process; right?
A. That is correct.
Q. And you say that the product produced by the '814 patent process has a different impurity profile than the product
01:32 produced by the '117 patent process; right?
A. That's correct.
Q. You also say that the '814 patent process gives you different yields than the '117 patent process; right?
A. That's correct.
01:33 Q. And in your direct testimony, you compared batches of treprostinil made by the '814 patent process, to batches made by the '117 patent process; right?
A. That's correct.
MR. STEINDLER: Let's go to PTX-100A.
01:33 Q. This is the chart that you used in your direct testimony

to set out the batches that you were relying on for your analysis; right?
A. That's one page of it, yes. There are several pages.
Q. Understood. This is a multiple page chart; right?
01:33 A. Yes.
Q. Now, the batches made by the '117 patent process, are commercial batches of treprostinil made by UTC; right?
A. No, they're both developmental and commercialized, both.
Q. But most of the batches are commercial batches; correct?
01:34 A. Yes, I would say that's correct. More of them are commercial, yes.
Q. And all of the batches that UTC made that you're relying on were developed -- strike that.
All of the batches that UTC made were made by processes
01:34 that were developed and optimized by UTC over a period of years; correct?
A. Yes.
MR. STEINDLER: Let's go to Dr. Aristoff's slide number 32.
01:34 Q. In your direct testimony you referred to an optimization memo from UTC; correct?
A. Yes.
Q. And that optimization memo describes UTC's efforts to optimize its commercial process for making treprostinil from
01:34 the time that it engaged Dr. Moriarty and his group in 1997;

right?
A. Yes.
Q. So, UTC was working on optimizing its commercial process for making treprostinil on the '117 patent method, over quite
01:35 a number of years; correct?
A. Yes.
MR. STEINDLER: Let's go to slide 27 in Dr. Aristoff's presentation.
Q. Are you with me?
01:35 A. Yes.
Q. You will recall that in your presentation you described the Bettis memo, which -- which describes additional improvements that were -- were made in optimizing UTC's process; right?
01:35 A. Well, they saw they had a more pure product.
Q. And this -- this Bettis memo reports that UTC was able to further optimize its commercial production process so that it could get purer and purer drug substance; right?
A. Yes.
01:36 MR. STEINDLER: Let's go to PTX-753, which is this Bettis memo. And can you go to the bottom, very bottom, very bottom and just blow up the date.
Q. You'll recall that the Bettis memo is dated March 16th, 2004; right?
01:36 A. That's correct.

Q. And this is seven years after the '117 patent is filed; right?
A. Yes.
Q. And UTC had been constantly working on optimizing its manufacturing process; right?
A. I don't know if they're constantly working it, but they were probably working on it.
MR. STEINDLER: Can we just blow up the summary section here in the Bettis memo.
Q. Again, this is a document that you were referring to in your direct testimony; right?
A. Yes.
Q. Now, the Bettis memo says that purer and purer drug substance has been produced over time using commercial production processes; right?
A. Yes.
Q. It's reporting that UTC had done such a good job of optimizing its commercial process, that it was getting very very low levels of impurities in its treprostinil drug substance; right?
A. Yes.
Q. And in fact, the level of impurities UTC was getting with this super optimized commercial production process was so low, that Bettis was recommending that UTC could tighten its specification for its GMP drug substance; right?

A. Yes.
Q. Now, let's go back to your slide 27. You recall that you testified with respect to this third bullet in slide 27, that under the proposed limits the average Upjohn lot wouldn't meet
01:38 the proposed revised limits for particular impurities; right?
A. That's correct.
Q. Now, those proposed limits aren't included in the '117 patent claims; right?
A. No.
01:38 Q. And what you've done in your analysis is to compare optimized and super optimized commercial embodiments of the '117 patent to the '814 patent; right?
A. What I did was start with Dr. Buchwald's analysis, and realized he left out a lot of lots that had been produced by
01:38 UTC. So I used all the data that was available to do the analysis, not just selected lots from UTC.
Q. And what you're doing is you're using optimized and super optimized lots from UTC's commercial product to compare to the '814 patent process; right?
01:39 A. I'm using the data that I had. I have no guarantee that the Upjohn would be able to improve on the process at all, from the '814 patent.
Q. But the '117 patent doesn't require that you use UTC's optimized or super optimized process, does it?
01:39 A. No, that's -- I used -- that's why I averaged all the --

all the data that I had available, because any one lot can give a high or lower value for impurities depending on that particular run, you have to average them.

Q. But the '117 patent just says all you have to do is use a Pauson-Khand cyclization step; right?

A. Yes.

Q. It doesn't specify any other steps in the process besides that one step; right?

A. No.

Q. So the comparison that you're using is to particular optimized commercial embodiments; correct?

A. They were made by the '117 patent process patent, in the '117 patent, so that's what I used.

MR. STEINDLER: So let's go to Dr. Aristoff's slide number 10, please.

Q. All that the '117 patent requires is that you cyclize the claim starting enyne, into the claim cyclized intermediate compound, using an intramolecular cyclization step; right?

A. Well, they require that you have a stereoselectively produced isomeric compound.

Q. Let's go back to the tutorial slide with the bridge that we saw at the outset of this trial. Do you remember seeing this slide that Dr. Williams had prepared?

A. Yes.

Q. All the claims of the '117 patent require is that you

have a particular enyne and a particular cyclized intermediate, and you use a claimed cyclization step; right?

A. And what it also requires that you have a stereoselectively produced product.

01:41 Q. The patent claims don't specify any reaction conditions even for the cyclization step; isn't that correct?

A. That's correct.

Q. And they don't even require that the cyclization be conducted using a Pauson-Khand reaction; correct?

01:41 A. That's correct.

Q. There are intramolecular cyclizations that are not Pauson-Khand reactions that would be covered by this claim; right?

A. I'm not aware of any that would work, but I'm only aware

01:41 of the Pauson-Khand doing that cyclization.

Q. But the claims don't require you to use the specific Pauson-Khand reaction that UTC uses in its optimized commercial manufacturing process; right?

A. They don't require it.

01:41 Q. Now, you understand that UTC spent a lot of time, effort and money to optimize just the Pauson-Khand step in its reaction process; right?

MR. CARSTEN: Your Honor, I object. I thought that Mr. Steindler objected to the witness as not a Pauson-Khand

01:42 expert, and now we're getting a series of questions directed

to the witness' knowledge of the Pauson-Khand reaction and what UT did or didn't do with respect to it. I think it's inappropriate.

MR. STEINDLER: I'm happy to have his entire direct
01:42 testimony stricken from the record, but he did talk about this. Mr. Carsten asked him about these kinds of things, so I'm allowed to go into it.

THE COURT: We did talk about it. So I remember at the beginning, though, Dr. Aristoff indicated that he wasn't a
01:42 Pauson-Khand expert; I don't recall having Pauson-Khand steps explained during his direct. But I thought the questions were whether the patent included a Pauson-Khand step and all he said was yes, he didn't explain what it was. So I'll allow the question.

01:42 MR. CARSTEN: Fair enough, your Honor.

BY MR. STEINDLER:

Q. You understand that UTC spent a lot of time, effort and money to optimize just --

THE COURT: We've already been through that
01:43 question. Next question.

MR. STEINDLER: I'm sorry; say that again?

THE COURT: I said we've already been through that question, next question.

MR. STEINDLER: I'm sorry; I understood you to say
01:43 that I could ask that question. I didn't get an answer to it.

THE COURT: I think he answered that question.
MR. STEINDLER: I don't think so, Judge. There was just an objection, I don't think he answered that question.
THE COURT: Please restate the question.
01:43 MR. STEINDLER: Sure.
THE COURT: I guess my problem is it seems like we're going over the same things we've been through for the last hour. So you may continue.
BY MR. STEINDLER:
01:43 Q. You understand that UTC spent a lot of time, effort and money to optimize just the Pauson-Khand step in its reaction process; correct?
A. Yes.
Q. So, even for this one step in UTC's commercial
01:44 manufacturing process, UTC had to optimize that step to get the yields that it ultimately achieved; correct?
A. You always optimize reactions when you're doing a process.
Q. But even for this single step in UTC's commercial
01:44 manufacturing process, UTC had to optimize that step in order to get the yields that it ultimately achieved; right?
A. Yes, but I'll point out even their unoptimized yields were better than the yield I had for my key cyclization step in the '814 patent.
01:44 Q. Well, let's go to PTX-493. And you recognize this is the

as optimization memorandum that we have seen earlier?
A. Yes.
MR. STEINDLER: Can you go to Bates number 203. And blow up the bottom.
01:45 Q. You'll recognize that it's now talking about this Pauson-Khand cyclization step; right?
A. Yes.
MR. STEINDLER: Let's go to the next page. And blow up just the developmental research paragraph.
01:45 Q. And you'll see that there's a discussion here that the yields were from 47 percent to 95 percent; right?
A. Yes.
Q. So they were getting yields as low as 47 percent in this -- some iterations of this reaction; right?
01:45 THE COURT: Hold on, Mr. Steindler. Is this talking about the yields within the Pauson-Khand step? Weren't we through -- I didn't think Dr. Aristoff testified about this.
MR. STEINDLER: He just -- he just said that in his -- in his previous testimony, and I'm now seeking to impeach
01:46 him with respect to the what the document says.
THE COURT: Mr. Carsten?
MR. CARSTEN: Your Honor, the only testimony that the witness gave on direct was with respect to the overall process yield between the '814 and the process -- and the
01:46 '117, and this is now parsing to a particular chemical

reaction. You know, I do object to it, your Honor.

THE COURT: So, I don't understand your point here --

MR. STEINDLER: Here's the basic point. What Dr. Aristoff is doing when he says he's comparing the '814 product to the '117 product is he's looking at particular highly optimized embodiments of the '117 patent product. And what I'm showing is that you can do the '117 patent process in all kinds of different ways, and get all kinds of different yields, like we see here, just for this one step, and that there are all kinds of ways that you can do to get -- to make the product under the '117 patent, that even under his construction is not different than what you got in the prior art.

THE COURT: It doesn't seem to me that you've asked that question. I think you should be more focused on your point.

BY MR. STEINDLER:

Q. Well, don't you agree that in some iterations of the Pauson-Khand step, this document is reporting that UTC was getting yields as low as 47 percent?

A. Yes, but I'll point out in my cyclization step the optimized -- you have the high optimized too was only three percent of the desired compound.

Q. And again that was for a particular example that you

were --
A. That was the best I ever came up with.
Q. All right.
MR. STEINDLER: So can we go then back to Dr. Aristoff's slide number 10?
Q. Now, again, the '117 patent doesn't require the optimized cyclization step that UTC did; right?
A. Can you restate that, please?
Q. The '117 patent doesn't require the optimized cyclization step used by UTC; right?
A. It requires this type of transformation which is commonly called a Pauson-Khand transformation.
Q. And that can be done under all kinds of different reaction conditions; correct?
A. Yes.
Q. Now, I notice in your slide you're referring to this intermediate compound as a compound, and the starting enyne as a compound; right?
A. That's correct.
Q. And so those are specific chemical molecules; correct?
A. Yes, when you draw the structure of a compound you show one specific molecular formula.
Q. And in fact, at this stage of the reaction process (indicating) you actually have a mixture in the flask; right?
A. Yes.

Q. So let's go back to the tutorial slide 20, the bridge slide. Now, there's no particular reaction conditions required for the Pauson-Khand step; right?
A. No, except to be a stereoselectively produced product.
01:49 Q. And there are many process steps that have to be undertaken before you get to the starting enyne compound; right?
A. Yes, there's several steps, yes.
Q. And there's steps that you have to take after the
01:50 cyclization step to get to the final treprostinil product; right?
A. That is correct.
Q. And the '117 patent is completely silent as to how these other steps are performed; right?
01:50 A. That's correct.
Q. It doesn't say what the steps should be, how they're to be performed, what reaction conditions are to be used, what reagent conditions are to be used; correct?
A. That's correct.
01:50 Q. So, all that the '117 patent requires is that those process steps before and after the cyclization step have to be performed because they're necessary to get to the final product; right?
A. That's correct.
01:50 Q. And how those steps are performed will impact the final

product; right?
A. Yes.
Q. Now, let's go to a slide that Dr. Buchwald presented. This is a depiction of the different steps that are used in the example in the '117 patent; right?
A. That's correct.
Q. And you agree with Dr. Buchwald that there were purifications that were done after 12 of the 15 steps in the process; right?
A. Yes, that's commonly done in any synthesis.
Q. And it also includes a purification after the final step of preparing the crude product; right?
A. Yes.
THE COURT: So, Mr. Steindler, we're looking at slide 37?
MR. STEINDLER: This is slide 37 from Dr. Buchwald's demonstrative slides, that is correct.
THE COURT: Okay, thank you.
So, have you seen this before, Dr. Aristoff?
THE WITNESS: Yes, during Dr. Buchwald's testimony.
THE COURT: So you understand what it is?
THE WITNESS: Yes, yes.
THE COURT: Okay.
BY MR. STEINDLER:
Q. Now, the '117 patent doesn't disclose the purity of the

crude product at the end of the last synthetic step prior to purification; correct?

A. No, you infer it from the yield of the last step.

Q. It also doesn't disclose the purity of the final purified product; correct?

A. No.

Q. And all of these purification steps will impact the purity of the final product; right?

A. Yes, but so will the stereoselective process that you use, the stereoselective transformation of the Pauson-Khand will also impact that final purity.

Q. Now, none of the final purification steps done in the example of the '117 patent are required by the '117 patent claims; correct?

A. No, the purification steps are not required.

Q. So, the example in the '117 patent is in fact a preferred embodiment; correct?

A. I'm not sure what that means.

MR. STEINDLER: Can we go into the patent at column 4. Starting at line 30.

Q. Do you see the patent describes this example as a preferred embodiment in the patent; right?

A. This says in one embodiment.

Q. But it is discussing in the title, a detailed description of the preferred embodiments, and there's only one example;

right?
A. Yes, I guess that's correct.
Q. So, the '117 patent claims cover treprostinil made without the purification steps described in this example;
01:53 right?
A. Now I'm confused by the question; can you say the question again?
THE COURT: All right, rephrase.
Q. The claims of the '117 patent can cover treprostinil made
01:53 without any of these purification steps; right?
A. You mean the purification steps that were shown on Dr. Buchwald's slide?
Q. Correct.
A. Oh, okay, I thought you meant in the patent. Okay. Yes.
01:53 Q. And there are -- strike that.
The '117 patent would cover treprostinil made without any purification steps; right?
A. It could, yes.
Q. Now, the claimed cyclization step doesn't impart any
01:54 specific level of purity or yield to the final product; right?
A. Yes, again I think we covered this, it's a stereoselective reaction, it's one of the many reasons you get a stereoselectively -- stereoselective isomeric compound, that step has to predominantly give one stereoisomer.
01:54 Q. Now, suppose that some inventive scientist discovers that

a 50/50 mixture of treprostinil and one of its stereoisomers, is actually a more effective medication than treprostinil alone; are you with me?

A. Not exactly. Can you did that one again?

01:55 THE COURT: So rephrase.

MR. STEINDLER: Sure.

THE COURT: This is a hypothetical question?

MR. STEINDLER: It's a hypothetical question, yes.

BY MR. STEINDLER:

01:55 Q. So, someone discovers that treprostinil and one of its stereoisomers together, is a more effective medicine than treprostinil alone; do you understand the hypothetical?

A. Okay, yes.

Q. If that were true, one could purposely make a 50/50

01:55 mixture of treprostinil and that stereoisomer using a process that includes the claimed cyclization step; right?

A. Say that again?

THE COURT: So you don't understand the question?

THE WITNESS: No. Could you could that one again?

01:56 I'm trying to figure out this hypothetical situation.

BY MR. STEINDLER:

Q. The hypothetical is that you discovered that treprostinil and one of its stereoisomers together is a more potent medicine than treprostinil alone; okay? Are you following me

01:56 so far?

A. Yes.
Q. In order to make that combination you could purposely make a 50/50 mixture of treprostinil and one of its stereoisomers using the Pauson-Khand cyclization step; right?
01:56 A. Well, no, it would depend on what --
THE COURT: Wait; there's an objection.
MR. CARSTEN: I object to the question. It's vague with respect to making; are we talking about the process here, or are we talking -- I don't even understand the question.
01:56 THE COURT: All right, then sustained. Rephrase.
MR. STEINDLER: Sure.
BY MR. STEINDLER:
Q. Under the circumstances of the hypothetical that I'm putting to you, you could put this other stereoisomer into the
01:57 mixture right after you make the cyclized intermediate; correct?
THE COURT: Do you understand that.
THE WITNESS: I think so. Let me make sure I understand. So you're saying you're going to do the
01:57 Pauson-Khand reaction which is stereoselective, and then you're going to add in this other diastereoisomer.
Q. Correct.
A. Okay.
Q. All right.
01:57 A. All right.

Q. And in that case, you would have made treprostinil in a process that's covered by the '117 patent claims, but you wouldn't necessarily have predominantly one stereoisomer in the product; right?

01:57 A. Yeah, because you added --

THE COURT: I didn't understand that question, so you better rephrase.

MR. STEINDLER: Well, the witness understood and answered it, Judge.

01:58 THE COURT: I'm sorry, but I don't understand the question. You have to rephrase.

BY MR. STEINDLER:

Q. I'll start from the beginning. A scientist discovers that treprostinil plus a stereoisomer is a more potent

01:58 medicine than treprostinil alone are; okay? Are you with me?

A. Yes.

Q. And so, the scientist sets out to make this product that's a combination of treprostinil and this other stereoisomer; correct?

01:58 A. Yes.

Q. And then you can add this other stereoisomer to the reaction mixture after you've done the cyclization step; correct?

A. Well, is it the stereoisomer that you want at the end

01:58 synthesis you would add at the end -- very end of the

synthesis, you wouldn't add it at that step.
Q. But you could add it at any step in the process after the cyclization step; right?
A. Yes, but its structure would change as you do some of the
01:59 reactions in the process, you wouldn't have that particular diastereoisomer anymore.
Q. But you could make this product that includes treprostinil and this other stereoisomer, following the '117 patent process and end up with a product that is not
01:59 predominantly one stereoisomer; right?
A. So again I'm confused as you're doing it. If you -- if you took this other diastereoisomer and added it at the very end of the process after you've made treprostinil and then added it in, yes, you would have a new product that would
01:59 contain treprostinil and this other diastereoisomer.
MR. STEINDLER: Let's go to Dr. Aristoff's slide 19.
Q. This is a slide that you presented comparing the '814 patent yield versus the '117 patent yield; right?
A. That's correct.
02:00 Q. And the three percent yield that you see is the yield of the '117 patent, that's a yield for a specific preferred embodiment, the example in the patent; correct?
A. There's one example in the patent, that's what I used for the yields.
02:00 Q. So you don't always get that kind of a yield if you

follow the '117 patent process; right?
A. Not every time, no.
Q. You're going to get all kinds of different yields if you make treprostinil using just the Pauson-Khand step; right?
02:00 A. Yes, but I used the same argument to make -- to calculate the yield for the '814 patent, that was the best yield I ever got .3 percent.
Q. So the product in the '117 patent is not necessarily going to be produced in any specific level of yield; right?
02:01 A. Well, every example I saw was three percent, in the patent I saw, in the IND it was actually nine percent based on the example there, that's the information that I had.
Q. But you can do processes for making treprostinil that are covered by the '117 patent that are not these specific
02:01 embodiments that you looked at; right?
A. Yes.
Q. And the '117 patent covers all kinds of ways to get to treprostinil as long as it includes a cyclization step.
A. Yes.
02:01 Q. So, the '117 patent product is not necessarily going to be produced at any particular level of yield; right?
A. Again, I just used the data that I had for both processes.
Q. So let's go to slide 20. Again, with respect to
02:01 theoretical yield, I want to clarify that you're looking at

the preferred embodiment here in the '117 patent to compare it to the '814 patent; right?

A. No, I'm saying that the '117 patent has a potential to give you a hundred percent theoretical yield, because you could have in theory a hundred percent of at each step of that process in the '814 patent process, that was not possible, I could at do best 50 percent.

Q. But the '117 patent covers all kind of different processes to make treprostinil; right?

A. Yes, but if you're thinking theoretical that means that you would use the process that did create a one hundred percent yield in the step.

Q. So your theoretical yield is something that might be possible under the '117 patent, but is not required for all of the different kinds of processes that would be covered under the '117 patent; right?

A. The one hundred percent theoretical yield is accurate, you never get a hundred percent yield, but that's what the theoretical yield would be for that process, there's no step in there that you've deliberately done as in my '814 synthesis that gives you a 50 percent.

Q. Let's go to the next slide, slide 21. You'll recall testifying that what Sandoz said in its invalidity contentions support your position with respect to the '814 patent yield being different than the '117 patent yield; right?

A. Yes.
Q. Now, it's really hard to read this in the slide, but in a portion that wasn't blown up, you'll see that Sandoz's invalidity contentions aren't talking about the '814 patent, are they?
A. They are at least talking about this -- I don't know -- I don't recall the rest of it, Sandoz's invalidity contentions.
Q. The passage that you relied on to support your position that the '814 patent has different yields than the '117 patent, doesn't mention the '814 patent at all; isn't that correct?
A. Not there, no.
Q. Now, were you aware that Sandoz didn't discuss the '814 patent anywhere in these invalidity contentions?
A. I don't recall the specifics.
Q. Were you aware that Sandoz actually had to move to amend its validity contentions to add the '814 patent and that Judge Goodman granted that motion over UTC's objection?
A. No, I don't know anything about that --
Q. So this invalidity contention that you're relying on to support your position that the '814 patent has different yields than the '117 patent actually doesn't address the '814 patent at all; does it?
A. It doesn't appear to here.
Q. Now, let's go to --

THE COURT: So it's 2 o'clock now you want break for lunch at this time.

MR. STEINDLER: Sure.

THE COURT: All right so, Doctor -- how long do you want to take for lunch, 30 minutes?

MR. STEINDLER: As short as possible given that we'd like to try get as much of the live witness testimony done today as we can.

THE COURT: We will be back at 20 to 3:00.

All right, Doctor, so you may step down.

THE WITNESS: Thank you.

THE COURT: Thank you.

MR. STEINDLER: Thank you.

(Luncheon recess.)

THE COURT: You may be seated.

You are still under oath, Doctor.

THE WITNESS: Yes, your Honor.

THE COURT: Mr. Steindler?

MR. STEINDLER: Thank you, your Honor.

BY MR. STEINDLER:

Q. Did you talk to anyone during the break about your testimony?

A. No.

Q. Can we go to another one of the slides that you used, Sandoz's D-Dem660, that was part of your slide deck in your

presentation. Do you recall this slide that you used?
A. Yes.
Q. Now, this slide is with respect to DTX-60, volume 1.2 of UTC's NDA at Bates number 21936. Right?
02:55 A. Yes.
Q. And it depicts a number of different lots of treprostinil; correct?
A. Yes.
Q. Lots WC and UA were made by the '814 patent method;
02:55 right?
A. Yes.
Q. And the other lots were made by the '117 patent method; right?
A. That's correct.
02:55 Q. And if you look at the purity levels, the table reports that lot WC had a purity level of 95.5; correct?
A. Yes.
Q. Lot UA had a purity level of 94.6; correct?
A. That's correct.
02:56 Q. And it then proceeds across to show purity levels of lots made by the '117 patent process; right?
A. Yes.
Q. And some of these lots had purity levels of 93.1, 92.8, 92.1; correct?
02:56 A. That's correct.

Q. And these lots with the purity levels that we just described were actually made by UTC's optimized process; right?
A. Yes.
02:56 Q. And those lots were purified after the end of the synthesis; right?
A. Yes.
Q. So you would agree with me that you don't necessarily get high levels of purity using the '117 patent process; right?
02:56 A. Not in -- no, not in any individual lot. That's why I averaged all the lots that I had available through 2004 -- early 2004.
Q. The product of the '117 patent doesn't necessarily have a higher level of purity than the product of the '814 patent;
02:57 right?
A. Well, again, I averaged because I thought okay, what's representative of the '117 product was what I saw from all this massive amount of information I had in the NDA. And that's where I got the average purities in my tables.
02:57 Q. But this table shows that for particular embodiments of the '814 patent, it's got purity levels that exceed particular embodiments of the '117 patent process; correct?
A. Yes, it can be variations in any individual lot.
MR. STEINDLER: Let's go to Dr. Buchwald's slide
02:57 D-Dem-659, which is part of this same table. It's again in

DTX-60, volume 1.2 of UTC's NDA at Bates number 21934.

Q. Do you recall this?

A. Yes.

Q. Now, again, with respect to these same lots WC and UA, it has certain information in the table about those lots; right?

A. Yes.

Q. And it reports that the lot size for lot WC made by the '814 process is 167 grams; right?

A. That's correct.

MR. STEINDLER: Let's turn to DTX-57, the Upjohn DMF, which is already in evidence.

Q. Are you familiar with the Upjohn DMF?

A. Yes, I've seen it, yes.

MR. STEINDLER: Can you go to the page Bates stamped 1161342, please.

Q. This describes the process for making treprostinil in Upjohn DMF; correct?

A. Yes.

Q. And the date at the top is September 17, 1986; right?

A. Yes.

MR. STEINDLER: Can we turn to Bates number 1161350, please. And if you can highlight the bottom of the first full paragraph here, and this second paragraph.

Q. Are you with me?

A. Yes, I see this.

Q. And it describes making a 167 gram batch of treprostinil; right?
A. Yes.
Q. And then it also describes a further 120 grams that were made in this process; right?
A. Yes.
Q. And this describes it all together 287 grams were made -- strike that.
This describes that all together, 287 grams of treprostinil were made here; correct?
A. Yes.
Q. And this is lot WC; right?
A. I don't know if the second part would have been considered lot WC, the first part would have.
Q. And the batch size that we have here is comparable to the size of some of UTC's commercial batches; right?
A. Smaller than many of them, but maybe some -- I don't recall actually all the numbers for the commercial lots.
Q. Well, you would agree with me that you didn't make one gram at a time here in making this lot WC; right?
A. That's true.
MR. STEINDLER: Now, let's go back to Dr. Buchwald's slide 661, please.
Q. This is a slide that reports a table set out at DTX-386, volume 1.6 of UTC's NDA at Bates number 22275; do you see

that?
A. Yes.
Q. Now, 10 years after lot WC was made by Upjohn, it was turned into a finished product and used by UTC in human clinical trials; right?
MR. CARSTEN: Your Honor, I object. I don't think we used this slide or talked anything about clinical trials in connection with Dr. Aristoff's testimony.
THE COURT: Well, what's the point of the question?
MR. STEINDLER: I'm getting to whether there are any functional differences between the prior art lots and the '117 patent lots.
THE COURT: Why can't you ask him that question?
MR. STEINDLER: Because I have to prove it.
THE COURT: This is a circuitous route. So, I don't think there was any direct testimony on this subject.
MR. STEINDLER: Well, let me also say this --
THE COURT: You keep adding on to your arguments, Mr. Steindler. Why don't you just give me one full argument up front, then I can analyze all the elements of it before I respond.
MR. STEINDLER: All right. We have an agreement as we heard at the beginning of trial that I'm entitled to call their witnesses in my case in chief.
MR. CARSTEN: I don't believe that agreement extends

to experts, your Honor.

MR. STEINDLER: That's news to me. But, in any event --

THE COURT: You don't have an agreement according to your adversaries.

MR. STEINDLER: Apparently that agreement's now been changed. Because that is certainly my understanding of the agreement. But having said that, this issue goes to whether there's structural and functional differences between the one product and the other, and I'm just trying to establish in the record here, with evidence that there's no functional difference between the '814 patent product and the '117 patent product.

THE COURT: All right. You may ask the question. Go ahead.

BY MR. STEINDLER:

Q. Well, let me ask it simply. You would agree with me that there's no functional difference between the product of the '814 patent and the product of the '117 patent; correct?

A. Actually I don't know that.

Q. Can't you see here -- strike that.

Don't you see here that the lot WC was used in clinical tests?

MR. CARSTEN: Your Honor, I object. You can't open the door to this by asking a question that's improper, and he

says I don't know and then say well, look here at this. That's improper.

THE COURT: I guess he's trying to see if he can change his testimony. It goes to credibility, so I'll allow it.

BY MR. STEINDLER:

Q. Isn't it true, sir, that 10 years after lot WC was made, it was turned into a finished product, batch Y7H0978A and used by UTC in human clinical trials?

A. Yes, that's what it says.

Q. And you don't have -- you don't dispute that it performed effectively in the human clinical trials, do you?

A. I don't know.

MR. CARSTEN: Objection, your Honor; it lacks foundation.

THE COURT: I'll let him answer the question.

THE WITNESS: Yeah, I don't know that's true.

BY MR. STEINDLER:

Q. You're not in your testimony contending that there's a functional difference between the product made in the prior art, and -- strike that. You're not contending that there's a functional difference between the product of the '814 patent and the product of the '117 patent; correct?

A. No, I don't know if there's a functional difference.

Q. Now, you understand that lot WC made by the Upjohn '814

patent method, met the treprostinil specification requirements that UTC had approved by the FDA; correct?

A. I believe that's the case.

MR. STEINDLER: Let's turn to Dr. Aristoff's slide 26.

Q. This is the slide that you presented to explain that there were in your view differences in purity profiles between the '814 patent and the '117 patent; right?

A. Yes.

Q. And just so that we're clear, for these differences that you're relying on, you're looking at UTC's optimized commercial embodiments; correct?

A. I was using all the development and commercial lots through early 2004 that I had data on from the NDA and a couple other sources, the IND amendment.

Q. Now, even using these optimized commercial lots for averages, the '814 patent has exactly the same kind of impurities as the optimized '117 patent, right, just at different levels of concentration; correct?

A. No, there were impurities in the '117 lot that were not present in the Upjohn lots, the -- the product of the '814 patent.

Q. In your slide here, you're not -- strike that.

Your slide here presents impurities that are present both in the '814 patent and the '117 patent; correct?

A. Yes, I started with Dr. Buchwald's analysis and these are the ones that he used so I used the same ones, I just added all -- he only selected some of the lots, I used all the lots.
Q. Now, again, to be clear when you say there are structural differences between the '814 patent product and the '117 patent product, what you mean is that there's a difference in these concentration levels of impurities contained in the mixture; right?
A. I'm saying that there's different relative amounts of impurities as well as different impurities.
Q. Now, the average from '814 patent that you're relying on here, shows four percent of impurities; right?
A. That's correct.
Q. That falls within UTC's specification for its treprostinil drug substance; correct?
A. Yes.
Q. So, setting aside the age of lot WC, for example, the '814 patent lot of treprostinil could be used with the Remodulin commercial product because it meets UTC's specification; correct?
A. It does meet the specifications, it doesn't meet what Dr. Bettis was proposing in his memo of improved specifications.
Q. But specifications that the FDA has approved for treprostinil would be met by the '814 patent product; correct?
A. Yes.

Q. So as far as the FDA is concerned, the '814 patent product is the same as the '117 patent product; correct?

MR. CARSTEN: Objection, your Honor; relevance.

THE COURT: Overruled. You can answer.

03:09 THE WITNESS: Oh yes. Well, I'm not -- I don't work for the FDA so I'm not -- I'm not sure I can answer that question.

BY MR. STEINDLER:

Q. So they meet both meet -- strike that.

03:09 The '814 patent product and '117 patent product both meet the same FDA approved specification for treprostinil; correct?

A. As far as I understand the analytical specifications.

MR. STEINDLER: Let's go to another demonstrative

03:09 used by Dr. Buchwald, number 65 -- strike that. It's number 56. It describes a passage from Burroughs Wellcome IND, DTX-58. It's a volume 1.2, at Bates number 0101559.

Q. Do you see this?

A. Yes.

03:10 Q. Now -- so, this is describing lot WA; correct?

A. Yes.

MR. STEINDLER: Then let's go to D-Dem-657, please.

Q. Again, DTX-59, the April 15, 1999 IND amendment, at Bates number 61839, there's a passage that's set out in this slide;

03:11 right?

A. Yes.
Q. And in this passage is a statement made by United Therapeutics to the FDA; correct?
A. Yes.
03:11 Q. The passage involves a comparison of an old reference standard lot, WA, made by the '814 patent process with a new reference standard lot, UT-15, RS-98-LO1, made by the '117 patent process; right?
A. Yes.
03:11 Q. And the -- strike that.
UTC is reporting to the FDA that the reference standard made by the '814 patent and the reference standard made by the '117 patent, are the same compound; right?
A. It says that.
03:12 Q. So the FDA is telling -- strike that.
UTC is telling the FDA that the '814 patent product is the same as the '117 patent product; correct?
A. Yes, but I would say any chemist would understand it doesn't mean they're a hundred percent identical. It means
03:12 they're substantially the same -- contain the same molecular formula of the major product. So I don't remember how pure each of these were, but primarily compounds the molecular structure of treprostinil. They're not identical.
MR. STEINDLER: Let's go to Buchwald D-Dem-58,
03:12 please.

Q. Within this same April 15, 1999 IND amendment in DTX-59, at Bates number 61857, UTC is representing to the FDA that by looking at and comparing the IR spectra and absorption bands you can tell that the two lots are the same material; correct?

03:13 A. Yes, but again you couldn't tell by IR, you have a hundred -- I don't even think by IR you can tell 98 percent. If there's a half a percent of impurity in one lot and -- and not in the other you can't tell that by IR.

Q. Again here, in the April 151999 IND amendment, at 61857,

03:13 UTC is representing to the FDA that the product of the '814 patent is the same as the product for the '117 patent; correct?

A. No, I disagree. A chemist at the FDA would understand that the primary molecular structure in both those lots would

03:14 have the molecular structure of treprostinil. There can still be different impurities in the two lots, it would be very small but they'd be there.

Q. So when UTC tells the FDA that the '814 patent product and the '117 patent product, are the same material they don't

03:14 really mean that; is that your testimony?

A. No, I'm saying a chemist would understand that means that the majority of the material has the same molecular structure in both those lots, any chemist would understand that.

Q. Now, let's go to your slide 29. So the difference that

03:15 you're looking at in impurities levels here for your averages

is the difference between 96 percent pure, and 99.04 percent pure; right?

A. Yes.

Q. And that 99.04 percent pure as we've said is from optimized UTC embodiments; right?

A. I said it was taken from the development and commercial lots of UTC, versus the lots from the development lots from Upjohn. That's all that data I had.

Q. All of those lots are optimized process; correct?

A. I don't know if I'd say they all were. Upjohn material must have been optimized, too so I'm having a hard time understanding the question.

Q. Let's go to your slide 30. Again, with respect to differences in yield, just to be clear, the product of the '117 patent that you're using here by comparison is the preferred embodiment set out in the '117 patent; right?

A. That's from claim 33, yes. Excuse me; from the '117 patent it's claim 3, from the '814 patent it's example 33.

Q. Just so that the record is clear, when you're comparing yields, you're comparing yields from an example in the '814 patent to an example in the '117 patent; right?

A. Yes. Yes. Those are the only two they had one example in each patent, so that's what I used.

Q. And the '117 patent would cover other ways of making treprostinil that didn't have these levels of yields; right?

A. It could.
Q. Let's go to your slide 31. You say the '117 patent is not obvious because the stereoselective reaction pathway reduces the need for purification; right?
03:17 A. That's correct.
Q. We saw earlier, though, that in the example in the '117 patent, 12 of the 15 steps involve purifications; right?
A. Yes. But here we're really talking about the final step where you have a 50/50 mixture in the '814 patent, and you
03:17 have primarily treprostinil in the '117 patent. So there's a lot more of impurities to get rid of even at the last step.
Q. But even in the '117 patent you still had to purify the crude product at the final step in that reaction; correct?
A. Yes.
03:17 Q. Now, you say that the '117 pathway creates a distinct product with a superior impurity profile; right?
A. Yes.
Q. But as we said, the '117 pathway is just a single step in multistep process; right?
03:18 A. Yes.
Q. And you can get all kinds of purity levels depending on the process you choose; right?
A. So again I used the data that was available, that's what I used to determine the impurity profile. I used the same
03:18 analysis that Dr. Buchwald did.

Q. So, even under your construction, where you say the claims are directed to a mixture, the '814 patent product can be the same as the '117 patent product; right?
A. No -- could you repeat that? I don't think I said that.
03:18 Q. Isn't that exactly what UTC told the FDA?
A. Could you repeat your question? I don't understand it.
THE COURT: Please rephrase.
MR. STEINDLER: Sure.
BY MR. STEINDLER:
03:18 Q. Didn't UTC tell the FDA that the '814 patent process can be the same as the '117 patent product?
A. Again, they're referring to the primary constituent of both the products is treprostinil, the molecular structure of treprostinil. They're not saying the impurity profiles are
03:19 the same.
Q. When you say to the FDA that the reference standard made by the '814 patent is the same material, as the reference standard made by the '117 patent, aren't you saying that the compound plus its impurities is the same?
03:19 A. I don't believe that.
Q. All right. Nothing further.
THE COURT: Thank you.
(REDIRECT EXAMINATION OF PAUL A. ARISTOFF, PH.D. BY MR. CARSTEN:)
03:19 Q. Hello, Dr. Aristoff.

A. Hi.
Q. You were just asked some questions about the reference standard made from material that had come from the '814 synthesis; do you remember that?
03:19 A. Yes.
Q. Okay. With respect to that reference standard material, how is that material purified?
A. Well, it came from lot WC which was actually one of the ones I used in my analysis, but my recollection that the lot
03:20 WC itself had about five to 10 recrystallizations at least, and then you need several more to get to the reference standard as well.
MR. STEINDLER: So, let's pull up DTX-57, please. And let's go to page 1161350.
03:20 Q. I think this is one of the pages that Mr. Steindler showed to you.
THE COURT: I didn't catch the document number.
MR. CARSTEN: It's DTX-57, five seven.
THE COURT: Thank you.
03:20 MR. CARSTEN: And page number is 1161350.
And Mr. Merisier, if you'd be so kind to pull up the same section that Mr. Steindler had asked.
BY MR. CARSTEN:
Q. Is this a section that Mr. Steindler directed you to on
03:21 this page?

A. Yes.
Q. Okay. And does this inform you in what the -- what purification process the WC material was subjected to?
A. Yes, I believe this is the one that we're referring to, yes.
Q. So can you just describe for the Court, what was done to this material after it came out of the reaction mixture?
A. So, again, after the crude product was recrystallized, is says as many times as necessary, so typically five to 10 recrystallizations were required. And at this point, they did -- it was further purified, they had to a chromatography, and then they did an -- let's see, then they did another crystallization.
Q. Do you recall offhand, Dr. Aristoff, what the -- what the purity of that material the WC material was roughly?
A. That was around 95 percent.
Q. Now, is this five to 10 recrystallization requirement and the chromatography, the additional recrystallization to get to WC, is that disclosed in the '814 patent?
A. No.
Q. Now, in order to get to the purified reference sample, there were two additional purifications; right?
A. Yes.
Q. And do you remember the solvent system that was used there?

A. No, I do not.
Q. Would it surprise it was ethanol water in some ratio?
MR. STEINDLER: Objection; leading.
THE COURT: Overruled. You may answer.
03:22 THE WITNESS: Thank you, your Honor. No, that would -- that would be normal solvent system.
BY MR. CARSTEN:
Q. Now, is that -- that ethanol water solvent recrystallization, is that disclosed in the '814 patent?
03:22 A. I don't recall that being disclosed.
Q. And do you recall how many times that material was recrystallized in that other solvent system to get to the reference purity standard?
A. I can't recall exactly, I think it was at least twice.
03:23 Q. Now, would you agree with me, Dr. Aristoff, that this is an unusual purification process?
A. Yes, this is a lot more recrystallizations than you would typically do.
Q. Would that reflect some kind of optimization of a
03:23 process?
A. It's telling me -- I mean it's the same experience I had on a much smaller scale, it's hard to get pure material and you suffer a lot of loss of material, even here they mention 12 percent, to even get that purity.
03:23 Q. Optimization of steps in a reaction sequence, is that --

is that routine?
A. Yeah, you always do that.
Q. Is it expected?
A. Yes.
03:23 Q. Mr. Steindler was asking you about super optimized processes; do you recall that?
A. Yes.
Q. Do you have any idea what super optimized means?
A. Not really.
03:24 Q. Have you ever heard that term?
A. No.
Q. Now let's turn to the -- well, before we move on from this point, purifications generally, do organic chemists use purification at the end of reaction sequence?
03:24 A. Yes.
Q. Why is that?
A. Well, very few reactions work perfectly or even close to perfectly and you almost always have side products, materials you have to get rid of, so you almost are always doing some
03:24 sort of purification.
Q. Now, Mr. Steindler --
MR. STEINDLER: Let's go to the claims of the '117 patent. That's PTX-2, your Honor.
And let's just pull out the first part of claim 1.
03:24 Q. Stereoselectively produced isomeric compound, that's a

term we've heard quite a bit about, Dr. Aristoff; right?
A. Yes.
Q. Now, I think Mr. Steindler was suggesting that you read this term to mean expressly a mixture; right?
03:25 A. Yes.
Q. Now, the claim uses the word compound here, doesn't it?
A. Yes.
Q. And your testimony with respect to -- and your analysis with respect to this claim has been consistent throughout the
03:25 case; right?
A. Yes.
Q. Did you change the way in which you applied this claim term?
A. No.
03:25 Q. Now, Mr. Steindler cited some deposition testimony to you about a solid, so I'd like to ask you a couple questions about that if I could. Do you remember that testimony?
A. Yes.
Q. Now, if you followed the '117 patent claims or example 1,
03:25 at the end what is it that you get following the purifications?
A. So at the end of the purifications you'll get a solid or an oil depending what -- what prostaglandin analog you're making.
03:25 Q. So for treprostinil it would be what, a solid --

A. It would be a solid for treprostinil.
Q. And that treprostinil solid, that was stereoselectively produced; right?
MR. STEINDLER: Objection; leading.
03:26 THE COURT: All right. Sustained. Next question.
BY MR. CARSTEN:
Q. Was that -- was that material stereoselectively produced?
MR. STEINDLER: Same objection.
THE COURT: Why don't you ask him about the
03:26 material. So rephrase.
MR. CARSTEN: Okay.
BY MR. CARSTEN:
Q. That treprostinil compound that's the solid at the end of the '117, do you have an opinion as to whether that was
03:26 stereoselectively produced following the steps of the '117 patent?
A. Well, yes, definitely the '117 patent describes a stereoselectively produced compound.
Q. Now, if a person of skill in the art took that compound,
03:26 that solid, and put it into solution, do you have an opinion as to whether the compound in that solution would still be stereoselectively produced or not?
A. Well, it would be yes, at that point.
Q. Does that change anything about that solid in some way to
03:27 make it not stereoselectively produced?

A. No.
Q. Does the '117 patent example 1 provide guidance as to how to get to stereoselectively produced treprostinil?
A. Yes, in example 1.
03:27 Q. Do you believe that example is sufficient to tell people how to get to -- those of skill in the art how to get to stereoselectively produced treprostinil?
A. Yes.
Q. Mr. Steindler asked you some questions about midway
03:27 through a synthesis you add some other product; do you remember that testimony?
A. Yes.
Q. Would a person of skill in the art ever do that?
A. No, I don't think that would be a wise thing to do.
03:27 Q. Why not?
A. Well, if you do that you're going to be changing that other compound, as you're doing the chemistry you're just complicating things for yourself.
MR. CARSTEN: Now, Mr. Merisier, can you put up
03:28 slide 23 please from Dr. Aristoff's direct testimony?
I'm sorry; I thought it was slide 23. I apologize. The one in which we quote the Sandoz invalidity contentions, please.
Q. Now, you remember you were asked about this on your
03:28 cross-examination, Dr. Aristoff?

A. Yes.
Q. And Mr. Steindler pulled up the first part of this upper paragraph; right?
A. Yes.
03:28 Q. And he said to you look, the '814 patent isn't cited there; right?
A. That's correct.
Q. Okay. Well, let's go back to -- now the remaining part of that paragraph says, early preparations of treprostinil
03:28 resulted in complex mixtures of diastereoisomers requiring separation and low yields. You see that; right?
A. Yes.
Q. And you -- what's your understanding about what that refers to?
03:29 A. Well, it was my work at Upjohn.
Q. Okay. Now, it goes on to a completely separate paragraph, and it says, other early efforts by Upjohn. Do you see that?
A. Yes.
03:29 Q. What's that referring to?
A. I assume that was my subsequent efforts at Upjohn.
Q. And what are your subsequent early efforts at Upjohn?
A. The '814 patent.
Q. You weren't asked to do any work on infringement in this
03:29 case; right?

A. No.
Q. Have you ever been an expert in a patent case where you've opined about infringement of patents?
A. No.
03:29 Q. Were you ever provided any legal standards relating to infringement of patents?
A. No.
Q. Now, you were cited I think in connection with the slide we just had up, something about numerous prior art
03:30 disclosures; do you remember that?
A. Yes.
Q. And that was relating to numerous prior art disclosures of treprostinil; right?
A. Yes.
03:30 Q. And you're familiar with each and every one of them; right?
A. Yes.
Q. Are you listed as an author and/or inventor on all if not -- or most or all of them?
03:30 A. Most, there's several that I'm not.
Q. As the inventor of treprostinil, did any one of those numerous prior art disclosures teach stereoselectively produced treprostinil compound?
A. No.
03:30 Q. Any doubt in your mind about that?

A. No, no doubt.

MR. CARSTEN: Pass the witness.

THE COURT: Do you have any --

MR. STEINDLER: No. No questions.

03:30 THE COURT: All right. So you may step down, Doctor. Thank you for coming.

THE WITNESS: Thank you, your Honor.

(Witness excused.)

THE COURT: Next witness.

03:31 MR. CARSTEN: Your Honor, United Therapeutics calls Dr. Richard Gering to the stand. My colleague Veronica Ascarrunz is going to be handling the direct examination of Dr. Gering.

In addition, your Honor, I understand this is a 03:31 fairly short witness, it's on the order of I believe a half an hour or so, maybe less; we're optimistic. But Dr. Gering has a scheduling conflict and he needs to be done today if at all possible, he can't come back on Thursday.

THE COURT: I'm not committing to that.

03:31 MR. CARSTEN: I understand, I'm just raising the issue. We had hoped that -- we didn't expect the cross-examination to go nearly twice as long as the direct examination of Dr. Aristoff.

MR. STEINDLER: Judge, if they have a problem with 03:31 timing of their witness, they can be short with this witness.

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

UNITED THERAPEUTICS CORPORATION,

Vs.

SANDOZ, INC.,
DEFENDANT

CIVIL NO.
12-1617 (PGS)
13-316

MAY 22, 2014
CLARKSON S. FISHER COURTHOUSE
402 EAST STATE STREET
TRENTON, NEW JERSEY 08608

B E F O R E: THE HONORABLE PETER G. SHERIDAN
U.S. DISTRICT COURT JUDGE
DISTRICT OF NEW JERSEY

TRIAL - DAY 12

Certified as true and correct as required
by Title 28, U.S.C. Section 753
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of that into today, we may be able to finish up the following Tuesday.

THE COURT: We had the wrong Tuesday when we were going to finish this, we were only off about a week.

00:01 MR. STEINDLER: That's exactly true, your Honor. But, in any event, obviously as Mr. Carsten says it's up your Honor's preference. But to the extent to which we're able to fit some of that deposition playing in today, I think it would help us to be able to get -- give us a shot of at being done

00:01 on the Tuesday after Memorial Day.

THE COURT: All right. So I can probably go to about 4:15 today, so we'll proceed with depositions from 3:00 to 4:00.

MR. CARSTEN: Very well, your Honor.

00:02 THE COURT: So that means you're under an obligation to finish up this witness by 2:00.

MR. CARSTEN: I think I can accept that challenge, your Honor.

THE COURT: All right, thank you.

00:02 MR. CARSTEN: May I proceed?

THE COURT: You may, Mr. Carsten.

MR. CARSTEN: Thank you, your Honor. UTC recalls to the stand, Professor Robert Williams.

THE COURT: All right.

00:02 (ROBERT M. WILLIAMS, PH.D., previously sworn,

resumes witness stand.)

THE COURT: Good morning, Doctor. So you're still under oath.

THE WITNESS: Yes, sir. Good morning, your Honor.

10:02 THE COURT: Good morning.

MR. CARSTEN: Your Honor, I have some materials to use with the witness; may I approach?

THE COURT: Yes, you may.

MR. CARSTEN: Thank you.

10:02 (Handing to witness and Court.)

THE COURT: So, Doctor, it's admirable how you stayed awake in the back there through all of this.

THE WITNESS: Chemistry is interesting.

(DIRECT EXAMINATION OF ROBERT M. WILLIAMS, PH.D. BY MR. 10:03 CARSTEN:)

Q. Good morning, Professor Williams.

A. Good morning.

Q. So, you were here earlier and you testified your opinions with respect to infringement; correct?

10:03 A. Correct.

Q. Okay. We've called you back because you've done more than just renders opinions on infringement in this case; correct?

A. That's correct.

10:03 Q. And what's your understanding of what you're going to

testify about today?
A. My understanding is I was going to testifying about my opinion regarding secondary considerations of nonobviousness.
Q. Have you prepared a slide that outlines the particular consideration that's you intend to testify about today?
A. Yes.
MR. CARSTEN: May I just have a moment, your Honor?
THE COURT: You may.
(Brief pause.)
MR. CARSTEN: Thank you, Mr. Merisier.
Thank you for the indulgence, your Honor.
BY MR. CARSTEN:
Q. Professor Williams, would you please summarize for the Court the particular considerations or secondary considerations upon which you intend to provide opinions today?
A. Yes, certainly. So I was asked to render opinions on whether or not there was a long felt need for the invention of the '117 patent; I was also asked to consider failure of others; I was also asked to opine on unexpected results; and finally I was asked to consider if there was a nexus between the '117 patent claims and the commercial success of Remodulin.
Q. Let's start with long felt need. Did you reach a conclusion about whether there was a long felt need for

stereoselectively produced isomeric treprostinil compound according to the '117 patent?

A. Yes.

Q. And what was your opinion?

A. My opinion is that there certainly was a long felt need.

MR. CARSTEN: I'd like to call up DTX-372, please.

Q. What is DTX-372 in evidence?

A. Yes, this is a process optimization report for the manufacture of treprostinil, UT-15, prepared by David Walsh.

MR. CARSTEN: And let's turn to page 173 of that document if we could.

Q. What is this?

A. Yes, this is parts of that report that was written by Dr. Moriarty, who is one of the named inventors on the '117 patent.

Q. Did this document -- the information contained in this document support your conclusion it was a long felt need?

A. Yes.

Q. Let's go back to the slide deck to a passage from pages 176 and 177. Are these the portions that you specifically considered?

A. Yes, well, among others, but here it sums it up. Dr. Moriarty said "At the planning stage in 1997 our initial approach was directed towards improving the known Upjohn Aristoff routes, summarized below in scheme 1, and a parallel

effort was directed towards finding a totally new route."

Then he goes on to say: Furthermore, reduction of the C11 keto group created another chiral center. This process could not allow the production of large-scale quantities of UT-15 -- which is treprostinil -- in an economical way because of the extensive separation problems, which resulted from the plethora of stereomers -- which is abbreviated for stereoisomer -- formed in this non-stereoselective process.

Q. So, what chemistry is being discussed here in the Moriarty memorandum?

A. Yeah, I believe this refers to the chemistry that Dr. Aristoff developed at Upjohn that's contained in the '814 patent.

Q. Now, did Dr. Moriarty and his group actually attempt the Upjohn route?

A. My understanding is that they actually didn't go in the laboratory and attempt it, they did an intellectual analysis of that chemistry.

Q. Now, how does -- how do these passages support your conclusion with respect to long felt need?

A. Well, Dr. Moriarty was faced with trying to come up with synthesized treprostinil and looking at the prior art, looked at what was available and all that was available was what Dr. Aristoff had done at Upjohn, and he concluded that what they had accomplished at Upjohn was not suitable for -- for

scale-up needs due to the non-stereoselective nature of the Upjohn synthesis, and in particular the extensive separation problems of the diastereoisomers, the stereoisomers that are created in that process.

Q. Were you here in court for the testimony of Dr. Rothblatt?

A. Yes, I was.

Q. Does that also confirm your opinions on long felt need?

A. Yes, indeed. Dr. Rothblatt told a very I thought engaging story of going to a lot expense and time and trouble to license in the patent portfolio from Burroughs Wellcome, which was indeed the Aristoff patents, and when she finally got them she was told well, you have these patents but they're unsuitable for actual manufacture of the drug, and she was very let down. And then she set up this call for proposals that Dr. Moriarty answered and he was funded and then solved this problem.

Q. Now, are you aware of any testimony from Alphora witnesses that confirm your conclusion that there was a long felt need?

A. Yes.

Q. And do you have a slide on that?

A. Yes, on the next one.

Q. Would you please describe for the Court what you're showing here?

A. Yes, so in deposition testimony, Dr. Boris Gorin, who is the director of research at Alphora, in reference to the first Upjohn synthesis, which is described in the '075 patent, he said "it's not feasible."

00:10 And then with respect to the '814 patent, which is the second Upjohn or Aristoff synthesis, he described as very kind of messy. And he also says: It doesn't look like the greatest chemistry, I don't think it's worth even going down that path. So, both prior art syntheses were dismissed out of 00:10 hand.

Q. And who are the two witnesses that you're talking about here?

A. These are both Ph.D.s who work at Alphora.

Q. And the first was with respect to the '075 synthesis, 00:10 that was Dr. Boris Gorin?

A. Yes.

Q. And who is he?

A. Director of research, I think I said that.

Q. And with respect to the second witness on the '814, who 00:11 is that?

A. That's Dr. Graham McGowan, who's the Alphora API project manager.

Q. And how do these quotations confirm your opinion with respect to long felt need?

00:11 A. Well, again it confirms my opinion that as of the late

1990s the prior art did not provide a suitable feasible method to make treprostinil at scale for actually developing and launching a real drug, a new medicine.

Q. Turning to failure of others, did you reach a conclusion regarding whether others had tried and failed to prepare stereoselectively produced treprostinil?

A. Yes.

Q. And what was that conclusion?

A. My conclusion is -- is that the Aristoff group at Upjohn particular that had the first syntheses of treprostinil, tried and failed to come up which a stereoselective route due to treprostinil.

Q. And turning back to the UTC process optimization memo, DTX-372, were there any passages there that supported your conclusion?

A. Yes.

Q. Do you have a slide?

A. Yes.

Q. What is this?

A. So this is again the process optimization report that we were just looking at a few minutes ago, and this is now Dr. Moriarty writing, and he says here quote "UT-15 --" which is treprostinil "-- was prepared by Upjohn chemists likewise using the above sequence, they obtained a crude product corresponding to a mixture of diastereoisomers of 1." And

compound numbered 1 corresponds to the treprostinil structure.

And then he goes on to say: Five to 10 recrystallizations were necessary to yield a product that was purified by chromatography on silica gel to give a product that was finally recrystallized from THF to give 167 grams, and that was from 1.24 kilograms of the initial product, which corresponds to about a 12 percent yield, just that one step.

Q. I'm sorry; a 12 percent yield?

A. 12 percent.

Q. Is that low?

A. That's low.

Q. And what does that 12 percent yield actually refer to?

A. It's referring to the purified 167 grams that started with 1.4 kilograms of material, that was a one-to-one mixture of diastereoisomers.

Q. In pounds how much is 1.4 kilograms?

A. Let's see, that's about three pounds.

Q. And how much is 167 grams?

A. A fraction of a pound.

Q. Would you consider the Upjohn route to be a failure in terms of making stereoselectively produced treprostinil suitable for scale-up?

A. Yes.

Q. Why?

A. Because in order to get even a couple hundred grams of

material they had to start with roughly 10 times that, and separations are very expensive, they're -- they generate a lot of waste, solvent waste, adds tremendously to the cost of the final product, so this is certainly not something that a real process chemist would have considered as a viable way to actually manufacture this drug.

Q. Were there any other passages on the same page, which is page 44 of DTX-372 that support your opinion?

A. Actually, just beneath this there's another passage on the next demonstrative. And Dr. Moriarty goes on to say: This prior work -- referring to '814 chemistry -- did not offer much guidance for our purification of the final product UT-15 -- treprostinil -- because they had a mixture of stereomers or stereoisomer at this stage; the unacceptably low recovery of the product was not relevant because in contrast on the Upjohn work, we have a pure steromer or stereoisomer, at the stage of triol 66 and 1 -- and there he's referring to the chemistry he developed that's in the '117 patent.

Q. How does this support your opinion with respect to failure of others?

A. Well, again he's saying that the unacceptably low recovery of the final product from the prior art, was just not useful for practical way to make and sell this drug.

Q. Now, let's turn to unexpected results. In your opinion, Professor Williams, is it unexpected that the claimed

intramolecular cyclization reaction was able to be used to prepare a selectively produced isomeric treprostinil compound?

A. Yes.

Q. And let me show you PTX-574. Do you recognize PTX-574, Doctor?

A. Yes.

Q. What is it?

A. This is a review article that was published in 2004, the title of which is When the Pauson-Khand and Pauson-Khand Type Reactions Can Be Go Awry, a Plethora of Unexpected Results.

Q. And did -- did you rely upon this document in rendering your opinions on secondary considerations?

A. Yes. This is one of the things I relied on.

MR. CARSTEN: Your Honor, I move to admit PTX-574, please.

MR. STEINDLER: No objection.

THE COURT: All right, admitted.

(Plaintiff's Exhibit 574 was marked into evidence.)

BY MR. CARSTEN:

Q. Did any particular passage from this unexpected results article support your opinion?

A. Yes, actually the article is full of relevant information, but Section 2.2 which is shown on this demonstrative slide, alternative -- titled Alternative Pathways, the authors actually classified into five different

families of undesirable side reactions that attempted the Pauson-Khand reactions have been documented the undergo. And for example, then in the first one there's something like seven, under A other modes of reaction there's like seven different types of reaction manifolds that were identified in the literature, again this is a review article. So there's five families of alternative pathways, and so clearly the literature taught that the Pauson-Khand type reactions are very unpredictable, you get all kinds of strange side products that are not the desired five membered ring with the double bond and the -- and the carbonyl group cyclopentanone that's formed in the classical Pauson-Khand reaction which is formed in the '117 patent process to make the tricyclic intermediate that we've been talking about the last couple weeks.

Q. How commonly are used Pauson-Khand or Pauson-Khand type reactions in the pharmaceutical manufacture?

A. To my knowledge extremely rare. In fact as far as I know, the manufacture of treprostinil is the only example of the industrial use of the Pauson-Khand reaction.

Q. I'd like to show you PTX-571. What is PTX-571?

A. Yes, this is another review article, titled the Medicinal Chemists Toolbox, An Analysis of Reactions Used in the Pursuit of Drug Candidates. And in this review article the authors analyze something like 3,500 drug candidates and drugs and the chemistry that was used to make those drug candidates and

drugs. And lists the most popular or commonly used reactions in pharmaceutical manufacture and the Pauson-Khand reaction is not on the list at all.

Q. Is this an article that you relied upon in rendering your opinions on secondary considerations?

A. Yes, it is.

MR. CARSTEN: Your Honor, we move to admit PTX-571.

MR. STEINDLER: No objection.

THE COURT: All right, it's admitted.

(Plaintiff's Exhibit 571 was marked into evidence.)

MR. CARSTEN: Thank you, your Honor.

BY MR. CARSTEN:

Q. Is there any particular passage from the -- this roughly review article PTX-571 that informed your opinions regarding unexpected results?

A. Yes. And so, here, on the -- on this demonstrative, which is from that review article, here's shown in terms of synthetic complexity the authors analyzed 3,566 compounds that were either drug candidates or drugs, and they're able to find traceable routes for almost three thousand of them. And they classified them into two different levels of complexity, one was the number of chemical steps that required in the synthesis of each of those drugs or drug candidates. And in the case of treprostinil as described in the '117 patent example 1, that's a 15 step synthesis, and the top chart here

shows the number of steps covering these roughly three thousand drugs and drug candidates, and this graph maxes out at 10 steps. So above 10 steps treprostinil would be, you know, off the charts. So in terms of sheer molecular complexity based on number of steps to put this molecule together treprostinil is -- is an outlier.

Q. What is the chart on the bottom of this -- this demonstrative show?

A. Yes. And so the second complexity criteria that they looked at were the number of stereogenic centers. And as you can see over at zero on the left-hand side most of the drug or drug candidates had zero stereogenic centers. Treprostinil has five stereogenic centers as we've heard in the last couple of weeks, and on this chart none of the drugs or drug candidates had five stereogenic centers. And ones with more than five is a very very diminishing tiny fraction of the total. So again, in terms of complexity with regard to stereogenic centers, treprostinil again is an outlier.

Q. So, how does this article inform your opinions with respect to the unexpected results of the intramolecular cyclization reaction, and the preparation of stereoselectively produced isomeric treprostinil compound?

A. Well, the fact that Pauson-Khand or Pauson-Khand type reactions are not mentioned in this article at all, so it certainly wasn't the go-to reaction to make multistep complex

drug candidates with multiple stereogenic centers.
Q. Just for the record, the page that we excerpted here is PTX-71 at Bates number 70000; right?
A. Yes. That's correct.
10:22 Q. Did you form any opinions relating to nexus of the claimed invention to any commercial success?
A. Yes.
Q. What's that opinion?
A. Yes. So my opinion is that there is a nexus between the
10:22 '117 patent claims and the commercial success of Remodulin.
Q. Why?
A. I think I have a demonstrative that speaks to that.
Q. Okay.
A. So this is from a Journal of Organic Chemistry article
10:22 that was written by Dr. Moriarty, and I lifted two quotes out of this article. And he says here first: Unfortunately this low level of stereo -- control of stereochemistry in the route led to significant separation problems in obtaining the final product, and could not be used to fulfill our scale-up needs
10:23 for development of UT-15, which is treprostinil. And there he's referring again to the prior art Upjohn synthesis, the '814 patent.
And he also says: With regard to both the '075 and the '814, these routes, although conceptually appealing were
10:23 deemed inadequate to the task of producing kilogram quantities

of UT-15, and accordingly a novel synthetic route was required.

Q. How does that support your opinion there's a nexus between the '117 patent claims and the commercial success of Remodulin?

A. Well, there was no previous commercial production of treprostinil using the prior art, methods, and the '117 patent was the -- the enabling technology that allowed the Remodulin drug to be launched and is now I think very commercially successful.

Q. Do you think Remodulin would exist without the '117 patent?

A. I don't think so.

Q. Did Dr. Rothblatt's testimony also support your opinion in any way?

A. Yes.

Q. How so?

A. Well, she again after going to great expense and of licensing in the patent portfolio from Upjohn by Burroughs Wellcome, she learned that she couldn't use the prior art to make and develop the drug, and actually ended up having to self -- she funded herself additional research to come up with a practical synthesis of this drug. And Dr. Moriarty and his group answered that call, and successfully tackled the problem and now "viola!", after the '117 patent technology was

invented reduced to practice, now we have a real drug.
Q. Have you summarized your opinions with respect to secondary considerations on a slide?
A. Yes.
10:25 Q. Can you just walk the Court through that, please?
THE COURT: Could you just go back to the prior slide? Could I have the Bates page?
MR. CARSTEN: I apologize, your Honor. This is from Dr. Moriarty's Journal of Organic Chemistry article, that's
10:25 DTX-171 in evidence, at pages 5997 seven and 5998.
THE COURT: All right, thank you.
BY MR. CARSTEN:
Q. Would you please describe or summarize your opinions related to secondary considerations, Professor Williams?
10:25 A. Certainly. So the summary of my opinion is shown here, and first there was in my opinion a long felt need for stereoselectively produced treprostinil. Secondly, others tried but failed to prepare stereoselectively produced treprostinil. Third, the claimed intramolecular cyclization
10:26 reaction, the Pauson-Khand reaction, was an unexpected result. And finally there is a nexus between the '117 patent claims and Remodulin's commercial success.
Q. Is there any doubt in your mind on any of those conclusions?
10:26 A. I have no doubt.

MR. CARSTEN: Pass the witness.

THE COURT: All right, thank you.

Mr. Steindler?

(CROSS-EXAMINATION OF ROBERT M. WILLIAMS, PH.D. BY MR. STEINDLER:)

Q. Good morning, Dr. Williams.

A. Good morning.

Q. The original IND for treprostinil was submitted by Burroughs Wellcome for the treatment of congestive heart failure; right?

A. I think that's correct.

Q. And the IND was terminated by Burroughs Wellcome because of a failure in a clinical trial; right?

A. I don't know if that was the exclusive reason.

MR. STEINDLER: Can we go to DTX-459, please?

Q. You recall this document, DTX-459, which is in evidence is the History and Process Validation Rationale For the Treprostinil Manufacturing Process; right?

A. Yes.

Q. You're familiar with this document; right?

A. Yes, I've seen this document.

MR. STEINDLER: Can we turn to the page Bates stamped 1096012, please. And just blow up the second paragraph.

Q. You'll see, among other things, it was stated that in the

last sentence that at a certain point Flolan failed as a treatment for congestive heart failure at Glaxo and this project was stopped at Wellcome; right?

A. That's what it says.

10:28 Q. So that -- strike that.

Burroughs Wellcome stopped the project for treprostinil because of a failure in a clinical trial, not anything to do with the manufacturing process; right?

MR. CARSTEN: Your Honor, I object; calls for

10:28 speculation.

THE COURT: Well, if you can answer the question, you may.

THE WITNESS: I think like I just said, there might have been other considerations as well. This certainly was

10:28 one.

BY MR. STEINDLER:

Q. But you don't know that there's any other reason besides the failure in the clinical trial that caused Burroughs Wellcome to decide to stop this project; right?

10:28 A. I don't know for sure.

Q. Now, at a certain point, Dr. Rothblatt got in touch with Glaxo and then decided that there would be a transfer to UTC of the patents and the pending IND for treprostinil; right?

A. I don't remember all the documents that were transferred,

10:29 but certainly I do recall that she said that she licensed the

patents.
Q. So -- and this took place at around the beginning of 1997; right?
A. I don't recall the exact date.
10:29 Q. Well, let's go to your slide number 3 that we just looked at. You're referring here to DTX-372 at pages 176 and 177; right?
A. Yes.
Q. And it says: At the planning stage in 1997, our initial
10:29 approach was directed towards improving the Upjohn lot. Right?
A. Yes, that's what it says.
Q. So to the extent to which there was a need for a new process to make treprostinil, that need began in 1997; right?
10:30 A. No.
Q. Let's turn to -- back to DTX-459, please.
MR. STEINDLER: And can we go to 1096011. And can you blow up these last two paragraphs.
Q. Again, this is a document that pertains to the history of
10:30 the treprostinil project at UTC; right?
A. May I read it?
Q. Of course.
(Witness reviewing.)
A. Okay, I've read the paragraph. What was your question?
10:31 Q. The question is, this is UTC's own document about its

process that led to the development of treprostinil; correct?
A. I didn't quite understand your question.
THE COURT: Please rephrase.
Q. Let's go back to the first page of this document, please.
10:31 DTX-459 is UTC's own document relating to the history of the treprostinil manufacturing process; correct?
A. Okay, yeah, that's the title of the document.
Q. So that's a correct statement, this is -- this is UTC's own document pertaining to the history of the treprostinil
10:32 manufacturing process; right?
A. Yes, that's UTC own document.
MR. STEINDLER: Then can we turn to 1096011 again and blow up these two paragraphs.
Q. Are you with me?
10:32 A. I'm with you.
Q. And it says, among other things, that Dr. Rothblatt approached Glaxo, licensed these patents and the last of the composition matter patents were licensed in January of 1997; right?
10:32 A. Yes, that's when the composition matter patents were licensed, that's correct.
Q. And then it says: The development of treprostinil as an improved treatment for pulmonary hypertension began in earnest. Right?
10:32 A. Yes.

Q. So, UTC's project to develop treprostinil, as an improved treatment for pulmonary hypertension, began in earnest in or around January of 1997; right?
A. No. So it says here that just reading from what you have
10:33 in front of me that it says it took Rothblatt seven months to license the compound from Glaxo, she founded United Therapeutics in 1996 and certainly there was a need before then, the disease didn't spontaneously start in 1997.
Q. But before then there was no project to develop
10:33 treprostinil for treating pulmonary hypertension; right?
A. Well, the project at Upjohn which was started in the late 1970s and early 1980s, was developing this family of prostacyclin derivatives way back then.
Q. The product that was developed at Upjohn was used in an
10:34 IND to treat congestive heart failure; right?
A. Yes, but that doesn't mean that's the only use that that type of prostacyclin could be used for its biological -- biological mode of action of prostacyclin is well known.
Q. There was never any application to the FDA to use
10:34 treprostinil to treat pulmonary hypertension until Dr. Rothblatt and UTC took over this application in 1997; right?
A. That part seems to be correct.
Q. And can we -- strike that.
The '117 patent was filed on October 24, 1997; right?
10:34 A. I don't have the patent in front of me, but I'll accept

your representation on the date.

Q. Let's just look at DTX-2, please, just so that we have the date straight here.

MR. STEINDLER: Can you blow up the -- and can you focus here on this filing date, October 24, 1997.

Q. Do you see that in the '117 patent?

(Witness reviewing.)

A. I don't see the date you're referring to.

Q. So if you look at the related U.S. application data, there's --

A. Oh, I see it.

Q. There's a date here October 24, 1997; right?

A. Yes.

Q. And you're aware that that's stipulated by the parties as the priority date for the '117 patent; right?

A. Yes.

Q. So what we're looking at in terms of long felt need is somewhere between January of 1997, and October 24, 1997; right?

A. No.

Q. So your view is that there was a need for this even though no one was working on treprostinil for pulmonary hypertension until UTC took this over; right?

A. Of course there was a need, yes.

MR. STEINDLER: Can we pull up DTX-494. It's

already in evidence.
Q. You'll recognize this document is a manufacturing agreement with -- between United Therapeutics and Steroids, Ltd.; right?
10:36 A. Yes, I see that.
MR. STEINDLER: May I approach, your Honor?
THE COURT: Yes, you may.
(Handing to Court and witness.)
THE COURT: Thank you.
10:37 BY MR. STEINDLER:
Q. Within this document, which is a -- strike that.
This document has a series of different documents within it as it was produced to us by UTC, and I'd like to turn to the page Bate stamped 686. Are you with me?
10:37 A. Yes.
Q. This is a proposal that Dr. Moriarty and his group made to UTC to develop a process for making treprostinil; right?
A. Yes. I haven't looked at this document recently, but I'm with you, go ahead.
10:38 Q. And the proposal is dated February 7, 1997; right?
A. Yes.
Q. And the patent was filed on October 24, 1997; right?
A. Yes.
Q. So Dr. Moriarty and his group were able to come up with a
10:38 new synthesis that is claimed in the '117 patent between

February 7, 1997, and October 24, 1997; right?
A. Yes.
Q. Now, you will recall that -- that Dr. Aristoff's group at Upjohn was able to make a 167 gram lot of treprostinil using
10:39 the '814 patent process; right?
A. Yes.
Q. And that 167 gram batch also had along with it an additional 127 -- strike that.
In addition to the 167 gram portion of it there was --
10:39 they also made another 120 grams in that same -- from that same material; right?
A. Yes.
Q. So all in, Upjohn was able to make a batch of 287 grams of treprostinil using the prior art process; right?
10:39 A. Yes, with an extraordinarily difficult separation that was -- and extremely low yield and recovery, yes.
Q. The purity level of that lot was above 95 percent; right?
A. That's my recollection, yes, that's correct.
Q. And that 287 gram batch would meet UTC's FDA approved
10:40 specification for treprostinil; right?
A. I believe that's correct.
Q. Now, let's turn back to DTX-459, the UTC history and process validation memo regarding the treprostinil manufacturing process. Okay?
10:40 A. I'm with you.

MR. STEINDLER: Can we go to the page Bate stamped 1096012, please. And blow up the second full paragraph on that page.

Q. Are you with me?

10:41 A. Yes.

Q. And you see in language that we've looked at before in this case, that their concern was that the prior art process was uneconomical since the cost per kilogram would be over a million dollars; right?

10:41 A. That's what it says, yes.

Q. Let's now turn to PTX-494. And within PTX-494 let's go to the page Bate stamped 681. Are you with me?

A. Yes.

Q. You recognize that this is a letter from what was then

10:42 called LungRX later UTC, to Dr. Moriarty; right?

A. I see that.

Q. And he's authorizing Dr. Moriarty to proceed based on a letter dated October 8th, 1997, to make an initial batch of treprostinil; correct?

10:42 A. I see that, yes.

Q. And the cost of that batch is -- strike that.

That was for a 300 gram batch; right?

A. That's what it says yes.

Q. And the cost of that 300 gram batch was going to be

10:42 $299,000; right?

A. Well, it says at a maximum cost of $299,000.
Q. $299,000 for 300 grams is just about a million dollars for a kilogram; right?
A. Well, they were giving him a generous budget during the development phase to make an initial batch of material.
Q. This is -- strike that.
This letter, which is dated 21 October 1997, is just three days before the '117 patent application was filed; right?
A. Yes.
Q. And at that time the cost using the '117 patent process was roughly a million dollars a kilogram; right?
A. Not necessarily, no.
Q. This letter is authorizing the cost to be about a hundred -- strike that.
This letter by LungRX dated 21 October 1997, is authorizing Dr. Moriarty and his group to make treprostinil using the '117 patent process at about a million dollars a kilogram; correct?
A. Yes, but like I said it's at a maximum cost number one; number two, this was a development phase of the project and very often when you're working things out an experimental run may fail, so he was given a budget, but I understand that the manufacturing cost is way below that.
Q. At this stage, just at the time the patent application

was being filed, the manufacturing cost was about comparable to the cost used in the Upjohn process; right?

A. Again, not necessarily, this is the budget he was given. I have no idea if he spent $299,000 to make 300 grams.

10:45 Q. All right.

MR. STEINDLER: Well, let's go to the page Bate stamped 678. And blow up the top paragraph.

Q. Now, this is a date -- strike that.

This is a letter -- this is a letter --

10:45 THE COURT: You can't read it, Mr. Steindler.

MR. STEINDLER: Judge, I realize that, but this is how it was produced to us by UTC, and I think we can read it. Its pertinent parts.

BY MR. STEINDLER:

10:45 Q. First of all, this is a letter dated October 8, 1997 that the previous letter that we just looked at was referring to; correct?

A. I don't know, I can't read it.

Q. So, in this sentence here it says: At the present stage

10:46 of development of our new synthesis the cost is $997 a gram. Right?

A. I can't read it.

Q. Well, this is how the document was produced to us by UTC.

THE COURT: Just ask questions, Mr. Steindler.

10:46 Q. Your testimony, sir, is that you cannot read that this

sentence says: At the present stage of development of our new synthesis the cost is $997 a gram?

A. I can read -- I can make out some of the words, but to me this is an illegible document.

10:47 Q. So let's go back to the previous page. This is LungRX referencing the previous letter that we looked at, of 8 October 1997; correct?

A. Yes, that's what it says.

Q. And by this letter we authorize you to proceed in the

10:47 production of this initial batch at a maximum cost of $299,000 for 300 grams. Right?

A. That's what it says.

Q. And that would work out to $997 a gram; right?

A. Okay, that math is accurate.

10:47 Q. So at this stage, at the time that UTC was -- strike that.

At this stage, at the time that UTC was filing its patent application on the '117 patent process, the cost of making treprostinil by the '117 patent, was essentially the

10:48 same as the cost of making treprostinil by the prior art '814 patent process; right?

A. No, not necessarily as I think I already answered. I think you've already asked me this question.

MR. STEINDLER: No further questions.

10:48 THE COURT: All right. Redirect?

(REDIRECT EXAMINATION OF ROBERT M. WILLIAMS, PH.D. BY MR. CARSTEN:)

Q. Professor Williams, before United Therapeutics took over the treprostinil compound, was Upjohn trying to improve the synthesis?

A. Yes.

Q. And with respect to Dr. Aristoff, did Dr. Aristoff say that he was trying to improve the '814 synthesis as well?

A. Yes, I heard him testify to that the other day.

Q. What did he say?

A. He said that he tried to make the '814 synthesis stereoselective, but he failed.

Q. I'd also like to show you PTX-1, if I could.

MR. STEINDLER: Mr. Merisier, would you be so kind?

Q. Are you familiar with the PTX-1?

A. Yes.

Q. What is PTX-1?

A. This is the so-called '222 patent.

Q. Now, did you consider the '222 patent in your analysis in this case?

A. Yes, I haven't looked at this in a while, but yes, I did.

MR. STEINDLER: Objection. I didn't cross him on the '222 patent and he didn't say anything about it in direct.

THE COURT: Sustained.

BY MR. CARSTEN:

Q. Do you recall Mr. Steindler suggested that no one had tested or had worked on treprostinil in connection with pulmonary hypertension until UT took it over in 1997; right?

MR. STEINDLER: That was not my testimony or -- that was not what I suggested, and I object to this question.

THE COURT: Frank, can you repeat the question?

(Question read back by the reporter.)

THE COURT: You're going to have to rephrase. So the objection is sustained.

MR. CARSTEN: Sure.

BY MR. CARSTEN:

Q. You recall Mr. Steindler asking you about the development work at UT for treprostinil beginning in earnest in early 1997; right?

A. Yes, I remember that question.

Q. And that was in connection with the development being done for pulmonary hypertension; right?

A. Yes.

Q. Did you see any evidence in connection with your work in this case that someone had been working with treprostinil in connection with pulmonary hypertension well before that date?

A. Yes, we were just looking at it in the '222 patent.

Q. I'm sorry; what was that?

A. We were just looking at it in the '222 patent.

Q. What about the '222 patent suggested to you that someone

was looking at treprostinil for pulmonary hypertension before 1997?

A. I don't remember the exact date, but I understand it's earlier.

10:51 Q. I'd like to put up PTX-1, the '222 patent.

MR. STEINDLER: Same objection, your Honor.

THE COURT: Well, you opened up the subject on whether or not there was research being done earlier, and I think that was the point of the question. So I'll allow it.

10:51 MR. CARSTEN: Thank you, your Honor.

BY MR. CARSTEN:

Q. Do you see that there's a related U.S. application data here?

A. Yes.

10:51 Q. And what's the date of the related U.S. application?

A. June 16th, 1989.

Q. How long before 1997 is that?

A. Let's say 18 years.

Q. I think it's eight years.

10:52 A. I'm sorry; eight years.

Q. Forget to carry the 1.

MR. CARSTEN: Your Honor's, move to admit PTX-1.

THE COURT: Any objections?

MR. STEINDLER: I'm going to object to it as on

10:52 relevance grounds.

THE COURT: I'll admit it for the limited purpose of determining the dates of that research, if that's what we're trying to do, which would be June 16, 1989.

MR. CARSTEN: Thank you, your Honor.

10:52 (Plaintiff's Exhibit 1 was marked into evidence.)

MR. CARSTEN: Just for clarity sake, can we go to the claims of the '222, please. And the claims are down at the bottom. On the right-hand column, Mr. Merisier.

THE COURT: So why are we going to the claims?

10:52 MR. CARSTEN: Your Honor, I just want to get on the record that the claims actually deal with the treprostinil molecule and for pulmonary hypertension.

BY MR. CARSTEN:

Q. Would you just describe your understanding of the claims

10:53 please, Professor Williams?

A. Yes. So I guess I'll just read: A method of treating pulmonary hypertension in the patient which comprises administering to said patient effective pulmonary hypertension treatment amount of the compound 9-deoxy-2 prime 9, et cetera,

10:53 et cetera, which is the complex chemical name of treprostinil.

Q. The treprostinil molecule?

A. Yes.

MR. CARSTEN: I have nothing further, your Honor.

THE COURT: All right. Any re --

10:53 MR. STEINDLER: Let's stay right on this claim here

with the '222 patent.

(RECROSS-EXAMINATION OF ROBERT M. WILLIAMS, PH.D. BY MR. STEINDER:)

Q. Does claim -- strike that.

Do any of the claims of the '222 patent, cover a stereoselectively produced isomeric compound that is treprostinil?

MR. CARSTEN: Your Honor, this goes well beyond the scope of my redirect.

THE COURT: Well, you know, the problem with it is that you opened it up now, you brought the claims in, now he wants to ask about the claims. So I'll allow it.

MR. CARSTEN: Thank you.

THE COURT: In a limited fashion. So, you are trying to say the claims don't relate to the issues that we're dealing with?

MR. STEINDLER: I'm trying to find out what this expert's opinion is on that subject, correct.

THE COURT: Okay.

THE WITNESS: What was the question?

THE COURT: Please restate it.

BY MR. STEINDLER:

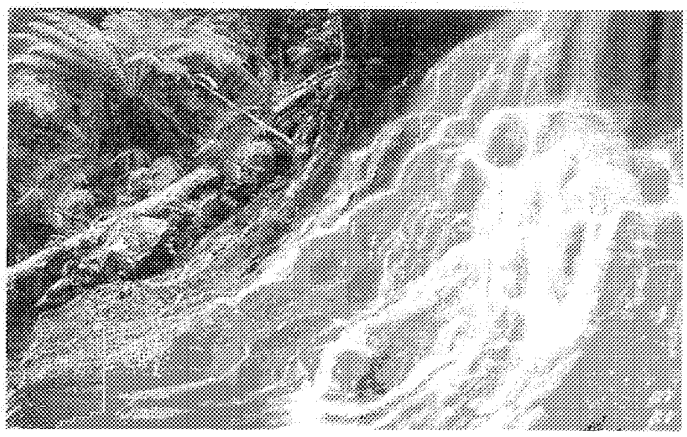
Q. Do any of the claims of the '222 patent, cover a stereoselectively produced isomeric compound that is the treprostinil compound?

A. I don't know, I haven't considered it.
Q. With respect to the '222 patent, there was no effort that you're aware of, to commercialize treprostinil for treating pulmonary hypertension, until Dr. Rothblatt and her team took over the IND from Burroughs Wellcome in 1997; right?
A. I don't know.
MR. STEINDLER: Nothing further.
THE COURT: All right. Okay, Doctor, thank you. You may step down.
THE WITNESS: Thank you, your Honor.
(Witness excused.)
THE COURT: How long is the next witness?
MR. JACKSON: I have a brief application to make, your Honor. I'm happy to do it now or after a break.
THE COURT: You can make an application now.
MR. JACKSON: Okay. I want to raise an issue that has come to our attention, when Dr. White was on the stand after both I was done with my direct and Mr. Steindler was done with his cross-examination, the Court asked a couple of questions of Dr. White.
Could you pull up the transcript at 1708?
And the Court was asking about whether or not certain things were obvious, about whether or not use of the SDF with the compound was obvious. And I think there was a miscommunication between the Court and Dr. White, about

Conceptual Chemistry

Understanding Our World of Atoms and Molecules

John Suchocki
Leeward Community College



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physical dependence A dependence characterized by the need to continue taking a drug to avoid withdrawal symptoms.

physical model A representation of a system that helps us predict how the system behaves.

physical property Any physical attribute of a substance, such as color, density, or hardness.

point source A specific, well-defined location where pollutants enter a body of water.

polar bond A chemical bond having a dipole.

polymer A long organic molecule made of many repeating units.

potential energy Stored energy.

power The rate at which energy is expended.

precipitate A solute that has come out of solution.

principal quantum number *n* An integer that specifies the quantized energy level of an atomic orbital.

probability cloud The pattern of electron positions plotted over time to show the likelihood of an electron being at a given position at a given time.

producer An organism at the bottom of a trophic structure.

product A new material formed in a chemical reaction, appearing after the arrow in a chemical equation.

protein A polymer of amino acids, also known as a polypeptide.

proton A positively charged subatomic particle of the atomic nucleus.

psychoactive Said of a drug that affects the mind or behavior.

psychological dependence A deep-rooted craving for a drug.

pure The state of a material that consists of a single element or compound.

quantum hypothesis The idea that light energy is contained in discrete packets called quanta.

quantum A small, discrete packet of light energy.

rad A unit for measuring radiation dosage, equal to 0.01 joule of radiant energy absorbed per kilogram of tissue.

radioactivity The tendency of some elements, such as uranium, to emit radiation as a result of changes in the atomic nucleus.

reactant A starting material in a chemical reaction, appearing before the arrow in a chemical equation.

reaction rate A measure of how quickly the concentration of products in a chemical reaction increases or the concentration of reactants decreases.

recombinant DNA A hybrid DNA composed of DNA strands from different organisms.

reduction The process whereby a reactant gains one or more electrons.

rem A unit for measuring radiation dosage, obtained by multiplying the number of rads by a factor that allows for the different health effects of different types of radiation.

replication The process by which DNA strands are duplicated.

reverse osmosis A technique for purifying water by forcing it through a semipermeable membrane.

ribonucleic acid A nucleic acid containing a fully oxygenated ribose sugar.

saccharide Another term for carbohydrate. The prefixes *mono-*, *di-*, and *poly-* are used before this term to indicate the length of the carbohydrate.

salinization The process whereby irrigated land becomes more salty.

salt An ionic compound formed from the reaction between an acid and a base.

saturated hydrocarbon A hydrocarbon containing no multiple covalent bonds, with each carbon atom bonded to four other atoms.

saturated solution A solution containing the maximum amount of solute that will dissolve.

scientific hypothesis A testable assumption often used to explain an observed phenomenon.

scientific law Any scientific hypothesis that has been tested over and over again and has not been contradicted. Also known as a scientific principle.

semipermeable membrane A membrane that allows water molecules to pass through its submicroscopic pores but not solute molecules.

sensory neuron A peripheral neuron that transmits electrical signals from the senses to the central nervous system.

soil horizon A layer of soil.

solid Matter that has a definite volume and a definite shape.

solubility The ability of a solute to dissolve in a given solvent.

soluble Capable of dissolving to an appreciable extent in a given solvent.

solute Any component in a solution that is not the solvent.

solution A homogeneous mixture in which all components are in the same phase.

solvent The component in a solution present in the largest amount.

specific heat capacity The quantity of heat required to change the temperature of 1 gram of a substance by 1 Celsius degree.

United States Patent [19]

Aristoff

[11] **Patent Number: 4,668,814**

[45] **Date of Patent: May 26, 1987**

[54] **INTERPHENYLENE CARBACYCLIN DERIVATIVES**

[75] Inventor: **Paul A. Aristoff**, Portage, Mich.

[73] Assignee: **The Upjohn Company**, Kalamazoo, Mich.

[21] Appl. No.: **690,803**

[22] Filed: **Jan. 11, 1985**

[51] **Int. Cl.**[4] **C07C 177/00**

[52] **U.S. Cl.** **560/51;** 544/155; 544/380; 546/203; 546/204; 546/283; 546/284; 546/285; 548/540; 549/66; 549/78; 549/79; 549/305; 549/465; 549/496; 549/499; 549/501; 549/502; 549/65; 560/45; 560/56; 562/444; 562/466; 562/499; 562/453; 564/80; 564/88; 564/89; 564/90; 564/92; 564/93; 564/95; 564/97; 564/98; 564/99; 564/152; 564/158; 564/171; 564/174; 564/374; 564/384; 564/427; 564/453; 564/454; 568/633; 568/808; 568/817

[58] **Field of Search** 560/51, 45, 56; 562/444, 466, 499, 453; 542/429; 544/155, 380; 564/80, 88, 89, 90, 92, 93, 95, 97, 98, 99, 171, 174, 152, 158, 374, 384, 427, 453

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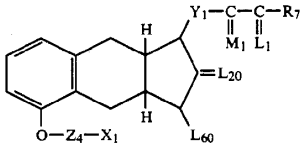
[57] **ABSTRACT**

A compound of the formula



and intermediates useful in preparing same.

11 Claims, No Drawings

INTERPHENYLENE CARBACYCLIN DERIVATIVES

FIELD OF THE INVENTION

The present invention relates to novel pharmaceutically useful compounds which are carbacyclin analogs having a tricyclic nucleus.

PRIOR ART

Related interphenylene carbacyclins are described and claimed in U.S. Pat. No. 4,306,075, U.S. Pat. No 4,306,076, and EP No. 87237 (Derwent No. 754477). Compounds having a 5-membered oxa ring are described in European Pat. No. 24-943 (Derwent No. 19801D).

Carbacyclin and closely related compounds are known in the art. See Japanese Kokai Nos. 63,059 and 63,060, also abstracted respectively as Derwent Farmdoc CPI Numbers 48154B/26 and 48155B/26. See also British published specifications No. 2,012,265 and German Offenlungsschrift No. 2,900,352, abstracted as Derwent Farmdoc CPI Number 54825B/30. See also British published applications Nos. 2,017,699 and 2,013,661 and U.S. Pat. No. 4,238,414.

The synthesis of carbacyclin and related compounds is also reported in the chemical literature, as follows: Morton, D. R., et al, J. Org. Chem., 44:2880-2887 (1979); Shibasaki, M., et al, Tetrahedron Lett., 433-436 (1979); Kojima, K., et al, Tetrahedron Lett., 3743-3746 (1978); Nicolaou, K. C., et al, J. Chem. Soc., Chemical Communications, 1067-1068 (1978); Sugie, A., et al, Tetrahedron Lett., 2607-2610 (1979); Shibasaki, M., Chem. Lett., 1299-1300 (1979), and Hayashi, M., Chem. Lett., 1437-40 (1979); Aristoff, P. A., J. Org. Chem. 46, 1954-1957 (1981); Yamazaki, M., et al, Chem. Lett., 1245-1248 (1981); and Barco, A., et al, J. Org. Chem. 45, 4776-4778 (1980); and Skuballa, W., et al, Angew. Chem. 93, 1080-1081 (1981). The utility and synthesis of compounds closely related to those claimed herein is described in Aristoff, P. A., and Harrison, A. W., Tetrahedron Lett. 23, 2067-2070 (1982) and in Advances in Prostaglandin, Thromboxane, and Leukotriene Research, Vol. 11, 267 (1983).

7-Oxo and 7-hydroxy-CBA_2 compounds are apparently disclosed in U.S. Pat. No. 4,192,891. 19-Hydroxy-CBA_2 compounds are disclosed in U.S. Pat. No. 4,225,508. CBA_2 aromatic esters are disclosed in U.S. Pat. No. 4,180,657. 11-Deoxy-Δ^{10}- or Δ^{11}-CBA_2 compounds are described in Japanese Kokai No. 77/24,865, published Feb. 24, 1979.

SUMMARY OF THE INVENTION

The present invention provides compounds of Formula I wherein:

X_1 is

(1) $-COOR_1$, wherein R_1 is
- (a) hydrogen;
- (b) (C_1-C_{12}) alkyl;
- (c) (C_3-C_{10}) cycloalkyl;
- (d) (C_7-C_{12}) aralkyl;
- (e) phenyl, optionally substituted with one, 2 or 3 chloro or (C_1-C_3) alkyl;
- (f) phenyl substituted in the para position by
  - (i) $-NHCOR_{25}$,
  - (ii) $-COR_{26}$,
  - (iii)

  - or
  - (iv) $-CH{=}N{-}NHCONH_2$ wherein R_{25} is methyl, phenyl, acetamidophenyl, benzamidophenyl, or $-NH_2$; R_{26} is methyl, phenyl, $-NH_2$, or methoxy; R_{54} is phenyl or acetamidophenyl; inclusive; or
- (g) a pharmocologically acceptable cation;

(2) $-CH_2OH$;

(3) $-COL_4$, wherein L_4 is
- (a) amino of the formula $-NR_{51}R_{52}$ wherein R_{51} and R_{52} are
  - (i) hydrogen,
  - (ii) (C_1-C_{12}) alkyl,
  - (iii) (C_3-C_{10}) cycloalkyl,
  - (iv) (C_7-C_{12}) aralkyl,
  - (v) phenyl, optionally substituted with one 2 or 3 chloro, (C_1-C_3) alkyl, hydroxy, carboxy, (C_2-C_5) alkoxycarbonyl, or nitro,
  - (vi) (C_2-C_5) cyanoalkyl,
  - (vii) (C_2-C_5) carboxyalkyl,
  - (viii) (C_2-C_5) carbamoylalkyl,
  - (ix) (C_3-C_6) acetylalkyl,
  - (x) (C_7-C_{11}) benzoalkyl, optionally substituted by one, 2 or 3 chloro, (C_1-C_3) alkyl, hydroxy, (C_1-C_3) alkoxy, carboxy, (C_2-C_5) alkoxy carbonyl, or nitro,
  - (xi) pyridyl, optionally substituted by one, 2 or 3 chloro, (C_1-C_3) alkyl, or (C_1-C_3) alkoxy,
  - (xii) (C_6-C_9) pyridylalkyl optionally substituted by one, 2 or 3 chloro, (C_1-C_3) alkyl, hydroxy, or (C_1-C_3) alkoxy,
  - (xiii) (C_1-C_4) hydroxyalkyl,
  - (xiv) (C_1-C_4) dihydroxyalkyl,
  - (xv) (C_1-C_4) trihydroxyalkyl, with the proviso that not more than one of R_{51} and R_{52} is other than hydrogen or alkyl;
- (b) cycloamino selected from the group consisting of pyrrolidino, piperidino, morpholino, piperazino, hexamethylenimino, pyrrolino, or 3,4-didehydropiperidinyl optionally substituted by one or 2 (C_1-C_{12}) alkyl of one to 12 carbon atoms, inclusive;
- (c) carbonylamino of the formula $-NR_{53}COR_{51}$ wherein R_{53} is hydrogen or (C_1-C_4) alkyl and R_{51} is other than hydrogen, but otherwise defined as above;
- (d) sulfonylamino of the formula $-NR_{53}SO_2R_{51}$, wherein R_{51} and R_{53} are defined in (c);

(4) $-CH_2NL_2L_3$ wherein L_2 and L_3 are hydrogen or (C_1-C_4) alkyl, being the same or different, or the pharmacologically acceptable acid addition salts thereof when X_1 is $-CH_2NL_2L_3$;

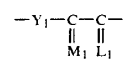
(5) $-CN$;

wherein Z_4 is $-CH_2-$, $-CH_2CH_2-$, $-CF_2-$ or $-CH_2CF_2$;

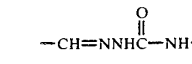
wherein L_{20} is α—OH,β—H; α—H,β—OH; H,H; α—CH_3,β—H; α—CH_2OH,β—H; =O; or $=CH_2$; wherein L_{60} is hydrogen or L_{20} and L_{60} taken together form a double bond between positions 10 and 11;

wherein Y_1 is $-CH_2CH_2-$, $-SCH_2-$, $-C{\equiv}C-$, trans—CH=CH—, or cis—CH=CH—;

wherein



taken together is



wherein M_1 is α—H:β—H; =O; α—OH:β—R_5; or α—R_5:β—OH; wherein R_5 is hydrogen or methyl;

wherein L_1 is

(1) α—R_3:β—R_4, α—R_4:β—R_3, or mixtures thereof wherein R_3 and R_4 are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R_3 and R_4 is fluoro only when the other is hydrogen or fluoro;

(2) or when M_1 is α—H:β—H, L_1 is α—OH:β—R_3, α—R_3:β—OH; or a mixture of α—OH:β—R_3 and α—R_3:β—OH wherein R_3 is hydrogen, methyl, vinyl, or ethynyl;

wherein R_7 is

(1) —$C_mH_{2m}CH_3$, wherein m is an integer from one to 8, inclusive;

(2) phenoxy optionally substituted by one, 2 or 3 chloro, fluoro, trifluoromethyl, (C_1–C_3) alkyl, or (C_1–C_3) alkoxy, with the proviso that not more than two substituents are other than alkyl with the proviso that R_7 is phenoxy or substituted phenoxy, only when R_3 and R_4 are hydrogen or methyl, being the same or different;

(3) phenyl, benzyl, phenylethyl, or phenylpropyl optionally substituted on the aromatic ring by one, 2 or 3 chloro, fluoro, trifluoromethyl, (C_1–C_3) alkyl, or (C_1–C_3) alkoxy, with the proviso that not more than two substituents are other than alkyl;

(4) cis—CH=CH—CH_2CH_3;

(5) —$(CH_2)_2$—CH(OH)—CH_3;

(6) —$(CH_2)_3$—CH=$C(CH_3)_2$;

(7) —$C_pH_{2p}CH$=CH_2 wherein p is an integer from 2 to 6, inclusive;

wherein

taken together is

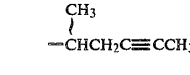
(1) (C_4–C_7) cycloalkyl optionally substituted by one to 3 (C_1–C_5) alkyl, or (C_1–C_5)alkenyl;

(2) 2-(2-furyl) ethyl;

(3) 2-(3-thienyl) ethoxy;

(4) 3-thienyloxymethyl; or

(5)



and the individual optical enantiomers thereof with the proviso that each compound is other than one formed when the substituents X_1, Z_4, L_{20}, Y_1, M_1, L_1, and R_7 have the following meanings:

X_1 is as defined above;

Z_4 is —CH_2—, —CF_2—, or —CH_2CF_2—;

L_{20} is α—OH,β—H; α—H,β—OH; H,H; α—CH_2OH,β—H;

Y_1 is —CH_2CH_2—, —C≡C—, trans—CH=CH—, or cis—CH=CH—;

M_1 is α—OH:β—R_5, or α—R_5:β—OH wherein R_5 is hydrogen or methyl;

L_1 is α—R_3:β—R_4, α—R_4:β—R_3, or a mixture thereof wherein R_3 and R_4 are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R_3 and R_4 is fluoro only when the other is hydrogen or fluoro; and

R_7 is as defined above except R_7 is other than —$(CH_2)_2$—CH=CH_2 and R_7 is other than —$C(L_1)R_7$ taken together is as defined above except —$C(L_1)R_7$ is other than (C_4–C_7)cycloalkyl optionally substituted with (C_1–C_5)alkenyl.

The present invention also provides a new procedure for preparing compounds of Formula I(a) wherein X_1 is

(1) —$COOR_1$, wherein R_1 is

(a) hydrogen;

(b) (C_1–C_{12}) alkyl;

(c) (C_3–C_{10}) cycloalkyl;

(d) (C_7–C_{12}) aralkyl;

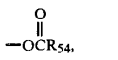
(e) phenyl, optionally substituted with one, 2 or 3 chloro or (C_1–C_3) alkyl;

(f) phenyl substituted in the para position by

(i) —$NHCOR_{25}$,

(ii) —COR_{26},

(iii)



or

(iv) —CH=N—$NHCONH_2$ wherein R_{25} is methyl, phenyl, acetamidophenyl, benzamidophenyl, or —NH_2; R_{26} is methyl, phenyl, —NH_2, or methoxy; R_{54} is phenyl or acetamidophenyl; inclusive; or

(g) a pharmacologically acceptable cation;

(2) —CH_2OH;

(3) —COL_4, wherein L_4 is

(a) amino of the formula —$NR_{51}R_{52}$ wherein R_{51} and R_{52}

(i) hydrogen,

(ii) (C_1–C_{12}) alkyl,

(iii) (C_3–C_{10}) cycloalkyl,

(iv) (C_7–C_{12}) aralkyl,

(v) phenyl, optionally substituted with one 2 or 3 chloro, (C_1–C_3) alkyl, hydroxy, carboxy, (C_2–C_5) alkoxycarbonyl, or nitro,

(vi) (C_2–C_5) cyanoalkyl,

(vii) (C_2–C_5) carboxyalkyl,

(viii) (C_2–C_5) carbamoylalkyl,

(ix) (C_3–C_6) acetylalkyl,

(x) (C_7–C_{11}) benzoalkyl, optionally substituted by one, 2 or 3 chloro, (C_1–C_3) alkyl, hydroxy, (C_1–C_3) alkoxy, carboxy, (C_2–C_5) alkoxy carbonyl, or nitro,

(xi) pyridyl, optionally substituted by one, 2 or 3 chloro, (C_1–C_3) alkyl, or (C_1–C_3) alkoxy,

(xii) (C_6–C_9) pyridylalkyl optionally substituted by one, 2 or 3 chloro, (C_1–C_3) alkyl, hydroxy, or (C_1–C_3) alkoxy,

(xiii) (C_1–C_4) hydroxyalkyl,

(xiv) (C_1–C_4) dihydroxyalkyl,

(xv) (C_1-C_4) trihydroxyalkyl,
with the proviso that not more than one of R_{51} and R_{52} is other than hydrogen or alkyl;

(b) cycloamino selected from the group consisting of pyrrolidino, piperidino, morpholino, piperazino, hexamethylenimino, pyrrolino, or 3,4-didehydropiperidinyl optionally substituted by one or 2 (C_1-C_{12}) alkyl of one to 12 carbon atoms, inclusive;

(c) carbonylamino of the formula $-NR_{53}COR_{51}$ wherein R_{53} is hydrogen or (C_1-C_4) alkyl and R_{51} is other than hydrogen, but otherwise defined as above;

(d) sulfonylamino of the formula $-NR_{53}SO_2R_{51}$, wherein R_{51} and R_{53} are defined in (c);

(4) $-CH_2NL_2L_3$ wherein L_2 and L_3 are hydrogen or (C_1-C_4) alkyl, being the same or different, or the pharmacologically acceptable acid addition salts thereof when X_1 is $-CH_2NL_2L_3$;

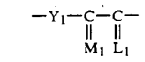
(5) —CN;

wherein Z_4 is $-CH_2-$, $-CH_2CH_2-$, $-CF_2-$ or $-CH_2CF_2$;

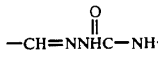
wherein L_{20} is α—OH,β—H; α—H,β—OH; H,H; α—CH_3,β—H; α—CH_2OH,β—H; =O; or =CH_2; wherein L_{60} is hydrogen or L_{20} and L_{60} taken together form a double bond between positions 10 and 11;

wherein Y_1 is $-CH_2CH_2-$, $-SCH_2-$, —C≡C—, trans—CH=CH—, or cis—CH=CH—;

wherein



taken together is



wherein M_1 is α—H:β—H; =O; α—OH:β—R_5; or α—R_5:β—OH; wherein R_5 is hydrogen or methyl;

wherein L_1 is

(1) α—R_3:β—R_4, α—R_4:β—R_3, or mixtures thereof wherein R_3 and R_4 are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R_3 and R_4 is fluoro only when the other is hydrogen or fluoro;

(2) or when M_1 is α—H:β—H, L_1 is α—OH:β—R_3, α'R_3:β—OH; or a mixture of α—OH:β—R_3 and α—R_3:β—OH wherein R_3 is hydrogen, methyl, vinyl, or ethynyl;

wherein R_7 is

(1) $-C_mH_{2m}CH_3$, wherein m is an integer from one to 8, inclusive;

(2) phenoxy optionally substituted by one, 2 or 3 chloro, fluoro, trifluoromethyl, (C_1-C_3) alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl with the proviso that R_7 is phenoxy or substituted phenoxy, only when R_3 and R_4 are hydrogen or methyl, being the same or different;

(3) phenyl, benzyl, phenylethyl, or phenylpropyl optionally substituted on the aromatic ring by one, 2 or 3 chloro, fluoro, trifluoromethyl, (C_1-C_3) alkyl, or (C_1-C_3) alkoxy, with the proviso that not more than two substituents are other than alkyl;

(4) cis—CH=CH—CH_2CH_3;

(5) $-(CH_2)_2-CH(OH)-CH_3$;

(6) $-(CH_2)_3-CH=C(CH_3)_2$;

(7) $C_pH_{2p}CH=CH_2$ where p is an integer from 2 to 6, inclusive;

wherein

taken together is

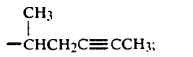
(1) (C_4-C_7) cycloalkyl optionally substituted by one to 3 (C_1-C_5) alkyl, or (C_1-C_5)alkyl;

(2) 2-(2-furyl) ethyl;

(3) 2-(3-thienyl) ethoxy;

(4) 3-thienyloxymethyl; or

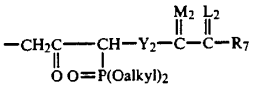
(5)



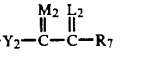
and the individual optical enantiomers thereof.

In the event it is not readily apparent the difference between the compounds of Formula I and those of Formula I(a) lies in the fact that certain compounds of Formula I are excluded by the proviso beginning on page 4, line 35. The compounds excluded by the proviso in Formula I are described and claimed in U.S. Pat. No. 4,306,075 and copending U.S. application Ser. No. 351,069 filed Feb. 22, 1982. The novel process described herein is applicable to the prior claimed compounds and the novel compounds described and claimed herein

Also, the present invention provides novel intermediates of Formulas I(b), I(c), I(d) and II as set forth in the Formula Chart. In Formulas I(b) and I(c) the group Q is cis-$CH_2CH=CH_2$, $-CH_2COOH$, or



wherein alkyl has from 1 to 4 carbon atoms; L is the same as L_1 in Formula I only any hydrous group is protected with an Rx group as defined below; Y_2 is $-SCH_2-$ or $-CH_2CH_2-$, M_2 is α-H,β-ORx, α-ORx,β-H or H,H wherein Rx is a protecting group as defined below, and R_7 has the meaning defined in Formula I(a). In Formula I(d) Q_2 is



as defined above or CO_2 alkyl wherein alkyl has from 1 to 4 carbon atoms. The intermediates of Formulas I(a), I(b), I(c), I(d) and II are useful in the preparation of the compounds of Formuls I and I(a).

The compounds of Formula I and I(a) have useful pharmacological properties as defined below.

DETAILED DESCRIPTION OF INVENTION

In the compounds of the present invention, and as used herein, (‴) denotes the α-configuration, ( ) denotes the β-configuration, (~) denotes α- and/or β-configuration or the E and/or Z isomer.

With regard to the divalent groups described above, i.e., L_{20}, M_1 and L_1 said divalent groups are defined in terms of an α-substituent and a β-substituent which means that the α-substituent of the divalent group is in the alpha configuration with respect to the plane of the C-8 to C_{12} cyclopentane ring and the β-substituent is in the beta configuration with respect to said cyclopentane ring.

The carbon atom content of various hydrocarbon containing groups is indicated by a prefix designating the minimum and maximum number of carbon atoms in the moiety. For example, in defining the moiety L_4 in the $-COL_4$ substituent group the definition (C_1-C_{12})alkyl means that L_4 can be an alkyl group having from one to 12 carbon atoms. Additionally, any moiety so defined includes straight chain or branched chain groups. Thus (C_1-C_{12})alkyl as set forth above includes straight or branched chain alkyl groups having from 1 to 12 carbon atoms and as additional illustration, when L_4 represents, for example, (C_2-C_5)carboxyalkyl, the alkyl moiety thereof contains from 1 to 4 carbon atoms and is a straight chain or a branched chain alkyl group. Similarly a C_3-C_5 alkenyl group as may be present on the cycloalkyl group represented by $-C(L_1)R_7$ contains from 3 to 5 carbon atoms and one double bond in the chain.

In Formula I when the hydrogen at position 9 is beta the compounds are named as 9-deoxy-2',9α-methano-3-oxa-4,5,6-trinor-3,7-(1',3'-interphenylene)PGF_1 compounds, and when it is alpha the compounds are named as 9-deoxy-2',9β-methano-3-oxa-4,5,6-trinor-3,7-(1',3'-interphenylene)PGF_1 compounds.

When Z_4 is $-CF_2-$ the compounds of Formula I are also characterized as 2,2-difluoro and when Z_4 is $-CH_2CF_2-$ the compounds are characterized as 2α-homo-2,2-difluoro.

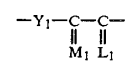
When R_5 is methyl, the carbacyclin analogs are all named as "15-methyl-" compounds. Further, except for compounds wherein Y_1 is cis-CH=CH—, *compounds wherein the* M_1 moiety contains an hydroxyl in the beta configuration are additionally named as "15-epi-" compounds.

For the compounds wherein Y_1 is cis-CH=CH—, then compounds wherein the M_1 moiety contains an hydroxyl in the alpha configuration are named as "15-epi-CBA" compounds. For a description of this convention of nomenclature for identifying C-15 epimers, see U.S. Pat. No. 4,016,184, issued Apr. 5, 1977, particularly columns 24–27 thereof.

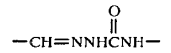
The compounds of the present invention which contain $-(CH_2)_2-$, cis-CH=CH—, trans —CH=CH— or —C≡C— as the Y_1 moiety, are accordingly referred to as "13,14-dihydro", "cis-13", "trans-13", or —13,14-didehydro" compounds, respectively. Compounds wherein Y_1 is $-SCH_2-$ are named as "13-thio" compounds.

Compounds wherein M_1 is H,H are named as "15-deoxy" compounds. Compounds wherein M_1 is =O are named as "15-oxo" compounds.

Compounds wherein

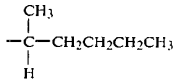


taken together is



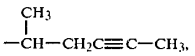
are are named as 13,14,15,16,17,18,19,20-octanor-12-[N-R_7-carbamoyl)hydrazono-methyl].

When R_7 is



the compounds so described are named as 17(S),20-dimethyl compounds.

When $-C(L_1)-R_7$ is



the compounds are named as "16-(R,S)methyl-18,19-tetradehydro" compounds.

When $-C(L_1)R_7$ is $-CH_2CH=CH_2$ the compounds so described are named as "19,20-didehydro".

When at least one of R_3 and R_4 is not hydrogen then there are described the "16-methyl" (one and only one of R_3 and R_4 is methyl), "16,16-dimethyl" (R_3 and R_4 are both methyl), "16-fluoro" (one and only one of R_3 and R_4 is fluoro), "16,16-difluoro" (R_3 and R_4 are both fluoro) compounds. For those compounds wherein R_3 and R_4 are different, the carbacyclin analogs so represented contain as asymmetric carbon atom at C-14. Accordingly, two epimeric configurations are possible: "(16S)" and "(16R)". Further, there is described by this invention the C-16 epimeric mixture: "(16RS)".

When X_1 is $-CH_2OH$, the compounds so described are named as "2-decarboxy-2-hydroxymethyl" compounds.

When X_1 is $-CH_2NL_2L_3$, the compounds so described are named as "2-decarboxy-2-aminomethyl" or "2-(substituted amino)methyl" compounds.

When X_1 is $-COL_4$, the novel compounds herein are named as amides. Further, when X_1 is $-COOR_1$ and R_1 is other than hydrogen the novel compounds herein are named as esters and salts.

When X_1 is CN the novel compounds herein are named as 2-decarboxy-2-cyano compounds.

Examples of phenyl esters substituted in the para position (i.e., X_1 is $-COOR_1$, R_1 is p-substituted phenyl) include p-acetamidophenyl ester, p-benzamidophenyl ester, p-(p-acetamidobenzamido)phenyl ester, p-(p-benzamidobenzamido)phenyl ester, p-amidocarbonylaminophenyl ester, p-acetylphenyl ester, p-benzoylphenyl ester, p-aminocarbonylphenyl ester, p-methoxycarbonylphenyl ester, p-benzoyloxyphenyl ester, p(p-acetamidobenzoyloxy)phenyl ester, and p-hydroxybenzaldehyde semicarbazone ester.

Examples of novel amides herein (i.e., X_1 is $-COL_4$) include the following:

(1) Amides within the scope of alkylamino groups of the formula NR_9R_{10} are methylamide, ethylamide, n-propylamide, isopropylamide, n-butylamide, n-pentylamide, tert-butylamide, neopentylamide, n-hexylamide, n-heptylamide, n-octylamide, n-nonylamide, n-decylamide, n-undecylamide, and n-dodecylamide, and isomeric forms thereof. Further examples are dimethyla-

mide, diethylamide, di-n-propylamide, diisopropylamide, di-n-butylamide, methylethylamide, di-tert-butylamide, methylpropylamide, methylbutylamide, ethylpropylamide, ethylbutylamide, and propylbutylamide. Amides within the scope of cycloalkylamino are cyclopropylamide, cyclobutylamide, cyclopentylamide, 2,3-dimethylcyclopentylamide, 2,2-dimethylcyclopentylamide, 2-methylcyclopentylamide, 3-tert-butylcyclopentylamide, cyclohexylamide, 4-tertbutylcyclohexylamide, 3-isopropylcyclohexylamide, 2,2-dimethylcyclohexylamide, cycloheptylamide, cyclooctylamide, cyclononylamide, cyclodecylamide, N-methyl-N-cyclobutylamide, N-methy-N-cyclopentylamide, N-methyl-N-cyclohexylamide, N-ethyl-N-cyclopentylamide, and N-ethyl-N-cyclohexylamide. Amides within the scope of aralkylamino are benzylamide, 2-phenylethylamide, and N-methyl-N benzyl-amide. Amides within the scope of substituted phenylamide are p-chloroanilide, m-chloroanilide, 2,4-dichloroanilide, 2,4,6-trichloroanilide, m-nitroanilide, p-nitroanilide, p-methoxyanilide, 3,4-dimethoxyanilide, 3,4,5-trimethoxyanilide, p-hydroxymethylanilide, p-methylanilide, m-methyl anilide, p-ethylanilide, t-butylanilide, p-carboxyanilide, p-methoxycarbonyl anilide, p-carboxyanilide and o-hydroxyanilide. Amides within the scope of carboxyalkylamino are carboxyethylamide, carboxypropylamide and carboxymethylamide, carboxybutylamide. Amides within the scope of carbamoylalkylamino are carbamoylmethylamide, carbamoylethylamide, carbamoylpropylamide, and carbamoylbutylamide. Amides within the scope of cyanoalkylamino are cyanomethylamide, cyanoethylamide, cyanopropylamide, and cyanobutylamide. Amides within the scope of acetylalkylamino are acetylmethylamide, acetylethylamide, acetylpropylamide, and acetylbutylamide. Amides within the scope of benzoylalkylamino are benzoylmethylamide, benzoylethylamide, benzoylpropylamide, and benzoylbutylamide. Amides within the scope of substituted benzoylalkylamino are p-chlorobenzoylmethylamide, m-chlorobenzoylmethylamide, 2,4-dichlorobenzoylmethylamide, 2,4,6-trichlorobenzoylmethylamide, m-nitrobenzoylmethylamide, p-nitrobenzoylmethylamide, p-methoxybenzoylmethylamide, 2,4-dimethoxy benzoylmethylamide, 3,4,5-trimethoxybenzylmethylamide, p-hydroxymethylbenzoylmethylamide, p-methylbenzoylmethylamide, m-methylbenzoylmethylamide, p-ethylbenzoylmethylamide, t-butylbenzoylmethylamide, p-carboxybenzoylmethylamide, m-methoxycarbonylbenzoylmethylamide, o-carboxybenzoylmethylamide, o-hydroxybenzoylmethylamide, p-chlorobenzoylethylamide, m-chlorobenzoylethylamide, 2,4-dichlorobenzoylethylamide, 2,4,6-trichlorobenzoylethylamide, m-nitrobenzoylethylamide, p-nitrobenzoylethylamide, p-methoxybenzoylethylamide, p-methoxybenzoylethylamide, 2,4-dimethoxybenzoylethylamide, 3,4,5trimethoxybenzoylethylamide, p-hydroxymethylbenzoylethylamide, p-methylbenzoylethylamide, m-methylbenzoylethylamide, p-ethylbenzoylethylamide, t-butylbenzoylethylamide, p-carboxybenzoylethylamide, m-methoxycarbonylbenzoylethylamide, o-carboxybenzoylethylamide, o-hydroxybenzoylethylamide, o-chlorobenzoylpropylamide, m-chlorobenzoylpropylamide, 2,4-dichlorobenzoylpropylamide, 2,4,6-trichlorobenzoylpropylamide, m-nitrobenzoylpropylamide, p-nitrobenzoylpropylamide, p-methoxybenzoylpropylamide, 2,4-dimethoxybenzoylpropylamide, 3,4,5-trimethoxybenzoylpropylamide, p-hydroxymethylbenzoylpropylamide, p-methylbenzoylpropylamide, m-methylbenzoylpropylamide, p-ethylbenzoylpropylamide, t-butylbenzoylpropylamide, p-carboxybenzoylpropylamide, m-methoxycarbonylbenzoylpropylamide, o-carboxybenzoylpropylamide, o-hydroxybenzoylpropylamide, p-chlorobenzoylbutylamide, m-chlorobenzoylbutylamide, 2,4-dichlorobenzoylbutylamide, 2,4,6-trichlorobenzoylbutylamide, m-nitrobenzoylmethylamide, p-nitrobenzoylbutylamide, p-methoxybenzoylbutylamide, 2,4-dimethoxybenzoylbutylamide, 2,4,5-trimethoxybenzoylbutylamide, p-hydroxymethylbenzoylbutylamide, p-methylbenzoylbutyamide, m-methylbenzoylbutylamide, p-ethylbenzoylbutyalmide, m-methylbenzoylbutylamide, p-ethylbenzoylbutylamide, t-butylbenzoylbutylamide, p-carboxybenzoylbutylamide, m-methoxycarbonylbenzoylbutylamide, o-carboxybenzoylbutylamide, o-hydroxybenzoylmethylamide. Amides within the scope of pyridylamino are α-pyridylamide, β-pyridylamide, and γ-pyridylamide. Amides within the scope of substituted pyridylamino are 4-methyl-α-pyridylamide, 4-methyl-β-pyridylamide, 4-chloro-α-pyridylamide, and 4-chloro-β-pyridylamide. Amides within the scope of pyridylalkylamino are α-pyridylmethylamide, β-pyridylmethylamide, γ-pyridylmethylamide, α-pyridylethylamide, β-pyridylethylamide, γ-pyridylethylamide, α-pyridylpropylamide, β-pyridylpropylamide, γ-pyridylpropylamide, α-pyridylbutylamide, β-pyridylbutylamide, and γ-pyridylbutylamide. Amides within the scope of substituted pyridylalkylamido are 4-methyl-α-pyridylmethylamide, 4-methyl-β-pyridylmethylamide, 4-chloro-α-pyridylmethylamide, 4- chloro-β-pyridylmethyl-amide, 4-methyl-α-pyridylpropylamide, 4-methyl-β-pyridylpropylamide, 4-chloro-α-pyridylpropylamide, 4-chloro-β-pyridylpropylamide, 4-methyl-α-pyridylbutylamide, 4-methyl-β-pyridylbutylamide, 4-chloro-α-pyridylbutylamide, 4-chloro-β-pyridylbutylamide, 4-chloro-γ-pyridylbutylamide. Amides within the scope of hydroxyalkylamino are hydroxymethylamide, β-hydroxyethylamide, β-hydroxypropylamide, γ-hydroxypropylamide, 1-(hydroxymethyl)ethyl-amide, 1-(hydroxymethyl)-propylamide, (2-hydroxymethyl)propylamide, and α,α,-dimethyl-hydroxyethylamide. Amides within the scope of dihydroxyalkylamino are dihydroxymethylamide, β,γ-dihydroxypropylamide, 1-(hydroxymethyl)2-hydroxymethylamide, β,γ-dihydroxybutylamide, β,δ-dihydroxybutyl-amide, γ,δ-dihydroxybutylamide, and 1,1-bis(hydroxymethyl)ethylamide. Amides within the scope of trihydroxyalkylamino are tris(hydroxymethyl)-methylamide and 1,3-dihydroxy-2-hydroxymethylpropylamide.

(2) Amides within the scope of cycloamino groups described above are pyrrolidylamide, piperidylamide, morpholinylamide, hexamethyleneiminylamide, piperazinylamide, pyrrolinylamide, and 3,4-didehydropiperidinylamide each of which may be optionally substituted with one or 2 straight or branched alkyl chains having from 1 to 12 carbon atoms.

(3) Amides within the scope of carbonylamino of the formula $-NR_{53}COR_{51}$ are methylcarbonylamide, ethylcarbonylamide, phenylcarbonylamide, and benzylcarbonylamide.

(4) Amides within the scope of sulfonylamino of the formula $-NR_{53}SO_2R_{51}$ are methylsulfonylamide, ethylsufonylamide, phenylsulfonylamide, p-tolylsulfonylamide, benzylsulfonylamide.

Examples of alkyl of one to 12 carbon atoms, inclusive, are methyl, ethyl, propyl, isopropyl, isobutyl, tert-

butyl, isopentyl, neopentyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, isomeric forms thereof.

Examples of (C_3–C_{10}) cycloalkyl which includes alkyl-substituted cycloalkyl, are cyclopropyl, 2-methylcyclopropyl, 2,2-dimethylcyclopropyl, 2,3-diethylcyclopropyl, 2-butylcyclopropyl, cyclobutyl, 2-methylcyclobutyl, 3-propylcyclobutyl, 2,3,4-triethylcyclobutyl, cyclopentyl, 2,2-dimethylcyclopentyl, 2-pentylcyclopentyl, 3-tert-butylcyclopentyl, cyclohexyl, 4-tert-butylcyclohexyl, 3-isopropylcyclohexyl, 2,2-dimethylcyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, and cyclodecyl.

Examples of (C_7–C_{12}) aralkyl are benzyl, 2-phenylethyl, 1-phenylethyl, 2-phenylpropyl, 4-phenylbutyl, 3-phenylbutyl, 2-(1-naphthylethyl), and 1-(2-naphthylmethyl).

Examples of phenyl substituted by one to 3 chloro or alkyl of one to 4 carbon atoms, inclsive, are p-chlorophenyl, m-chlorophenyl, 2,4-dichlorophenyl, 2,4,6-trichlorophenyl, p-tolyl, m-tolyl, o-tolyl, p-ethylphenyl, p-tert-butylphenyl, 2,5-dimethylphenyl, 4-chloro-2methylphenyl, and 2,4-dichloro-3-methylphenyl.

The compounds of Formulas I and I(a) produce certain prostacyclin-like pharmacological responses. Accordingly, the novel formula I compounds are useful as agents in the study, prevention, control, and treatment of diseases, and other undesirable physiological conditions, in mammals, particularly humans, valuable domestic animals, pets, zoological specimens, and laboratory animals (e.g., mice, rats, rabbits and monkeys). In particular, these compounds are useful as anti-ulcer agents and anti-asthma agents, and as antithrombotic agents as indicated below.

(a) Platelet Aggregation Inhibition

The compounds of Formulas I and I(a) are useful whenever it is desired to inhibit platelet aggregation, to reduce the adhesive character of platelets, or to remove or prevent the formation of thrombi in mammals, including man. For example, these compounds are useful in the treatment and prevention of myocardial infarcts, to treat and prevent post-operative thrombosis, to promote patency of vascular grafts following surgery, to treat peripheral vascular diseases, and to treat conditions such as atherosclerosis, arteriosclerosis, blood clotting defects due to lipemia, and other clinical conditions in which the underlying etiology is associated with lipid imbalance or hyperlipidemia. Other in vivo applications include geriatric patients to prevent cerebral ischemic attacks and long term prophylaxis following myocardial infarcts and strokes. For these purposes, these compounds are administered systemically, e.g., intravenously, subcutaneously, intramuscularly, and in the form of sterile implants for prolonged action. For rapid response, especially in emergency situations, the intravenous route of administration is preferred.

The preferred dosage route for these compounds is oral, although other non-parenteral routes (e.g., buccal, rectal, sublingual) are likewise employed in preference to parenteral routes. Oral dosage forms are conventionally formulated as, e.g., tablets or capsules and administered 2–4 times daily. Doses in the range of about 0.05 to 100 mg per kg of body weight per day are effective in treating the aforedescribed conditions associated with the inhibition of platelet aggregation. Doses in the range about 0.01 to about 10 mg per kg of body weight per day are preferred, the exact dose depending on the age, weight, and condition of the patient or animal, and on the frequency and route of administration.

The addition of these compounds to whole blood provides in vitro applications such as storage of whole blood to be used in heart-lung machines. Additionally whole blood containing these compounds can be circulated through organs, e.g., heart and kidneys, which have been removed from a donor prior to transplant. They are also useful in preparing platelet rich concentrates for use in treating thrombocytopenia, chemotherapy, and radiation the therapy. In vitro applications utilize a dose of 0.001–1.0 μg per ml of whole blood. The compounds of the present invention are useful in the treatment of peripheral vascular diseases, in the same manner as described in U.S. Pat. No. 4,103,026.

(b) Gastric Secretion Reduction

Compounds of Formulas I and I(a) are useful in mammals, including man and certain useful animals, e.g., dogs and pigs, to reduce and control gastric secretion, thereby to reduce or avoid gastrointestinal ulcer formation, and accelerate the healing of such ulcers already present in the gastrointestinal tract. For this purpose, these compounds are injected or infused intravenously, subcutaneously, or intramuscularly in an infusion dose range of about 0.1 μg to about 20 μg per kg of body weight per minute, or in a total daily dose by injection or infusion in the range about 0.01 to about 10 mg per kg of body weight per day, the exact dose depending on the age, weight, and condition of the patient or animal, and on the frequency and route of administration.

Preferably, however, these novel compounds are administered orally or by other non-parenteral routes. As employed orally, one to 6 administrations daily in a dosage range of about 0.001 to 100 mg per kg of body weight per day is employed. Once healing of the ulcers has been accomplished the maintenance dosage required to prevent recurrence is adjusted downward so long as the patient or animals remains asymptomatic.

The final products of specific Examples 6 and 7 contained herein demonstrate good cytoprotective properties with relatively low blood pressure effects in rats rendering said compounds preferred embodiments of the present invention.

(c) NOSAC-Induced Lesion Inhibition

Compounds of Formulas I and I(a) are also useful in reducing the undesirable gastrointestinal effects resulting from systemic administration of anti-inflammatory prostaglandin synthetase inhibitors, and are useful for that purpose by concomitant administration of said compounds of Formulas I and I(a) and the anti-inflammatory prostaglandin synthetase inhibitor. See Partridge, et al., U.S. Pat. No. 3,781,429, for a disclosure that the ulcerogenic effect induced by certain non-steroidal anti-inflammatory agents in rats is inhibited by concomitant oral administration of certain prostaglandins of the E series. Accordingly these novel Formulas I and I(a) compounds are useful, for example, in reducing the undesirable gastrointestinal effects resulting from systemic administration of known prostaglandin synthetase inhibitors, e.g., indomethacin, phenylbutazone, and aspirin, in the same manner as described by Partridge, et al, for the PGE compounds in U.S. Pat. No. 3,781,429.

The anti-inflammatory synthetase inhibitor, for example, indomethacin, aspirin, or phenylbutazone is admin-

istered in any of the ways known in the art to alleviate an inflammatory conditions, for example, in any dosage regimen and by any of the known routes of systemic administration.

(d) Bronchodilation (Anti-asthma)

The compounds of Formulas I and I(a) are also useful in the treatment of asthma. For example, these compounds are useful as bronchodilators or as inhibitors of mediator-induced bronchoconstriction, such as SRS-A, and histamine which are released from cells activated by an antigen-antibody complex. Thus, these compounds control spasm and facilitate breathing in conditions such as bronchial bronchitis, bronchiectasis, pneumonia and emphysema. For these purposes, these compounds are administered in a variety of dosage forms, e.g., orally in the form of tablets, capsules, or liquids; rectally in the form of suppositories, parenterally, subcutaneously, or intramuscularly, with intravenous administration being preferred in emergency situations; by inhalation in the form of aerosols or solutions for nebulizers; or by insufflation in the form of powder. Doses in the range of about 0.01 to 5 mg per kg of body weight are used 1 to 4 times a day, the exact dose depending on the age, weight, and condition of the patient and on the frequency and route of administration. For the above use Formulas I and I(a) compounds can be combined advantageously with other anti-asthmatic agents, such as sympathomimetics (isoproterenol, phenylephrine, ephedrine, etc.); xanthine derivatives (theophylline and aminophylline); and corticosteroids (ACTH and prednisolone).

The pharmacologically useful Formulas I and I(a) compounds are effectively administered to human asthma patients by oral inhalation or by aerosol inhalation. For administration by the oral inhalation route with conventional nebulizers or by oxygen aerosolization it is convenient to provide the instant active ingredient in dilute solution, preferably at concentrations of about one part of medicament to from about 100 to 200 parts by weight of total solution. Entirely conventional additives may be employed to stabilize these solutions or to provide isotonic media, for example, sodium chloride, sodium citrate, citric acid, sodium bisulfite, and the like can be employed. For administration as a self-propelled dosage unit for administering the active ingredient in aerosol form suitable for inhalation therapy the composition can comprise the active ingredient suspended in an inert propellant (such as a mixture of dichlorodifluoromethane and dichlorotetrafluoroethane) together with a co-solvent, such as ethanol, flavoring materials and stabilizers. Suitable means to employ the aerosol inhalation therapy technique are described fully in U.S. Pat. No. 3,868,691, for example.

When X_1 is $—COOR_1$, the novel Formula I and I(a) compounds so described are used for the purposes described above in the free acid form, in ester form, or in pharmacologically acceptable salt form. When the ester form is used, the ester is any of those within the above definition of R_1. However, it is preferred that the ester be alkyl of one to 12 carbon atoms, inclusive. Of the alkyl esters, methyl and ethyl are especially preferred for optimum absorption of the compound by the body or experimental animal system; and straight-chain octyl, nonyl, decyl, undecyl, and dodecyl are especially preferred for prolonged activity.

Pharmacologically acceptable salts of the novel compounds of Formula I and I(a) for the purposes described above are those with pharmacologically acceptable metal cations, ammonia, amine cations, or quaternary ammonium cations. Illustrative pharmacological acceptable cations which R_5 may represent are the following.

Especially preferred metal cations are those derived from the alkali metals, e.g., lithium, sodium, and potassium, and from the alkaline earth metals, e.g., magnesium and calcium, although cationic forms of other metals, e.g., aluminum, zinc, and iron are within the scope of this invention.

Pharmacologically acceptable amine cations are those derived from primary, secondary, and tertiary amines. Examples of suitable amines are methylamine, dimethylamine, trimethylamine, ethylamine, dibutylamine, triisopropylamine, N-methylhexylamine, decylamine, dodecylamine, allylamine, crotylamine, cyclopentylamine, dicyclohexylamine, benzylamine, dibenzylamine, α-phenylethylamine, β-phenylethylamine, ethylenediamine, diethylenetriamine, adamantylamine, and the like aliphatic, cycloaliphatic, araliphatic amines containing up to and including about 18 carbon atoms, as well as heterocyclic amines, e.g., piperidine, morpholine, pyrrolidine, piperazine, and lower-alkyl derivatives thereto, e.g., 1-methylpiperidine, 4-ethylmorpholine, 1-isopropylpyrrolidine, 2-methylpyrrolidine, 1,4-dimethylpiperazine, 2-methylpiperidine, and the like as well as amines containing water-solubilizing or hydrophilic groups, e.g., mono-, di-, and triethanolamine, ethyldiethanolamine, N-butylethanolamine, 2-amino-1-butanol, 2-amino-2-ethyl-1,3-propanediol, 2-amino-2-methyl-1-propanol, tris-(hydroxymethyl) aminomethane, N-phenylethanolamine, N-(p-tert-amylphenyl)-diethanolamine, galactamine, N-methylglycamine, N-methylglucosamine, ephedrine, phenylephrine, epinephrine, procaine, and the like. Further useful amine salts of the basic amino acid salts, e.g., lysine and arginine.

Examples of suitable pharmacologically acceptable quaternary ammonium cations are tetramethylammonium, tetraethylammonium, benzyltrimethylammonium, phenyltriethylammonium, and the like.

When X_1 is $—CH_2NL_2L_3$, the Formula I and I(a) compounds so described are used for the purposes described in either free base or pharmacologically acceptable acid addition salt form.

The acid addition salts of the 2-decarboxy-2-aminomethyl- or 2-(substituted aminomethyl)- Formula I compounds provided by this invention are, for example, the hydrochlorides, hydrobromides, hydriodides, sulfates, phosphates, cyclohexanesulfamates, methanesulfonates, ethanesulfonates, benzenesulfonates, toluenesulfonates and the like, prepared by reacting the appropriate compound of Formula I with the stoichiometric amount of the acid corresponding to the pharmacologically acceptable acid addition salt.

To obtain the optimum combination of biological response specificity, potency, and duration of activity, certain compounds within the scope of this invention are preferred. Preferred compounds of the present invention are Formula I compounds wherein Z_4 is $—CH_2—$, and of these compounds those wherein Y is $—CH_2CH_2—$, $—C≡C—$ or trans $—CH=CH—$ and/or X_1 is $—COOR_1$ are preferred especially when R_1 is hydrogen, methyl, ethyl, or a pharmacologically acceptable cation such as sodium. Compounds of Formula I wherein R_7 is cyclohexyl, n-pentyl or $—(CH_2)_3—CH=C(CH_3)_2$ are preferred. And compounds

wherein Y_1 is $-SCH_2-$ or M_1 is H,H or β-H,α-OH are also preferred.

In describing the preparation of the compounds of the present invention reference is made to Chart A to Chart K. In the Charts the various substituent groups have the following meanings. In Chart A: R_7, L_{60}, Z_4, X_1, L_{20}, M_1, and L_1 have the meanings defined in Formula I(a); alkyl is a hydrocarbon chain of from 1 to 4 carbon atoms and is straight or branched, e.g., methyl, ethyl, etc.; Y_2 is $-CH_2CH_2-$ or $-SCH_2-$; M_2 is =O protected as a ketal, α-H:β-ORx, α-ORx:β-H, or H,H where Rx is a protecting group as defined below; L_2 is the same as L_1 in Formula I(a) only any hydroxyl groups are protected as ORx where Rx is as defined below; L_{21} is the same as L_{20} in Formula I(a) only L_{21} is not =O and any hydroxy groups are protected as ORx where Rx is as defined below; L_{22} is the same as L_{20} in Formula I(a) only any hydroxyl groups are protected as ORx where Rx is as defined below; and W_1 has the meaning defined in Chart A. In Chart B: W_2 has the meaning defined in Chart B; L_{60} and R_7 have the meanings defined in Formula I(a); Y_3 is $-CH_2CH_2-$; cis—CH=CH—, trans—CH=Ch— or —C≡C—; alkyl, L_2 and L_{22} have the meanings defined above in Chart A; M_3 is α-H:β-OH or α-OH:β-H; M_1 is =O, α-H:β-ORx, α-ORx:β-H; Ra is the same as R_7 in Formula I(a) only Ra is not a group containing any unsaturation; Rb is an unsaturated group defined by R_7 in Formula I(a) wherein the double bond is protected by bromine or an epoxide group; Rc represents an unsaturated R_7 group; and Rd represents an unsaturated group of R_7 only the double bond is protected with an epoxide function. In Chart C: L_{60} is as defined in Formula I and L_{22} has the meaning defined in Chart A above. In Chart D: Ph is phenyl; L_{60} has the meaning defined in Formula I(a); and L_{21} is as defined in Chart A above. In Chart E: Ph is phenyl; L_{60}, M_1, L_1, R_7, Z_4 and X_1 have the meanings defined in Formula I(a); Y_3 has the meaning defined in Chart B; and L_{22} has the meaning defined in Chart A above. In Chart F the groups Y_2, L_2, M_2 and R_7 have the meanings defined in Chart A and alkyl has from 1 to 4 carbon atoms.

During the preparation of the compounds of the present invention it may be necessary or desirable to protect the various hydroxyl groups at positions 11, 15, 16 or those contained in substituent R_7 as ORx groups where Rx is a suitable protecting group. Many suitable protecting groups are known in the art and are described, for example in U.S. Pat. No. 4,401,824, particularly column 11, line 21 through column 13, line 15, wherein such groups are described as is the manner of adding and removing such groups on the hydroxyl. The aforesaid portions of U.S. Pat. No. 4,401,824 are incorporated herein by reference. Although any of these protecting groups may be employed those preferred are tetrahydropyranyl (THP), tetrahydrofuran (THF), tert-butyldimethylsilyl and tert-butyldiphenylsilyl. It may be useful, of course, to use protecting groups which may be hydrolyzed selectively and also when group R_7 contains an hydroxyl to be protected generally this hydroxyl is protected using the same type of group that is used at positions C-11, C-15 or C-16.

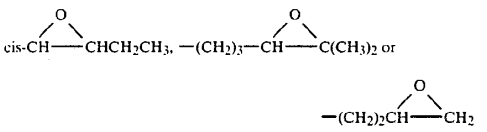
The compounds of the present invention are prepared by various means utilizing 2,3,3A,4-tetrahydro-5-methoxy-2-oxo-naphtho[2,3-B]furan depicted as Formula II. Although in describing the preparation of the compounds of Formulas I and I(a) only one optical enantiomer may be depicted the processes are applicable to both the D and L optical isomers or mixtures thereof unless, of course, a particular step is stereoselective. The compounds of Formula I(a) wherein Y_1 is $-CH_2CH_2-$ or $-SCH_2-$ are prepared as depicted in Chart A. The enollactone (II) is alkylated with two equivalents of a phosphonate anion (III) followed by one equivalent of acetic acid after which the reaction is warmed to effect the intramolecular Wadsworth-Emmons reaction, this procedure being an improved modification of the procedure of C. A. Henrick, et al., J. Am. Chem. Soc. 90, 5926 (1968). The resulting enone (IV) is reduced to the ketone (V) by procedures known in the art. For example the enone is hydrogenated over palladium catalyst in ethanol at 3 atmospheres pressure and may be followed by oxidation if necessary using, for example, Jones reagent. Equilibration to the thermodynamically favored ketone is achieved typically under basic conditions using, for example, potassium hydroxide in ethanol by procedures known in the art. When in compounds of Formula IV R_7 is a group containing a double bond such double bond is protected prior to reduction of the enone. For example the double bond can be protected by treatment of compound IV with one equivalent of bromine in carbon tetrachloride and following reduction of the enone and conversion to intermediate VI (see below) the double bond is deprotected by treatment of the ketone by heating with zinc in acetic acid or ethanol. Also the double bond can be protected by treatment of compound IV with metachloroperbenzoic acid (MCPBA) in methylene chloride to give an epoxide which can be removed, restoring the double bond following reduction of the enone and conversion (see below) to intermediate VI, by treatment with tri-n-butylphosphine with heating (see M. J. Boskin and D. B. Denney, Chem. Ind., London, 330, 1959) or treatment with tungsten hexachloride and lithium iodide with heating (see K. B. Sharpless, et. al., J. Am. Chem. Soc. 94, 6538 (1972)). The ketone (V) is then used to prepare compounds of Formula I(a) or the intermediates (VI) which are utilized in preparing compounds of Formula I(a).

To prepare intermediates (VI) wherein L_{21} is α-H,β-OH, or α-OH,β-H the ketone (V) is reduced by procedures known in the art, for example using sodium borohydride. Conversion of the ketone (V) to the intermediate (VI) where L_{21} is methylene, i.e., $=CH_2$, typically is achieved via a Wittig-type procedure, for example, using methylenetriphenylphosphorane by generally known procedures. Alternatively, the methylene group can be prepared by treatment of ketone (V) with the anion of methyl phenyl-N-methyl sulfoxime in tetrahydrofuran followed in a subsequent step by sulfoxime elimination with aluminum amalgam (see Aristoff, P. A. and Harrison, A. W., Tetrahedron Lett. 23, 2067–2070 (1982)). The methylene intermediate can be used to prepare compounds IX as depicted in Chart A or can be reduced to the corresponding compound wherein L_{21} is α-CH_3,β-H, for example, via hydrogenation over palladium catalyst by procedures known in the art. The methylene intermediate can also be used to prepare the corresponding compound wherein L_{21} is α-CH_2OH,β-H by hydroboration using, for example, borobicyclononane (9-BBN) followed by work-up with basic hydrogen peroxide. The intermediates of (VI) wherein L_{21} and L_{60} taken together form a double bond are prepared by treating the ketone (V) with a hydrazine derivative, such as, tosylhydrazine, followed by a Shapiro reaction on the resulting tosylhydrazone (see R. H. Shapiro,

Chapter 3 in Organic Reactions, Volume 23, pp. 405–507). The 10,11-didehydro intermediate thus obtained can be used to prepare compounds (IX) as depicted in Chart A or can be hydrogenated, e.g., using palladium over charcoal, to intermediates (VI) wherein L_{21} is H,H.

The compounds of (V) and (VI) are converted to the phenols (VII) by, for example, treatment with lithium diphenylphosphide in tetrahydrofuran as generally described by R. E. Ireland and D. M. Walba, Tetrahedron Letters, 1071 (1976). Other methods for aryl methyl ether cleavages are known and may be employed, e.g., see M. V. Bhatt and S. U. Kulkarni, Synthesis 249 (1983). The phenols are converted to compounds (VIII)(a) by selective alkylation, for example, using potassium carbonate and a nitrile of the formula Cl-Z_4-CN wherein Z_4 has the meaning defined in Formula I(a) by procedures generally known in the art. The phenols are converted to compounds (VIII)(b) by treatment with one equivalent of base, e.g., sodium hydride, and an appropriate halo alkanoate, e.g., alkyl bromo alkanoate of the formula BrZ_4-COOalkyl wherein alkyl has, e.g., from 1 to 4 carbon atoms and Z_4 has the meaning defined in Formula I(a). The compounds (VIII)(a) and (b) are hydrolyzed to the corresponding carboxylic acids of (VIII)(c) by procedures known in the art, for example, by using aqueous potassium hydroxide in methanol. The carboxylic acids of (VIII)(c) are converted to the final products (IX) wherein X_1 is COOH upon hydrolysis of any protecting groups at positions 11, 15 or 16 and the ketal protecting the C-15 is carbonyl. The carboxylic acids of (VIII)(c) can also be converted to compounds IX wherein X_1 is other than COOH by conventional means. For example, the carboxylic acid derivative can be reduced to (IX) wherein X_1 is $-CH_2OH$ by treatment with lithium aluminum hydride. The thus formed C-1 alcohols, i.e., compounds IX wherein X_1 is CH_2OH can be oxidized to the corresponding carboxaldehyde which on treatment with a salt of hydroxylamine gives the oxime which is dehydrated to give the nitrile, i.e., compounds (IX) wherein X_1 is CN. The carboxylic acid derivative also can be converted to the various esters and amides defined in Formula I(a), and the amides can be reduced to the corresponding amines by using lithium aluminum hydride as generally described in U.S. Pat. No. 4,073,808. Following the conversions to the various X_1 groups any protecting groups present at C-11, C-15 or C-16 may be removed by hydrolysis as described hereinabove.

Compounds of Formula I(a) wherein Y_1 is other than $-SCH_2-$ are prepared using the aldehyde depicted in Chart B as Formula XI. By the procedures generally described in Chart U of U.S. Pat. No. 4,306,075 the Formula XI aldehyde is reacted with an alkyl phosphonate of Formula X under the conditions of a Wittig reaction to give a ketone of Formula XII. The ketone can be used to prepare final products of Formula I(a) or can be reduced by hydride reduction to the trans-vinyl α- or β-alcohol, i.e., compounds of formula XIII wherein M_3 is α-OH,β-H or α-H,β-OH. The trans-vinyl alcohol of XIII can be used to prepare final products of Formula I(a) or when R_7 is other than a group containing unsaturation can be hydrogenated to give compounds of Formula XIV wherein Ra is R_7 except it is other than a group containing unsaturation. If prior to the initial reaction of the aldehyde of Formula XI and the phosphonate X any double bond present in the group R_7 is protected, as for example by treatment with one equivalent of bromine or by treatment with MCPBA as generally described hereinabove in connection with compounds of Formula IV in Chart A, the corresponding compounds of Formulas XII(a), XIII(a) and XIV(a) are obtained wherein Rb is one of the unsaturated groups of R_7 defined in Formula I(a) except that any unsaturation is protected by bromine or an epoxide function. Thus the compounds of Formula XIV(a) can be deprotected by treatment with zinc in acetic acid or ethanol when halogen protection is employed or by treatment with tributylphosphine or tungsten hexachloride and lithium iodide when epoxide protection is employed to give compounds of Formula XV wherein Rc is an R_7 unsaturated group as defined in Formula I(a). The compounds of Formulas XII and XIII wherein R_7 is other than a group containing unsaturation and of Formulas XII(a) and XIII(a) can be dihalogenated at C-13, C-14 and subsequently dehydrohalogenated by procedures well known in the art, e.g., see U.S. Pat. No. 4,029,681 or C. Gandolfi, et al., Il Farmaco, Ed. Sci. 27, 1125 (1972), to give compounds of Formula XVI wherein R_7 has the meaning defined in Formula I(a) and of Formula XVI(a) wherein Rd is



The compounds of Formula XVI can be used to prepare final products of Formula I(a) or the compounds of Formulas XVI and XVI(a) can be hydrogenated using a Lindlar catalyst to give the cis-vinyl alcohols of Formulas XVII and XVII(a) wherein R_7 and Rd are as defined above. The compounds of Formula XVII can be used to prepare final products of Formula I(a) or can be selectively oxidized to the cis-vinyl ketones of Formula XVIII using, e.g., DDQ or manganese dioxide, by procedures known in the art. The epoxides of Formula XVII(a) can be treated with tributylphosphine or tungsten hexachloride and lithium iodide as described hereinabove to remove the epoxide protecting groups. When R_5 in the M_1 substituent of Formula I(a) is methyl the appropriate starting materials are obtained by oxidizing the alcohols of Formulas XIV, XV and XVI to the corresponding ketones by procedures known in the art and then the resulting ketones as well as the vinyl ketones of Formulas XII and XVIII are treated with methyl lithium or a methyl Grignard by well known procedures. The compounds of Formulas XIII, XIV, XV, XVI and XVII wherein M_3 is α-H,β-OH or α-OH,β-H can be treated with a leaving group, e.g., converting the M_3 OH to OTs followed by a displacement reaction using, e.g., lithium aluminum hydride, to give the corresponding compounds wherein M_3 is H,H.

Collectively and for convenience all the starting materials prepared in connection with Chart B are depicted by Formula XIX in Chart B wherein M_1, L_{60}, and R_7 have the meanings defined in Formula I; M_3 is α-H,β-OH or α-OH,β-H;; and L_2 and L_{22} are the same as L_1 and L_{20} respectively in Formula I(a) only any hydroxyl group present is protected. The compounds of Formula XIX are converted to final products of Formula I(a) by the same procedures set forth in Chart A for converting compounds VI and V to compounds IX. Prior to making these conversions any hydroxyl groups

at positions 11, 15, 16 or in the R_7 group can be protected as ORx as described hereinabove.

The compounds of Formula XI are prepared as set forth in Chart C and Chart D. In Chart C the 2,3,3A,4-tetrahydro-5-methoxy-2-oxo-naphtho[2,3-B] furan (Formula II) is treated with the anion of trimethylphosphonoacetate followed by cyclization as generally described in connection with the reaction of compounds of Formulas II and III in Chart A. Alternatively the lactone (II) is treated at low temperature with the anion of methyl acetate (or ethyl acetate to give the ethyl ester analog) followed by warming to effect the cyclization. Compounds XX are reduced to the ketone XXI by means known in the art, e.g., by hydrogenation using palladium catalyst. The ketone XXI is reduced to the C-11 alcohol by, e.g., treatment with sodium borohydride after which the carboxy ester is reduced to the hydroxymethyl compound (XXII) using, e.g., excess diisobutylaluminum hydride. The compound of formula XXII is converted to the aldehyde of formula XI by procedures known in the art, e.g., by protection of the C-13 alcohol with an ORx group followed by oxidation of the C-11 alcohol to the ketone, e.g., with Collins reagent, followed by conversion of the C-11 ketone to any of the L_{22} groups as previously described, hydrolysis of the C-13 protecting group and oxidation to the aldehyde.

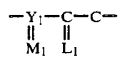
In Chart D the lactone II is alkylated with the anion of dimethylphosphonate in a manner similar to that described for the reaction of compounds II and III in Chart A. The enone of Formula XXIII is reduced, e.g., by hydrogenation at room temperature over palladium catalyst by procedures known in the art to give the ketone of Formula XXIV the ketone enolate of which is alkylated using benzylchloromethyl ether by procedures known in the art to give compounds of Formula XXV wherein Ph is phenyl. The ketones of Formula XXV are converted to the various C-11 analogs of Formula XXVI by the same general procedures described for the conversion of compounds V to compounds VI in Chart A. Any hydroxyl group present at the C-11 substituent is protected appropriately as described hereinbefore prior to proceeding to compounds of Formula XXVII. Cleavage of the benzyl ethers of Formula XXVI by hydrogenation, procedures known in the art, gives the 12-hydroxymethyl compounds of Formula XXVII which are oxidized to the aldehydes of Formula XI using Collins reagent by known procedures.

The compounds of Formula IV in Chart A can also be prepared as depicted in Chart F. The 2,2-ethylenedioxy-5-methoxynaphthalen-3-ylacetic acid (Formula XXXVI) is reacted with two equivalents of a phosphonate of Formula III as generally described in connection with the preparation of compounds of Formula IV in Chart A to give the compounds of Formula XXXVII. The Formula XXXVII compound is deketalized by means known in the art, e.g., by treatment with aqueous acid followed by reprotection of any hydroxyl groups in the $-C(M_2)C(L_2)R_7$ chain as generally described herein. The ketone of Formula XXXVIII is then treated with base, e.g., sodium hydride in glyme to give the enone of Formula IV.

Compounds of Formula I(a) wherein Y_1 is other than $-SCH_2-$ can also be prepared as depicted in Chart E. Compounds XXVIII are obtained as depicted in Chart D (see compounds XXV and XXVI) and are converted to the phenols of Formula XXIV by cleavage of the methyl ether using lithium diphenylphosphide in tetrahydrofuran as generally described hereinabove in connection with the preparation of compounds VII in Chart A. The phenols of Formula XXIX are converted to the compounds of XXX by the general procedures described in connection with the compounds of Formula VII to compounds of Formula IX in Chart A. The compounds of Formula XXX are converted to the aldehydes of Formula XXXIV by the general procedures described in connection with the preparation of compounds XI from compounds XXVI in Chart D, and the aldehydes of Formula XXXIV in turn are converted to the compounds of Formula XXXV by the general procedures described in Chart B for preparing compounds XIX.

Compounds of Formula I(a) also can be prepared as depicted in Chart E beginning with compounds of Formula XXXI which are obtained as described in Chart C (see Formulas XXI and XXII). Cleavage of the methyl ether of XXXI is accomplished using lithium diphenylphosphide in tetrahydrofuran as described hereinbefore followed by esterification, e.g., using diazomethane, and the resulting phenols (XXXII) are converted to the compounds of Formula XXXIII by the general procedures described in connection with the conversion of compounds VII to compounds IX in Chart A. The compounds of XXXIII are then converted to the corresponding aldehydes of XXXIV as generally described in Chart C (i.e., XXII to XI).

The compounds of Formula I(a) wherein



taken together is

are prepared by treating an aldehyde of Formula XXXIV (see Chart E) with a semicarbizide of the formula $H_2NNC(=O)NH-R_7$ by procedures known in the art. The semicarbazides are obtained by procedures generally known in the art by converting an R_7CHO compound to the corresponding imine which is reduced to an amine. The amine is treated with dimethylcarbonate to give the corresponding carbamate which is treated with hydrazine hydrate to give the semicarbazide.

The phosphonates of Formulas III (Chart A) and X (Chart B) are known in the art or are prepared by procedures known in the art (see, for example, U.S. Pat. Nos. 4,029,681 and 4,401,824 and as depicted in Charts G. H and J.

In Chart G the cyclohexylcarboxaldehyde (1) is alkylated with vinyl Grignard or vinyl lithium to give the vinyl alcohol (5) by procedures known in the art. Kinetic resolution of the vinyl alcohol (5) to give compound (6) is accomplished by the method of Sharpless (Martin, V. S., et al., J. Am. Chem. Soc. 103, 6237 (1981). Alternatively, the cyclohexylcarboxyaldehyde is alkylated with acetylene anion by known procedures to give the ethynyl alcohol (2) which is oxidized to the ketone (3) using, e.g., Jones reagent, by known procedures. The ketone (3) is reduced assymetrically using chiral reagents by known procedures. See, e.g., Mid-

land, M. M., J. Org. Chem. 47, 2815 (1982); J. Org. Chem. 46, 3933 (1981), and J. Am. Chem. Soc. 102, 867 (1980); and also, Cohen, N., J. Org. Chem. 45, 583 (1980) and Brinkmeyer, R. S., and Kapoor, V., J. Am. Chem. Soc. 99, 8339 (1977). The ethynyl alcohol (4) is then partially reduced using, e.g., sodium bis(2-methoxyethoxy)aluminum hydride in toluene or hydrogenation over Lindlar catalyst by known procedures. The vinyl alcohol (6) is then protected, e.g., as a tetrahydropyranyl group, and either subjected to iodoboration by the general procedures of H. C. Brown, "Organic Synthesis via Boranes," John Wiley, N.Y., 1975, pp. 101–102, to give compound (11) or is subjected to hydroboration and oxidation using, e.g., 9-borabicyclononane followed by alkaline peroxide work-up by known procedures to give 4-cyclohexyl-4-ORx-propanol. The propanol is converted to compound 11 by direct replacement of the primary OH with iodide using iodine and a triaryl phosphine as generally described by B. R. Castro, "Organic Reactions," 29, p. 1, ed., W. G. Dauben, John Wiley, N.Y., 1983. Alternatively the primary OH of the propanol is selectively activated, e.g., via tosylation followed by displacement of the tosylate with iodide in acetone and diisopropylamine to give compound (11). Compound (11) is treated with the anion of dialkyl methyl phosphonate to give compound (12).

As depicted in Chart G, the protected vinyl alcohol (7) may also be converted to the alcohol (8) by, e.g., ozonolysis and treatment with a reducing agent such as sodium borohydride. The alcohol (8) can be converted to the iodide (9) directly or via the tosylate as described above in connection with the preparation of compound (11). The iodide (9) is then alkylated with a dialkyl methylthio phosphonate following the general methods outlined by M. Mikolajczk, et al., J. Org. Chem. 44, 2967 (1979) to give compound (10). The alcohol (8) can also be obtained from D-mandelic acid (15) as depicted in Chart G by hydrogenating the acid over rhodium catalyst by known procedures, e.g., T. Hirano, et al., Makrmol. Chem. 177, 3237 (1976) to give α-hydroxycyclohexaneacetic acid (14) which is converted to the ester (13) by generally known procedures. The ester (13) is then reduced to give compound (8) using, e.g., excess diisobutylaluminum hyrdide. D-mandelic acid (15) can also be used to prepare compound (19) in Chart G. The hydroxyl group of the acid is protected using, e.g., as a tetrahydropyranyl group, then the acid is reduced to the alcohol, using. e.g., sodium bis(2-methoxyethoxy)aluminum hydride in toluene or using lithium aluminum hydride after which the alcohol is converted to the iodide (16) directly or via the tosylate in the manner generally described in connection with the preparation of compound (11). The iodide (16) is then alkylated using, e.g., vinyl Grignard or vinyl lithium with nickel or copper catalysis by generally known procedures to give the vinyl compund (17) which is converted to the iodide (18) in the same manner as described above for the conversion of compound (7) to compound (11). The iodide (18) is treated with trimethylphosphite under the conditions of an Arbuzov reaction to give the phosphonate (19).

In Chart H there is described additional means of obtaining phosphonates useful in preparing compounds of this invention. The acetylene (20) is partiallly reduced to the trans vinyl compound (21) using, e.g., sodium bis(2-methoxyethoxy)aluminum hyrdide by known procedures. The vinyl alcohol is subjected to Sharpless asymetric epoxidation as generally described by B. E. Rossiter, et al., J. Am. Chem. Soc. 103, 464 (1981) and T. Katsuki and K. B. Sharpless, J. Am. Chem. Soc. 102, 5974 (1980) to give compound (22) which is reduced to the alcohol (23) by general procedures described by J. M. Finan and Y. Kishi, Tetrahedron Lett. 23, 2719 (1982). By selective activation the primary hydroxyl of compound (23) is tosylated to give (24), the tosylate of which is converted to the iodide using, e.g., sodium iodide to give compound (25). The secondary hydroxyl of compound (25) is protected and the compound is alkylated with the anion of dialkyl methylphosphonate to give compound (27) by general procedures known in the art.

Chart J also sets forth means for obtaining phosphonates for use in preparing the compounds of this invention. Alkylation of 4-bromo-2-methyl-2-butene, compound (28), is achieved with allyl magnesium bromide using, e.g., copper or nickel catalysis by known procedures to give compound (29) which is subjected to hydroboration and oxidation using. e.g., 9-borabicyclononane, followed by hydrogen peroxide workup to give the alcohol (30) which is converted to the iodide, compound (31) e.g., by the procedures described in connection with the preparation of compound (11) in Chart G. Alternatively compound (29) can be subjected to hydroboration and iodination to give compound (31) by known procedures. Compound (31) is then alkylated with the dianion of propargyl alcohol by known procedures to give compound (32) which is partially reduced to give 33, e.g., using sodium bis(2-methoxyethoxy)aluminum hydride, then converted to the phosphonate (34) by procedures generally described hereinabove.

Although Charts G, H, and J depict the preparation of specific phosphonates wherein R_7 is cyclohexyl, phenyl, alkyl or alkenyl, the methods there described are applicable generally to the phosphonates used herein.

The compound of Formula II is prepared as depicted in Chart K and as described in Example 1.

EXAMPLE 1

2,3,3A-4-Tetrahydro-5-methoxy-2-oxo-naphtho[2,3-B]furan

(a)

3,4-Dihydro-2-hydroxy-5-methoxynaphthalenecarboxylic acid methyl ester (Chart K, Compound 35)

A solution of 5-methoxy-β-tetralone (20.6 g, 117 mmol) and 350 ml of dimethylcarbonate was cooled to 0° to 5°, then treated with 32 ml (140 mmol) of 25 sodium methoxide in oxygen-free methanol. The resulting dark brown solution was stirred for 30 minutes at 0°, then heated to 70°, stirred for 18 hours under a nitrogen atmosphere, then cooled to 0° to 5° and quenched with 200 ml of cold 1N degassed aqueous hydrochloric acid. The solution was extracted with ethyl acetate (2×150 ml). The combined organic layers were washed with brine (2×200 ml), dried over magnesium sulfate, filtered, and rotary evaporated at 50°. The resulting red-brown oil was crystallized from 80 ml of 1:1 ether/hexane in the freezer to give 14.43 g (53%) of yellow crystals, m.p. 56°–58°. A second crop of yellow crystals (3.6 g, 14%) can be obtained from 20 ml 1:1 ether/hexane, m.p. 55°–58°. The mother liquor (~12 g) was chromatographed on 100 g of silica gel 60 slurry packed in 300 ml of hexane. Eluting with 2% ethyl acetate in hexane gave 5.1 g (19%) of the title compound (a) in

fractions 17–28, m.p. 53°–58°. Total yield of compound (a) was 23.1 g (85%).

NMR ($CDCl_3$, TMS): δ 2.3–2.7 (m, 2H), 2.8–3.0 (m, 2H), 3.80 (s, 3H), 3.90 (s, 3H), 6.6–7.5 (m, 3H), 13.35 (s, 1H).

Infrared: ν_{max} (mull): 1640, 1598, 1587, 1566, 1422, 1378, 1311, 1277, 1220, 1207, 1086, 1052, 1030, 892, 787, 769, 721 cm^{-1}.

TLC (Silica Gel GF): RF=0.47 in 10% ethyl acetate in hexane.

(b) 3,4-Dihydro-2-hydroxy-3-(3-propene)-5methoxy naphthalenecarboxylic acid methyl ester (Chart K, Compound 36)

A solution of 300 ml of tetrahydrofuran and 39 ml (282 mmol) of diisopropylamine under nitrogen, was cooled to −50° C. and treated with 170 ml (272 mmol) of 1.6M n-butyllithium in hexane dropwise maintaining the temperature at −50° C. The solution was stirred at −50° for 15 minutes, then at 0° for 15 minutes. A solution of 30.0 g (128.1 mmol) of 3,4-dihydro-2-hydroxy-5-methoxynaphthalenecarboxylic acid methyl ester in 70 ml of tetrahydrofuran was added dropwise to maintain the temperature at 0°. The resulting yellow suspension was treated with 13.5 ml (160 mmol) of allyl bromide in 50 ml of tetrahydrofuran dropwise maintaining the temperature at 0°. The cooling bath was removed and the orange solution was stirred at ambient temperature for 1 hour, then cooled to 10° to 15° C. and 500 ml of 1N degassed aqueous hydrochloric acid was added dropwise maintaining the temperature below 15°. The layers were separated and the aqueous layer extracted with 400 ml of ethyl acetate. The organic layers were combined and washed with 500 ml of brine, dried over anhydrous magnesium sulfate, filtered and concentrated via rotary evaporation and then house vacuum to give 44.2 g of the title compound (b), m.p. 70°–71°.

NMR ($CDCl_3$, TMS): δ1.8–3.2 (m, 5H), (3H singlets at 3.80 δ and 3.90 δ; 6H) 4.7–5.4 (m, 2H), 5.5 α 6.1 (m, 1H), 6.5–7.6 (m, 3H), 13.4 (s, 1H).

Infrared: ν_{max} 2925, 2956, 1237, 1598, 1440, 1270, 1257, 1051, 1002, 885, 790, 772 cm^{-1}.

TLC (Silica Gel GF): Rf=0.34 in 10% ethyl acetate in hexane.

(c) 1,2,3,4-Tetrahydro-5-methoxy-3-(3-propene)naphthalen-2-one (Chart K, Compound 37)

A mixture of 44.1 g of 3,4-dihydro-2-hydroxy-5-methoxy-3-(3-propene)naphthalenecarboxylic acid methyl ester and 110 ml of dimethyl sulfoxide was degassed with nitrogen and heated to ~50° under nitrogen to effect dissolution. The resulting orange solution was treated with 6.0 g (142 mmol) of anhydrous lithium chloride and 7.5 ml of deionized water and heated to 150° under nitrogen, then stirred at 150° for 4 hours. The solution was cooled to 10° to 15°, diluted with 500 ml of 1:1 brine/water and extracted with three 200 ml portions of ethyl acetate. The organic layers were combined and washed with three 200 ml portions of water, two 200 ml portions of brine, dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to give 28.3 g of the title compound (c), m.p. 39°–40°.

NMR ($CDCl_3$, TMS): δ 1.8–2.8 (m, 4H), 3.0–4.3 (m, including 2H broad singlet at 3.53 δ and 3H singlet at 3.80 δ, 6H), 4.8–5.4 (m, 2H), 5.5–6.1 (m, 1H), 6.5–7.4 (m, 3H).

Infrared: ν_{max} 2922, 1713, 1642, 1599, 1588, 1472, 1441, 1436, 1258, 1081, 910, 771, 719, 609 cm^{-1}.

TLC (Silica Gel GF): Rf=0.32 in 10% ethyl acetate in hexane.

(d) The 2-ethylenedioxy ketal of 1,2,3,4-tetrahydro-5-methoxy-3-(3-propene)naphthalen-2-one (Chart K, Compound 38)

A solution of 27.8 g (128 mmol) of 1,2,3,4-tetrahydro-5-methoxy-3-(3-propene)naphthalen-2-one, 450 ml of methylene chloride, 150 ml (2.2 mmol) of ethylene glycol, 60 ml (450 mmol) of triethylorthoformate, and 270 mg (1.41 mmol) of p-toluenesulfonic acid monohydrate was degassed with nitrogen and stirred at room temperature under nitrogen for 22 hours after which the reaction was quenched with 7.5 ml (52 mmol) of triethylamine, diluted with 500 ml of 1:1 saturated aqueous sodium bicarbonate/water and the layers were separated. The aqueous layer was extracted with 200 ml of methylene chloride. The combined organic layers were washed with three 500 ml portions of water and 500 ml of brine, then concentrated by rotary evaporation to give ~40 g of a red oil. The red oil was dissolved in 200 ml of hexane and treated with 200 ml of water. The mixture was degassed and stirred under nitrogen for one hour. The layers were separated and the organic layer was dried with anhydrous magnesium sulfate, then filtered and concentrated in vacuo to give ~35 g of an orange oil. The orange oil was filtered through 100 g of silica gel 50 washing with 800 ml of 10% ethyl acetate in hexane. The filtrate was concentrated in vacuo to give 31.5 g (94%) of the title compound (d), m.p. 34°–35°.

NMR ($CDCl_3$, TMS)''δ 1.7–3.3 (m, including 2H broad singlet at 2.90 δ, 7H), 3.4–4.4 (m, including 3H singlet at 3.77 δ, 7H), 4.8–5.3 (m, 2H), 5.6–6.2 (m, 1H), 6.5–7.4 (m, 3H).

Infrared: ν_{max} (film): 2940, 2890, 1620, 1590, 1470, 1440, 1260, 1155, 1075, 950, 770 cm^{-1}.

TLC (Silica Gel GF): Rf=0.35 in 10% ethyl acetate in hexane.

(e) 2,2-Ethylenedioxy-5-methoxy-1,2,3,4-tetrahydro-naphthalen-3-ylacetic acid (Chart K, Compound 39)

To a mixture of 1400 ml of deionized water and 66.5 g (310 mmol) of sodium metaperiodate was added 1.0 g (6.4 mmol) of potassium permanganate. The purple solution was stirred for 30 minutes at room temperature then treated in sequence with 5.0 g (36 mmol) of anhydrous potassium carbonate, then 350 ml of t-butanol, followed by 8.9 g (34 mmol) of the ethylenedioxy ketal of 1,2,3,4-tetrahydro-5-methoxy-3-(3-propene)naphthalen-2-one in 350 ml of t-butanol. The resulting reddish-purple suspension was stirred at room temperature for 2 hours. The reaction was quenched with 10 ml (150 mmol) of ethylene glycol and stored at room temperature for 2.5 hours. Approximately 30% of the solvent was removed via rotary evaporation, and the remaining material was acidified to pH 3–4 with 100 ml of 1M aqueous hydrochloric acid and extracted with three 500 ml portions of ethyl acetate. The organic layers were combined and washed with two 500 ml portions of brine, dried over anhydrous sodium sulfate, filtered, and the solvents removed in vacuo to give 8.5 g (89%) of the title compound (e), m.p. 129°–130°.

Infrared: ν_{max} 2927, 1703, 1587, 1471, 1266, 1143, 1082, 1059, 948, 873, 765 cm^{-1}.

NMR ($CDCl_3$, TMS): δ 1.8–3.4 (m, 6H), 3.9–4.5 (m, including 3H singlet at 3.77 δ, 8H), 6.4–7.4 (m, 3H), 10.27 broad singlet, 1H).

TLC (Silica Gel GF): Rf=0.20 in 30% ethyl acetate in hexane.

(f)

5-Methoxy-2-oxo-1,2,3,4-tetrahydronaphthalen-3-ylacetic acid (Chart K, Compound 40)

A solution of 8.0 g (28.7 mmol) of 2,2-ethylenedioxy-5-methoxy-1,2,3,4-tetrahydronaphthalen-3-ylacetic acid, 80 ml of 3N aqueous hydrochloric acid, and 80 ml of acetone was degassed and heated to 60° under nitrogen then stirred under nitrogen at 60° for 4 hours. The reaction was cooled to room temperature, approximately 50% of the solvent was removed by rotary evaporation, diluted with 100 ml of brine, and extracted with three 100 ml portions of ethyl acetate. The organic layers were combined and washed with two 100 ml portions of brine, dried over anhydrous sodium sulfate, filtered, and concentrated via rotary evaporation to give an orange solid. The orange solid was triturated with 10 ml of ether and filtered to give 4.9 g (73%) of the title compond (f), m.p. 129°–131°.

NMR ($CDCl_3$, TMS): δ 2.2–3.2 (m, 4H), 3.3–4.0 (m, including 2H broad singlet at 3.67 δ and 3H singlet at 3.85 δ, 6H), 6.4–6.9 (m, 2H), 7.1–7.3 (m, 1H), 10.2 (bs, 1H).

Infrared: ν_{max} 2908, 2855, 1730, 1714, 1676, 1471, 1454, 1446, 1266, 1202, 1195, 1184, 1091, 776, 747, 724, cm^{-1}.

TLC (Silica Gel GF): Rf=0.22 in 35% ethyl acetate in hexane with 1% acetic acid.

(g)

2,3,3A,4-Tetrahydro-5-methoxy-2-oxo-naphtho[2,3-B]furan (Chart K, Compound 41)

A solution of 5-methoxy-2-oxo,1,2,3,4-tetrahydronaphthalen-3-yl-acetic acid (1.75 g, 7.49 mmol) in 88 ml of ethyl acetate was treated all at once with 88 ml of a reagent prepared immediately before use as follows: 20.0 ml of a solution of 0.40 ml of 70% perchloric acid in 100 ml of ethyl acetate was added to 50 ml of ethyl acetate, then 19.2 ml (0.20 mmol) of acetic anhydride was added and the reagent diluted to a total volume of 100 ml with ethyl acetate. The solution was stirred for 10 minutes at room temperature under nitrogen then quenched with 100 ml of saturated aqueous sodium bicarbonate. The layers were separated and the organic layer was washed with 100 ml of brine, dried with anhydrous sodium sulfate, filtered and concentrated in vacuo. To remove the excess acetic anhydride, the red oil was treated with 10 drops of pyridine and 200 ml of methanol. The solvents were removed in vacuo (rotovap bath below 30°); then to remove the pyridine 100 ml of toluene was added and the solvents were removed in vacuo (rotovap bath below 35°). An additional 100 ml of toluene was added and concentrated in vacuo to give a yellow solid. The yellow solid was recrystallized from ethyl acetate and hexane to give 890 mg (55%) of the title compound (g) as a white solid, m.p. 139°–141°.

NMR ($CDCl_3$, TMS): δ 2.0–4.1 (m, including 3H singlet at 3.86 δ, 8H), 6.0–6.2 (d, J=3 Hz, 1H), 6.6–7.0 (m, 2H), 7.0–7.4 (m, 1H).

Infrared: ν_{max} 2926, 1800, 1686, 1571, 1472, 1444, 1267, 1075, 964, 865, 850, 780 cm^{-1}.

CMR ($CDCl_3$, TMS): δ ppm (relative intensity): 173.94 (14), 156.31 (17), 154.89 (18), 134.98 (17), 127.79 (92), 121.42 (11), 119.48 (90), 109.60 (97), 101.09 (81), 55.48 (64), 34.76 (88), 33.17 (88), 27.29 (85).

UV: 218 nm (ε=17,650), 267 nm (ε=7,150), 293 nm (sh, ε=2,000), 303 nm (sh, ε=1,150).

TLC (Silica Gel GF): Rf=0.32 in 15% ethyl acetate in hexane.

EXAMPLE 2

Dimethyl[(4S)-tetrahydropyran-2-yloxy-nonyl]phosphonate

(a) 2-Octen-1-ol (Chart H, Compound 21)

A solution of 200 ml of dry tetrahydrofuran, degassed with nitrogen and cooled to 0° to 5°, and 85 ml (289 mmol) of 3.4M solution of sodium bis(2-methoxyethoxy) aluminum hydride in toluene was treated with 30.0 g (238 mmol) of 2-octyn-1-ol in 200 ml of dry tetrahydrofuran dropwise over one hour maintaining the temperature at 0° to 5°. The solution was removed from the cooling bath and stirred at ambient temperature for 3 hours then cooled to below −20° and carefully quenched (vigorous evolution of hydrogen occurs) with 1M aqueous sulfuric acid (~10 ml) until the evolution of gas ceases. The quenched reaction mixture was poured into 1 L of cold 1M aqueous sulfuric acid, the layers separated, and the aqueous layer extracted with three 300 ml portions of ethyl acetate. The organic layers were combined and washed with 400 ml of brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to give 30.4 (100%) of the title compound (a) which was distilled at 60° at 1 mm Hg to provide an analytical sample.

NMR ($CDCl_3$, TMS): δ 0.9 (t, J=6 Hz, 3H), 1.1–1.8 (m, 6H), 1.8–2.2 (m, 2H), 2.97 (s, 1H), 4.0–4.2 (m, 2H), 5.6–5.8 (m, 2H).

CMR ($CDCl_3$, TMS): δ 133.38, 129.00, 63.69, 32.24, 31.45, 28.90, 22.56, 14.02.

Infrared: ν_{max} (film) 3331, 2927, 2858, 1671, 1468, 1379, 1089, 1001, 969 cm^{-1}.

TLC (Silica Gel GF): Rf=0.26 in 10% ethyl acetate in hexane (the plate was developed twice).

(b) 2,3-Epoxyoctan-1-ol (Chart H, Compound 22)

To 2.0 L of methylene chloride, degassed with nitrogen and cooled to −20° under nitrogen, was added 70.8 ml (238 mmol) of titanium (IV) isopropoxide followed by 44.8 ml (262 mmol) of (+)-diethyl-L-tartrate maintaining the temperature below −15°. The mixture was stirred for 10 minutes. A solution of 30.4 g (240 mmol) of 2-octen-1-ol was added in 30 ml of methylene chloride dropwise maintaining the temperature below −15°. An additional 10 ml of methylene chloride was added and the solution stired for 10 minutes after which 104 ml (480 mmol) of t-butylhydroperoxide (4.6M in 1,2-dichloroethane) was added dropwise maintaining the temperature below −15°. The reaction solution was stirred for 24 hours at −20°. The pale yellow reaction solution was cannulated using nitrogen pressure into a 0° to 5° solution of 1400 ml of deionized water containing 400 g of ferrous sulfate and 200 g of d-tartaric acid vigorously stirred. The yellow-green emulsion was stirred for 30 minutes at ambient temperature then filtered through celite, the layers separated, and the aqueous layer extracted with two 500 ml portions of methylene chloride which had been used to wash the filter cake. The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to give a colorless oil. The oil was dissolved in

600 ml of hexane and 300 ml of t-butylmethyl ether, degassed with nitrogen, and cooled to 0° under nitrogen after which the solution was treated with 500 ml of ice cold 1N aqueous sodium hydroxide and vigorously stirred for 30 minutes under nitrogen at 0°. The aqueous layer was saturated with sodium chloride. The layers were separated and the aqueous layer extracted with two 150 ml portions of 2:1 hexane/t-butylmethyl ether. The organic layers were combined, washed with two 300 ml portions of brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to give ~25 g of colorless oil. The oil was chromatographed on 300 g of silica gel 60 eluting with 20% ethyl acetate in hexane to give (57%) of the title compound (b).

NMR ($CDCl_3$, TMS): δ 0.9 (t, J=6 Hz, 3H), 1.0–2.1 (m, 8H), 2.6–3.2 (m, 3H), 3.4–4.2 (m, 2H).

CMR ($CDCl_3$, TMS): 67 62.08, 58.90, 56.26, 31.67, 25.69, 22.61, 13.97.

Infrared: ν_{max} (mull) 3115, 2961, 2854, 1584, 1037, 1008, 991, 877, 730 cm^{-1}.

TLC (Silica Gel GF): Rf=0.19 in 30% ethyl acetate in hexane.

Specific Rotation: $[\alpha]_D = -35°$ (95% ethanol).

(c) 1,3-Octandiol (Chart H, Compound 23)

To a solution of 250 ml of dry tetrahydrofuran, degassed with nitrogen and cooled to 0° to 5° under nitrogen, and 46.0 ml (156 mmol) of 3.4M solutions of sodium bis(2-methoxyethoxy) aluminum hydride in toluene was added 15.0 g (104 mmol) of 2,3-epoxyethan-1-ol in 120 ml of dry tetrahydrofuran dropwise over one hour. An additional 10 ml of dry tetrahydrofuran was added and the mixture was stirred at 0° to 5° for 16 hours. The reaction solution was then quenched at 0° to 5° with 10 ml of 1M aqueous sulfuric acid, and the resulting white slurry was poured into 1 L of ice cold 1M aqueous sulfuric acid. The layers were separated and the aqueous layer was extracted with three 250 ml portions of ethyl acetate. The organic layers were combined, washed with 250 ml of saturated aqueous sodium bicarbonate and 250 ml of brine, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give 14.4 g (95%) of the title comoound (c).

NMR ($CDCl_3$, TMS): δ 0.9 (t, J=6 Hz, 3H), 1.0–1.8 (m, 10H), 3.2–4.0 (m, 5H).

Infrared: ν_{max} (film): 3345, 2872, 2860, 1468, 1460, 1379, 1130, 1056 cm^{-1}.

TLC (Silica Gel GF): Rf=0.30 in 70% ethyl acetate in hexane.

Specific Rotation: $[\alpha]_D = +8°$ (in 95% ethanol).

(d) 2-(p-Toluenesulfonyloxy)octan-3-ol (Chart H, Compound 24)

A solution of 14.2 g (97.1 mmol) of 1,3-octandiol and 200 ml of dry pyridine degassed with nitrogen and cooled to 0° was treated with 19.4 g (102 mmol) of p-toluenesulfonyl chloride and stirred for 18 hours at 0° under nitrogen. The reaction mixture was then poured onto 500 g of ice and stirred until the ice dissolved. The mixture was extracted with three 200 ml portions of ethyl acetate. The organic layers were combined, washed with 200 ml of brine, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo at room temperature using two 200 ml portions of toluene to azeotropically remove the pyridine to give 24.5 g (84%) of the title compound (d).

NMR ($CDCl_3$, TMS): δ 0.9 (t, J=6 Hz, 3H), 1.0–2.2 [m, including broad singlet (1H) at 2.1 11H], 2.43 (s, 3H), 3.5–3.9 (m, 1H), 4.0–4.4 (m, 2H), 7.4 (d, J=9 Hz, 2H), 7.75 (d, J=9 Hz, 2H).

Infrared: ν_{max} (film) 3545, 3432, 2955, 2930, 2859, 1598, 1358, 1189, 1176, 1097, 958, 911, 814, 665 cm^{-1}.

TLC (Silica Gel GF): Rf=0.5 in 50% ethyl acetate in hexane.

(e) 1-Iodooctan-3-ol (Chart H, Compound 25)

A solution of 24.5 g of 1-(p-toluenesulfonyloxy)octan-3-ol and 75 g (500 mmol) of sodium iodide was degassed with nitrogen and heated to 50° under nitrogen, then stirred at 50° for one hour. The suspension was cooled to 25° and most of the acetone was removed in vacuo at room temperature. The resulting red-orange solid was dissolved with 500 ml of ethyl acetate and 500 m of 1:1 brine/water. The layers were separated and the aqueous layer extracted with 100 ml of ethyl acetate. The organic layers were combined, washed with 100 ml of 5% aqueous sodium thiosulfate, 200 ml of brine, and dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give 19.84 g of title compound (e).

(f) 1-Iodooctan-3-ol, 0-tetrahydropyranyloxy (Chart H, Compound 26)

A solution of 19.84 g of 1-iodooctan-3-ol and 100 ml of methylene chloride, degassed with nitrogen, was combined with 15 ml (150 mmol) of dihydropyran and 100 mg of pyridine hydrochloride and then stirred at room temperature under nitrogen for 18 hours. The reaction solution was washed with 100 ml of saturated aqueous sodium bicarbonate, 100 ml of brine, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The crude product was chromatographed on 300 g of silica gel 60 slurry packed with hexane, eluting with 3% ethyl acetate in hexane to give 11.47 g of the title compound (f).

NMR ($CDCl_3$, TMS): δ 0.9 (t, J=6 Hz, 3H), 1.1–2.3 (m, 16H), 3.0–4.1 (m, 5H), 4.8 (bs, 1H).

Infrared: ν_{max} (film) 2932, 2858, 1465, 1455, 1440, 1209, 1200, 1132, 1077, 1024, 871 cm^{-1}.

TLC (Silica Gel GF): Rf=0.40 in 5% ethyl acetate in hexane.

(g) Dimethyl[(4S)-tetrahydropyran-2-yloxynonyl]phosphonate (Chart H, Compound 27)

To 300 ml of dry tetrahydrofuran, degassed with nitrogen and cooled to −40° under nitrogen, was added 6.0 ml (57.5 mmol) of diethylamine. The solution was treated with 34.0 ml (52.7 mmol) of n-butyllithium (1.55M in hexane) dropwise maintaining the temperature below −30° and stirred at −35° to −30° for 15 minutes, then cooled to −75°. A solution of 6.54 g (52.7 mmol) of dimethylmethylphosphonate in 50 ml of dry tetrahydrofuran was added dropwise maintaining the temperature below −70°. Stirring was continued for 30 minutes at −75° to −70° after which 16.31 g (47.9 mmol) of 1-iodooctan-3-ol, 0-tetrahydropyranyloxy in 100 ml of dry tetrahydrofuran was added dropwise maintaining the temperature below −70°. The mixture was stirred at −70° for one hour and the reaction mixture allowed to warm to −10° over 4 to 5 hours. The mixture was carefully quenched with 500 ml of 1:1 brine/water and extracted with two 400 ml portions of ethyl acetate. The organic layers were combined, washed with 500 ml of brine, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give a crude product which was chromatographed on

300 g of silica gel 60 slurry packed in ethyl acetate. The product was eluted with 1 L of ethyl acetate followed by 2 L of 15% acetone in ethyl acetate to give 11.47 g of the title compound (g).

NMR ($CDCl_3$, TMS): δ 0.9 (t, J=6 Hz, 3H), 1.1–2.1 (m, 20H), 3.3–4.1 (m, including two 3H singlets at 3.70 and 3.80, 9H), 4.67 (bs, 1H).

Infrared: ν_{max} (film) 2952, 1464, 1456, 1246, 1200, 1183, 1133, 1076, 1062, 1030, 995, 831, 813 cm^{-1}.

TLC (Silica Gel GF): Rf=0.24 in ethyl acetate.

EXAMPLE 3

9-Deoxy-13,14-dihydro-2',9α-methano-3-oxa-4,5,6-trinor-3,7-(1',3-interphenylene)-PGF_1

(a)

8,12-Didehydro-9,11-dideoxy-13,14-dihydro-2',9α-methano-3-oxa-11-oxo-1,4,5,6-tetranor-3,7-(1',3'-interphenylene)-PGF_1, 15-(tetrahydropyranyl ether)

A solution of 11.90 g (35.37 mmol) of dimethyl[(4S)-tetrahydropyran-2-yloxynonyl]phosphonate and 450 ml of dry tetrahydrofuran, degassed and flushed with nitrogen, was cooled to −78° C. The stirred solution was treated with 22.5 ml (36.0 mmol) of 1.60M n-butyllithium dropwise over 15 to 20 minutes then stirred for one hour at −78° C. A solution of 3.71 g (17.17 mmol) of 2,3,3A,4-tetrahydro-5-methoxy-2-oxo-naptho[2,3-B]furan in 70 ml of dry tetrahydrofuran, degassed and flushed with nitrogen and cooled to −78° C. under nitrogen, was added via cannula and under nitrogen pressure dropwise over 30 minutes. The resulting solution was stirred for 4 hours while allowing the temperature to rise slowly to −10° after which the solution was treated dropwise with 1.03 ml (18 mmol) of glacial acetic acid. The reaction mixture was stirred for 15 minutes at ambient temperature and heated at 60° to 65° for 6 hours. The resulting yellow-green solution was cooled to 5°, neutralized to about pH 6 to 7 with 500 ml of brine containing 18 ml (18 mmol) of 1M aqueous hydrochloric acid, and extracted with three 250 ml portions of ethyl acetate. The organic layers were combined and washed with 200 ml of 3:1 brine/saturated aqueous sodium bicarbonate and then with 400 ml of brine and dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The resulting crude product was chromatographed on 200 g of silica gel 60 degassed with nitrogen eluting with 1 L of 20% ethyl acetate in hexane. The elution was continued with 1 L of ethyl acetate followed by 2 L of 25% acetone in ethyl acetate to give 4.96 g (68%) of title compound 3(a).

NMR ($CDCl_3$, TMS): δ 0.9 (t, J=6 Hz, 3H), 1.0–3.1 (m, 22H), 3.3–4.2 (m, including 3H singlet at 3.83 δ, 9H), 4.63 (bs, 1H), 6.6–7.3 (m, 3H).

Infrared ν_{max} (film): 1700, 1652, 1584, 1471, 1456, 1439, 1268, 1252, 1133, 1091, 1077, 1032, 771 cm^{-1}.

UV (95% ethanol): λ nm (ϵ_{max}) 229 (17,050), 272 (3,500), 281 (3,150).

TLC (Silica Gel GF): Rf 0.26 in 20% ethyl acetate in hexane.

(b) 9,11-DIDEOXY-13,14-DIHYDRO-2',9∇-METHANO-3-oxa-11-oxo-1,4,5,6-tetranor-3,7-(1',3'-interphenylene)-12-epi-PGF_1, 15-(tetrahydropyranyl ether)

To a solution of 4.95 G (11.6 mmol) of the compound of Example 3(a) in 250 ml of degassed absolute ethanol was added a solution of 1.67 g of 10% palladium on carbon and 112 mg (0.81 mmol) of anhydrous potassium carbonate. The resulting mixture was hydrogenated at 50 psi (3.4 atm) for 42 hours after which the mixture was filtered through a pad of 1:1 celite/anhydrous magnesium sulfate. The filter cake was washed with two 200 ml portions of ethyl acetate. The colorless solution was concentrated in vacuo using 200 ml of toluene to azeotrope the last traces of water and ethanol to give 5.2 g of colorless oil. [TLC(Silica gel GF; 20% ethyl acetate in hexane): 2 spots (neither visible under UV light) R_f=0.28 and 0.38.] The colorless oil was dissolved in 65 ml of acetone then degassed and flushed with nitrogen and cooled to −40° to −35° C. The solution was treated dropwise with 4.78 ml (12.8 mmol) of Jones Reagent over 10 to 15 minutes and stirred at −40° to −35° for 2 hours under nitrogen. The excess Jones Reagent was quenched with 3.1 ml (40 mmol) of 2-propanol at −40° to 35° and the mixture was stirred for 30 minutes after which 3 g of solid sodium bicarbonate was added. The mixture was stirred for 15 minutes at ambient temperature after which the green suspension was filtered through celite and the filter cake was washed with four 70 ml portions of ethyl acetate. The combined filtrates were washed with two 100 ml portions of saturated aqueous sodium bicarbonate and 100 ml of brine. The aqueous washes were combined and back extracted with 100 ml of ethyl acetate. The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The resulting dark brown oil was filtered through 20 g of silica gel 60 washing with 500 ml of 20% ethyl acetate in hexane. The filtrate was concentrated in vacuo to give 4.7 g (95%) of compound 3(b) as a pale brown oil.

NMR ($CDCl_3$, TMS): δ 0.9 (t, J=6 Hz, 3H), 1.0–4.2 (m, including 3H singlet at 3.83 ppm, 33H), 4.6 (bs, 1H), 6.6–6.9 (m, 2H), 6.9–7.3 (m, 1H).

TLC (Silica Gel GF): R_f=0.38 in 20% ethyl acetate in hexane.

(c)

9,11-Dideoxy-13,14-dihydro-2',9α-methano-3-oxa-11-oxo-1,4,5,6-tetranor-3,7-(1',3'-interphenylene)-PGF_1, 15-(tetrahydropyranyl ether)

To 4.7 g (10.9 mmol) of the compound of Example 3(b) in 450 ml of 95% ethanol was added 90 ml of 10% aqueous sodium hydroxide and the resulting solution was degassed and flushed with nitrogen and heated at reflux (bath temperature 105°) for 7.5 hours under nitrogen. The reaction was cooled to room temperature and approximately two-thirds of the solvent was removed in vacuo at room temperature and the remaining material was diluted with 500 ml of brine and extracted with three 200 ml portions of ethyl acetate. The combined organics were washed with 200 ml of brine, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The crude product was flash chromatographed on 240 g of silica gel (230–400 mesh ASTM) eluting with 10% ethyl acetate in hexane collecting 200 ml fractions to give 4.41 g (94%) of the title compound 3(b) as a colorless oil.

NMR ($CDCl_3$, TMS): δ 0.9 (t, J=6 Hz, 3H), 1.0–4.2 (m, including 3H singlet at 3.83 ppm, 33H), 4.6 (bs, 1H), 6.6–6.9 (m, 2H), 6.9–7.3 (m, 1H).

Infrared ν_{max} (film): 1738, 1588, 1469, 1440, 1257, 1200, 1133, 1113, 1091, 1077, 1050, 1032, 1023, 993, 769 cm^{-1}.

TLC (Silica Gel GF): R_f=0.41 in 20% ethyl acetate in hexane.

(d)
9-Deoxy-13,14-dihydro-2',9α-methano-3-oxa-1,4,5,6-tetranor-3,7-(1',3'-interphenylene)-PGF_1

To 2.80 g (74.0 mmol) of sodium borohydride, degassed and flushed with nitrogen, and cooled to −30°, was slowly added 350 ml of absolute methanol and the resulting material was stirred for 10 minutes and treated with a solution of 10.2 g (23.8 mmol) of the compound of Example 3(c) in 15 ml of dry methylene chloride and 76 ml of absolute methanol dropwise maintaining the temperature of the solution at −30°. The resulting solution was stirred at −30° for 4 hours, then at −25° for 2.5 hours after which the reaction was quenched with 19.0 ml of glacial acetic acid then diluted with 600 ml of brine and extracted with four 250 ml portions of ethyl acetate. The organic layers were combined and washed with 300 ml of saturated aqueous sodium bicarbonate, then washed with 300 ml of brine, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give 10.1 g of a colorless oil [TLC(Silica gel GF; 20% ethyl acetate in hexane): 5 spots with the major spot at R_f=0.20.] The oil was dissolved in 60 ml of tetrahydrofuran and diluted with 180 ml of glacial acetic acid and 90 ml of deionized water, degassed and flushed with nitrogen, and stirred at 40° to 45° under nitrogen for 3 hours. The solution was then cooled to room temperature, diluted with 500 ml of brine and extracted with three 250 ml portions of 3:2 ethyl acetate/hexane. The organic layers were combined and washed with four 300 ml portions of brine. The aqueous layers were combined and back extracted with two 250 ml portions of 3:2 ethyl acetate/hexane. All the organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo using two 300 ml portions of toluene to azeotrope the acetic acid. The resulting colorless oil was chromatographed on 700 g of silica gel 60 eluting with 40% ethyl acetate in hexane to give 5.28 g (64%) of the title compound 3(d).

NMR ($CDCl_3$, TMS): δ 0.9 (t, J=6 Hz, 3H), 1.0–3.1 (m, including 2H singlet at 2.30 δ, 23H), 3.5–3.9 (m, including 3H singlet at 3.83 δ, 5H), 6.6–6.9 (m, 2H), 7.0–7.3 (m, 1H).

TLC (Silica Gel GF): R_f0.25 in 50% ethyl acetate in hexane.

Infrared: ν_{max} (film): 3343, 1587, 1477, 1472, 1461, 1455, 1441, 1341, 1327, 1263, 1104, 1077, 1034, 734 cm^{-1}.

(e)
9-Deoxy-13,14-dihydro-2',9α-methano-3-oxa-1,4,5,6-pentanor-3,7-(1',3'-interphenylene)-PGF_1

A solution of 250 ml of dry tetrahydrofuran and 8.3 ml (47.7 mmol) of diphenylphosphine, degassed and cooled to 0° to 5° C. under introgen, was treated with 30.0 ml (46.5 mmol) of n-butyllithium (1.55M in hexane) dropwise over 15 minutes then stirred an additional 30 minutes at ambient temperature after which 5.6 g (16.2 mmol) of the compound of Example 3(d) in 50 ml of dry tetrahydrofuran was added under nitrogen pressure over 15 minutes. An additional two 10 ml portions of tetrahydrofuran were added and the mixture was heated at reflux for 8 hours under nitrogen. The solution was cooled to 0° to 5° C. after which 11.0 ml (63.6 mmol) of diphenylphosphine was added, then treated with 41.0 ml (63.6 mmol) of n-butyllithium (1.55M in hexane) dropwise over 10 to 15 minutes. The solution was stirred at ambient temperature for 30 minutes then refluxed for 16 hours all under nitrogen pressure. The solution was then cooled to 0° to 5° C. and poured into 465 ml of ice cold brine containing 125 ml of 1N aqueous hydrochloric acid (pH 3–4) and extracted with three 200 ml portions of ethyl acetate. The organic layers were combined, washed with 200 ml of brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The resulting colorless oil was chromatographed on 400 g of silica gel 60 eluting with 50% ethyl acetate in hexane to give the product.

NMR ($CDCl_3$, TMS): δ 0.9 (t, J=6 Hz, 3H), 1.0–3.0 (m, 21H), 3.3–3.9 (m, 2H), 4.4 (bs, 3H), 6.5–7.1 (m, 3H).

Infrared: ν_{max} (film): 3345, 1590, 1465, 1280, 775 cm^{-1}.

TLC (Silica Gel GF): R_f=0.18 in 50/5 ethyl acetate in hexane.

(f)
2-Decarboxy-2-cyano-9-deoxy-13,14-dihydro-2',9α-methano-3-oxa-4,5,6-trinor-3,7-(1',3'-interphenylene)-PGF_1,

The phenol from 3(e) (5.12 g, 15.4 mmol) was combined with 22.8 g (165 mmol) of anhydrous potassium carbonate, and 17.8 ml (281 mmol) of chloroacetylnitrile and 150 ml of acetone. The solution was degassed and flushed with nitrogen and refluxed for 24 hours under nitrogen and cooled to 15° to 20° C., diluted with 200 ml of 1:1 brine/water and extracted with 600 ml of ethyl acetate. The organic layer was washed with 200 ml of brine. The aqueous layers were combined and extracted with 200 ml of ethyl acetate. The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The resulting oil was chromatographed on 400 g of silica gel 60 eluting with 20% acetone in methylene chloride to give the product.

NMR ($CDCl_3$, TMS): δ 0.9 (t, J=6 Hz, 3H), 1.0–3.0 (m, 21H), 3.20 (bs, 2H), 3.4–3.9 (m, 2H), 4.73 (s, 2H), 6.7–7.3 (m, 3H).

Infrared: ν_{max} (film): 3360, 1610, 1585, 1470, 1455, 1415, 1265, 1235, 1105, 1080, 1040, 770, 740, 735 cm^{-1}.

TLC (Silica Gel GF): R_f 0.26 in 20% acetone in methylene chloride.

(g) The nitrile from 3(f) (4.9 g, 13.2 mmol) was combined with 100 ml (445 mmol) of 25% aqueous potassium hydroxide, degassed and flushed with nitrogen. The solution was refluxed for 6 hours, cooled to 0° to 5°, acidified to pH 6 with 400 ml of ice cold 1N aqueous hydrochloric acid in 1 L of brine, and extracted with four 300 ml portions of ethyl acetate. The combined organic layers were washed with 500 ml of brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The resulting pink to red solid was chromatographed on 400 g of CC-4 acid washed silica gel eluting with 2 L of 50% ethyl acetate in hexane followed by 3 L of 70% ethyl acetate in hexane to give 5.10 g of solid which was crystallized from hot tetrahydrofuran and hexane to give 1.20 g of 9-deoxy-13,14-dihydro2',9α-methano-3-oxa-4,5,6-trinor-3,7-(1',3-interphenylene)-PGF_1 (m.p. 122°–124° C.).

NMR

$$\overset{O}{\overset{\|}{}}$$
(CD_3CCD_3, TMS):

δ0.9 (t, J=6 Hz, 3H), 1.0–3.1 (m, 21H), 3.3–3.9 (m, 2H), 4.3–5.3 (m including 2Hs at δ 4.67, 5H), 6.6–7.2 (m, 3H).

Specfic Rotation: $[\alpha]_D+34°$ (c 0.901, 95% etOH).

Infrared: ν_{max} (mull): 3440, 3380, 2720, 2670, 2580, 1740 (weak), 1710, 1610, 1585, 1425, 1260, 1145, 1120, 1090, 1025 cm^{-1}.

EXAMPLE 4

Dimethyl [(4R)-4-cyclohexyl-4-tetrahydropyran-2-yloxybutyl]-phosphonate

(a) 1-Cyclohexylprop-2-enol (Chart G, Compound 5)

To 140 ml of dry tetrahydrofuran, degassed and flushed with nitrogen (3×) and cooled to 0° C. under nitrogen, was added 1.3M vinyl magnesium bromide (195 ml, 253.5 mmol) in tetrahydrofuran rapidly and dropwise over 5 minutes. The resulting solution was stirred for 5 minutes at 0° C. under nitrogen after which a solution of 24.0 g (223 mmol) of cyclohexylcarboxaldehyde in 40 ml of dry tetrahydrofuran was added via syringe at 0° C. The resulting mixture was stirred for 3.75 hours at 0° to 5° C. under a nitrogen atmosphere after which the reaction was quenched at 0° C. by careful addition of saturated aqueous ammonium chloride. The resulting suspension was poured into 1 L of ice cold, saturated, aqueous ammonium chloride and extracted with three 600 ml portions of ethyl acetate. The ethyl acetate extracts were combined and washed with 1 L of saturated aqueous ammonium chloride, 1 L of saturated aqueous sodium bicarbonate, then twice with 1 L each of brine. The ethyl acetate extract was dried thoroughly over magnesium sulfate, filtered, and concentrated at room temperature via rotovap to give 31.0 g of 1-cyclohexylprop-2-enol.

NMR ($CDCl_3$, TMS): δ 0.73–2.67 (m, 12H, CH_2, CH), 3.87 (t, 1H, CH—O, J=6 Hz), 5.07–5.43 (m, 2H, CH=), 5.67–6.13 (m, 1H, CH=).

Infrared (film): 3370, 2925, 1450, 1020, 990, 975, 890 cm^{-1}.

TLC (Silica Gel GF): R_f=0.54 in 25% ethyl acetate in hexane.

(b) (R)-1-Cyclohexylprop-2-enol (Chart G, Compound 6)

To 2.2 L of methylene chloride, degassed and flushed with nitrogen and cooled to −25° C. under nitrogen, was added 72.2 ml of titanium tetraisopropoxide (242.5 mmol) at −25° C. under nitrogen. The solution was stirred for 3 to 5 minutes at −25° C. after which 62.16 ml of (−)-diisopropyl(D)tartrate (290 mmol) was added at −25° C. under nitrogen. A solution of 31.0 g (214 mmol) of 1-cyclohexylprop-2-enol in 50 ml of methylene chloride was added to the reaction mixture at −25° C. under nitrogen. The resulting solution was stirred for 5–10 minutes at −25° C. under nitrogen after which 3M t-butylhydroperoxide in dichloroethane (48.5 ml, 145.5 mmol) was added at −25° C. under nitrogen. The mixture was stirred for 10 minutes at −25° to −20° C. under nitrogen, then stirred for 3 days at −20° C. The reaction was quenched by cannulating the reaction mixture (at −20° C.) into a mechanically stirred tartaric acid-ferrous sulfate solution (200 g/400 g in 2 L water) at 0° C. The resulting suspension was stirred at 0° C. for 20 to 30 minutes and filtered through a pad of celite, washing the pad thoroughly with methylene chloride. The filtrate layers were separated and the aqueous layer was extracted with methylene chloride (2×500 ml each). The organic extracts were combined and washed with brine (2×1000 ml each), dried over magnesium sulfate, filtered and concentrated at room temperature via rotovap to give the title compound 4(b) as a yellow oil which was purified as follows: The oil was dissolved in 650 ml of hexane and cooled to 0° C. under nitrogen then treated with aqueous 1N sodium hydroxide (550 ml) at 0° C. under nitrogen. The resulting suspension was stirred for 40 minutes at 0° C. under nitrogen after which the layers were separated and the aqueous layer was extracted with hexane (2×500 ml each). The organic extracts were combined, washed with brine (500 ml), dried over sodium sulfate, filtered and concentrated at room temperature via rotovap to a yellow oil. The yellow oil was chromatographed on silica gel (1200 g) packed with 10% ethyl acetate in Skellysolve B (SSB) eluting with 12% in SSB to give 9.59 g of the title compound 4(b).

NMR ($CDCl_3$, TMS): δ 0.73–2.67 (m, 12H, CH_2, CH), 3.87 (ε, 1H, CH—O), 5.07–5.43 (m, 2H, CH=), 5.67–6.13 (m, 1H, CH=).

Infrared (film): 3370, 2925, 1450, 1020, 990, 975, 890 cm^{-1}.

TLC (Silica Gel GF): R_f=0.54 in 25% ethyl acetate in hexane.

(c) 3-Cyclohexyl-3-tetrahydropyranyloxy-prop-1-ene (Chart G, Compound 7)

A solution of 22.07 g of (R)-1-cyclohexylprop-2-enol in 300 ml of methylene chloride, degassed and washed with nitrogen, was treated at ambient temperature under nitrogen with pyridinehydrochloride (0.145 g) and then with dihydropyran (44.4 ml, 466 mmol). The reaction mixture was stirred overnight at ambient temperature under nitrogen, then cooled using an ice bath and treated with aqueous sodium bicarbonate (15 ml). The resulting solution was diluted with saturated aqueous sodium bicarbonate (200 ml), stirred for 5 minutes after which the layers were permitted to separate. The organic layer was washed with 200 ml of brine, dried over anhydrous sodium sulfate, filtered and the filtrate concentrated via rotovap to give 35.0 g of compound 4(c) as a yellow oil.

NMR ($CDCl_3$, TMS): δ 0.63–2.20 (m, 17H, CH_2, CH), 3.27–4.10 (m, 3H, CH—O, CH_2O), 4.67 (bs, 1H, CH—O, THP), 4.93–5.33 (m, 2H, CH=), 5.40–6.13 (m, 1H, CH=).

Infrared (film): 2925, 2855, 1130, 1115, 1080, 1035, 1020, 1015, 995, 980 cm^{-1}.

TLC (Silica Gel GF): R_f=0.62 in 25% ethyl acetate in hexane.

(d) 3-Cyclohexyl-3-tetrahydropyranyloxypropanol (Chart G, Compound 8)

A solution of 35.0 g of 3-cyclohexyl-3-tetrahydropyranolprop-1-ene (157 mmol) in 795 ml of dry tetrahydrofuran, degassed and flushed with nitrogen, then cooled to 0° C., was treated dropwise at 0° C. with 0.5M 9-BBN in tetrahydrofuran (795 ml, 398 mmol). The resulting solution was stirred for one hour at 0° C. after which the cooling bath was removed and stirring was continued at ambient temperature for 6 hours. The reaction mixture was then cooled to 0° C. and treated slowly with 30% hydrogen peroxide (231 ml), then treated with 3N potassium hydroxide (231 ml) all at once. The resulting suspension was stirred for 35 minutes at 0° C. after which the cooling bath was removed and the reaction suspension was stirred for one hour at ambient temperature. The reaction mixture was then diluted with brine (1 L), the layers separated and the aqueous

layer was extracted with three 700 ml portions of ethyl acetate. The organic layers were combined and washed with three 500 ml portions of brine, dried over anhydrous sodium sulfate, filtered and the filtrate concentrated in vacuo at ~25° C. The resulting product was chromatographed on silica gel (1750 g) packed with 5% ethyl acetate in SSB, eluting with 8 L of 5% ethyl acetate in SSB, 6 L of 10% ethyl acetate in SSB, 6 L of 20% ethyl acetate in SSB, 6 L of 25% ethyl acetate in SSB, and 4 L of 30% ethyl acetate in SSB to give 27.19 g of compound 4(d).

NMR ($CDCl_3$, TMS): δ 0.63–2.90 (m, 20H, CH_2, CH, C—OH), 3.23–4.13 (m, 5H, CH—O, CH_2—O), 4.03–4.87 (m, 1H, CH—O, THP).

Infrared (film): 3435, 2930, 2855, 1450, 1160, 1135, 1075, 1025, 990 cm^{-1}.

TLC (Silica Gel GF): R_f=0.21–0.38 in 30% ethyl acetate in hexane.

(e) The 1-p-toluenesulfonyl derivative of 3-cyclohexyl-3-tetrahydropyranyloxypropanol

A solution of 27.19 g (112 mmol) of 3-cyclohexyl-3-tetrahydropyranyloxypropanol in 136 ml of dry pyridine, degassed with nitrogen and cooled to 0° C., was treated with 25.7 g (135 mmol) of p-toluenesulfonyl chloride. The reaction mixture was stirred for 20 hours at 0° C. under nitrogen after which 350 g of ice was added and the cooling bath was removed. The reaction mixture was stirred for 75 minutes, then diluted with 600 ml of water, and extracted with three 500 ml portions of ethyl acetate. The organic layers were combined, washed with 600 ml of saturated aqueous sodium bicarbonate, 600 ml of water, and 600 ml of brine, and dried over anhydrous sodium sulfate, filtered and the filtrate concentrated via rotovap at room temperature. The residual pyridine was removed azeotropically at room temperature via rotovap using two 300 ml portions of toluene to give 38.09 g of compound 4(e).

NMR ($CDCl_3$, TMS): δ 0.63–2.20 (m, 19H, CH_2, CH), 2.47 (s, 3H, $ArCH_3$), 3.23–4.40 (m, 5H, CH—O, CH_2—O), 4.47 (m, 1, CH—O, THP), 7.37 (D, 2H, ArH; J=10, 5 Hz), 7.87 (D, 2H, ArH; J=10, 5 Hz).

Infrared (film): 2930, 2860, 1600, 1445, 1375, 1175, 905, 815, 670 cm^{-1}.

TLC (Silica Gel GF): R_f=0.48 in 20% ethyl acetate in hexane.

(f) (1-Tetrahydropyranyloxy-3-iodopropyl)cyclohexane (Chart G, Compound 11)

A solution of 36.74 g (92.65 mmol) of the compound from Example 4(e), 1.5 ml of diisopropylethylamine, 360 ml of acetone and 83.33 g (550 mmol) of sodium iodide was stirred at room temperature under nitrogen for 20 hours. The solution was then cooled using an ice bath and concentrated via rotovap at room temperature to give a red-orange solid. The solid was dissolved in 1L of ethyl of ethyl acetate. The organic layers were washed with 525 ml of 5% aqueous sodium thiosulfate then with 1 L of brine, dried over anhydrous magnesium sulfate, filtered and the filtrate concentrated via rotovap at room temperature to give a yellow oil. The oil was chromatographed on 900 g of silica gel packed with SSB, eluting with 4 L of SSB, then with 3% ethyl acetate in SSB to give 27.47 g of compound 4(f).

NMR ($CDCl_3$, TMS): δ 0.63–2.53 (m, 19H, CH_2, CH), 3.07–3.70 (m, 4H, CH_2—O, CH_2—I), 3.77–4.10 (m, 1H, CH—O), 4.48–4.82 (m, 1H, CH—O, THP).

Infrared (film): 2925, 2850, 1450, 1200, 1130, 1115, 1075, 1065, 1035, 1023, 980 cm^{-1}.

TLC (Silica Gel GF): R_f=0.47 in 10% ethyl acetate in hexane.

(g) [(4R)-4-Cyclohexyl-4-tetrahydropyran-2-yloxybutyl]-phosphonate (Chart G, Compound 12)

To 500 ml of dry tetrahydrofuran cooled to −40° C. under nitrogen was added 9.98 ml (96.7 mmol) of diethylamine. The solution was treated with 60 ml (93 mmol) of n-butyllithium (1.55M in hexane) dropwise maintaining the temperature below −30° C. The solution was stirred at −35° to −30° C. for 15 minutes then cooled to −75° C. A solution of 10.6 g (85.4 mmol) of dimethylmethyl phosphonate in 50 ml of dry tetrahydrofuran was added dropwise maintaining the temperature below −70° C. The solution was stirred for 30 minutes at −75° to −70° C. after which 27.29 g (77.5 mmol) of (1-tetrahydropyranyloxy-3-iodopropyl)cyclohexane in 100 ml of dry tetrahydrofuran was added dropwise maintaining the temperature below −70° C. The reaction mixture was stirred at −70° C. for one hour then allowed to warm to −10° C. over 4 hours. The reaction was quenched with 800 ml of 1:1 brine/water and the layers separated. The aqueous layer was extracted with two 650 ml portions of ethyl acetate. The organic layers were combined, washed with 800 ml of brine, dried over anhydrous sodium sulfate, filtered and the filtrate concentrated in vacuo. The resulting product was chromatographed on 500 g of silica gel packed with ethyl acetate eluting the product with 2 L of ethyl acetate and then with 6 L of 5% acetone in ethyl acetate to give 18.14 g of compound 4(g).

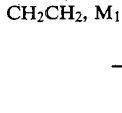
NMR ($CDCl_3$, TMS): δ 0.63–2.53 (m, 23H), 3.23–4.20 (m, 3H), 3.70 (s, 3H), 3.83 (s, 3H), 4.60 (bs, 1H).

Infrared (film): 2930, 3850, 1450, 1245, 1200, 1130, 1115, 1060, 1030, 990, 835, 815 cm^{-1}.

TLC (Silica Gel GF): Rf=0.14 in ethyl acetate.

EXAMPLE 5

15-Cyclohexyl-9,11-dideoxy-13,14-dihydro-2',9α-methano-11α-methyl-4,5,6,16,17,18,19,20-octanor-3,7-(1',3'-interphenylene)-PGF_1 (Formula I where X_1 is CO_2H, Z_4 is CH_2, L_{60} is H, L_{20} is α-CH_3,β-H, Y_1 is CH_2CH_2, M_1 is α-OH,β-H and



is cyclohexyl

(a) 15-Cyclohexyl-8,12-didehydro-9,11-dideoxy-13,14-dihydro-2',9a-methano-3-oxa-11-oxo-1,4,5,6,16,17,18,19,20-nonanor-3,7-(1',3'-interphenylene)-PGF_1, 15-(tetrahydropyranyl ether)

A solution of 11.9-g (35.37) mmol of the product of Example 4 and 450 ml of dry tetrahydrofuran, degassed and flushed with nitrogen, was cooled to −78° C. The stirred solution was treated with 22.5 ml (36.0 mmol) of 1.60M n-butyllithium dropwise over 15 to 20 minutes, then stirred for one hour at −78° C. A solution of 3.71 g (17.17 mmol) of 2,3,3A,4-tetrahydro-5-methoxy-2-oxo-naphtho[2,3-B]furan in 70 ml of dry tetrahydrofuran, degassed and flushed with nitrogen and cooled to

−78° C. under nitrogen, was added via cannula and under nitrogen pressure dropwise over 30 minutes. The resulting solution was stirred for 4 hours while allowing the temperature to rise slowly to −10° C. after which the solution was treated dropwise with 1.03 ml (18 mmol) of glacial acetic acid. The reaction mixture was stirred for 15 minutes at ambient temperature and heated at 60° to 65° for 6 hours. The resulting yellow-green solution was cooled to 5°, neutralized to about pH 6 to 7 with 500 ml of brine containing 18 ml (18 mmol) of 1M aqueous hydrochloric acid, and extracted with three 250 ml portions of ethyl acetate. The organic layers were combined and washed with 200 ml of 3:1 brine/saturated aqueous sodium bicarbonate and then with 400 ml of brine and dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The resulting crude product was chromatographed on 200 g of silica gel to give the title compound 5(a).

(b)
15-Cyclohexyl-9,11-dideoxy-13,14-dihydro-2',9a-methano-3-oxa-11-oxo-1,4,5,6,16,17,18,19,20-nonanor-3,7-(1',3'-interphenylene)-12-epi-PGF_1, 15-(tetrahydropyranyl ether)

To a solution of 4.95 g of the compound of Example 5(a) in 250 ml of degassed ethanol was added a solution of 1.67 g (1.56 g/atom) of 10% palladium on carbon and 112 mg (0.81 mmol) of anhydrous potassium carbonate. The resulting mixture was hydrogenated at 50 psi 93.4 atm) for 42 hours after which the mixture was filtered through a pad of 1:1 celite/anhydrous magnesium sulfate (30 g). The filter cake was washed with two 200 ml portions of ethyl acetate. The colorless solution was concentrated in vacuo using 200 ml of toluene to azeotrope the last traces of water and ethanol to give 5.2 g of colorless oil which was filtered through 20 g of silica gel 60 washing with 500 ml of 20% ethyl acetate in hexane to give compound 5(b).

(c) 15-Cyclohexyl-9,11-dideoxy-13,14-dihydro-2',9a-methano-3-oxa-11-oxo-1,4,5,6,16,17,18,19,20-nonanor-3,7-(1',3'-interphenylene)-PGF_1, 15-(tetrahydropyranyl ether)

To 4.7 g of the compound of Example 5(b) in 450 ml of 95% ethanol was added 90 ml of 10% aqueous sodium hydroxide and the resulting solution was degassed and flushed with nitrogen and heated at reflux (bath temperature 105°) for 7.5 hours under nitrogen. The reaction was cooled to room temperature and approximately two-thirds of the solvent was removed in vacuo at room temperature and the remaining material was diluted with 500 ml of brine and extracted with three 200 ml portions of ethyl acetate. The combined organics were washed with 200 ml of brine, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The crude product was flash chromatographed on silica gel to give the title compound 5(c).

(d)
(15R)-15-Cyclohexyl-9,11-dideoxy-13,14-dihydro-2',9α-methano-11-methylene-1,4,5,6,16,17,18,19,20-nonanor-3-oxa-3,7-(1',3'-interphenylene)-PGF_1, 15-(tetrahydropyranyl ether)

A degassed solution of methyl phenyl-N-methyl sulfoxmine (1.502 g, 8.88 mmol) in freshly distilled tetrahydrofuran (26.6 ml) was cooled to −78° C. under nitrogen and treated dropwise with 2.9M methylmagnesium chloride in tetrahydrofuran (3.06 ml, 8.88 mmol). The resulting solution was stirred for 35 minutes at −78° C. and for 15 minutes at 0° C., cooled to −78° C. and treated with a solution of the product 5(c) (1.92 g, 4.36 mmol) in freshly distilled tetrahydrofuran (10 ml). Residual ketone starting material was transferred to the reaction with two 4 ml aliquots of freshly distilled tetrahydrofuran. The reaction was stirred for 1.75 hours while the temperature was permitted to go from −78° C. to 0° C., then was stirred for 2 hours at 0° C. The reaction was diluted with ice-cold brine (80 ml) and extracted with diethyl ether (3×110 ml). The ether extracts were washed with brine (80 ml), 0.2M aqueous potassium bisulfate (80 ml), aqueous saturated sodium bicarbonate (80 ml) and brine (80 ml), dried over magnesium sulfate, filtered and concentrated in vacuo to a yellow oil (3.49 g).

A degassed solution of the crude sulfoximine (3.37 g; theory 2.65 g) in freshly distilled tetrahydrofuran (66) was cooled to 0° C. under nitrogen and treated with 50% acetic acid/water (20 ml), followed immediately by aluminum amalgam which had been prepared by washing 20 mesh aluminum powder (3.55 g) with ether (75.5 ml) methanol (2×75.5 ml) then 3.57 g of mercuric chloride in water (122 ml) followed by methanol (75.5 ml) and ether (75.5 ml).

The resulting black suspension was permitted to stir for 2.75 hours while the reaction temperature was allowed to go slowly from 0° C. to 10° C., cooled to 0° C., diluted with ethyl acetate (100 ml) and stirred for 30 minutes at 0° C. The suspension was filtered through celite, and the filtercake was washed with ethyl acetate. The combined filtrate was washed with brine (135 ml) 0.2M aqueous potassium bisulfate (135 ml) and brine (135 ml), dried over sodium sulfate, filtered and concentrated to a yellow oil.

The crude product was chromatographed on silica gel in 5% ethyl acetate in hexane

NMR ($CDCl_3$, TMS): δ 0.73–3.10 (m, 30), 3.27–3.63 (m, 2), 3.77–4.23 (m, 1), 3.80 (S, 3), 4.53–4.73 (m), 4.77–4.97 (m, 2), 6.63–6.90 (m, 2), 7.13 (d of d, 1, $J_1=J_2=7.5$ Hz).

Infrared (film): 2930, 2860, 1652, 1605, 1595, 1475, 1455, 1405, 1260, 1240, 1205, 1135, 1115, 1095, 1080, 1028, 995, 865, 768 cm^{-1}.

TLC (Silica Gel GF): Rf=0.58 in 1% ethyl acetate in hexane.

(e)
15-Cyclohexyl-9,11-dideoxy-13,14-dihydro-2',9α-methano-11-methyl-1,4,5,6,16,17,18,19,20-nonanor-3-oxa-3,7-(interphenylene)-PGF_1, 15-tetrahydropyranyl ether

A degassed solution of the product of 5(d) (0.156 g, 0.36 mmol) in absolute ethanol (11.15 ml) was treated at room temperature under nitrogen with 10% palladium on charcoal (0.052 g) and anhydrous potassium carbonate (0.06 g). The resulting suspension was alterntely degassed and flushed with nitrogen then degassed and flushed with hydrogen and hydrogenated at 50 p.s.i. for 22 hours. The suspension was evacuated and flushed with nitrogen, filtered through 1:1 celite/magnesium sulfate (3 g). The filtercake was washed with ethyl acetate and the combined filtrate was concentrated in vacuo to give 0.155 g of the title compound (e) as a crude oil.

NMR ($CDCl_3$, TMS): δ 0.70–3.21 (m, including doublet, 3, CH_3 at 0.90, J=6 Hz), 3.27–3.70 (m, 2), 3.80–4.30

(m, 1), 3.83, (s, 3), 4.60–4.90 (m, 1), 6.70–7.03 (m, 2), 7.13 (d of d, 1, $J_1=J_2=7.5$ Hz).

TLC (Silica Gel GF): Rf=0.58 in 10% ethyl acetate/hexane.

(f)

15-Cyclohexyl-9,11-dideoxy-13,14-dihydro-2′,9α-methano-11-methyl-1,4,5,6,16,17,18,19,20-nonanor-3-oxa-3,7-(1′,3′-interphenylene)-PGF_1

The crude product of example 5(e) in 8 ml of 4:2:2 acetic acid/water/tetrahydrofuran was stirred at 45° C. under nitrogen for 3 hours, cooled, diluted with brine and extracted with ethyl acetate. The organics were washed with brine, dried over sodium sulfate, filtered and concentrated to a yellow oil.

The crude product was chromatographed on silica gel in 10% ethyl acetate in hexane to give 0.116 g (90%) of the title compound (f).

NMR ($CDCl_3$, TMS): δ 0.07–3.03 (m, 29, including doublet, 3, J=6 Hz), 3.20–3.53 (m, 1), 3.83 (s, 3), 6.63–6.97 (m, 2), 7.13 (d of d, 1, $J_1=J_2=7.5$ Hz).

Infrared (film): 3370, 2930, 2850, 1605, 1595, 1475, 1444, 1375, 1330, 1310, 1260, 1100, 1080, 1045, 970, 895, 775, 735 cm^{-1}.

TLC (Silica Gel GF): Rf=0.51 in 25% ethyl acetate in hexane.

(g)

15-Cyclohexyl-1,2,4,5,6,16,17,18,19,20-decanor-9,11-dideoxy-13,14-dihydro-2′,9α-methano-11-methyl-3-oxa-3,7-(1′,3′-interphenylene)-PGF_1

A degassed solution of diphenylphosphine (0.173 ml, 0.973 mmol), in freshly distilled tetrahydrofuran (5.5 ml) was cooled to 0° C under nitrogen and treated with 1.58M n-butyllithium (0.60 ml, 0.95 mmol). The resulting red solution was stirred for 5 min at 0° C. and for 30 min at room temperature then treated at ambient temperature with a solution of the product of 5(f) (0.116 g, 0.325 mmol) in freshly distilled tetrahydrofuran (1.1 ml). Residual 52 was transferred to the reaction vessel with two 0.27 ml aliquots of freshly distilled tetrahydrofuran, and the reaction was stirred at reflux for 6 hours, cooled to 0° C., treated with diphenylphosphine (0.52 ml, 2.92 mmol) followed by n-butyllithium (1.8 ml, 2.85 mmol). The reaction was stirred for 5 min at 0° C., 20 min at ambient temperature and 18 hours at reflux, cooled to 0° C., acidified with cold, aqueous 1N HCl (12 ml) and diluted with ice-cold brine. The resulting suspension was extracted with ethyl acetate and the organics were washed with brine, dried over sodium sulfate, filtered and concentrated to a semi-solid.

The crude product was chromatographed on silica gel in 15% ethyl acetate in hexane to give 0.106 g (95%) of the title compound (g).

NMR ($CDCl_3$, TMS): δ 0.70–3.00 (m, 29, including doublet, 3 at 0.90, J=6 Hz), 3.23–3.57 (m, 1), 5.33–6.43 (m, 1), 6.63–6.90 (m, 2), 7.07 (d of d, 1).

Infrared (film): 3350, 2930, 2850, 1605, 1595, 1470, 1455, 1380, 1290, 1245, 1085, 1050, 1000, 895, 775, 740 cm^{-1}.

TLC (Silica Gel GF): Rf=0.31 in 25% ethyl acetate in hexane.

(h)

2-Cyano-15-cyclohexyl-2-decarboxy-9,11-dideoxy-13,14-dideoxy-2′,9α-methano-11-methyl-1,4,5,6,17,18,19,20-nonanor-3-oxa-3,7-(1′,3′-interphenylene)-PGF_1 and its 8,9,11,12-tetra-epi-isomer

A degassed solution of the product of 5(g) (0.106 g, 0.309 mmol) in acetone (5 ml) was treated at ambient temperature under nitrogen with anhydrous potassium carbonate (0.915 g, 6.62 mmol), followed by chloroacetonitrile (0.71 ml, 11.25 mmol). The resulting suspension was stirred at reflux for 22 hours and was incomplete. Additional potassium carbonate (0.915 g, 6.62 mmol) and chloroacetonitrile (0.71 ml, 11.25 mmol) was added, and the reaction was stirred at reflux for 24 hours, cooled and diluted with 1:1 brine/water (75 ml). The suspension was extracted with ethyl acetate (3×75 ml), and the combined extracts were washed with brine (2×75 ml), dried over sodium sulfate, filtered and concentrated to a brown oil.

The crude product was chromatographed on silica gel acetone in methylene chloride to give 0.077 g (65%) of title compound (h).

NMR ($CDCl_3$, TMS): δ 0.70–3.03 (m, 29, including doublet, 3, J=6 Hz at 0.90), 3.20–3.53 (m, 1), 4.77 (s, 2), 6.73–7.03 (m, 2), 7.17 (d of d, $J_1=J_2=7.5$ Hz).

Infrared (film): 3400, 2930, 2850, 1605, 1590, 1480, 1475, 1375, 1260, 1235, 1100, 1045, 980, 895, 775, and 740 cm^{-1}.

TLC (Silica Gel GF): Rf=0.80 in 5% acetone in methylene chloride.

(i)

15-Cyclohexyl-9,11-dideoxy-13,14-dihydro-2′,9α-methano-11-methyl-4,5,6,16,17,18,19,20-octanor-3-oxa-3,7-(1′,3′-interphenylene)-PGF_1

A degassed solution of the nitrile compound 5(h) (0.077 g, 0.202 mmol) in anhydrous methanol (4.56 ml) was treated at ambient temperature under nitrogen with 25% aqueous potassium hydroxide (1.4 ml). The resulting solution was stirred at reflux for 5.5 hours, cooled to 0° C., acidified with aqueous 1N HCl (10 ml) and diluted with ice-cold brine (40 ml). The resulting suspension was extracted with ethyl acetate (3×50 ml), and the combined extracts were washed with brine (2×50 ml), dried over sodium sulfate, filtered and concentrated to an off-white solid which was recrystallized from ethyl acetate/hexane to give 0.056 g, (69%) of title compound (i), m.p. 123°–125° C.

NMR ($CDCl_3$, TMS): δ 0.70–3.10 (m, 28, including doublet, 3, J=6 Hz at 0.90), 3.20–3.53 (m, 1), 4.30 (bs, 2), 4.63 (s), 6.45–7.45 (m, 3).

Infrared (mull): 3430, 2970, 2860, 2720, 2580, 1740, SH(1705), 1605, 1590, 1465, 1425, 1380, 1260.

TLC (Silica Gel GF): Rf=0.32 in 1:1 A-IX-cyclohexane.

EXAMPLE 6

(a)

15-Cyclohexyl-9,11-dideoxy-13,14-dihydro-2′,9α-methano-11-methylene-1,4,5,6,16,17,18,19,20-nonanor-3-oxa-3,7-(1′,3′-interphenylene)-PGF_1

A solution of example 5(a) (0.195 g, 0.44 mmol) in acetic acid (6 ml) water (3 ml) and tetrahydrofuran (1.5 ml) was stirred for 3 hours at 45° C. under nitrogen, cooled, diluted with brine (75 ml) and extracted with ethyl acetate (3×75 ml). The organics were washed

with brine (75 ml), aqueous saturated sodium bicarbonate (3×75 ml), and brine (2×75 ml), dried over sodium sulfate, filtered and the filtrate concentrated in vacuo to give a pale yellow oil.

The crude product was chromatographed in 10% ethyl acetate in hexane to afford 0.109 g (70%) of title compound (a).

NMR ($CDCl_3$, TMS): δ 0.73–3.10 (m, 24), 3.20–3.63 (m, 1 3.83 (s, 3), 4.77–5.07 (m, 2), 6.73–6.97 (m, 2), 7.13, (d of d, 1, $J_1=J_2=7.5$ Hz), 7.27–7.80 (m, 1).

Infrared (film): 3400, 3330, 2930, 2860, 1660, 1605, 1595, 1475, 1450, 1335, 1330, 1270, 1255, 1130, 1100, 1070, 1035, 965, 895, 875, 775, 754 cm^{-1}.

TLC (Silica Gel GF): Rf=0.47 in 20% ethyl acetate in hexane.

(b)

15-Cyclohexyl-1,2,4,5,6,16,17,18,19,20-decanor-9,11-dideoxy-13,14-dihydro-2',9α-methano-11-methylene-3-oxa-3,7-(1',3'-interphenylene)-PGF_1

A degassed solution of diphenylphosphine (0.16 ml, 0.90 mmol) in freshly distilled tetrahydrofuran (5 ml) was cooled to 0° C. under nitrogen and treated with 1.58M n-butyllithium in hexane (0.55 ml, 0.87 mmol). The resulting red solution was stirred at 0° C. for 5 minutes and at ambient temperature for 30 minutes then treated at room temperature with a solution of the methyl ester from 6(a) (0.106 g, 0.30 mml) in freshly distilled tetrahydrofuran (1 ml). The reaction was stirred at reflux for 6 hours, cooled to 0° C., treated with diphenylphosphine (0.32 ml, 1.80 mmol) followed by 1.58M n-butyllithium in hexane (1.10 ml, 1.74 mmol). The reaction was stirred at 0° C. for 5 minutes, at ambient temperature for 15 minutes and at reflux for 18 hours. The reaction was cooled to 0° C., diluted with brine (40 ml) containing 5 ml of 1N HCl, and extracted with ethyl acetate (3×35 ml). The organics were washed with brine (3×50 ml), dried over sodium sulfate, filtered and concentrated to a semi-solid.

The crude product was chromatographed on silica gel with 15% ethyl acetate in hexane to give 0.065 g (64%) of title product (b).

NMR ($CDCl_3$, TMS): δ 0.73–3.03 (m, 25), 3.27–3.6-(m, 1), 4.87 (d, 2, J=7 Hz), 5.10–5.97 (bs, 1), 6.70 (2d, 2, J1=J2=7.5 Hz).

Infrared (film): 3340, 2930, 2850, 1710 (weak), 1655, 1590, 1465, 1455, 1445, 1330, 1285, 1060, 1040, 880, 775, 735 cm^{-1}.

TLC (Silica Gel GF): Rf=0.29 in 25% in ethyl acetate in hexane.

(c)

2-Cyano-15-cyclohexyl-2-decarboxy-9,11-dideoxy-13,14-dihydro-2',9α-methano-11-methylene-1,4,5,6,16,17,18,19,20-nonanor-3-oxa-3,7-(1',3'-interphenylene)-PGF_1

A degassed solution of the phenol compound 6(b) (0.065 g, 0.19 mmol) in acetone (3 ml) was treated at ambient temperature under nitrogen with anhydrous potassium carbonate (0.566 g, 4.09 mmol) followed by chloroacetonitrile (0.44 ml, 6.97 mmol). The resulting suspension was stirred at reflux for 29.5 hours at reflux, cooled and diluted with 1:1 brine/water (50 ml). The suspension was extracted with ethyl acetate (3×50 ml), and the organics were washed with brine (2×50 ml), dried over sodium sulfate, filtered and concentrated to a brown oil.

The crude product was chromatographed on silica gel with ethyl acetate in hexane to give 0.067 g (93%) of title compound (c).

NMR ($CDCl_3$, TMS): δ 0.73–3.10 (m, 25), 3.23–3.63 (m, 1), 4.80 (s, 2), 4.87 (d, 2, J=7 HZ), 6.87 (2d, 2, $J_1=J_2=7.5$ Hz), 7.2 (d of d, 1, $J_1=J_2=7.5$ Hz).

Infrared (film): 3400, 3065, 2930, 2860, 1645, 1590, 1475, 1450, 1265, 1235, 1100, 885, 765 cm^{-1}.

TLC (Silica Gel GF): Rf=−0.54 in 5% acetone in methylene chloride.

(d)

15-Cyclohexyl-9,11-dideoxy-13,14-dihydro-2',9α-methano-11-methylene-4,5,6,16,17,18,19,20-octanor-3-oxa-3,7-(1',3'-interphenylene)-PGF_1

A degassed solution of the nitrile compound 6(c) (0.067 g, 0.177 mmol) in absolute methanol (4 ml) was treated at ambient temperature under nitrogen with 25% aqueous potassium hydroxide (1.4 ml). The resulting solution was stirred at reflux for 6 hours, cooled to 0° C., acidified to ~pH 4 with 1N aqueous HCl (9.5 ml) and diluted with brine 35 (35 ml). The aqueous suspension was extracted with ethyl acetate (3×35 ml), and the combined organics were washed with brine (2×45 ml), dried over sodium sulfate, filtered and concentrated to a light yellow solid.

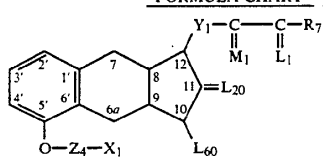
The crude product was recrystallized from ethyl acetate-hexane ~1:10 to give a total of 60 mg (85%) of title compound (d).

NMR ($CDCl_3$, TMS): δ 0.73–3.10 (m, 24), 3.20–3.80 (m, 3), 4.63 (s, 2), 4.80 (d, 2, J=7 HZ), 6.58 (d, 1, J=7.5 Hz), 6.78 (d, 1, J=7.5 Hz), 7.05 (d of d, 1, $J_1=J_2=7.5$ Hz).

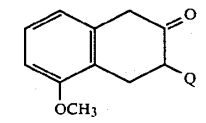
Infrared (nujol mull): 3350, 2930, 2860, 2550, 2430, 1715, 11605, 1590, 1470, 1440, 1375, 1335, 1255, 1235, 1115, 1040, 875 and 770 cm^{-1}.

TLC (Silica Gel GF): Rf=0.43 in 2 A-IX:1 cyclohexane, Rf=0.31 in 1:1-A-IX-cyclohexane.

FORMULA CHART



Formula I and Formula I(a)



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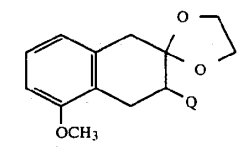

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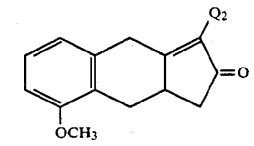

Formula I(d)

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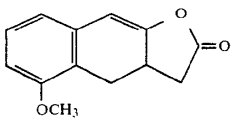
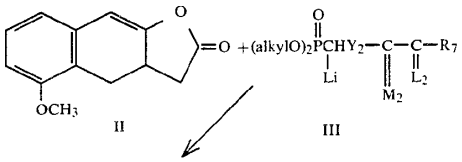
FORMULA CHART

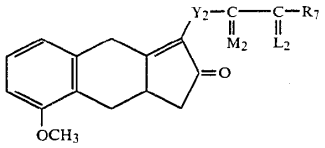


Formula II

CHART A



II III



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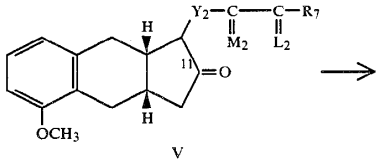

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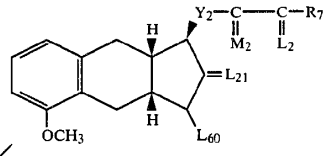

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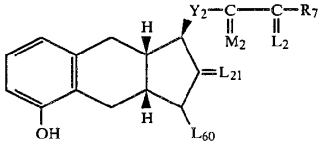

VII

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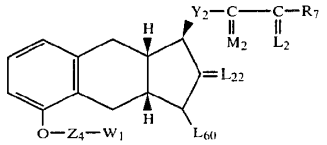
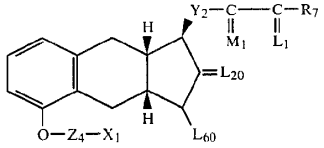
CHART A



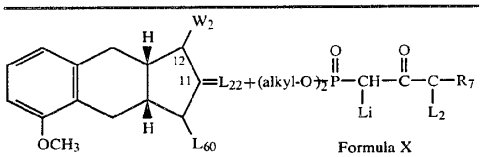
VIII

(a) W_1 = COOalkyl
(b) W_1 = CN
(c) W_1 = COOH



IX

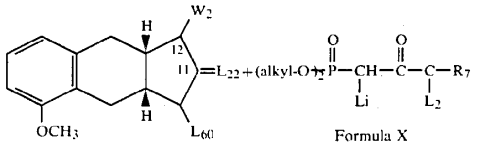
CHART B



Formula X

Formula	W_2
XI	CHO
XII	trans-CH=CH—C(=O)—C(L_2)—R_7
XII(a)	trans-CH=CH—C(=O)—C(L_2)—Rb
XIII	trans-CH=CH—C(M_3)(L_2)—R_7
XIII(a)	trans-CH=CH—C(M_3)(L_2)—Rb
XIV	—CH_2CH_2—C(M_3)(L_2)—Ra
XIV(a)	—CH_2CH_2—C(M_3)(L_2)—Rb
XV	—CH_2CH_2—C(M_3)(L_2)—Rc
XVI	—C≡C—C(M_3)(L_2)—R_7
XVI(a)	—C≡C—C(M_3)(L_2)—Rd

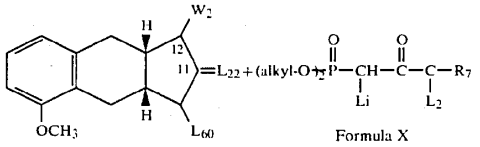
CHART B-continued



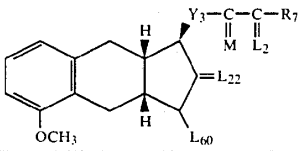
Formula X

Formula	W_2
XVII	$-cis\text{-}CH{=}CH-\underset{\underset{M_3}{\|}}{C}-\underset{\underset{L_2}{\|}}{C}-R_7$
XVII(a)	$-cis\text{-}CH{=}CH-\underset{\underset{M_3}{\|}}{C}-\underset{\underset{L_2}{\|}}{C}-Rd$
XVIII	$-cis\text{-}CH{=}CH-\underset{\underset{O}{\|}}{C}-\underset{\underset{L_2}{\|}}{C}-R_7$

CHART B-continued



Formula X

Formula	W_2
XIX	

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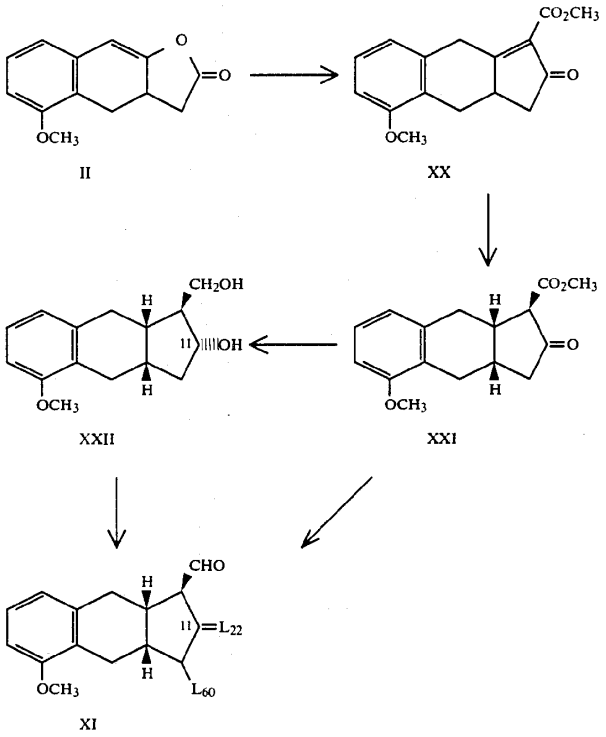
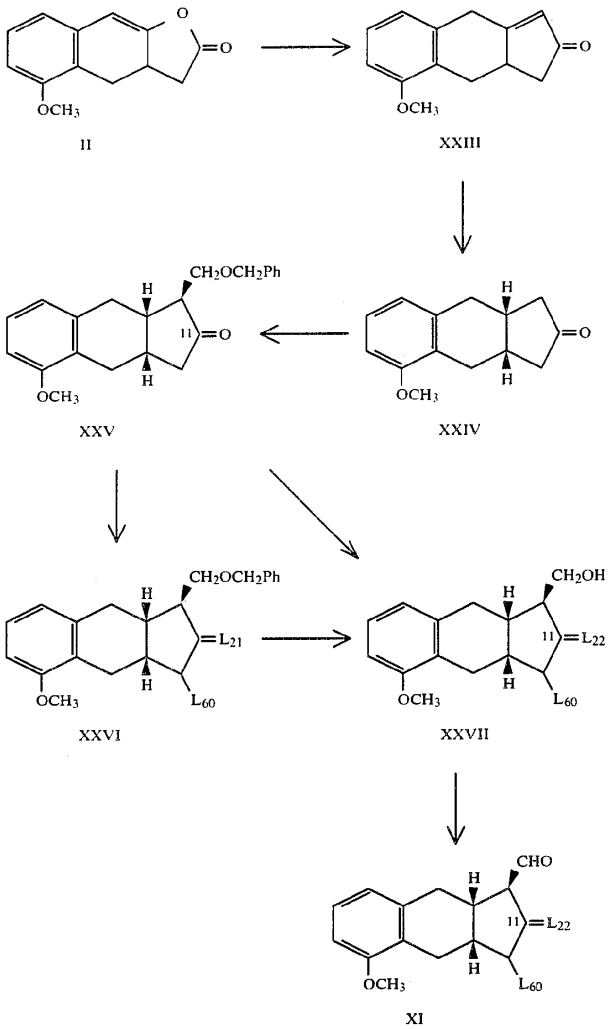


II XX XXI XXII XI

CHART D



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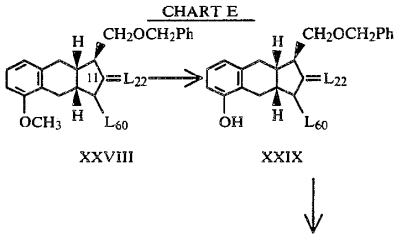

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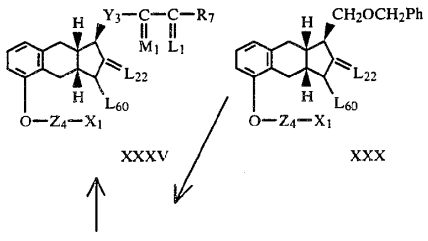

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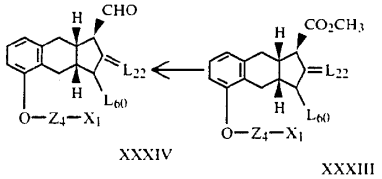
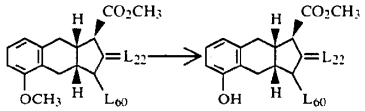
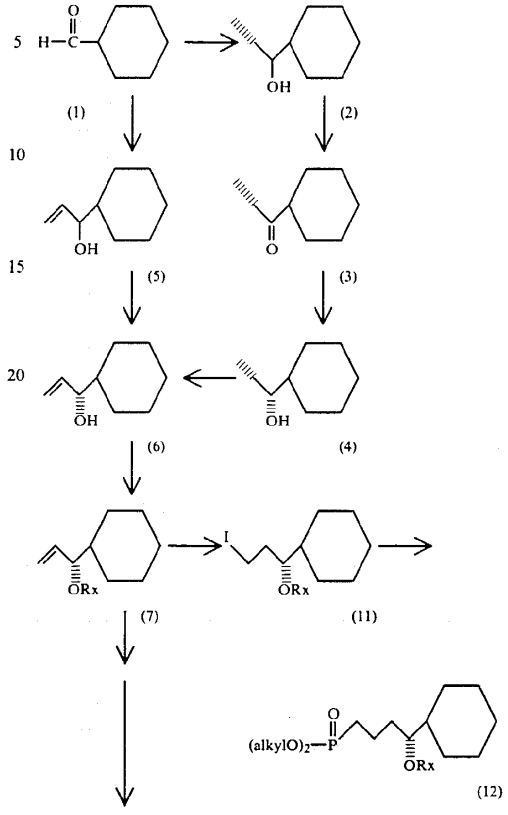


XXXIV XXXIII



XXXI XXXII

CHART G



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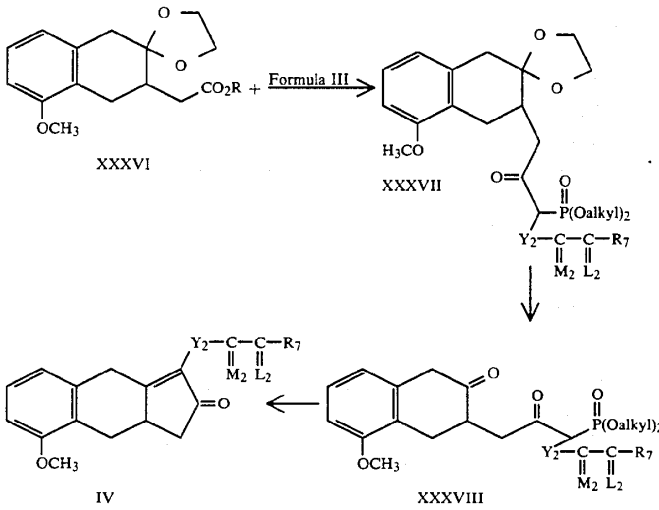

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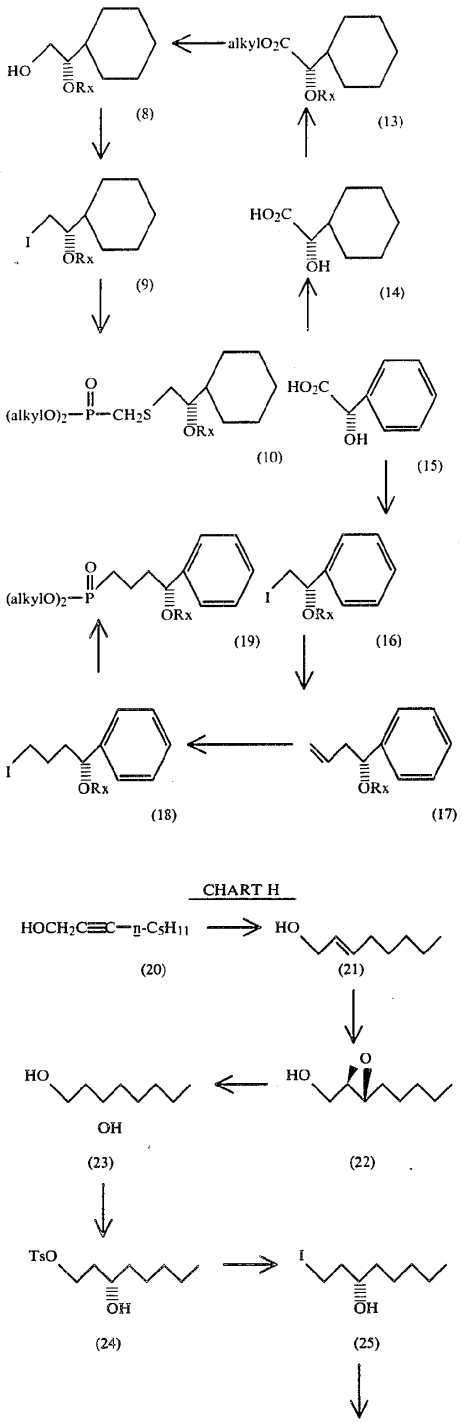

CHART H

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CHART H

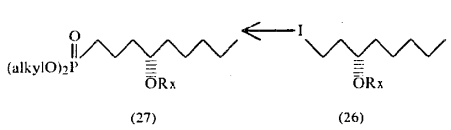

CHART J

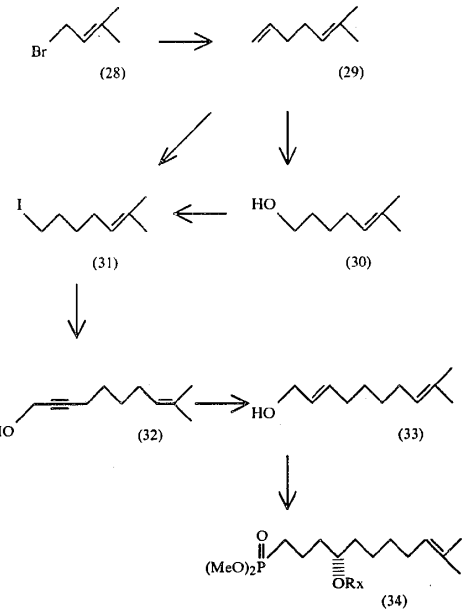

CHART K

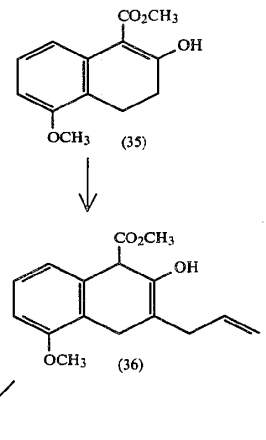

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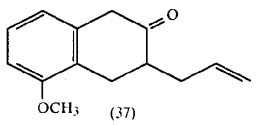
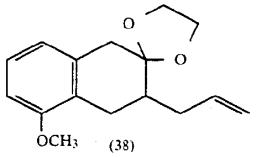
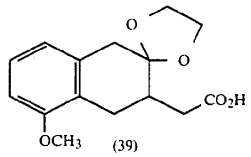
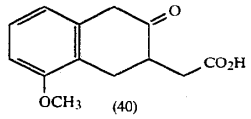
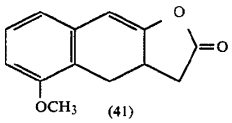
CHART K





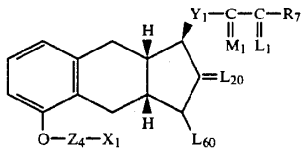






I claim:

1. A compound of the formula



wherein X_1 is

(1) —$COOR_1$, wherein R_1 is
- (a) hydrogen;
- (b) (C_1–C_{12}) alkyl;
- (c) (C_3–C_{10}) cycloalkyl;
- (d) (C_7–C_{12}) aralkyl;
- (e) phenyl, optionally substituted with one, 2 or 3 chloro or (C_1–C_3) alkyl;
- (f) phenyl substituted in the para position by
  - (i) —$NHCOR_{25}$,
  - (ii) —COR_{26},
  - (iii)

or
- (iv) —CH=N—$NHCONH_2$ wherein R_{25} is methyl, phenyl, acetamidophenyl, benzamidophenyl, or —NH_2; R_{26} is methyl, phenyl, —NH_2, or methoxy; R_{54} is phenyl or acetamidophenyl; inclusive; or

(g) a pharmacologically acceptable cation;

(2) —CH_2OH;

(3) —COL_4, wherein L_4 is
- (a) amino of the formula —$NR_{51}R_{52}$ wherein R_{51} and R_{52} are
  - (i) hydrogen,
  - (ii) (C_1–C_{12}) alkyl,
  - (iii) (C_3–C_{10}) cycloalkyl,
  - (iv) (C_7—C_{12}) aralkyl,
  - (v) phenyl, optionally substituted with one 2 or 3 chloro, (C_1–C_3) alkyl, hydroxy, carboxy, (C_2–C_5) alkoxycarbonyl, or nitro,
  - (vi) (C_2–C_5) cyanoalkyl,
  - (vii) (C_2–C_5) carboxyalkyl,
  - (viii) (C_2–C_5) carbamoylalkyl,
  - (ix) (C_3–C_6) acetylalkyl,
  - (x) (C_7–C_{11}) benzoalkyl, optionally substituted by one, 2 or 3 chloro, (C_1–C_3) alkyl, hydroxy, (C_1–C_3) alkoxy, carboxy, (C_2–C_5) alkoxy carbonyl, or nitro,
  - (xi) pyridyl, optionally substituted by one, 2 or 3 chloro, (C_1–C_3) alkyl, or (C_1–C_3) alkoxy,
  - (xii) (C_6–C_9) pyridylalkyl optionally substituted by one, 2 or 3 chloro, (C_1–C_3) alkyl, hydroxy, or (C_1–C_3) alkoxy,
  - (xiii) (C_1–C_4) hydroxyalkyl,
  - (xiv) (C_1–C_4) dihydroxyalkyl,
  - (xv) (C_1–C_4) trihydroxyalkyl, with the proviso that not more than one of R_{51} or R_{52} is other than hydrogen or alkyl;
- (b) cycloamino selected from the group consisting of pyrolidino, piperidino, morpholino, piperazino, hexamethylenimino, pyrrolino, or 3,4-didehydropiperidinyl optionally substituted by one or 2 (C_1–C_{12}) alkyl of one to 12 carbon atoms, inclusive;
- (c) carbonylamino of the formula —$NR_{53}COR_{51}$ wherein R_{53} is hydrogen or (C_1–C_4) alkyl and R_{51} is other than hydrogen, but otherwise defined as above;
- (d) sulfonylamino of the formula —$NR_{53}SO_2R_{51}$, wherein R_{51} and R_{53} are defined in (c);

(4) —$CH_2NL_2L_3$ wherein L_2 and L_3 are hydrogen or (C_1–C_4) alkyl, being the same or different, or the pharmacologically acceptable acid addition salts thereof when X_1 is —$CH_2NL_2L_3$;

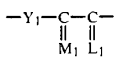
(5) —CN;

wherein Z_4 is —CH_2—, —CH_2CH_2—, —CF_2—, or —CH_2CF_2;

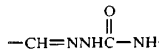
wherein L_{20} is α-OH,β-H; α-H,β-OH; H,H; α-CH_3,β-H; α-CH_2OH,β-H; =O; or =CH_2; wherein L_{60} is hydrogen or L_{20} and L_{60} taken together form a double bond between positions 10 and 11;

wherein Y_1 is —CH_2CH_2—, —SCH_2—, —C≡C—, trans —CH=CH—, or cis —CH=CH—;

wherein



taken together is



wherein M_1 is α-H:β-H; =O; α-OH:β-R_5; or α-R_5:β-OH; wherein R_5 is hydrogen or methyl;

wherein L_1 is

(1) α-R_3:β-R_4, α-R_4:β-R_3, or mixtures thereof wherein R_3 and R_4 are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R_3 and R_4 is fluoro only when the other is hydrogen or fluoro;

(2) or when M_1 is α-H:β-H L_1 is α-OH:β-R_3, α-R_3:β-OH; or a mixture of α-OH:β-R_3 and α-R_3:β-OH wherein R_3 is hydrogen, methyl, vinyl, or ethynyl;

wherein R_7 is

(1) $-C_mH_{2m}CH_3$, wherein m is an integer from one to 8, inclusive;

(2) phenoxy optionally substituted by one, 2 or 3 chloro, fluoro, trifluoromethyl, (C_1-C_3) alkyl, or (C_1-C_3) alkoxy, with the proviso that not more than two substituents are other than alkyl with the proviso that R_7 is phenoxy or substituted phenoxy, only when R_3 and R_4 are hydrogen or methyl, being the same or different;

(3) phenyl, benzyl, phenylethyl, or phenylpropyl optionally substituted on the aromatic ring by one, 2 or 3 chloro, fluoro, trifluoromethyl, (C_1-C_3) alkyl, or (C_1-C_3) alkoxy, with the proviso, that not more than two substituents are other than alkyl;

(4) cis $-CH=CH-CH_2CH_3$;

(5) $-(CH_2)_2-CH(OH)-CH_3$;

(6) $-(CH_2)_3-CH=C(CH_3)_2$;

(7) $-(CH_2)_2-CH=CH_2$;

wherein

taken together is

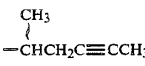
(1) (C_4-C_7) cycloalkyl optionally substituted by one to 3 (C_1-C_5) alkyl or (C_1-C_5) alkenyl;

(2) 2-(2-furyl)ethyl;

(3) 2-(3-thienyl)ethoxy;

(4) 3-thienyloxymethyl;

(5)



and the individual optical enantiomers thereof with the proviso that each compound is other than one formed when the substituents X_1, Z_4, L_{20}, Y_1, L_1, and R_7 have the following meanings:

wherein X_1 is as defined above;

wherein Z_4 is $-CH_2-$, $-CF_2$, or $-CH_2CF_2-$;

wherein L_{20} is α-OH,β-H; α-H,β-OH; H,H; α-CH_2OH,β-H;

wherein Y_1 is $-CH_2CH_2-$, $-C\equiv C-$, trans $-CH=CH-$, or cis $-CH=CH-$;

wherein M_1 is α-OH:β-R_5, or α-R_5:β-OH wherein R_5 is hydrogen or methyl;

wherein L_1 is

(1) α-R_3:β-R_4, α-R_4:β-R_3, or a mixture of α-R_3:β-R_4, wherein R_3 and R_4 are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R_3 and R_4 is fluoro only when the other is hydrogen or fluoro; and

wherein R_7 is as defined above except R_7 is other than $-(CH_2)_2-CH=CH_2$ and $C(L_1)R_7$ taken together is as defined above except $C(L_1)R_7$ is other than (C_4-C_7) cycloalkyl optionally substituted with (C_1-C_5) alkenyl.

2. A compound of claim **1** wherein M_1 is α-H,β-OH; α-OH,β-H, or H,H.

3. A compound of claim **2** wherein L_{20} is α-CH_3,β-H or α-OH,β-H.

4. A compound of claim **3** wherein Z_4 is $-CH_2-$.

5. A compound of claim **3** wherein X_1 is $COOR_1$.

6. A compound of claim **5** wherein R_1 is hydrogen, or (C_1-C_{12}) alkyl or a pharmaceutically acceptable cation.

7. A compound of claim **3** wherein R_7 is $-C_mH_{2m}CH_3$ wherein m is an integer from one to 8 inclusive, $-(CH_2)_2-CH=CH_2$, or $-(CH_2)_3-CH=CH(CH_3)_2$.

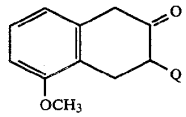
8. A compound of claim **3** wherein $-C(L_1)R_7$ taken together is (C_4-C_7) cycloalkyl.

9. A compound of claim **1** which is (11RS,15R)-15-cyclohexyl-9,11-dideoxy-13,14-dihydro-2',9α-methano-11-methyl-4,5,6,16,17,18,18,20-octanor-3-oxa-3,7-(1',3'-interphenylene)PGF_1 and salts and isomers thereof.

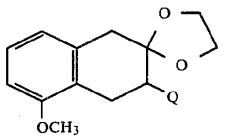
10. A compound of claim **1** which is (15R)-15-cyclohexyl-9,11-dideoxy-13,14-dihydro-2',9α-methano-11-methylene-4,5,6,16,17,18,19,20-octanor-3-oxa-3,7-(1',3'-interphenylene)PGF_1 and salts and isomers thereof.

11. A compound of formula

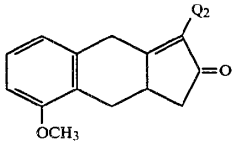
Formula I(b)



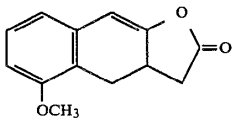
Formula I(c)



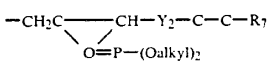
Formula I(d)



Formula II



wherein Q is cis-$-CH_2CH=CH_2$, $-CH_2COOH$, or



wherein alkyl has from 1 to 4 carbon atoms, Y_2 is $-SCH_2-$ or CH_2CH_2-, M_2 is α-H:β-OR_x, α-OR_x:β-H or H,H wherein R_x is a protecting group; L_2 is α-R_3:β-R_4, α-R_4:β-R_3 or mixture thereof wherein R_3 and R_4 are hydrogen, methyl or fluoro, being the same or different with the proviso that one of R_3 and R_4 is fluoro only when the other is hydrogen or fluoro, or when M_2 is H,H, L_2 is α-OR_x:β-R_3, α-R_3:β-OR_x, or a mixture thereof wherien R_3 is hydrogen, methyl, vinyl or ethynyl and R_x is a protecting group; and R_7

(1) $-C_mH_{2m}CH_3$, wherein m is an integer from one to 8, inclusive;

(2) phenoxy optionally substituted by one, 2 or 3 chloro, fluoro, trifluoromethyl, (C_1-C_3) alkyl, or (C_1-C_3) alkoxy, with the proviso that not more than two substituents are other than alkyl with the proviso that R_7 is phenoxy or substituted phenoxy, only when R_3 and R_4 are hydrogen or methyl, being the same or different;

(3) phenyl, benzyl, phenylethyl, or phenylpropyl optionally substituted on the aromatic ring by one, 2 or 3 chloro, fluoro, trifluoromethyl, (C_1-C_3) alkyl, or (C_1-C_3) alkoxy, with the proviso that not more than two substituents are other than alkyl;

(4) cis-$CH=CH-CH_2CH_3$;

(5) $-(CH_2)_2-CH(OH)-CH_3$;

(6) $-(CH_2)_3-CH=C(CH_3)_2$;

(7) $-C_pH_{2p}CH=CH_2$ wherein p is an integer from 2 to 6, inclusive;

or C—R_7 taken together is

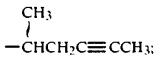
(1) (C_4-C_7) cycloalkyl optionally substituted by one to 3 (C_1-C_5) alkyl, or (C_1-C_5)alkenyl;

(2) 2-(2-furyl)ethyl;

(3) 2-(3-thienyl)ethoxy;

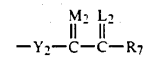
(4) 3-thienyloxymethyl; or

(5)



and

Q_2 is



wherein Y_2, M_2, L_2 and R_7 are as defined above or Q_2 is $-CO_2$ alkyl wherein alkyl has from 1 to 4 carbon atoms.

* * * * *

UNITED STATES PATENT OFFICE

CERTIFICATE OF CORRECTION

Patent No. 4,668,814 Dated 26 May 1987

Inventor(s) Paul A. Aristoff

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

Column 1, line 9, should read:

CROSS REFERENCE TO RELATED APPLICATIONS: This application is a C-I-P of U.S. application Serial No. 587,337, filed March 8,]984, now abandoned.

Signed and Sealed this

Ninth Day of August, 1988

Attest:

DONALD J. QUIGG

Attesting Officer

Commissioner of Patents and Trademarks

[redacted]

UNITED THERAPEUTICS CORP

FORM 10-K
(Annual Report)

Filed 02/24/15 for the Period Ending 12/31/14

Address	1040 SPRING ST SILVER SPRING, MD 20910
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Symbol	UTHR
SIC Code	2834 - Pharmaceutical Preparations
Industry	Biotechnology & Drugs
Sector	Healthcare
Fiscal Year	12/31

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ITEM 8. FINANCIAL STATEMENTS AND SUPPLEMENTARY DATA

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UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549

FORM 10-K

(Mark One)

☒ **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934.**

For the fiscal year ended December 31, 2014

OR

☐ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934.**

For the transition period from to

Commission file number 0-26301

United Therapeutics Corporation
(Exact Name of Registrant as Specified in Its Charter)

Delaware	**52-1984749**
(State or Other Jurisdiction of Incorporation or Organization)	(I.R.S. Employer Identification No.)
1040 Spring Street, Silver Spring, MD	**20910**
(Address of Principal Executive Offices)	(Zip Code)

(301) 608-9292
Registrant's Telephone Number, Including Area Code

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	**Name of each exchange on which registered**
Common Stock, par value $.01 per share and associated preferred stock purchase rights	NASDAQ Global Select Market

Securities registered pursuant to Section 12(g) of the Act:

None
(Title of Class)

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ☒ No ☐

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes ☐ No ☒

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Website, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes ☒ No ☐

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§229.405 of this chapter) is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company. See definitions of "large accelerated filer," "accelerated filer," and "smaller reporting company" in Rule 12b-2 of the Exchange Act. (Check one):

Large accelerated filer ☒	Accelerated filer ☐	Non-accelerated filer ☐ (Do not check if a smaller reporting company)	Smaller reporting company ☐

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act). Yes ☐ No ☒

The aggregate market value of the Common Stock held by non-affiliates of the registrant, based on the closing price on June 30, 2014, as reported by the NASDAQ Global Select Market was approximately $3,053,391,425.

The number of shares outstanding of the issuer's common stock, par value $0.01 per share, as of February 17, 2015, was 46,665,517.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive proxy statement for the registrant's 2015 annual meeting of shareholders scheduled to be held on June 26, 2015, are incorporated by reference in Part III of this Form 10-K.

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PART I

ITEM 1. BUSINESS

United Therapeutics Corporation is a biotechnology company focused on the development and commercialization of innovative products to address the unmet medical needs of patients with chronic and life-threatening conditions.

Our key therapeutic products and product candidates include:

- *Prostacyclin Analogues.* Prostacyclin analogues are stable synthetic forms of prostacyclin, an important molecule produced by the body that has powerful effects on blood vessel health and function. Our lead product is Remodulin ® (treprostinil) Injection (Remodulin), which is administered subcutaneously (under the skin) or intravenously (in the vein) for the treatment of pulmonary arterial hypertension (PAH) to diminish symptoms associated with exercise. The United States Food and Drug Administration (FDA) approved Remodulin for subcutaneous and intravenous administration in 2002 and 2004, respectively. Outside the United States, Remodulin is approved in 39 countries, most of which have approved both routes of administration. We are developing new technologies to make Remodulin delivery more convenient, such as implantable pump systems for intravenous Remodulin and pre-filled, semi-disposable pumps for subcutaneous Remodulin. In 2009, the FDA approved Tyvaso ® (treprostinil) Inhalation Solution (Tyvaso), an inhaled prostacyclin therapy for the treatment of PAH to improve exercise ability. In December 2013, the FDA approved Orenitram ® (treprostinil) Extended-Release Tablets (Orenitram), which commenced sales during the second quarter of 2014. Our wholly-owned subsidiary, Lung Biotechnology Inc., is developing another oral prostacyclin analogue for the treatment of PAH called esuberaprost.

- *Phosphodiesterase Type 5 (PDE-5) Inhibitor.* PDE-5 inhibitors act to inhibit the degradation of cyclic guanosine monophosphate (cyclic GMP) in cells. Cyclic GMP is activated by nitric oxide (NO), a naturally occurring substance in the body that mediates the relaxation of vascular smooth muscle. Our PDE-5 inhibitor is Adcirca ® (tadalafil) tablets (Adcirca), a once-daily oral therapy for the treatment of PAH. We acquired exclusive U.S. commercialization rights to Adcirca from Eli Lilly and Company (Lilly) in 2008. In 2009, the FDA approved Adcirca for the treatment of PAH to improve exercise ability.

- *Monoclonal Antibody (MAb).* MAbs act by targeting tumor-associated antigens located on the surfaces of cancer cells to activate a patient's immune system against the cancer cells. We are developing the antibody Ch14.18 MAb for the treatment of neuroblastoma, under an agreement with the National Cancer Institute (NCI) of the United States National Institutes of Health (NIH). In December 2013, our marketing authorization application (MAA) for this antibody was accepted for review by the European Medicines Agency (EMA), and in June 2014, the FDA accepted our biologics license application (BLA) for review.

- *Glycobiology Antiviral Agents.* Glycobiology antiviral agents are a novel class of small, sugar-like molecules that have shown preclinical indications of efficacy against a broad range of viruses. In 2011, we were awarded a contract from the National Institute of Allergy and Infectious Diseases (NIAID) of the NIH for studies directed at the development of a broad spectrum antiviral drug based on our glycobiology antiviral platform. During the third quarter of 2014, we commenced a phase I clinical trial of our lead antiviral candidate, an alpha-glucosidase inhibitor called UV-4B.

- *Cell-Based Therapy.* In 2011, we entered into a license agreement with Pluristem Ltd. (Pluristem) to develop and commercialize its cell-based product known as PLacental eXpanded (PLX) cells for the treatment of PAH. We commenced a phase I clinical study in Australia in 2013.

- *Lung Transplantation.* The only reported cure for PAH is a lung transplant. Using the xenotransplantation technology we acquired through our acquisition of Revivicor Inc. (Revivicor) and several regenerative medicine technologies that we have licensed, we are in the early preclinical stage of developing engineered lungs and lung tissue for transplant into patients suffering from PAH and other lung diseases. We are also developing technologies to increase the supply of donated lungs through ex-vivo perfusion of donor lungs prior to transplant.

We devote most of our research and development resources to developing these key products and product candidates.

We generate revenues from the sale of Remodulin, Tyvaso, Adcirca and Orenitram (which we refer to as our commercial products). We commenced sales of Orenitram during the second quarter of 2014. We expect that sales of our existing commercial products will continue to be our primary sources of revenues for the next several years. Our sales and marketing staff supports the availability of our commercial products in the countries in which they are approved. These efforts are supplemented by contracted specialty pharmaceutical distributors in the United States and other distributors internationally.

United Therapeutics was incorporated in Delaware in June 1996. Our principal executive offices are located at 1040 Spring Street, Silver Spring, Maryland 20910 and at 55 T.W. Alexander Drive, Research Triangle Park, North Carolina 27709.

Unless the context requires otherwise or unless otherwise noted, all references in this Annual Report on Form 10-K to "United Therapeutics" and to the "company", "we", "us" or "our" are to United Therapeutics Corporation and its subsidiaries.

Our Products

Our product portfolio includes the following:

Product	Mode of Delivery	Indication	Current Status	Our Territory
Remodulin	Continuous subcutaneous	PAH	Commercial in the U.S., most of Europe*, Argentina, Brazil, Canada, Chile, China, Israel, Japan, Mexico, Peru, Puerto Rico, Saudi Arabia, South Korea, Taiwan and Venezuela	Worldwide
Remodulin	Continuous intravenous	PAH	Commercial in the U.S., most of Europe*, Argentina, Canada, China, Israel, Japan, Mexico, Peru, Puerto Rico, Saudi Arabia, South Korea and Switzerland	Worldwide
Tyvaso	Inhaled	PAH	Commercial in the U.S. and Puerto Rico; also approved in Israel	Worldwide
Adcirca	Oral	PAH	Commercial in the U.S. and Puerto Rico	United States and Puerto Rico
Orenitram	Oral	PAH	Commercial in the U.S.	Worldwide
Ch14.18 MAb	Intravenous	High-risk neuroblastoma	MAA filed with the EMA in December 2013; BLA filed with the FDA in June 2014	Worldwide
Remodulin Implantable System	Continuous intravenous via implantable pump	PAH	PMA submitted by Medtronic Inc. to the FDA in December 2014. We submitted an NDA to the FDA in January 2015	United States, United Kingdom, Canada, France, Germany, Italy and Japan
Orenitram Combination Therapy	Oral	PAH	Phase III	Worldwide

Product	Mode of Delivery	Indication	Current Status	Our Territory
Esuberaprost	Oral	PAH	Phase III	North America, Europe, Mexico, South America, Egypt, India, South Africa and Australia
Ex-Vivo Lung Perfusion	Pre-transplant service providing extended preservation and assessment of donor lungs.	End-stage lung disease	Phase III	U.S.
PLX Cells	Intravenous	PAH	Phase I	Worldwide
UV-4B	Oral	Dengue and influenza	Phase I	Worldwide
Remodulin	Subcutaneous via pre-filled, semi-disposable pump	PAH	Preclinical	Worldwide
Glycobiology Antiviral Agents	Oral	Broad-spectrum agents against viral infectious diseases	Preclinical	Worldwide
Lung Transplantation	Various	End-stage lung disease	Preclinical	Worldwide

* We have obtained approval for subcutaneous and intravenous Remodulin in 24 member countries of the European Economic Area (EEA), as well as other non-EEA countries in Europe, and have received pricing approval in most of these countries.

Products to Treat Cardiopulmonary Diseases

Pulmonary Arterial Hypertension

PAH is a life-threatening disease that affects the blood vessels in the lungs and is characterized by increased pressure in the pulmonary arteries, which are the blood vessels leading from the heart to the lungs. The elevated pressure in the pulmonary arteries strains the right side of the heart as it pumps blood to the lungs. This eventually leads to right heart failure and, ultimately, death. PAH is characterized by structural changes in blood vessel walls, aggregation of platelets and alteration of smooth muscle cell function. We believe that PAH affects about 500,000 individuals worldwide. We have seen increases in the number of people diagnosed with the disease, but due to the rarity of the disease and the complexity of diagnosing it, only a small fraction of patients with PAH are being treated.

Currently, FDA-approved therapies for PAH focus on three distinct molecular pathways that have been implicated in the disease process: the prostacyclin pathway, the NO pathway, and the endothelin (ET) pathway. The three classes of drugs that target these three pathways are:

- *Prostacyclin Analogues.* Patients with PAH have been shown to have reduced levels of prostacyclin, a naturally occurring substance that has the effect of relaxing the pulmonary blood vessels, preventing platelet aggregation, and inhibiting the proliferation of smooth muscle cells in the pulmonary vessels. Therefore, drugs that mimic the action of prostacyclin, known as prostacyclin analogues, are established PAH treatments.

- *PDE-5 Inhibitors.* Patients with PAH have also been shown to have reduced levels of the enzyme responsible for producing NO, a naturally occurring substance in the body that causes relaxation of the pulmonary blood vessels. NO produces this effect by increasing intracellular levels of cyclic GMP. Therefore, another established therapeutic approach has been to inhibit the degradation of cyclic GMP, using drugs that are known as PDE-5 inhibitors.

- *Endothelin Receptor Antagonists.* PAH patients have also been shown to have elevated levels of endothelin-1, a naturally occurring substance in the body that causes constriction of, and structural changes to, the pulmonary blood vessels. Therefore, another established therapeutic approach has been to block the action of endothelin with drugs that are known as endothelin receptor antagonists (ETRAs).

Because any or all of the three pathways may be therapeutic targets in a patient, these three classes of drugs are used alone or in combination to treat patients with PAH. We currently market drugs in two of these three classes. Remodulin, Tyvaso and Orenitram are prostacyclin analogues, and Adcirca is a PDE-5 inhibitor.

Remodulin

One of our lead products for treating PAH is Remodulin, the active pharmaceutical ingredient of which is a prostacyclin analogue known as treprostinil. We sell Remodulin to specialty pharmaceutical distributors in the United States and to pharmaceutical distributors internationally. We recognized approximately $553.7 million, $491.2 million and $458.0 million in Remodulin revenues, representing 43 percent, 44 percent and 50 percent of our total net revenues for the years ended December 31, 2014, 2013 and 2012, respectively. The FDA approved Remodulin as a continuous subcutaneous infusion therapy in 2002, and as a continuous intravenous infusion therapy in 2004. Remodulin is indicated to treat patients with PAH (World Health Organization (WHO) Group 1), which includes multiple etiologies such as idiopathic and heritable PAH, as well as PAH associated with connective tissue diseases, to diminish symptoms associated with exercise. Studies establishing effectiveness included patients with New York Heart Association (NYHA) Functional Class II-IV (moderate to severe) symptoms. In 2006, the FDA expanded its approval to include transition of patients to Remodulin from Flolan ®, the first FDA-approved prostacyclin therapy for PAH. In 2007, the results of a prospective, open-label study demonstrated that stable patients with PAH can be safely transitioned from Flolan to intravenous Remodulin using a rapid switch protocol.

Outside of the United States, Remodulin is approved for the treatment of PAH in 39 countries by continuous subcutaneous administration and in 33 countries by continuous intravenous administration. Applications for approval of both subcutaneous and intravenous Remodulin are under review in other countries. We continue to work toward commercializing Remodulin in new territories.

We believe Remodulin has many qualities that make it an appealing alternative to competitive therapies. Remodulin is stable at room temperature, so it does not need to be cooled during infusion and patients do not need to use cooling packs or refrigeration to keep it stable. Treprostinil is highly soluble, which enables us to produce Remodulin in highly concentrated solutions. This allows therapeutic concentrations of Remodulin to be delivered at very low flow rates via miniaturized infusion pumps for both subcutaneous and intravenous infusion. Remodulin can be continuously infused for up to 48 hours intravenously or 72 hours subcutaneously before refilling the infusion pump, and is packaged as an aqueous solution so patients do not have to reconstitute the drug before refilling their pumps.

In 2008, the FDA approved Teva Pharmaceuticals USA, Inc.'s (Teva) version of generic epoprostenol (the active ingredient in Flolan) for the treatment of PAH via intravenous delivery. Also in 2008, the FDA approved another intravenous version of epoprostenol, which is currently marketed by Actelion Pharmaceuticals Ltd (Actelion) under the name Veletri ®. Actelion also markets Tracleer ® and Opsumit ®, both ETRAs, and Ventavis ®, an inhaled prostacyclin. Flolan and generic epoprostenol are not stable at room temperature, but Veletri may be stable at room temperature depending on its concentration. Flolan, generic epoprostenol, and Veletri have shorter half-lives than Remodulin, require mixing and daily pump refills, and are not administered with miniaturized infusion pumps. None of these products may be administered via subcutaneous infusion.

There are serious adverse events associated with Remodulin. When infused subcutaneously, Remodulin causes varying degrees of infusion site pain and reaction (redness and swelling) in most patients. Patients who cannot tolerate the infusion site pain related to use of subcutaneous Remodulin may instead use intravenous Remodulin. Intravenous Remodulin is delivered continuously through a surgically implanted central venous catheter, similar to Flolan, Veletri and generic epoprostenol. Patients who receive therapy through implanted venous catheters have a risk of developing blood stream infections and a serious systemic infection known as sepsis. Other common side effects associated with both subcutaneous and intravenous Remodulin include headache, diarrhea, nausea, jaw pain, vasodilation and edema.

International Regulatory Review of Subcutaneous and Intravenous Remodulin

Remodulin is approved in 39 countries outside the United States. In 33 of these countries, it is approved for both subcutaneous and intravenous use. In the other six countries, Remodulin is approved for subcutaneous use only.

We used the mutual recognition process, described more fully below in *Governmental Regulation—Marketing Pharmaceutical Products Outside the United States* , to obtain approval of subcutaneous Remodulin in most countries in the European Union (EU) in 2005. Our reference member state for the mutual recognition process was the French regulatory agency, *L'Agence Nationale de Sécurité du Médicament et des Produits de Santé* (ANSM). In 2011, we received regulatory approval for intravenous Remodulin by ANSM, which allows us to market intravenous Remodulin in the EEA countries where subcutaneous Remodulin has already been approved and where we have obtained pricing approval and approval of our risk management plan (RMP).

In Europe, an RMP is routinely required as part of the regulatory approval process for new medicines and also for significant variations involving a change to the route of administration, formulation or indication. For intravenous Remodulin, we have implemented an RMP focused on minimizing the known risks of central venous catheter-related blood stream infections associated with intravenous administration. To date, our RMP for intravenous Remodulin has been approved in 20 EEA countries, with pricing approval in 16 of these.

In March 2013, the China Food and Drug Administration approved intravenous and subcutaneous Remodulin for PAH in the People's Republic of China. In March 2014, Japan's Ministry of Health, Labor and Welfare approved Remodulin for the treatment of PAH by subcutaneous and intravenous administration. Remodulin is sold in Japan under the brand name Treprost™. In the second and third quarters of 2014, we commenced sales of Remodulin to our distributors in China and Japan, respectively.

Intravenous Remodulin Administered via Implantable Pump

A majority of the patients who die of PAH in the United States each year have not initiated treatment with an infused prostacyclin analogue, which is a complex and burdensome form of medical therapy. In 2009, we entered into an agreement with exclusive rights in the United States, UK, Canada, France, Germany, Italy and Japan, with Medtronic, Inc. (Medtronic) to develop its proprietary intravascular infusion catheter to be used with Medtronic's SynchroMed ® II implantable infusion pump and related infusion system components (together referred to as the Remodulin Implantable System) in order to deliver Remodulin for the treatment of PAH. If the Remodulin Implantable System is successful, it could reduce many of the patient burdens associated with infused prostacyclin analogues. In September 2013, Medtronic released the results of the *DelIVery* clinical trial, which we funded, in order to study the safety of the Remodulin Implantable System while administering Remodulin. The primary endpoint of the study was to demonstrate a rate of catheter-related complications below 2.5 per 1,000 patient-days while using the Remodulin Implantable System to deliver Remodulin.

Medtronic informed us that this primary objective was met ($p<0.0001$). In December 2014, Medtronic completed other stability, compatibility and technical assessments of the Remodulin Implantable System, including modifications to its hardware and software, and filed a premarket approval application (PMA) seeking FDA approval for the catheter and labeling changes. Medtronic is responsible for addressing any FDA requests for additional information concerning the Remodulin Implantable System. In January 2015, we submitted new labeling requesting FDA approval to allow the use of Remodulin with the Remodulin Implantable System. The FDA has indicated that our submission will be treated as a new NDA.

Subcutaneous Remodulin Administered via Pre-Filled, Semi-Disposable Pump

In December 2014, we entered into an exclusive agreement with DEKA Research & Development Corp. (DEKA) to develop a pre-filled, semi-disposable pump system for subcutaneous delivery of Remodulin. Under the terms of the agreement, we will fund all of the development costs related to the semi-disposable pump system and will pay product fees and a single-digit royalty to DEKA based on commercial sales of the system and the Remodulin sold for use with the system. Our goal is to be in a position to receive FDA approval for this delivery system by the end of 2018.

Tyvaso

We commenced commercial sales of Tyvaso in the United States in 2009. We sell Tyvaso to the same specialty pharmaceutical distributors in the United States that distribute Remodulin. For the years ended December 31, 2014, 2013 and 2012, we recognized approximately $463.1 million, $438.8 million and $325.6 million in Tyvaso revenues, representing 36 percent, 39 percent and 36 percent, respectively, of our total net revenues.

Tyvaso, which contains the active ingredient treprostinil, is administered four times a day by inhaling up to nine breaths during each two- to three-minute treatment session. Tyvaso is required to be administered using our proprietary Tyvaso Inhalation System, which consists of an ultra-sonic nebulizer that provides a dose of Tyvaso on a breath-by-breath basis. A single ampule containing Tyvaso is emptied into the Tyvaso Inhalation System once per day, so the Tyvaso Inhalation System only needs to be cleaned once each day.

Tyvaso was generally well tolerated in our trials, during which adverse events appeared to be similar to those previously reported for treprostinil or due to administration by inhalation. The most common adverse events were transient cough, headache, nausea, dizziness and flushing. We completed an open-label study in the United States to investigate the clinical effects of switching patients from Ventavis to Tyvaso. Patients in this study saved an average of approximately 1.4 hours per day when administering Tyvaso compared to Ventavis.

Ventavis is the only other FDA-approved inhaled prostacyclin analogue and is marketed by Actelion in the United States and by Bayer Schering Pharma AG (Bayer) in Europe. The active ingredient in Ventavis is iloprost. Patients need to inhale Ventavis six to nine times per day via a nebulizer. According to its package insert, each Ventavis inhalation consists of four to ten minutes of continuous inhalation via the nebulizer. Ventavis can cause a decrease in systemic (body-wide) blood pressure if the drug is administered at too high a dose.

Regulatory Approval of Tyvaso

In 2009, the FDA approved Tyvaso for the treatment of PAH in WHO Group 1 patients to improve exercise capacity using the Tyvaso Inhalation System. Studies establishing effectiveness included predominately patients with NYHA Functional Class III symptoms.

In connection with the Tyvaso approval, we agreed to a post-marketing requirement (PMR) and certain post-marketing commitments (PMCs). PMRs and PMCs are studies that sponsors conduct after FDA approval to gather additional information about a product's safety, efficacy, or optimal use. PMRs are required studies, whereas a sponsor voluntarily commits to conduct PMCs.

Under the PMCs, we modified certain aspects of the Tyvaso Inhalation System. We also performed a usability analysis incorporating the evaluation and prioritization of user-related risk followed by a human factors study. In 2012, the FDA acknowledged we had satisfied our PMCs and approved our modifications to the Tyvaso Inhalation System. The Tyvaso Inhalation System now includes a nebulizer called TD-100, which incorporates these modifications. In addition, we are developing further enhancements to make the Tyvaso Inhalation System easier for patients to use.

In accordance with our PMR, we are required to complete a long-term observational study in the United States that includes 1,000 patient years of follow-up in patients treated with Tyvaso, and 1,000 patient years of follow-up in control patients receiving other PAH treatments, to evaluate the potential association between Tyvaso and oropharyngeal and pulmonary toxicity. We have completed this study and are preparing to submit the results of the study by the FDA's deadline of June 30, 2015. While we believe we are on schedule to complete the PMR by this deadline, any failure or delay could result in penalties, including fines or withdrawal of Tyvaso from the market, unless we are able to demonstrate good cause for the failure or delay.

In June 2010, the FDA granted orphan drug designation for Tyvaso. Such a designation, coupled with an approval of the product for the orphan indication, confers an exclusivity period through July 2016, during which the FDA may not approve any application to market the same drug for the same indication, except in limited circumstances.

We are not seeking EMA approval of Tyvaso as a standalone treatment of PAH, but we are planning to seek EMA approval to market Tyvaso in combination with esuberaprost, if the BEAT study described below under *Esuberaprost* is successful. Tyvaso is approved in Israel, and we are in the process of updating its registration to include the TD-100 device so that we can commence commercial sales through our Israeli distributor, Rafa Laboratories Ltd.

Orenitram

Orenitram is an extended-release, oral tablet form of treprostinil, which we launched commercially in the United States during the second quarter of 2014. Orenitram is the only FDA-approved, orally administered prostacyclin analogue. We sell Orenitram to the same specialty pharmaceutical distributors in the United States that distribute Remodulin and Tyvaso. For the year ended December 31, 2014, we recognized approximately $41.3 million in Orenitram revenues, representing 3 percent of our total net revenues.

Regulatory Approval of Orenitram

In December 2013, the FDA approved Orenitram for the treatment of PAH in WHO Group 1 patients to improve exercise capacity. The primary study that established efficacy (FREEDOM-M) included predominately patients with WHO functional class II-III symptoms and etiologies of idiopathic or heritable PAH (75%) or PAH associated with connective tissue disease (19%). Orenitram's label also notes that Orenitram is probably most useful to replace subcutaneous, intravenous, or inhaled treprostinil, but these uses have not yet been studied. The most common side effects observed were headache, nausea and diarrhea.

FREEDOM-M was a 12-week monotherapy study of Orenitram (meaning patients were not on any background PAH therapy), which met its primary endpoint of improvement in six-minute walk distance at week 12. Analysis of the FREEDOM-M results demonstrated that patients receiving Orenitram

improved their six-minute walk distance by a median of approximately 23 meters (p=0.0125, Hodges-Lehmann estimate and non-parametric analysis of covariance in accordance with the trial's pre-specified statistical analysis plan) as compared to patients receiving the placebo. The median change from baseline at week 12 was 25 meters for patients receiving Orenitram and –5 meters for patients receiving the placebo.

Orenitram Combination Therapy

In addition to the successful monotherapy study noted above, we also conducted two unsuccessful phase III studies of Orenitram in combination with other approved therapies. We believe that in order for Orenitram to reach its full commercial potential, we need to complete further studies to support an amendment to Orenitram's label to include data demonstrating that Orenitram delays morbidity and mortality in patients who are on an approved oral background therapy. As such, we are enrolling up to 610 patients in a phase IV clinical trial called FREEDOM-EV, which began in 2012. FREEDOM-EV is a placebo-controlled study of patients who enter the study on an approved oral background therapy, and one of the two primary endpoints of the study is the time to clinical worsening. The other primary endpoint is change in six-minute walk distance from baseline to week 24.

We currently plan to seek approval of Orenitram in Europe upon completion of the FREEDOM-EV study. In 2005, the EMA announced that Orenitram had been designated an orphan medicinal product for the treatment of PAH. A request for orphan drug designation for Orenitram is pending before the FDA.

Adcirca

We began selling Adcirca in 2009. Adcirca is a PDE-5 inhibitor, the active pharmaceutical ingredient of which is tadalafil. Tadalafil is also the active pharmaceutical ingredient in Cialis ®, which is marketed by Lilly for the treatment of erectile dysfunction. We acquired the commercial rights to Adcirca for the treatment of PAH in the United States and Puerto Rico from Lilly in 2008. We sell Adcirca at prices established by Lilly, which are at parity with Cialis pricing and are typically set at a discount from an average wholesale price to pharmaceutical wholesalers. For the years ended December 31, 2014, 2013 and 2012, we recognized approximately $221.5 million, $177.0 million and $122.5 million in Adcirca revenues, representing 17 percent, 16 percent and 13 percent, respectively, of our net revenues.

Patients with PAH have been shown to have reduced levels of the enzyme responsible for producing NO, a naturally occurring substance in the body that has the effect of relaxing vascular smooth muscle cells. NO works to relax pulmonary blood vessels by increasing intracellular levels of cyclic GMP. Because cyclic GMP is degraded by PDE-5, an established therapeutic approach in the treatment of PAH is to use PDE-5 inhibitors to increase levels of cyclic GMP in blood vessels and improve cardiopulmonary function in PAH patients.

In September 2014, Gilead announced the results of a study of ambrisentan (an ETRA) and tadalafil in PAH patients as a first-line treatment, compared to treating PAH patients with only ambrisentan or tadalafil. In the study, first-line treatment with both therapies reduced the risk of clinical failure compared to a monotherapy treatment by 50 percent (p=0.0002).

Prior to the approval of Adcirca, Revatio ®, which is marketed by Pfizer Inc. (Pfizer), was the only PDE-5 inhibitor approved for the treatment of PAH. Sildenafil citrate, the active ingredient in Revatio, is also the active ingredient in Viagra ®, which is marketed by Pfizer for the treatment of erectile dysfunction. In 2012, several companies launched generic formulations of sildenafil citrate. Revatio and generic sildenafil citrate are dosed three times daily. Adcirca is dosed once daily.

FDA Approval of Adcirca

In 2009, the FDA approved Adcirca with a recommended dose of 40 mg, making it the first once-daily PDE-5 inhibitor for the treatment of PAH. Adcirca is indicated to improve exercise ability in patients with PAH (WHO Group 1), which encompasses patients with various etiologies, such as idiopathic and heritable PAH as well as PAH associated with connective tissue diseases. Studies establishing effectiveness included predominately patients with NYHA Functional Class II-III symptoms. Headaches were the most commonly reported side effect.

Commercial Rights to Adcirca

In 2008, we entered into several agreements with Lilly, including a license agreement and a manufacturing and supply agreement. Pursuant to the license agreement, Lilly granted us an exclusive license for the right to develop, market, promote and commercialize Adcirca for the treatment of pulmonary hypertension. Pursuant to the manufacturing and supply agreement, Lilly agreed to manufacture Adcirca and distribute it on our behalf via its wholesaler network, in the same manner that it distributes its own pharmaceutical products. See *Patents and Other Proprietary Rights, Strategic Licenses and Market Exclusivity* below for more details on these agreements.

Esuberaprost

We have the exclusive right to develop and market a modified-release formulation of beraprost in North America, Europe, and certain other territories for the treatment of cardiovascular indications, pursuant to our license agreement with Toray Industries, Inc. (Toray), which is described below under *Patents and Other Proprietary Rights, Strategic Licenses and Market Exclusivity—Toray Amended License Agreement* . Beraprost is a chemically stable, orally bioavailable prostacyclin analogue. Like natural prostacyclin and treprostinil, beraprost is believed to dilate blood vessels and prevent both platelet aggregation and proliferation of smooth muscle cells surrounding blood vessels, via a unique profile of pulmonary vascular receptor selectivity.

In 2012, we completed a phase I safety trial of esuberaprost (formerly known as 314d), a reformulated, single-isomer version of beraprost, and the data suggested that dosing esuberaprost four times a day would be well-tolerated. We believe that esuberaprost and treprostinil have differing prostacyclin receptor-bindings profiles, and thus could provide benefits to certain groups of patients with differing sets of safety and efficacy profiles. We also believe Tyvaso and esuberaprost have complimentary pharmacokinetic and pharmacodynamic profiles, which indicates they could provide greater efficacy in combination. As a result, in 2013, we began enrolling a phase III study called BEAT (***BE*** raprost 314d ***A*** dd-on to ***T*** yvaso) to evaluate the clinical benefit and safety of esuberaprost in combination with Tyvaso for patients with PAH who show signs of deterioration on inhaled treprostinil or have a less than optimal response to inhaled treprostinil treatment. We intend to enroll 240 patients in the study, which will have a primary endpoint of time to clinical worsening.

Cell-Based Therapy

In 2011, we entered into a license agreement with Pluristem to develop and commercialize a cell-based therapy for the treatment of PAH using Pluristem's proprietary cell technology known as PLacental eXpanded (PLX) cells. We commenced a phase I clinical study in Australia in 2013.

Lung Transplantation

PAH has not been reported to reoccur in end-stage patients who have received a lung transplant. We believe fewer than 100 PAH patients in the United States receive a lung transplant each year (out of almost 2,000 performed) due to a shortage of available lungs for transplant, as a result of the demand for transplantable lungs by patients with end-stage pulmonary diseases, such as chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis, and delays in listing PAH patients for transplant.

In 2011, we acquired all of the outstanding stock of Revivicor, a company focused on developing genetic biotechnology platforms to provide alternative tissue sources for the treatment of human degenerative disease through tissue and organ xenotransplantation. We have focused this platform on the goal of providing transplantable lungs for human patients.

In May 2014, we completed a $50.0 million preferred stock investment in Synthetic Genomics Inc. (SGI). We also entered into a separate multi-year research and development collaboration agreement with SGI whereby SGI will develop engineered primary pig cells, cells taken directly from living tissue and established for growth in vitro, with modified genomes for use in our xenotransplantation program, which is principally focused on lungs. Under this agreement, each party will assume its own research and development costs and SGI may receive royalties and milestone payments from development and commercialization of organs.

We are also engaged in preclinical development of several regenerative technologies for creating transplantable lung tissue and whole lungs for patients with end-stage lung disease, as well as other technologies intended to improve outcomes for lung transplant recipients. We are preparing to commence a clinical trial in the United States to study the use of ex-vivo lung perfusion technology originally developed in Canada (where it is already used commercially) to provide extended preservation and assessment of donated lungs that are initially rejected for transplantation. In 2014, we completed the construction of the only laboratory facility in the United States devoted to performing ex-vivo lung perfusion on a fee-for-service basis. This facility is located in Silver Spring, Maryland.

Products to Treat Cancer

Ch14.18 Antibody

In 2010, we entered into a Cooperative Research and Development Agreement (CRADA) with the NCI to collaborate on the late-stage development and regulatory agency submissions of Chimeric Monoclonal Antibody 14.18 (ch14.18) for children with high-risk neuroblastoma and patients with other forms of cancers. Ch14.18 is an antibody that has shown potential in the treatment of certain types of cancer by targeting GD2, a glycolipid on the surface of tumor cells. Neuroblastoma is a rare cancer of the sympathetic nervous system mainly affecting children. It is the most common extracranial, outside the skull, solid cancer in children and the most common cancer in infants. There are fewer than 1,000 new cases of neuroblastoma diagnosed each year in the United States. Ch14.18 is a chimeric, composed of a combination of mouse and human DNA, monoclonal antibody that induces antibody-dependent cell-mediated cytotoxicity, a mechanism of cell-mediated immunity whereby the immune system actively targets a cell that has been bound by specific antibodies.

Results of the NCI's phase III study were published in September 2010. In that study, immunotherapy with ch14.18 significantly improved patient outcome compared with standard therapy in patients with high risk neuroblastoma. Specifically, the two-year estimate for event-free survival was 66%±5% in the ch14.18 immunotherapy group and 46%±5% in the standard therapy group (p=0.01 without adjustment for interim analyses). The ch14.18 immunotherapy group was also significantly better than the standard therapy group in the estimated rate of overall survival (86%±4% vs. 75%±5% at two years, p=0.02 without adjustment for interim analyses). The most common serious adverse reactions were infections, pain, hypotension, infusion reactions, hypokalemia, fever, and capillary leak syndrome. This study was coordinated by the Children's Oncology Group, a national consortium of researchers supported by the NCI.

Under the terms of the CRADA, the NCI completed a second phase III clinical trial with 105 patients to define more clearly the safety and toxicity profile of ch14.18 immunotherapy in children, and we have developed the commercial production capability for the antibody. Collectively, related NCI-supported studies and our production data were used as the foundation for our MAA, which the EMA accepted for review in December 2013, and a BLA, which the FDA accepted for review in June

2014. We previously received orphan drug designation for ch14.18 from both the FDA and the EMA. In lieu of a royalty payment to the NCI, we have an ongoing obligation to provide the NCI with ch14.18 for its studies free of charge.

Products to Treat Infectious Diseases

Glycobiology Antiviral Agents

Pursuant to our research agreement with the University of Oxford (Oxford), we have the exclusive right to commercialize a platform of glycobiology antiviral drug candidates for the treatment of a wide variety of viruses. Through our research agreement with Oxford, we are also supporting research into new glycobiology antiviral drug candidates and technologies. We are currently testing many of these compounds in preclinical studies and Oxford continues to synthesize new agents that we may elect to test.

In 2011, we were awarded a cost plus fixed fee contract with an aggregate value of up to $45.0 million under a Broad Agency Announcement from NIAID for studies directed toward the development of a broad spectrum antiviral drug with a primary indication for dengue and a secondary indication for influenza, based on our glycobiology antiviral platform. There are eight milestone-based options to expand the project and funding under the contract. To date, we have received contract modifications exercising five of these options, increasing total committed contract funding to $28.1 million. We recognize revenue under this contract to the extent of allowable costs incurred, plus a proportionate amount of fees earned. Related revenues are included under the caption *Other Revenues* on our consolidated statements of operations.

Pursuant to our contract with NIAID, we began enrolling a phase I clinical trial of our lead antiviral candidate, an alpha-glucosidase inhibitor called UV-4B, in the third quarter of 2014. In November 2014, the FDA granted orphan drug designation for UV-4B for the treatment of acute dengue illness. We are also performing preclinical studies of UV-4B for the treatment of patients with ebola.

Sales and Marketing

Our marketing strategy for our commercial products is to use our sales and marketing teams to reach out to the prescriber community to: (1) increase PAH awareness; (2) increase understanding of the progressive nature of PAH; and (3) increase awareness of our commercial products and how they fit into the various stages of disease progression and treatment. Our sales and marketing teams consisted of approximately 155 employees as of December 31, 2014. We have divided our domestic sales force into two teams. One team sells Remodulin, Tyvaso and Orenitram, while the other team sells Adcirca.

Distribution of Commercial Products

United States Distribution of Remodulin, Tyvaso and Orenitram

We distribute Remodulin, Tyvaso and Orenitram throughout the United States and Puerto Rico through two contracted specialty pharmaceutical distributors: Accredo Health Group, Inc. (Accredo) and CVS Caremark (Caremark). These distributors are required to maintain certain minimum inventory levels in order to ensure an uninterrupted supply to patients who are prescribed our therapies. We compensate Accredo and Caremark on a fee-for-service basis for certain ancillary services in connection with the distribution of these products. If any of our distribution agreements expire or terminate, we may, under certain circumstances, be required to repurchase any unsold Remodulin, Tyvaso or Orenitram inventory held by our distributors.

These specialty pharmaceutical distributors are responsible for assisting patients with obtaining reimbursement for the cost of our treprostinil-based products and providing other support services. Under our distribution agreements, we sell each of our treprostinil-based products to these distributors at a transfer price that we establish. We have generally increased the price of Tyvaso by 4.9 percent annually, with the last such price increase becoming effective on January 1, 2015. We have not increased the price of Remodulin since 2010. We have also established patient assistance programs in the United States, which provides our treprostinil-based products to eligible uninsured or under-insured patients at no charge. Accredo and Caremark assist us with the administration of these programs.

United States Distribution of Adcirca

We sell Adcirca to pharmaceutical wholesalers at a discount from an average wholesale price. Under our manufacturing and supply agreement with Lilly (see *Patents and Other Proprietary Rights, Strategic Licenses and Market Exclusivity* below for more details), Lilly manufactures Adcirca and distributes it via its wholesaler network, which includes Accredo and Caremark, in the same manner that it distributes its own pharmaceutical products. Under the terms of this agreement, we take title to Adcirca upon completion of its manufacture by Lilly. Adcirca is shipped to customers in accordance with purchase orders received by Lilly. When customers take delivery of Adcirca, Lilly sends an invoice and collects the amount due from the customer subject to customary discounts and rebates, if any. Although Lilly provides these services on our behalf, we maintain the risk of loss as it pertains to inventory, product returns and non-payment of invoices. The manufacturing and supply agreement will continue in effect until expiration or termination of the license agreement. Lilly retains authority under the license agreement for all regulatory activities with respect to Adcirca, as well as its retail pricing, which has been and is expected to be at price parity with Cialis. Since receiving FDA approval of Adcirca, Lilly has generally increased the net wholesale price of Adcirca two or three times each year. During 2013, Lilly increased the net wholesale price of Adcirca by 9.5 percent in January and July and by 9.0 percent in December. During 2014, Lilly increased the net wholesale price of Adcirca by 9.1 percent in July and by 9.9 percent in December. We have also established a patient assistance program in the United States, which provides Adcirca to eligible uninsured or under-insured patients at no charge for a certain period of time.

International Distribution of Remodulin

We currently sell subcutaneous and intravenous Remodulin outside the United States to various distributors, each of which has exclusive distribution rights in one or more countries within Europe, Israel and the Middle East, Asia and South and Central America. We also distribute Remodulin in Canada through a specialty pharmaceutical wholesaler. In some of the European markets where we are not licensed to market Remodulin, such as Spain and the United Kingdom, we sell (but do not market) Remodulin on a named-patient basis in which therapies are approved for individual patients by a national medical review board, hospital or health plan on a case-by-case basis. We continue to work on expanding our sales of Remodulin into new territories through our existing network of distributors.

Patents and Other Proprietary Rights, Strategic Licenses and Market Exclusivity

Our success depends in part on our ability to obtain and maintain patent protection for our products, preserve trade secrets, prevent third parties from infringing upon our proprietary rights and operate without infringing upon the proprietary rights of others in the United States and worldwide. Many of these proprietary rights stem from licenses and other strategic relationships with third parties. In addition to intellectual property rights, U.S. and international regulatory authorities often provide periods of market exclusivity for manufacturers of biopharmaceutical products.

Patents provide the owner with a right to exclude others from practicing an invention. Patents may cover the active ingredients, uses, formulations, doses, administrations, delivery mechanisms,

manufacturing processes and other aspects of a product. The period of patent protection for any given product generally depends on the expiration date of various patents and may differ from country to country according to the type of patents, the scope of coverage and the remedies for infringement available in a country. Most of our commercial products and investigational products are protected by patents that expire on varying dates.

Significant legal questions exist concerning the extent and scope of patent protection for biopharmaceutical products and processes in the United States and elsewhere. Accordingly, there is no certainty that patent applications owned or licensed by us will be issued as patents, or that our issued patents will afford meaningful protection against competitors. Once issued, patents are subject to challenge through both administrative and judicial proceedings in the United States and other countries. Such proceedings include re-examinations, *inter partes* reviews, post-grant reviews and interference proceedings before the U.S. Patent and Trademark Office, as well as opposition proceedings before the European Patent Office. Litigation may be required to enforce, defend or obtain our patent and other intellectual property rights. Any administrative proceeding or litigation could require a significant commitment of our resources and, depending on outcome, could adversely affect the scope, validity or enforceability of certain of our patent or other proprietary rights.

Remodulin, Tyvaso and Orenitram Proprietary Rights

We have a number of issued patents and pending patent applications covering the stable prostacyclin analogue known as treprostinil, which is the active pharmaceutical ingredient in Remodulin, Tyvaso and Orenitram.

In January 1997, we acquired patents covering the use of treprostinil for PAH from GlaxoSmithKline PLC (formerly Glaxo Wellcome, Inc.) (Glaxo) in exchange for certain payments including a royalty on sales of any product containing treprostinil. All of these patents expired in October 2014, as did our royalty payment obligation to Glaxo.

In October 1997, we filed patent applications for a new synthesis method for treprostinil in the United States, Europe and various other countries. This application resulted in the grant of three patents in the United States, all of which expire in October 2017, as well as granted patents in a number of other countries, expiring in October 2018.

We continue to conduct research into new methods to synthesize treprostinil and have filed a number of additional patent applications relating to production of treprostinil, several of which have already been granted in the United States. One such patent was granted last year and is now listed in the Orange Book for Remodulin, Tyvaso and Orenitram, expiring in 2028.

In addition to the treprostinil patents noted above, we have additional patents specific to our individual treprostinil-based products, including the following:

- *Remodulin.* We have been granted three U.S. patents covering an improved diluent for Remodulin, which expire in 2028 and 2029. All three of these patents are listed in the FDA Orange Book.
- *Tyvaso.* We have been granted two U.S. patents, as well as patents in other countries, for Tyvaso that cover methods of treating PAH by inhaled delivery. These patents will expire in the United States in 2018 and in various countries throughout the world in 2020.
- *Orenitram.* Our patents for Orenitram cover methods of use for treating PAH, orally administered formulations, controlled moisture storage and production methods, as well as those covering controlled release formulations licensed to us by Supernus Pharmaceuticals Inc. (Supernus). These patents will expire in the United States between 2024 and 2031 and in various countries throughout the world between 2024 and 2027.

We have additional pending U.S. and international patent applications relating to Remodulin, Tyvaso and Orenitram.

Orange Book

In seeking approval of a drug through an NDA or BLA or upon issuance of new patents following approval of an NDA or BLA, applicants are required to submit to the FDA each patent that has claims covering the applicant's product or a method of using the product. Each of the patents submitted is then published in the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations, commonly known as the Orange Book. See *Governmental Regulation-Hatch—Waxman Act* below for further details. Remodulin currently has five unexpired Orange Book-listed patents with expiration dates ranging from 2017 to 2029. Tyvaso currently has four unexpired Orange Book listed patents with expiration dates ranging from 2017 to 2028. Orenitram currently has eight unexpired Orange Book listed patents with expiration dates ranging from 2017 to 2031. Additional patent applications are pending, and if granted, may be eligible for listing in the Orange Book.

Regulatory Exclusivity

In June 2010, the FDA granted orphan drug designation for Tyvaso. This designation confers an exclusivity period through July 2016, during which the FDA may not approve any application to market the same drug for the same indication, except under limited circumstances. As a result of FDA approval of our NDA for Orenitram as a new dosage form, Orenitram has three years of market exclusivity for PAH expiring in December 2016. A request for orphan drug designation for Orenitram is pending with the FDA.

Remodulin is protected in the European Union by data protection regulations, which prevent the grant of an abbreviated marketing approval for a product containing treprostinil for the treatment of PAH for a period of either six or ten years from the date of the grant of the first marketing authorization in the European Union. In those countries where protection runs for six years, that period has expired, while in those countries where protection runs for ten years, this period expires in February 2015.

Generic Challenges

We have received notice of ANDAs filed by Sandoz Inc. (Sandoz) and Teva requesting FDA approval to market a generic version of Remodulin. After we received notice, we filed lawsuits against Sandoz and Teva in the U.S. District Court for the District of New Jersey alleging patent infringement. In August 2014, the U.S. District Court for the District of New Jersey ruled that our Orange Book patent expiring in October 2017 was both valid and enforceable against Sandoz, and enjoined Sandoz from marketing its generic product until the expiration of that patent. Sandoz has appealed this ruling. For further details, see the sections below entitled *Governmental Regulation—Hatch-Waxman Act* and *Item 3.—Legal Proceedings.* There can be no assurance that we will prevail in our defense of our patent rights against Teva and Sandoz, or that additional challenges from other ANDA filers will not surface with respect to Remodulin or our other treprostinil-based products. Our existing patents could be invalidated, found unenforceable or found not to cover a generic form of Remodulin, Tyvaso or Orenitram. If any ANDA filer were to receive approval to sell a generic version of Remodulin, Tyvaso or Orenitram and/or prevail in any patent litigation, the affected product would become subject to increased competition and our revenue would decrease.

Supernus License

In 2006, we entered into an exclusive license agreement with Supernus to use certain of its technologies in producing Orenitram. Under the agreement, we paid Supernus certain amounts upon

the achievement of specified milestones based on the development of Orenitram and a $2.0 million milestone payment upon its commercial launch in 2014. In addition, the agreement provides that we will pay a single-digit royalty to Supernus based on net worldwide sales. Any such royalty will be paid for approximately twelve years commencing with the first product sale and is subject to adjustments as specified in the agreement.

NEBU-TEC Agreement of Sale and Transfer

In 2008, we entered into an agreement with NEBU-TEC International Med Products Eike Kern GmbH (NEBU-TEC) to purchase its line of business relating to the manufacture of the Tyvaso Inhalation System which provided for future contingent milestone payments of up to €10.0 million (of which we have already paid €3.0 million as of December 31, 2014). The transaction closed in 2009 after we received FDA approval for Tyvaso. Through 2013, we managed all aspects of the manufacturing process for the Tyvaso Inhalation System and NEBU-TEC supplied the labor to assemble the devices in a facility we leased from NEBU-TEC. In December 2013, we ceased manufacturing at the NEBU-TEC leased facility and are using a U.S.-based manufacturer to produce the Tyvaso Inhalation System.

Lilly Agreements Related to Adcirca

In 2008, we entered into several agreements with Lilly regarding Adcirca, including a license agreement and a manufacturing and supply agreement.

License Agreement

Under the terms of the license agreement, Lilly granted us an exclusive license for the right to develop, market, promote and commercialize Adcirca for the treatment of pulmonary hypertension in the United States and Puerto Rico. We agreed to pay Lilly royalties equal to five percent of our net sales of Adcirca, as a pass through of Lilly's third-party royalty obligations, for so long as Lilly is required to make such payments.

Lilly retained the exclusive rights to develop, manufacture and commercialize pharmaceutical products containing tadalafil, the active pharmaceutical ingredient in Adcirca, for the treatment of pulmonary hypertension outside of the United States and Puerto Rico and for the treatment of other diseases worldwide. Lilly retained authority for all regulatory activities with respect to Adcirca, including retail pricing, which has been and is expected to continue to be at price parity with Cialis.

The license agreement will continue in effect until the later of: (1) expiration, lapse, cancellation, abandonment or invalidation of the last claim to expire within a Lilly patent covering the commercialization of Adcirca for the treatment of pulmonary hypertension in the United States and Puerto Rico; or (2) expiration of any government-conferred exclusivity rights to use Adcirca for the treatment of pulmonary hypertension in the United States and Puerto Rico.

We have the right to terminate the license agreement upon six months written notice to Lilly. Lilly has the right to terminate in the event of a change of control of our company. Either party may terminate upon a material breach by the other party of the license agreement or the manufacturing and supply agreement, described above.

The U.S. patent for Adcirca for the treatment of pulmonary hypertension will expire in November 2017.

Manufacturing and Supply Agreement

Under the terms of the manufacturing and supply agreement, Lilly agreed to manufacture Adcirca and distribute it on our behalf via its pharmaceutical wholesaler network, in the same manner that it distributes its own pharmaceutical products. Under the terms of this agreement, we take title to

Adcirca upon its manufacture by Lilly. Adcirca is shipped to customers, generally pharmaceutical wholesalers, in accordance with customers' purchase orders received by Lilly. Lilly invoices and collects amounts due from the customer subject to customary discounts and rebates, if any, and remits the collections to us. Although Lilly is providing these services on our behalf, we maintain the risk of loss as it pertains to inventory, product returns and nonpayment of sales invoices. The manufacturing and supply agreement will continue in effect until expiration or termination of the license agreement.

We also agreed to purchase Adcirca at a fixed manufacturing cost. The agreement provides a mechanism, generally related to the increase in the national cost of pharmaceutical manufacturing, pursuant to which Lilly may raise the manufacturing cost of Adcirca.

National Cancer Institute

In 2010, we entered into a CRADA with the NCI to collaborate on the late-stage development and regulatory agency submissions of ch14.18 for children with high-risk neuroblastoma and patients with other cancers. For further details, refer to the section above entitled *Products to Treat Cancer—Ch14.18 Antibody.*

Medtronic

In 2009, we entered into an exclusive agreement with Medtronic, which was amended in 2011, to collaborate on the development and commercialization of Medtronic's proprietary intravascular infusion catheter to be used with Medtronic's Synchromed II implantable infusion pump and related infusion system components (together referred to as the Remodulin Implantable System) in order to deliver Remodulin for the treatment of PAH in the U.S., UK, Canada, France, Germany, Italy and Japan. Under the amended agreement, we have been working together at our expense to develop the Remodulin Implantable System, conduct a clinical trial and obtain regulatory approval for the use of Remodulin with the Remodulin Implantable System. If this development program is successful, our agreement provides that, upon commercialization, we will purchase infusion pumps and supplies from Medtronic and will also pay a royalty to Medtronic based on net sales of Remodulin for use in the Remodulin Implantable System within the exclusive territories, subject to certain adjustments specified in the agreement. The Remodulin Implantable System will be exclusive to Remodulin so long as we purchase a minimum percentage of our annual requirement for implantable pump systems from Medtronic. We will be solely responsible for all marketing and promotion of the Remodulin Implantable System in the exclusive territories.

Toray Amended License Agreement

In 2000, we licensed from Toray the exclusive right to develop and market beraprost for cardiovascular indications. Beraprost is a chemically stable oral prostacyclin analogue in a sustained release formulation, which is approved to treat PAH in Japan and certain other countries. This license gives us exclusive rights to develop beraprost and its variants throughout North America, Europe, and certain other territories. We are currently developing esuberaprost under this license agreement.

In 2007, we issued 400,000 shares of our common stock to Toray in exchange for the cancellation of Toray's existing right under the 2000 agreement to receive an option grant to purchase 1,000,000 shares of our common stock. Toray has the right to request that we repurchase the 400,000 shares of our common stock upon 30 days prior written notice at the price of $27.21 per share. The 2007 amendment also provided for certain milestone payments during the development period and upon receipt of regulatory approval for beraprost in the United States or the European Union.

In 2011, we amended our license agreement with Toray. The amendment did not materially change the terms of our license agreement, except for a reduction in royalty rates. In exchange for the reduction in royalty rates, we agreed to pay Toray $50.0 million in equal, non-refundable payments over the five-year period ending in 2015. As of December 31, 2014, we have $10.0 million remaining under this obligation, which is recorded as a current liability on our consolidated balance sheet. Toray has the right to terminate the license agreement in the event of a change of control of our company under certain circumstances.

Pluristem License Agreement

In 2011, we entered into a license agreement with Pluristem for exclusive worldwide rights to develop and commercialize a cell-based product for the treatment of PAH using Pluristem's proprietary PLX cell technology. The agreement provides for milestone payments to Pluristem at various stages of the product's development, as well as royalties on commercial sales.

Oxford

We maintain a research agreement with Oxford to develop antiviral compounds. Research under this agreement is performed by Oxford Glycobiology Institute, which is headed by a member of our Board of Directors and our scientific advisory board. Under the terms of the agreement, we are required to fund related research activities and make milestone payments for the successful completion of clinical trials. We are also obligated to pay royalties to Oxford equal to a percentage of our net sales from any discoveries and products developed by Oxford. Milestone payments and royalties are subject to reduction depending upon third-party contributions to discoveries and/or third-party licenses necessary to develop products. In August 2010, the term of the research agreement was extended through September 2016. In connection with the extension of the term, we agreed to pay Oxford a total of $2.9 million (using the then-prevailing exchange rate) in 60 equal monthly installments. As of December 31, 2014, approximately $1.1 million remains outstanding under this 2010 agreement. In addition, in December 2012, we amended our agreement with Oxford, under which we agreed to pay Oxford an additional $871,000 in the aggregate (using the exchange rate as of the amendment date) in 36 equal monthly installments beginning in January 2013 for additional work supporting the development of our virology platform. For additional details regarding our virology program, please see the section above entitled *Products to Treat Infectious Diseases—Glycobiology Antiviral Agents* .

DEKA

In December 2014, we entered into an exclusive agreement with DEKA to develop a pre-filled, semi-disposable pump system for subcutaneous delivery of Remodulin. Under the terms of the agreement, we will fund the development costs related to the semi-disposable pump system and will pay product fees and a single-digit royalty to DEKA based on commercial sales of the system and the Remodulin sold for use with the system. Our goal is to be in a position to receive FDA approval for this delivery system by the end of 2018.

Other

We are party to various other license agreements relating to therapies under development. These license agreements require us to make payments based on a percentage of sales, if we are successful in commercially developing these therapies, and may require other payments upon the achievement of certain milestones.

Research & Development Expenditures

We are engaged in research and development and have incurred substantial expenses for these activities. These expenses generally include the cost of acquiring or inventing new technologies and products, as well as new product development (both preclinical and clinical studies and manufacturing cost for unapproved products). Research and development expenses during the years ended December 31, 2014, 2013 and 2012 totaled approximately $242.5 million, $299.3 million and $173.4 million, respectively. See *Item 7—Management's Discussion and Analysis of Financial Condition and Results of Operations—Major Research and Development Projects* for additional information regarding expenditures related to major research and development projects. Research and development expense is significantly impacted by fluctuations in our stock price, due to the cash payment obligations created by our share-based compensation programs. For further details, see *Item 7—Management's Discussion and Analysis of Financial Condition and Results of Operations—Operating Expenses—Share-Based Compensation.*

Production and Supply

We produce our primary supply of Remodulin, Tyvaso and Orenitram at our own facilities. In particular, we synthesize treprostinil, the active ingredient in Remodulin and Tyvaso, and treprostinil diolamine, the active ingredient in Orenitram, at our facility in Silver Spring, Maryland. We also produce finished Tyvaso and Remodulin at our Silver Spring facility. We produce Orenitram and we warehouse and distribute Remodulin, Tyvaso and Orenitram, at our facility in Research Triangle Park, North Carolina.

We maintain a two-year inventory of Remodulin, Tyvaso and Orenitram based on expected demand, and we also contract with third-party contract manufacturers to supplement our capacity, in order to mitigate the risk that we might not be able to produce sufficient quantities to meet patient demand. For example, Baxter Pharmaceutical Solutions, LLC (Baxter) is approved by the FDA, the EMA and various other international regulatory agencies to produce Remodulin for us. In the case of Tyvaso, we rely on Catalent Pharma Solutions, Inc. (Catalent) to serve as an additional producer of Tyvaso, and we rely entirely on Minnetronix Inc. to manufacture the nebulizer used in our Tyvaso Inhalation System. We are working to obtain FDA approval of a third party to serve as an additional producer of Orenitram.

Although we believe that additional third parties could provide similar products, services and materials, there are few companies that could replace our existing third-party producers and suppliers. A change in supplier or producer could cause a delay in the production, distribution and research efforts associated with our respective products or result in increased costs. See also *Item 1A—Risk Factors* included in this Annual Report on Form 10-K.

Competition

Many drug companies engage in research and development to commercialize products to treat cardiovascular and infectious diseases and cancer. For the treatment of PAH, we compete with many approved products in the United States and the rest of the world, including the following:

- *Flolan, Veletri and generic epoprostenol.* Flolan (epoprostenol) is a prostacyclin that is delivered by intravenous infusion. Glaxo began marketing Flolan in the United States in 1996, and the generic exclusivity period for Flolan expired in 2007. In 2008, the FDA approved Teva's version of generic epoprostenol for the treatment of PAH. In 2010, Actelion commenced sales of Veletri, which is another version of epoprostenol;

- *Ventavis and Ilomedin ®.* Approved in 2004 in the United States and in 2003 in Europe, Ventavis (iloprost) is an inhaled prostacyclin analogue. Ventavis is currently marketed by Actelion in the

United States and by Bayer in Europe as Iloprost. Iloprost is also marketed by Bayer in certain countries outside the United States in an intravenous form known as Ilomedin;

- *Tracleer.* Tracleer (bosentan), an oral ETRA therapy for treatment of PAH, was approved in 2001 in the United States and in 2002 in Europe. Tracleer is marketed worldwide by Actelion;

- *Letairis* ®. Approved in 2007 in the United States, Letairis (ambrisentan) is an oral ETRA therapy marketed by Gilead for the treatment of PAH. In 2008, Glaxo received marketing authorization from the EMA for Letairis in Europe, where it is known as Volibris ®;

- *Revatio and generic sildenafil citrate.* Approved in 2005 in the United States, Revatio (sildenafil citrate) is an oral PDE-5 inhibitor therapy marketed by Pfizer. Revatio contains sildenafil citrate, the same active ingredient as Viagra. In the fourth quarter of 2012, several companies began marketing generic formulations of sildenafil citrate;

- *Opsumit.* Approved in October 2013 in the United States and December 2013 in the European Union, Opsumit (macitentan) is an oral ETRA developed by Actelion for the treatment of PAH; and

- *Adempas* ®. Approved in August 2013 in the United States and March 2014 in the European Union, Adempas (riociguat) is a soluble guanylate cyclase stimulator, which targets a similar vasodilatory pathway as PDE-5 inhibitors and is approved for chronic thromboembolic pulmonary hypertension and PAH. Adempas is an oral therapy marketed by Bayer.

There are also a variety of investigational PAH therapies in the later stages of development, including the following:

- *Uptravi* ® *(selexipag)* , an oral prostacyclin receptor agonist being developed jointly by Actelion and Nippon Shinyaku Co., Ltd. in Japan, and by Actelion outside Japan. In June 2014, Actelion announced that Uptravi met the primary endpoints of its phase III clinical trial. In December 2014, Actelion submitted applications with the EMA and the FDA seeking approval of Uptravi for the treatment of patients with PAH;

- *Gleevec* ® *(imatinib)* , a small molecule kinase inhibitor in an oral tablet form approved for treating various cancers, is being studied for the treatment of PAH. Novartis Pharmaceuticals Corporation (Novartis) completed a phase III trial of Gleevec for the treatment of PAH in September 2011. During the third quarter of 2012, Novartis withdrew its NDA in order to submit additional data to the FDA and during the first quarter of 2013 withdrew the MAA it had filed with the EMA;

- *Ralinepag,* an oral prostacyclin receptor agonist being developed by Arena Pharmaceuticals, Inc. (Arena). Arena commenced a phase II clinical trial of ralinepag in 2014; and

- *Trevyent* ®, a formulation of treprostinil being developed by SteadyMed Ltd. (SteadyMed) for delivery via its pre-filled, disposable PatchPump ®. SteadyMed has announced that it plans to submit an NDA for Trevyent in the first quarter of 2016, and an MAA in the first half of 2016.

Oral non-prostacyclin therapies (such as PDE-5 inhibitors and ETRAs) are commonly prescribed as first-line treatments for the least severely ill PAH patients (NYHA Class II patients). As patients progress in their disease severity (NYHA Class III and IV), less convenient approved therapies, such as inhaled prostacyclin analogues (such as Tyvaso) or infused prostacyclin analogues (such as Remodulin) are commonly added. Orenitram is the first approved oral prostacyclin therapy for PAH in the United States. We anticipate that it will face competition with existing oral PAH therapies, and will be regarded as a less invasive and more convenient alternative therapy to Tyvaso and Remodulin. The use of available oral therapies could delay many patients' need for inhaled or infused prostacyclin therapy. As a result, the availability of oral therapies affects demand for our inhaled and infused products.

We could also face competition from generic pharmaceutical companies in the future. For example, two generic companies have filed ANDAs requesting FDA approval to market a generic version of Remodulin. For details, see the sections below entitled *Governmental Regulation—Hatch-Waxman Act* and *Item 3.—Legal Proceedings.* In addition, certain Revatio patents expired in 2012, leading several manufacturers to launch generic formulations of sildenafil citrate, which physicians could prescribe for the treatment of PAH. Generic sildenafil citrate's lower price, relative to Adcirca, could lead to an erosion of Adcirca's market share and limit its growth potential. Although we believe Adcirca's once-daily dosing regimen is an appealing alternative to generic sildenafil citrate's dosing regimen of three times per day, we expect government payers and private insurance companies to favor over time the use of the less expensive generic sildenafil citrate instead of Adcirca.

We compete with the developers, manufacturers and distributors of all of the PAH products noted above for customers, funding, access to licenses, personnel, third-party collaborators, product development and commercialization. Almost all of these companies have substantially greater financial, marketing, sales, distribution and technical resources, and more experience in research and development, product development, manufacturing and marketing, clinical trials and regulatory matters, than we have.

Governmental Regulation

Pharmaceutical Product Approval Process

The research, development, testing, manufacture, promotion, marketing, distribution, sampling, storage, approval, labeling, record keeping, post-approval monitoring and reporting, and import and export of pharmaceutical products (drugs or biological products, hereinafter collectively drugs) are extensively regulated by governmental agencies in the United States and in other countries. In the United States, failure to comply with requirements under the Federal Food, Drug, and Cosmetic Act (FDC Act), the Public Health Service Act (PHSA), and other federal statutes and regulations, may subject a company to a variety of administrative or judicial sanctions, such as FDA refusal to approve pending NDAs or BLAs, warning letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, civil penalties, and criminal prosecution.

Satisfaction of FDA pre-market approval requirements typically takes many years, and the actual time required may vary substantially based upon the type, complexity and novelty of the product or disease. Drugs are subject to rigorous regulation by the FDA in the United States, the EMA in the EU and similar regulatory authorities in other countries. The steps ordinarily required before a new drug may be marketed in the United States, which are similar to steps required in most other countries, include:

- Preclinical laboratory tests, preclinical studies in animals, formulation studies and the submission to the FDA of an investigational new drug application (IND) for a new drug, which must become effective before clinical testing may commence;
- Clinical studies in healthy volunteers;
- Clinical studies in patients to explore safety, efficacy and dose-response characteristics;
- Adequate and well-controlled clinical trials to establish the safety and efficacy of the drug for each indication;
- The submission of an NDA or BLA to the FDA; and
- FDA review and approval of the NDA or BLA prior to any commercial sale or shipment of the drug.

Preclinical tests include laboratory evaluation of product chemistry and formulation, as well as animal studies to explore toxicity and for proof-of-concept. The conduct of the preclinical tests must comply with federal regulations and requirements including good laboratory practices. In the United States, the results of preclinical testing are submitted to the FDA as part of an IND, along with other information including information about product chemistry, manufacturing and controls and a proposed clinical trial protocol. Long-term preclinical tests, such as animal tests of reproductive toxicity and carcinogenicity, may continue after the IND is submitted. Absent FDA objection within 30 days after submission of an IND, the IND becomes effective and the clinical trial proposed in the IND may begin. At any time during this 30-day period or at any time thereafter, the FDA may halt proposed or ongoing clinical trials. The IND process may be extremely costly and may substantially delay development of our products. Moreover, positive results of preclinical tests will not necessarily indicate positive results in clinical trials.

Clinical trials involve the administration of the investigational new drug or biologic to healthy volunteers or patients under the supervision of a qualified investigator. Clinical trials must be conducted: (a) in compliance with federal regulations; (b) in compliance with good clinical practices (GCP), an international standard meant to protect the rights and health of patients and to define the roles of clinical trial sponsors, administrators, and monitors; and (c) under protocols detailing the objectives of the trial, the parameters to be used in monitoring safety and the criteria to be evaluated. Each protocol involving testing on U.S. patients and subsequent protocol amendments must be submitted to the FDA as part of the IND.

The FDA may order the temporary or permanent discontinuation of a clinical trial at any time or impose other sanctions if it believes that the clinical trial is not being conducted in accordance with FDA requirements or presents an unacceptable risk to the clinical trial patients. The study protocol and informed consent information for patients in clinical trials must also be approved by an institutional review board (IRB). An IRB may also require the clinical trial at a site to be halted temporarily or permanently for failure to comply with the IRB's requirements, or may impose other conditions.

Clinical trials in support of an NDA or a BLA are typically conducted in three sequential phases, but the phases may overlap. During phase I, the initial introduction of the drug into healthy human subjects or patients, the drug is tested to assess metabolism, pharmacokinetics, pharmacological actions, side effects associated with increasing doses, and, if possible, early evidence on effectiveness. Phase II usually involves studies in a limited patient population to assess the efficacy of the drug in specific, targeted indications, assess tolerance and optimal dosage and identify possible adverse effects and safety risks. If a compound is found to be potentially effective and to have an acceptable safety profile in phase II evaluations, then a meeting may be requested at the end of phase II to determine the safety of proceeding to phase III. Phase III trials, also called pivotal studies, major studies or advanced clinical trials, are undertaken to demonstrate clinical efficacy and safety in a larger number of patients, typically at geographically diverse clinical study sites, and to permit the FDA to evaluate the overall benefit-risk relationship of the drug and to provide adequate information for the labeling of the drug.

After successful completion of the required clinical testing, an NDA or a BLA is typically submitted to the FDA in the United States, and an MAA is typically submitted to the EMA in the EU. FDA approval of the NDA or BLA is required before marketing of the product may begin in the United States. The NDA or BLA must include the results of all preclinical, clinical and other testing and a compilation of data relating to the product's pharmacology, chemistry, manufacture, and controls. The cost of preparing and submitting an NDA or BLA is substantial. Under federal law, the submission of most NDAs and BLAs is additionally subject to a substantial application fee, currently exceeding $2.3 million, and the manufacturer and/or sponsor of an approved NDA or BLA is also subject to annual product and establishment fees, currently exceeding $110,000 per product and $569,000 per establishment. These fees are typically increased annually. However, the application fees may be waived for orphan drugs if certain requirements are met.

The FDA has 60 days from its receipt of an NDA or a BLA to determine whether the application will be accepted for filing based on the agency's threshold determination that it is sufficiently complete to permit substantive review. Once the submission is accepted for filing, the FDA begins an in-depth review. The FDA may instead ask for additional information, in which case, the application must be amended and resubmitted with the requested information. The FDA has agreed to certain performance goals in the review of NDAs. Most such applications for non-priority drugs are reviewed within ten to twelve months, while most applications for priority review drugs are reviewed in six to eight months. Priority review can be applied to drugs that the FDA determines offer major advances in treatment, or provide a treatment where no adequate therapy exists. For biologics, priority review is further limited to drugs intended to treat a serious or life-threatening disease. The review process may be extended by the FDA for three additional months to consider certain information submitted during FDA review, including information intended to clarify information already provided or to address any deficiencies identified in the submission. The FDA may also refer applications for novel pharmaceutical products or pharmaceutical products that present difficult questions of safety or efficacy to an advisory committee, typically a panel that includes clinicians and other experts, for review, evaluation and a recommendation as to whether the application should be approved. The FDA is not bound by the recommendation of an advisory committee, but it generally follows such recommendations. During the review process, the FDA also reviews the drug's product labeling to ensure that appropriate information is communicated to health care professionals and consumers. In addition, before approving an NDA or a BLA, the FDA will typically inspect one or more clinical sites to assure compliance with GCP. Additionally, the FDA will inspect the facility or the facilities at which the drug is manufactured. The FDA will not approve the product unless compliance with the FDA's current Good Manufacturing Practices (cGMP) and GCP is satisfactory and the NDA or BLA contains data that provide substantial evidence that the pharmaceutical product is safe and effective for purposes of the indication studied.

In the United States, after the FDA evaluates the NDA or BLA and the manufacturing facilities, the FDA may issue either an approval letter or a complete response letter. A complete response letter generally outlines the deficiencies in the submission and may require substantial additional testing or information in order for the FDA to reconsider the application. If and when those conditions have been addressed to the FDA's satisfaction in a resubmission of the NDA or BLA, the FDA will issue an approval letter. The FDA has committed to reviewing such resubmissions in two or six months depending on the type of information included. A Class 1 resubmission may contain only limited information such as labeling, safety updates, stability updates, or minor analysis updates or clarifying information and is subject to a two-month review period. All other resubmissions are categorized as Class 2 and are subject to a six-month review period. Even after such a resubmission, the FDA may decide that the application does not satisfy the regulatory criteria for approval.

An approval letter authorizes commercial marketing of the drug with specific prescribing information for specific indications. As a condition of NDA or BLA approval, the FDA may require a risk evaluation and mitigation strategy (REMS) to help ensure that the benefits of the drug outweigh the potential risks. A REMS can include medication guides, communication plans for healthcare professionals, and elements to assure safe use (ETASU). ETASU can include, but are not limited to, special training or certification for prescribing or dispensing, dispensing only under certain circumstances, special monitoring, and the use of patient registries. The requirement for a REMS can materially affect the potential market and profitability of the drug. To continue marketing our products after approval, applicable regulations require us to maintain a positive risk-benefit profile, maintain regulatory applications through periodic reports to regulatory authorities, fulfill pharmacovigilance requirements, maintain manufacturing facilities according to cGMP requirements, and successfully complete regulatory agency inspections, among other requirements. Our manufacturing facilities are subject to continual review and periodic inspections. Once granted, product approvals may be withdrawn if compliance with regulatory standards is not maintained or problems are identified following initial marketing.

Disclosure of Clinical Trial Information

Sponsors of clinical trials of FDA-regulated drugs and other products are required to register and disclose certain clinical trial information related to the product, patient population, phase of investigation, study sites and investigators, and other aspects of the clinical trial. This clinical trial information is then made public as part of the sponsor's registration. Sponsors are also obligated to disclose the results of their clinical trials after completion. Competitors may use this publicly-available information to gain knowledge regarding the progress of development programs.

Orphan Drugs

Under the Orphan Drug Act, an applicant can request the FDA to designate a product as an "orphan drug" in the United States if the drug is intended to treat a rare disease or condition affecting fewer than 200,000 people in the United States. Orphan drug designation must be requested before submitting an NDA or BLA. After the FDA grants orphan drug designation, the generic identity of the drug and its potential orphan use are disclosed publicly by the FDA. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process. The first NDA or BLA applicant to receive orphan drug designation and FDA approval for a particular active ingredient to treat a particular disease is entitled to a seven-year exclusive marketing period in the United States for that product, for that indication. During the seven-year period, the FDA may not approve any other application to market the same drug for the same disease, except in limited circumstances, such as a showing of clinical superiority to the product with orphan drug exclusivity or the inability of the NDA or BLA holder for the product with orphan drug exclusivity to assure availability of sufficient quantities of the drug to meet the needs of patients with the rare disease or condition. Orphan drug exclusivity does not prevent the FDA from approving a different drug for the same disease or condition, or the same drug for a different disease or condition. Among the other benefits of orphan drug designation are tax credits for certain research and a waiver of the NDA or BLA application user fee.

The FDA granted orphan drug designation for the active ingredient treprostinil for the treatment of PAH as a continuous infusion. However, this designation does not preclude us from seeking orphan drug designation for other formulations or routes of administration, such as oral or inhaled, of treprostinil to treat PAH, or for treprostinil used to treat other orphan diseases. In order for the FDA to grant orphan drug designation for other formulations or routes of administration of treprostinil to treat PAH, we must demonstrate that such new formulation or route of administration is clinically superior to the formulation or route of administration previously granted orphan drug designation. The FDA has granted orphan drug designation for Tyvaso. A request for orphan drug designation for Orenitram is pending.

Pediatric Information

Under the Pediatric Research Equity Act of 2007 (PREA), NDAs, BLAs and supplements to NDAs and BLAs must contain data to assess the safety and effectiveness of the drug for the claimed indication(s) in all relevant pediatric subpopulations and to support dosing and administration for each such pediatric subpopulation for which the drug is safe and effective. The FDA may grant deferrals for submission of data or full or partial waivers. Unless otherwise required by regulation, the PREA does not apply to any drug for an indication for which orphan drug designation has been granted.

The Best Pharmaceuticals For Children Act (BPCA) provides NDA holders a six-month extension of any exclusivity, patent or non-patent, for a drug if certain conditions are met. Conditions for exclusivity include the FDA's determination that information relating to the use of a new drug in the pediatric population may produce health benefits in that population, the FDA making a written request for pediatric studies, and the applicant agreeing to perform, and reporting on, the requested studies

within the requested time frame. Applications under the BPCA are treated as priority applications, with all of the benefits that designation confers.

Hatch-Waxman Act

The Hatch-Waxman Act (also known as the Drug Price Competition and Patent Term Restoration Act) was passed in 1984 to encourage research and development of new drugs and competition between brand and generic pharmaceutical companies. It created a faster approval process for generic drugs, called the abbreviated new drug application (ANDA), while providing protection to brand pharmaceuticals by extending their patent protection, in some cases, to compensate for patent life lost during the product development and approval process and providing periods of market exclusivity to encourage continuing research on, for example, new uses, strengths or dosage forms for existing drugs.

In seeking approval of a drug through an NDA, applicants are required to submit to the FDA each patent whose claims cover the applicant's product or FDA-approved method of using this product. Upon approval of a drug, each of the patents listed in the application is then published in the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations, commonly known as the Orange Book. Drugs listed in the Orange Book can, in turn, be cited by potential competitors in support of approval of an ANDA. Generally, an ANDA provides for marketing of a drug product that has the same active ingredients in the same strength(s), route of administration, and dosage form as the listed drug and has been shown through bioequivalence testing to be therapeutically equivalent to the listed drug. ANDA applicants are not required to conduct or submit results of preclinical or clinical tests to prove the safety or effectiveness of their drug product, other than the requirement for bioequivalence testing. Drugs approved in this way are commonly referred to as "generic equivalents" to the listed drug, and can often be substituted by pharmacists under prescriptions written for the original listed drug.

The ANDA applicant is required to certify to the FDA concerning any patents listed for the approved product in the FDA's Orange Book. Specifically, the applicant must certify that: (a) the required patent information has not been filed; (b) the listed patent has expired; (c) the listed patent has not expired, but will expire on a particular date and approval is sought after patent expiration; or (d) the listed patent is invalid or will not be infringed by the new product. A certification that the new product will not infringe the already approved product's listed patents or that such patents are invalid is called a Paragraph IV certification. If the applicant does not challenge the listed patents, the ANDA application will not be approved until all the listed patents claiming the referenced product have expired. Alternatively, for a patent covering an approved method of use, an ANDA applicant may submit a statement to the FDA that the company is not seeking approval for the covered use.

If the ANDA applicant has submitted a Paragraph IV certification to the FDA, the applicant must also send notice of the Paragraph IV certification to the NDA and patent holders once the ANDA has been accepted for filing by the FDA. The NDA and patent holders may then initiate a patent infringement lawsuit in response to the notice of the Paragraph IV certification. The filing of a patent infringement lawsuit within 45 days of the receipt of a Paragraph IV certification automatically prevents the FDA from approving the ANDA until the earlier of 30 months, expiration of the patent, settlement of the lawsuit or a decision in the infringement case that is favorable to the ANDA applicant.

The ANDA application also will not obtain final approval until any non-patent exclusivity, such as exclusivity for obtaining approval of an NDA for a new chemical entity, has expired. Federal law provides a period of five years following approval of a drug containing no previously approved active moiety, during which ANDAs for generic versions of those drugs cannot be submitted unless the submission contains a Paragraph IV certification, in which case the submission may be made four years following the original product approval. Following approval of an application to market a drug that contains previously approved active ingredients in a new dosage form, route of administration or

combination, or for a new condition of use that was required to be supported by new clinical trials conducted by or for the sponsor, the FDC Act provides for an exclusivity period of three years, during which the FDA cannot grant effective approval of an ANDA for such new condition of use, dosage form or strength that meets certain statutory requirements. Both of the five-year and three-year exclusivity periods, as well as any unexpired patents listed in the Orange Book for the listed drug, can be extended by six months if the FDA grants the NDA sponsor a period of pediatric exclusivity based on studies submitted by the sponsor in response to a written request.

The Hatch-Waxman Act provides that patent terms may be extended to compensate for some of the patent life that is lost during the FDA regulatory review period for a product. This extension period would generally be one-half the time between the effective date of an IND and the submission date of an NDA, plus all of the time between the submission date of an NDA and its approval, subject to a maximum extension of five years. Similar patent term extensions are available under European laws. Following FDA approval, we filed a patent term extension application with the United States Patent and Trademark Office for our patent covering the method of treating PAH using Remodulin. The application was approved in February 2005 with the maximum patent term extension of five years for a patent that expired on October 6, 2014.

We have received Paragraph IV certification letters from Sandoz and Teva advising that each has submitted an ANDA to the FDA requesting approval to market a generic version of Remodulin. For further details, see *Item 3.—Legal Proceedings.*

Section 505(b)(2) New Drug Applications

Most drug products (other than biological products) obtain FDA marketing approval pursuant to an NDA submitted under Section 505(b)(1) of the FDCA, or an ANDA. A third alternative is a special type of NDA submitted under Section 505(b)(2) of the FDCA, commonly referred to as a Section 505(b)(2) NDA, which enables the applicant to rely, in part, on the FDA's finding of safety and efficacy data for an existing product, or published literature, in support of its application.

Section 505(b)(2) NDAs may provide an alternate path to FDA approval for new or improved formulations or new uses of previously approved products. Section 505(b)(2) permits the filing of an NDA in which the applicant relies, at least in part, on information from studies made to show whether a drug is safe or effective that were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use. A Section 505(b)(2) applicant may eliminate the need to conduct certain preclinical or clinical studies, if it can establish that reliance on studies conducted for a previously-approved product is scientifically appropriate. The FDA may also require companies to perform additional studies or measurements to support the change from the approved product. The FDA may then approve the new product candidate for all or some of the labeled indications for which the referenced product has been approved, as well as for any new indication for which the Section 505(b)(2) NDA applicant has submitted data.

To the extent that the Section 505(b)(2) applicant is relying on prior FDA findings of safety and efficacy, the applicant is required to certify to the FDA concerning any patents listed for the previously approved product in the Orange Book to the same extent that an ANDA applicant would. Thus, approval of a Section 505(b)(2) NDA can be delayed until all the listed patents claiming the referenced product have expired, until any non-patent exclusivity, such as exclusivity for obtaining approval of a new chemical entity, listed in the Orange Book for the referenced product has expired, and, in the case of a Paragraph IV certification and subsequent patent infringement suit, until the earlier of 30 months, settlement of the lawsuit or a decision in the infringement case that is favorable to the Section 505(b)(2) applicant.

Other Regulatory Requirements

Once an NDA or a BLA is approved, the product will be subject to continuing regulations. For instance, the FDA closely regulates the post-approval marketing, labeling and advertising of prescription drugs, including the standards and regulations for direct-to-consumer advertising, off-label promotion, industry-sponsored scientific and educational activities and promotional activities involving the internet. Pharmaceutical products may be marketed only for their approved indications and in accordance with the provisions of their approved labeling. The FDA and other agencies actively enforce the laws and regulations prohibiting promotion of off-label uses, and a company that is found to have engaged in off-label promotion may be subject to significant liability.

Certain changes to the conditions established in an approved application, including changes in indications, labeling, equipment, or manufacturing processes or facilities, will require submission and FDA approval of an NDA or BLA or supplement thereto before the change can be implemented. An NDA or BLA supplement for a new indication typically requires clinical data similar to that in the original application, and the FDA uses the same procedures and actions in reviewing supplements as it does in reviewing NDAs or BLAs.

Adverse event reporting and submission of periodic reports continue to be required following FDA approval of an NDA or a BLA. The FDA also may require post-marketing testing, including phase IV clinical studies, risk minimization action plans, and surveillance to monitor the effects of an approved product or may place conditions on an approval that could restrict the distribution or use of the product. In addition, quality control as well as drug manufacture, packaging, and labeling procedures must continue to conform to cGMP requirements. Manufacturers and certain of their contractors are required to register their establishments with the FDA and certain state agencies, and are subject to periodic unannounced inspections by the FDA and these state agencies, to assess compliance with cGMP requirements. Accordingly, manufacturers must continue to expend time, money and effort in the areas of production and quality control to maintain compliance with cGMP requirements. Regulatory authorities may withdraw product approvals or request product recalls if a company fails to comply with regulatory standards or if previously unrecognized problems are subsequently discovered. Later discovery of previously unknown problems with a product, including adverse events or problems with manufacturing processes of unanticipated severity or frequency, or failure to comply with regulatory requirements, may also result in (1) revisions to the approved labeling to add new safety information; (2) imposition of post-market studies or clinical trials to assess new safety risks; or (3) imposition of distribution or other restrictions under a REMS program. Other potential consequences include, among other things, (1) restrictions on the marketing or manufacturing of the product; (2) fines, warning letters or holds on post-approval clinical trials; (3) refusal of the FDA to approve pending NDAs or supplements to approved NDAs, or suspension or revocation of product license approvals; (4) product seizure or detention, or refusal to permit the import or export of products; or (5) injunctions or the imposition of civil or criminal penalties.

Marketing Pharmaceutical Products Outside the United States

Outside of the United States, our ability to market our products is also contingent upon receiving marketing authorizations from regulatory authorities. The foreign regulatory approval process may include some or all of the risks associated with the FDA review and approval process set forth above, and the requirements governing the conduct of clinical trials and marketing authorization vary widely from country to country.

In the EU, marketing authorizations may be submitted through a centralized body or through a decentralized/mutual recognition or a national level process. The centralized procedure is mandatory for the approval of certain products, such as officially designated orphan medicines and medicines derived from biotechnology and high technology processes, and may be available at the applicant's option for other products that are a significant therapeutic, scientific or technical innovation or for which approval would be in the interest of public health. The centralized procedure provides for the grant of a single marketing authorization that is valid in the EEA, which consists of the EU member countries and Norway, Iceland, and Lichtenstein. The decentralized/mutual recognition procedures are available for all medicinal products that are not subject to the centralized procedure. Each EU member country has its own procedure for approval. A company may use the decentralized procedure to submit applications for marketing authorization in more than one EU country simultaneously for a product that has not previously been authorized in an EU country. In addition, the mutual recognition procedure provides for mutual recognition of national approval decisions, changes existing procedures for national approvals and establishes procedures for coordinated EU actions on products, suspensions and withdrawals. Under this procedure, the holder of a national marketing authorization for which mutual recognition is sought may submit an application to one or more EU member countries, certify that the dossier is identical to that on which the first approval was based, or explain any differences and certify that identical dossiers are being submitted to all EU member countries for which recognition is sought. Within 90 days of receiving the application and assessment report, each EU member country is required to decide whether to recognize approval. The procedure encourages member states to work with applicants and other regulatory authorities to resolve disputes concerning mutual recognition. Arbitration may be initiated when member countries fail to reach agreement. Following receipt of marketing authorization in an EU member country, the applicant is then usually (depending on the country) required to engage in pricing discussions and negotiations with a separate prescription pricing authority in that country. Commercial sales typically only commence in a country once pricing approval has been obtained.

To secure European regulatory approvals for subcutaneous Remodulin for PAH, we used the mutual recognition process. Under the rules then applicable, centralized filing was not required and we perceived the decentralized/mutual recognition procedure to be the most effective means for approval. We filed our first MAA in France in February 2001. Review of our application was completed in 2005. As a result, Remodulin was approved in 23 member countries of the EEA under the mutual recognition process described above. We withdrew applications in Spain, the United Kingdom and Ireland and are currently evaluating resubmitting applications in Spain and Ireland. In December 2011, we received approval for intravenous Remodulin in all of the 23 EEA member nations where subcutaneous Remodulin is approved.

To secure European regulatory approval for Tyvaso, we submitted an MAA to the EMA via the centralized process in 2008. Regulations in Europe have changed since we made our initial filing for Remodulin and all therapies for orphan diseases must now use the centralized process. In February 2010, we withdrew our MAA from consideration by the EMA, and do not currently intend to resubmit it as a standalone treatment for PAH, due to the EMA's major objection related to findings of non-compliance with good clinical practice at two clinical sites. The EMA stated that these findings would preclude a recommendation for approval of Tyvaso in the EU. The EMA had no major objections at the time of withdrawal related to the safety or efficacy of Tyvaso.

Biologics

Biological products used for the prevention, treatment, or cure of a disease, or condition, of a human being are subject to regulation under the FDC Act and the Public Health Service Act (PHSA). Biological products are approved for marketing via a BLA that follows an application process and approval requirements that are very similar to those for NDAs. To help reduce the increased risk of the

introduction of adventitious agents, the PHSA emphasizes the importance of manufacturing control for products whose attributes cannot be precisely defined. The PHSA also provides authority to the FDA to immediately suspend licenses in situations where there exists a danger to public health, to prepare or procure products in the event of shortages and critical public health needs, and to authorize the creation and enforcement of regulations to prevent the introduction, or spread, of communicable diseases in the United States.

After a BLA is approved, the product may also be subject to official lot release. As part of the manufacturing process, the manufacturer is required to perform certain tests on each lot of the product before it is released for distribution. If the product is subject to official lot release by the FDA, the manufacturer submits samples of each lot of product to the FDA together with a release protocol showing a summary of the history of manufacture of the lot and the results of all of the manufacturer's tests performed on the lot. The FDA may also perform certain confirmatory tests on lots of some products, such as viral vaccines, before releasing the lots for distribution by the manufacturer. In addition, the FDA conducts laboratory research related to the regulatory standards on the safety, purity, potency, and effectiveness of biological products. As with drugs, after approval of biologics, manufacturers must address any safety issues that arise, are subject to recalls or a halt in manufacturing, and are subject to periodic inspection after approval.

The Patient Protection and Affordable Care Act of 2010, as amended by the Health Care and Education Reconciliation Act of 2010 (PPACA), included a subtitle called the Biologics Price Competition and Innovation Act of 2009, or BPCI Act, which created an abbreviated approval pathway for biological products shown to be similar to, or interchangeable with, an FDA-licensed reference biological product. This is conceptually similar to the Hatch-Waxman Act in that it attempts to minimize duplicative testing. Biosimilarity, which requires that there be no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency must be shown through analytical studies, animal studies, and at least one clinical study absent a waiver. Interchangeability requires that a product must demonstrate that it can be expected to produce the same clinical results as the reference product and, for products administered multiple times, the biologic and the reference biologic may be switched after one has been previously administered without increasing safety risks or risks of diminished efficacy relative to exclusive use of the reference biologic. However, intricacies associated with the larger, and often more complex, structures of biological products, as well as the processes by which such products are manufactured, pose significant hurdles to implementation that are still being addressed by the FDA. In August 2014, the FDA issued draft guidance to address how biological products approved under the PHSA are granted periods of exclusivity.

A reference biologic is granted twelve years of exclusivity from the time of first licensure of the reference product. The first biologic product submitted under the abbreviated approval pathway that is determined to be interchangeable with the reference product has exclusivity against other biologics submitted under the abbreviated approval pathway for the lesser of (a) one year after first commercial marketing; (b) eighteen months after approval of the initial application if there is no legal challenge; (c) eighteen months after the resolution in the applicant's favor of a lawsuit challenging the biologics' patents if an application has been submitted; or (d) 42 months after the application has been approved if a lawsuit is ongoing within the 42 month period.

Because biologically sourced raw materials are subject to unique contamination risks, their use may be restricted in some countries.

Cell and Tissue Based Biologics

Manufacturers of cell and tissue based products must comply with the FDA's current good tissue practices (cGTP), which are FDA regulations that govern the methods used in, and the facilities and

controls used for, the manufacture of such products. The primary intent of the cGTP requirements is to ensure that cell and tissue based products are manufactured in a manner designed to prevent the introduction, transmission and spread of communicable diseases. Cell and tissue based products may also be subject to the same approval standards, including demonstration of safety and efficacy, as other biologic and drug products, if they meet certain criteria such as if the cells or tissues are more than minimally manipulated or if they are intended for a non-homologous use (a use different from the cell's origin).

U.S. Regulation of Medical Devices

Medical devices are also subject to FDA approval and extensive regulation under the FDC Act. Under the FDC Act, medical devices are classified into one of three classes: Class I, Class II, or Class III. The classification of a device into one of these three classes generally depends on the degree of risk associated with the medical device and the extent of control needed to ensure safety and effectiveness.

Class I devices are those for which safety and effectiveness can be assured by adherence to a set of general controls. These general controls include compliance with the applicable portions of the FDA's Quality System Regulation (QSR), which sets forth good manufacturing practice requirements; facility registration and product listing; reporting of adverse medical events; truthful and non-misleading labeling; and promotion of the device only for its cleared or approved intended uses. Class II devices are also subject to these general controls and to any other special controls as deemed necessary by the FDA to ensure the safety and effectiveness of the device. Review and clearance by the FDA for these devices is typically accomplished through the so-called 510(k) pre-market notification procedure. A Class III device requires approval of a premarket approval application (PMA), an expensive, lengthy and uncertain process that can require many years to complete. Most Class II and Class III medical devices may only be marketed in the United States if the FDA has approved a PMA application for the device or cleared the device in response to a 510(k) submission. There is also an alternative pathway to approval for low or moderate risk devices that are not classified and for which no predicate device exists, known as de novo classification.

When 510(k) clearance is sought, a sponsor must submit a pre-market notification demonstrating that the proposed device is substantially equivalent to a previously marketed device, also referred to as a "predicate" device. If the FDA agrees that the proposed device is substantially equivalent to the predicate device, then 510(k) clearance to market will be granted. After a device receives 510(k) clearance, any modification that could significantly affect its safety or effectiveness, or that would constitute a major change in its intended use, requires a new 510(k) clearance or could require pre-market approval.

Clinical trials are almost always required to support a PMA and are sometimes required for a 510(k) pre-market notification. These trials generally require FDA approval by submitting an application for an investigational device exemption, or IDE application. An IDE application must be supported by preclinical data, such as animal and laboratory testing results, which show that the device is safe to test in humans and that the study protocols are scientifically sound. Studies of devices that pose a significant risk require approval from both the FDA and an Institutional Review Board (IRB) prior to initiation of the study. A "nonsignificant" risk device study does not require submission of an IDE application to the FDA but does require IRB approval prior to initiation of the study. Nonsignificant risk device studies must comply with abbreviated IDE requirements.

Both before and after a medical device is commercially distributed, manufacturers and marketers of the device have ongoing responsibilities under FDA regulations. The FDA reviews design and manufacturing practices, labeling and record keeping, and manufacturers' required reports of adverse experiences and other information to identify potential problems with marketed medical devices.

Device manufacturers are subject to periodic and unannounced inspection by the FDA for compliance with the QSR, current good manufacturing practice requirements that govern the methods used in, and the facilities and controls used for, the design, manufacture, packaging, servicing, labeling, storage, installation, and distribution of all finished medical devices intended for human use.

If the FDA finds that a manufacturer has failed to comply or that a medical device is ineffective or poses an unreasonable health risk, it can institute or seek a wide variety of enforcement actions and remedies, ranging from a public warning letter to more severe actions such as:

- fines, injunctions, and civil penalties;
- recall or seizure of products;
- operating restrictions, partial suspension or total shutdown of production;
- refusing requests for 510(k) clearance or PMA approval of new products;
- withdrawing 510(k) clearances or PMA approvals already granted; and
- criminal prosecution.

The FDA also has the authority to require repair, replacement or refund of the cost of a medical device under certain circumstances.

The FDA also administers certain controls over the import and export of medical devices to and from the United States. Additionally, each foreign country subjects such medical devices to its own regulatory requirements. In the EU, a single regulatory approval process has been created, and approval is represented by the CE Mark.

The nebulizer used with our Tyvaso Inhalation System was included in our NDA for Tyvaso as a combination product, and was cleared by the FDA subject to compliance with the QSR as it applies to combination products. In 2012, we received FDA approval for a modified Tyvaso Inhalation System using an updated nebulizer (TD-100) based on the results of the completion of the QSR compliance commitments.

Government Reimbursement of Pharmaceutical Products

In the United States, many independent third-party payers, as well as the Medicare and State Medicaid programs, reimburse buyers of our commercial products. Medicare is the federal program that provides health care benefits to senior citizens and certain disabled and chronically ill persons. Medicaid is the federal program jointly funded and administered by the states to provide health care benefits to certain indigent persons. The Medicare contractors who administer the program provide reimbursement for Remodulin at a rate equal to 95% of the published average wholesale price as of October 1, 2003 (the Medicare Part B payment formula, under the Durable Medical Equipment Regional Carrier Guidelines, for drugs infused through durable medical equipment) and for Tyvaso at a rate of 106% of the average sales price (the Medicare Part B payment formula for drugs inhaled through durable medical equipment and also under the Durable Medical Equipment Regional Carrier Guidelines). Adcirca and Orenitram, oral drugs, are reimbursed under the Medicare Part D program. The State Medicaid programs also generally provide reimbursement for our commercial products, at reimbursement rates that are below the published average wholesale price and that vary from state to state. In return for including our pharmaceutical commercial products in the Medicare Part B and Medicaid programs, we have agreed to pay a rebate to State Medicaid agencies that provide reimbursement for those products. We have also agreed to sell our commercial products under contracts with the Department of Veterans Affairs, Department of Defense, Public Health Service and numerous other federal agencies as well as certain hospitals that are designated as 340B covered entities (entities designated by federal programs to receive drugs at discounted prices) at prices that are

significantly below the price we charge to our specialty pharmaceutical distributors. These programs and contracts are highly regulated and impose restrictions on our business. Failure to comply with these regulations and restrictions could result in a loss of our ability to continue receiving reimbursement for our drugs, exclusion of our products from reimbursement under the federal healthcare programs, or debarment, and expose us to liability under federal and state false claims laws. We estimate that between 35-50% of Remodulin, Tyvaso, Orenitram and Adcirca sales are reimbursed under the Medicare and Medicaid programs.

Anti-Kickback, False Claims Laws and The Prescription Drug Marketing Act

In addition to FDA restrictions on marketing pharmaceutical, biological and medical device products, several other types of state and federal laws have been applied to restrict certain marketing practices in the pharmaceutical and medical device industries in recent years. These laws include anti-kickback statutes and false claims statutes. The federal healthcare program anti-kickback statute prohibits, among other things, knowingly and willfully offering, paying, soliciting or receiving remuneration to induce or in return for purchasing, leasing, ordering or arranging for the purchase, lease or order of, or referring an individual for the furnishing of, any healthcare item or service reimbursable under Medicare, Medicaid or other federally financed healthcare programs. This statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on the one hand and prescribers, purchasers and formulary managers on the other. Violations of the anti-kickback statute are punishable by imprisonment, criminal fines, civil monetary penalties and exclusion from participation in federal healthcare programs. Although there are a number of statutory exemptions and regulatory safe harbors protecting certain common activities from prosecution or other regulatory sanctions, the exemptions and safe harbors are drawn narrowly, and practices that involve remuneration intended to induce prescribing, purchases or recommendations may be subject to scrutiny if they do not qualify for an exemption or safe harbor.

The federal False Claims Act prohibits any person from, among other things, knowingly presenting, or causing to be presented, a false claim for payment to the federal government, or knowingly making, or causing to be made, a false statement material to a false claim. Many pharmaceutical and other healthcare companies have been prosecuted under the False Claims Act for allegedly inflating drug prices they report to pricing services, which in turn were used by the government to set Medicare and Medicaid reimbursement rates, and for allegedly providing free product to customers with the expectation that the customers would bill federal programs for the product. In addition, companies have been prosecuted under the False Claims Act on the basis of allegations relating to marketing practices, including off-label promotion. The majority of states also have statutes or regulations similar to the federal anti-kickback statute and False Claims Act, which apply to items and services reimbursed under Medicaid and other state programs, or, in several states, apply regardless of the payer. Sanctions under these federal and state laws may include civil penalties, exclusion of a manufacturer's products from reimbursement under government programs, criminal fines, and imprisonment.

In December 2013, we received a subpoena from the Office of the Inspector General of the Department of Health and Human Services reflecting a civil investigation by the United States Department of Justice, principally represented by the United States Attorney's Office for the District of Maryland. The subpoena requests documents regarding Remodulin, Tyvaso and Adcirca, including our marketing practices relating to these products. For further details, see *Item 3.—Legal Proceedings.*

As part of the sales and marketing process, pharmaceutical companies frequently provide samples of approved drugs to physicians. The Prescription Drug Marketing Act (PDMA) imposes requirements and limitations upon the distribution of drugs and drug samples, and prohibits states from licensing distributors of prescription drugs unless the state licensing program meets certain federal guidelines that include minimum standards for storage and handling, as well as record keeping requirements for information regarding sample requests and distribution. The PDMA sets forth civil and criminal

penalties for violations. In addition, PPACA requires manufacturers and distributors to submit similar drug sample information to FDA.

Patient Protection and Affordable Care Act of 2010

PPACA is intended to expand healthcare coverage within the United States. Several provisions of the law, which have varying effective dates, have impacted us and have increased certain of our costs. PPACA imposes an annual fee on pharmaceutical manufacturers, based on the manufacturer's sale of branded pharmaceuticals and biologics (excluding orphan drugs) to certain U.S. government programs during the preceding year; expands the 340B drug discount program (excluding orphan drugs) including the creation of new penalties for non-compliance; and includes a 50% discount on brand name drugs for Medicare Part D participants in the coverage gap, or "donut hole." Effective beginning in 2010, the law also revised the definition of "average manufacturer price" for reporting purposes, which could increase the amount of the Medicaid drug rebates paid to states.

As noted above under *Governmental Regulation—Biologics* , the PPACA also created a regulatory pathway for the abbreviated approval of biological products that are demonstrated to be "biosimilar" or "interchangeable" with an FDA-approved biological product. In addition, PPACA imposes new annual reporting requirements for pharmaceutical, biological and device manufacturers with regard to payments or other transfers of value made to physicians and teaching hospitals. In addition, pharmaceutical, biological and device manufacturers are required to report annually investment interests held by physicians and their immediate family members during the preceding calendar year. Such information was required to be made publicly available by the Secretary of Health and Human Services in a searchable format beginning on September 30, 2014. CMS has stated that it plans to publish the 2014 payment data and make any applicable updates to the 2013 data in June 2015. Failure to submit required information may result in civil monetary penalties of up to $150,000 per year (and up to $1 million per year for "knowing failures") for all payments, transfers of value or ownership or investment interests not reported in an annual submission. Further, the PPACA amends the intent requirement of the federal anti-kickback and criminal health care fraud statute. A person or entity no longer needs to have actual knowledge of these statutes or specific intent to violate them. In addition, the government may assert that a claim including items or services resulting from a violation of the federal anti-kickback statute constitutes a false or fraudulent claim for purposes of the False Claims Act.

State Pharmaceutical and Medical Device Marketing Laws

If not preempted by the PPACA, several jurisdictions, including the District of Columbia, Maine, Massachusetts, Minnesota, Vermont and West Virginia, require pharmaceutical companies to report expenses relating to the marketing and promotion of pharmaceutical products and to report gifts and payments to healthcare practitioners in those jurisdictions. Some of these jurisdictions also prohibit various marketing related activities. Still other states require the posting of information relating to clinical studies and their outcomes. In addition, certain states, such as California, Connecticut, Nevada, and Massachusetts, require pharmaceutical companies to implement compliance programs or marketing codes and several other states are considering similar proposals. Compliance with these laws is difficult and time consuming, and companies that do not comply with these state laws face civil penalties or other civil enforcement action.

Employees

We had 740 employees as of February 7, 2015. The success of our business is highly dependent on attracting and retaining highly talented and qualified personnel.

Industry Segments and Geographic Areas

Since March 2011, our core business has been pharmaceuticals, in which we closely monitor the revenues and gross margins generated by our commercial products. We sell our products in the United States and throughout the rest of the world. The information required by Item 101 (b) and 101(d) of Regulation S-K relating to financial information about industry segments and geographical areas, respectively, is contained in Note 17 —*Segment Information* to our consolidated financial statements included in this Annual Report on Form 10-K.

Corporate Website

Our Internet website address is *http://www.unither.com* . Our filings on Form 10-K, Form 10-Q, Form 3, Form 4, Form 5, Form 8-K and any and all amendments thereto are available free of charge through this internet website as soon as reasonably practicable after they are filed with or furnished to the Securities and Exchange Commission (SEC). They are also available through the SEC at *http://www.sec.gov/edgar/searchedgar/companysearch.html* .

EXECUTIVE OFFICERS OF THE REGISTRANT

The following is a list, as of February 17, 2015, setting forth certain information regarding our executive officers. Each executive officer holds office until the first meeting of the Board of Directors after the annual meeting of shareholders, and until his or her successor is elected and qualified or until his or her earlier resignation or removal. Each executive officer's employment will end pursuant to the terms of his or her employment contract. Each of the employment contracts generally provides for an initial term of service of five years, which five-year term may be renewed after each year for additional one-year periods.

Name	Age	Position
Martine A. Rothblatt, Ph.D., J.D., M.B.A.	60	Chairman, Co-Chief Executive Officer and Director
Roger Jeffs, Ph.D.	53	President, Co-Chief Executive Officer and Director
David Zaccardelli, Pharm.D.	50	Executive Vice President and Chief Operating Officer
John M. Ferrari	60	Chief Financial Officer
Paul A. Mahon, J.D.	51	Executive Vice President, General Counsel and Corporate Secretary

Martine A. Rothblatt, Ph.D., J.D., M.B.A ., founded United Therapeutics in 1996 and has served as Chairman and Chief Executive Officer since its inception. In January 2015, she became United Therapeutics' Co-Chief Executive Officer upon the promotion of Roger Jeffs to Co-Chief Executive Officer. Prior to United Therapeutics, she founded and served as Chairman and Chief Executive Officer of SiriusXM Satellite Radio. She is a co-inventor on three of our patents pertaining to treprostinil.

Roger Jeffs, Ph.D., received his undergraduate degree in chemistry from Duke University and his Ph.D. in pharmacology from the University of North Carolina. Dr. Jeffs joined United Therapeutics in September 1998 as Director of Research, Development and Medical. He was promoted to Vice President of Research, Development and Medical in 2000 and to President and Chief Operating Officer in 2001. In January 2015, Dr. Jeffs was promoted to Co-Chief Executive Officer. On From 1993 to 1995, Dr. Jeffs worked at Burroughs Wellcome & Company where he was a member of the clinical research team that developed Flolan, the first FDA-approved therapy for patients with PAH. From 1995 to 1998, Dr. Jeffs worked at Amgen, Inc. where he served as the worldwide clinical leader

of the Infectious Disease Program. Dr. Jeffs currently leads our global clinical, commercial, manufacturing, regulatory, pharmacovigilance and business development efforts.

David Zaccardelli , Pharm.D., received his doctor of pharmacy from the University of Michigan. Dr. Zaccardelli joined United Therapeutics in 2004 as Vice President, Pharmaceutical Development. He was promoted to Senior Vice President, Pharmaceutical Development in 2006, to Executive Vice President, Pharmaceutical Development in 2007, Executive Vice President, Pharmaceutical Development & Operations in April 2008 and to Chief Manufacturing Officer and Executive Vice President, Pharmaceutical Development in November 2008. In January 2015, Dr. Zaccardelli was promoted to Executive Vice President and Chief Operating Officer. From 1988 to 1996, Dr. Zaccardelli worked at Burroughs Wellcome & Company and Glaxo Wellcome, Inc. in a variety of clinical research positions. He also served as Director of Clinical and Scientific Affairs for Bausch & Lomb Pharmaceuticals, Inc. from 1996 to 1997. Dr. Zaccardelli founded and led a startup company focused on contract pharmaceutical development services from 1997 through 2003.

John M. Ferrari joined United Therapeutics in May 2001 as Controller. Mr. Ferrari was promoted to Vice President of Finance in December 2003 and to Vice President of Finance and Treasurer in June 2004. In August 2006, Mr. Ferrari was promoted to Chief Financial Officer. Prior to joining United Therapeutics, Mr. Ferrari served as Controller for Blackboard, Inc., from 1998 to 2001. Prior to his employment with Blackboard, Inc., Mr. Ferrari served in various senior financial management positions since beginning his accounting career in 1984.

Paul A. Mahon, J.D., has served as General Counsel and Corporate Secretary of United Therapeutics since its inception in 1996. In June 2001, Mr. Mahon joined United Therapeutics full-time as Senior Vice President, General Counsel and Corporate Secretary. In November 2003, Mr. Mahon was promoted to Executive Vice President, General Counsel and Corporate Secretary. Prior to June 2001, he served United Therapeutics, beginning with its formation in 1996, in his capacity as principal and managing partner of a law firm specializing in technology and media law.

ITEM 1A. RISK FACTORS

Forward-Looking Statements

This Annual Report on Form 10-K contains forward-looking statements made pursuant to the safe harbor provisions of Section 21E of the Securities Exchange Act of 1934 (the Exchange Act) and the Private Securities Litigation Reform Act of 1995. These statements, which are based on our beliefs and expectations as to future outcomes, include, among others, statements relating to the following:

- Expectations of revenues, expenses, profitability, and cash flows, including our expectation that Orenitram ® (treprostinil) Extended Release Tablets (Orenitram) cost of product sales as a percentage of its net revenue will become comparable to our other treprostinil-based products;
- The sufficiency of current and future working capital to support operations;
- Our ability to obtain financing;
- Our expectations that we will pay the full principal balance due on the converting Convertible Notes upon settlement of early conversions or upon its maturity and that we have sufficient financial resources available to pay all amounts due;
- The value of our common stock and our ability and plans to complete our current common stock repurchase program;
- The maintenance of domestic and international regulatory approvals;
- The expected volume and timing of sales of our existing commercial products—Remodulin ® (treprostinil) Injection (Remodulin), Tyvaso ® (treprostinil) Inhalation Solution (Tyvaso),

Orenitram and Adcirca ® (tadalafil) Tablets (Adcirca)—and potential future commercial products such as ch14.18, our antiviral drugs and esuberaprost;

- The timing and outcome of clinical studies, regulatory filings, product launches and sales, including: (1) our plans to complete our FREEDOM-EV study of Orenitram; (2) our aim to obtain United States Food and Drug Administration (FDA) approval for Orenitram as a combination therapy; (3) our plan to file for approval of Orenitram in Europe upon the successful completion of the FREEDOM-EV study; (4) our program with Medtronic, Inc. (Medtronic) to develop an implantable pump to administer intravenous Remodulin; (5) the outcome of our FDA biologics license application and European Medicines Agency (EMA) marketing authorization application for ch14.18; (6) our phase III clinical trial of esuberaprost in combination with Tyvaso; and (7) our collaboration with DEKA Research & Development Corp. to develop a pre-filled, semi-disposable pump system for subcutaneous Remodulin.
- The outcome of potential future regulatory actions, including audits and inspections, by the FDA and international regulatory agencies;
- The impact of competing therapies, including generic products (such as generic sildenafil) and newly-developed therapies (such as selexipag, also known as Uptravi ®), on sales of our commercial products;
- The expectation that we will be able to produce sufficient quantities and maintain adequate inventories of our commercial products, through both our in-house production capabilities and third-party production sites, and our ability to obtain and maintain related approvals by the FDA and other regulatory agencies;
- The adequacy of our intellectual property protections and the validity and expiration dates of the patents we own or license;
- Our expectations regarding our ability to defend our intellectual property relating to Remodulin against generic and other challenges, including but not limited to our ongoing litigation with Sandoz Inc. (Sandoz) and Teva Pharmaceuticals USA, Inc. (Teva);
- Our expectations regarding the subpoena by the Office of Inspector General (OIG) of the U.S. Department of Health and Human Services relating to Remodulin, Tyvaso and Adcirca, including our marketing practices relating to these products, and the related investigation by the United States Department of Justice;
- Any statements that include the words "believe," "seek," "expect," "anticipate," "forecast," "project," "intend," "estimate," "should," "could," "may," "will," "plan," or similar expressions; and
- Other statements contained or incorporated by reference in this Annual Report on Form 10-K that are not historical facts.

The statements identified as forward-looking statements may appear in *Item 7—Management's Discussion and Analysis of Financial Condition and Results of Operations* or elsewhere in this Annual Report on Form 10-K. These statements are subject to risks and uncertainties and our actual results may differ materially from anticipated results. Factors that may cause such differences include, but are not limited to, those discussed below. We undertake no obligation to publicly update forward-looking statements, whether as a result of new information, future events or otherwise.

Risks Related to Our Business

We rely heavily on sales of Remodulin, Tyvaso and Adcirca to generate revenues and support our operations.

Sales of Remodulin, Tyvaso and Adcirca comprise substantially all of our revenues. A wide variety of events, many of which are described in other risk factors below, could cause sales of these products to decline. For instance, we would be unable to sell any of these products if their regulatory approvals were withdrawn. Any substantial change in the prescribing practices or dosing patterns of patients using Remodulin, Tyvaso or Adcirca due to combination or competing therapies, side effects, adverse events, deaths or any other reasons could decrease related revenues. We also face potential generic competition. For example, during the fourth quarter of 2012, generic sildenafil became commercially available, which could negatively affect future demand for Adcirca. We are also defending our intellectual property related to Remodulin against generic challenges by Sandoz and Teva. In addition, we rely on third parties to produce, market, distribute and sell Remodulin, Tyvaso and Adcirca. The inability of any one of these third parties to perform these functions satisfactorily could result in a reduction in sales. In addition, any failure to effectively manage our internal production processes could result in an inability to meet patient demand. Because we are highly dependent on sales of Remodulin, Tyvaso and Adcirca, a reduction in sales of any one of these products could have a negative and material adverse impact on our operations.

If our products fail in clinical trials, we will be unable to obtain or maintain FDA and international regulatory approvals and will be unable to sell those products.

To obtain regulatory approvals from the FDA and international regulatory agencies such as the EMA, we must conduct clinical trials demonstrating that our products are safe and effective. In the past, several of our product candidates failed or were discontinued at various stages in the development process. Moreover, we may need to amend ongoing trials or the FDA and/or international regulatory agencies may require us to perform additional trials beyond those we planned. Such occurrences could result in significant delays and additional costs, and related clinical trials may be unsuccessful. Approval of a new drug application or biologics license application could be subject to delays if the FDA determines that it cannot review or approve the application as submitted. In such a case, the FDA would issue a refuse-to-file letter or a complete response letter outlining deficiencies in the submission, and the FDA may require substantial additional studies, testing or information in order to complete its review of the application. We may fail to address any of these deficiencies adequately and consequently would be unable to obtain FDA approval to market the product candidate.

In addition, we are enrolling a phase IV clinical trial called FREEDOM-EV, which is a study of Orenitram in combination with other approved pulmonary arterial hypertension (PAH) therapies. One primary endpoint of the study is time to clinical worsening. The primary endpoint of our phase III study of esuberaprost in combination with Tyvaso is also time to clinical worsening. We have not previously conducted a study with a time to clinical worsening primary endpoint. Our inexperience with this type of trial design may impact our ability to conduct these trials appropriately and achieve positive results, or complete the trials within our anticipated timetable. In particular, failure to prove the efficacy of Orenitram in combination with other PAH therapies could materially limit the commercial potential of Orenitram and impede our growth.

The length of time that it takes for us to complete clinical trials and obtain regulatory approval for marketing varies by product, product use and country. Furthermore, we cannot predict with certainty the length of time it will take to complete necessary clinical trials or obtain regulatory approval of our future products.

Our clinical trials may be discontinued, delayed or disqualified for various reasons. These reasons include:

- The drug is ineffective, or physicians and/or patients believe that the drug is ineffective;
- We fail to reach agreement with the FDA or non-U.S. regulatory agencies regarding the scope or design of our clinical trials;
- Patients do not enroll in our studies at the rate we expect;
- We are unable to obtain approval from institutional review boards to conduct clinical trials at their respective sites;
- Ongoing or new clinical trials conducted by drug companies in addition to our own clinical trials reduce the availability of patients for our trials;
- Other investigational or approved therapies are viewed as more effective or convenient by physicians or patients;
- Our clinical trial sites, contracted clinical trial administrators or clinical studies conducted entirely by third parties do not adhere to trial protocols and required quality controls under FDA good clinical practice (GCP) regulations and similar regulations outside the United States;
- Patients experience severe side effects during treatment or die during our trials because of adverse events related to the trial drug, advanced disease, or other medical complications; and
- The results of our clinical trials conducted in countries outside of the United States are not acceptable to the United States or other countries, and the results of our clinical trials conducted in the United States are not acceptable to regulators in other countries.

In addition, the FDA and its international counterparts have substantial discretion over the approval process for pharmaceutical products. As such, these regulatory agencies may not agree that we have demonstrated the requisite level of product safety and efficacy to grant approval.

We may not compete successfully with established and newly developed drugs or products, or the companies that develop and market them.

We compete with well-established drug companies for, among other things, funding, licenses, expertise, personnel, clinical trial patients and investigators, consultants and third-party collaborators. We also compete with these companies for market share. Most of these competitors have substantially greater financial, marketing, manufacturing, sales, distribution and technical resources, and a larger number of approved products, than we do. These competitors also possess greater experience in areas critical to success such as research and development, clinical trials, sales and marketing and regulatory matters. There are several treatments that compete with our commercial therapies, as well as several other therapies under development, such as Actelion's Uptravi (selexipag) drug candidate, which is an oral prostacyclin IP receptor agonist. For the treatment of PAH, we compete with a number of approved products in the United States and worldwide, including the following: Flolan ®, Ventavis ®, Ilomedin ®, Tracleer ®, Revatio ®, Letairis ®, Veletri ®, Adempas ®, Opsumit ®, generic epoprostenol and generic sildenafil citrate. Patients and doctors may perceive these competing products, or products developed in the future, as safer, more effective, more convenient and/or less expensive than our therapies. Alternatively, doctors may reduce the prescribed doses of our products if they prescribe them in combination with our competitors' products. In addition, many competing PAH therapies are less invasive than Remodulin and the use of these products may delay or prevent initiation of Remodulin therapy. Any of these circumstances could negatively impact our operating results.

Development of new products or technologies by others may make our products obsolete or seemingly inferior.

Other companies may introduce new products that may render all or some of our technologies and products obsolete or noncompetitive. For example, both Adempas and Opsumit were recently approved by the FDA for the treatment of PAH. Our commercial therapies may also have to compete with investigational products currently in development, including Uptravi, which was submitted by Actelion in December 2014 to the FDA and EMA for approval to treat PAH. In addition, alternative approaches to treating chronic diseases, such as gene therapy or cell therapy, may make our products obsolete or noncompetitive. If introduced into the market, investigational therapies for PAH could be used in combination with, or as a substitute for, our therapies. If this occurs, doctors may reduce or discontinue the use of our products for their patients.

Sales of our products are subject to reimbursement from government agencies and other third parties. Pharmaceutical pricing and reimbursement pressures may negatively impact our sales.

The commercial success of our products depends, in part, on the availability of reimbursements by governmental payers such as Medicare and Medicaid, and private insurance companies. An estimated 35-50% of Remodulin, Tyvaso and Adcirca sales in the United States are reimbursed under the Medicare and Medicaid programs. In the United States, the European Union and other potentially significant markets for our products such as China and Japan, government payers and/or third-party payers are increasingly attempting to limit or regulate the price of medicinal products and frequently challenge the pricing of new and expensive drugs. Our prostacyclin analogue products (Remodulin, Tyvaso and Orenitram) are expensive therapies. Consequently, it may be difficult for our distributors to obtain adequate reimbursement for our products from third-party payers to motivate such distributors to support our products. Alternatively, third-party payers may reduce the amount of reimbursement for our products based on changes in pricing of other therapies for PAH. If third-party payers do not approve our products for reimbursement, or limit reimbursements, patients and physicians could choose competing products that are approved for reimbursement or provide lower out-of-pocket costs.

In the United States, the federal government and others are increasingly focused on analyzing the impact of various regulatory programs on the federal deficit, which could result in increased pressure on federal programs to reduce costs. In addition, financial pressures may cause the federal government or other third-party payers to seek cost containment more aggressively through mandatory discounts or rebates on our products, policies requiring the automatic substitution of generic products, more rigorous requirements for initial reimbursement approvals for new products or other similar measures. For example, there have been proposals to reduce reimbursement rates and/or adopt mandatory rebates under Medicare Part B, which covers Remodulin and Tyvaso. A reduction in the availability or extent of reimbursement from government health care programs could have a material adverse effect on our business and results of our operations.

In Europe, the success of our commercial products and future products depends largely on obtaining and maintaining government reimbursement at acceptable levels. In many European countries, patients are unlikely to use prescription drugs that are not reimbursed by their governments. Countries in Europe are under increasing pressure to reduce the cost of health care. Changes to current reimbursement policies may adversely affect our ability to sell our products or sell our products on a profitable basis. In many markets outside the United States, governments control the prices of prescription pharmaceuticals through the implementation of reference pricing, price cuts, rebates, revenue-related taxes and profit control. Furthermore, international governments expect prices of prescription pharmaceuticals to decline over the life of the product or as prescription volumes increase. In addition, in December 2011, we received marketing approval for the intravenous use of Remodulin in most of the countries that are members of the European Economic Area (EEA); however, we are in the process of obtaining approval of our risk management plan on a country-by-country basis, and must

obtain pricing approval in each of these member countries before we can market Remodulin. Delays in obtaining these approvals, or failure to obtain satisfactory pricing approvals, could impact our future sales growth. Additionally, in granting pricing approval for the intravenous use of Remodulin, a member country may approve a lower reimbursement price for intravenous Remodulin than for subcutaneous Remodulin, or reduce the reimbursement price for both methods of administering Remodulin. Any regulatory action reducing the reimbursement rates for intravenous and subcutaneous Remodulin could have a material adverse effect on our revenues, results of operations and our business.

Our production strategy exposes us to significant risks.

We must be able to produce sufficient quantities of our commercial products to satisfy the growing demand for our products. We produce Remodulin, Tyvaso and Orenitram, including the active ingredient in each of these products, at our own facilities and rely on third parties for additional production capacity and to produce advanced pharmaceutical ingredients. We rely on Minnetronix, Inc. as the sole manufacturer of the Tyvaso Inhalation System, and on Eli Lilly and Company (Lilly) as the sole manufacturer of Adcirca.

We substantially rely on third parties to adhere to and maintain production processes in accordance with all applicable regulatory requirements. If any of these critical third-party production and supply arrangements are interrupted for compliance issues or other reasons, we may not have sufficient inventory to meet future demand. In addition, any change in suppliers and/or service providers could interrupt the production of our commercial products and impede the progress of our commercial launch plans and clinical trials.

In addition, our internal production process also subjects us to risks as we engage in increasingly complex production processes. For example, Remodulin, Tyvaso and ch14.18 must be formulated in a sterile environment, which is challenging to maintain on a commercial scale. In addition, ch14.18 is a monoclonal antibody. As with all biologic products, monoclonal antibodies are inherently more difficult to produce than our treprostinil-based products and involve increased risk of viral and other contaminants. Finally, we have limited experience producing Orenitram on a commercial scale, and currently all Orenitram production is performed at our own facilities. It could take substantial time to establish an FDA-approved contract manufacturer as an additional supplier of Orenitram, or this process may not be successful at all.

Additional risks we face with our production strategy include the following:

- We and our third-party producers are subject to the FDA's current Good Manufacturing Practices and similar international regulatory standards. We are limited in our ability to exercise control over regulatory compliance by our third-party producers;
- As we expand our production operations to include new elements of the production process or new products, we may experience difficulty designing and implementing processes and procedures to ensure compliance with applicable regulations;
- Even if we and our third-party producers are in compliance with applicable domestic and international drug production regulations, the sterility and quality of the products being produced could be substandard and, therefore, such products would be unavailable for sale or use or subject to recalls;
- If we had to replace our own production operations or a third-party producer, the FDA and its international counterparts would require new testing and compliance inspections. Furthermore, a new producer would have to be familiarized with the processes necessary to produce and commercially validate our products, as producing our treprostinil-based and biologic products is complex;

- We may be unable to contract with needed producers on satisfactory terms or at all; and
- The supply of materials and components necessary to produce and package our products may become scarce or unavailable. Disruptions to the supply of these materials could delay the production and subsequent sale of such products. Any products produced with substituted materials or components would be subject to approval from the FDA and international regulatory agencies before they could be sold. The timing of any such regulatory approval is difficult to predict.

Any of these factors could disrupt sales of our commercial products, delay clinical trials or commercialization of new products, result in product liability claims and product recalls, and entail higher costs. Interruptions in our production process could be significant given the length of time and complexity involved in obtaining necessary regulatory approvals for alternative arrangements, through either third parties or internal manufacturing processes.

We rely in part on third parties to perform activities that are critical to our business. Our ability to generate commercial sales or conduct clinical trials could suffer if our third-party suppliers and service providers fail to perform.

Third parties assist us in: (1) producing our commercial products; (2) conducting clinical trials, preclinical studies and other research and development activities; (3) obtaining regulatory approvals; (4) conducting pharmacovigilance-related and product complaint activities, including drug safety, reporting adverse events and product complaints; and (5) marketing and distributing our products. The involvement of third parties is necessary because we do not possess the internal capacity, and in certain cases the expertise, to perform all of these functions. Accordingly, the success of these third parties in performing their contractual obligations is critical to our operations.

For risks relating to the involvement of third parties in our production process, see the risk factor above, entitled *Our production strategy exposes us to significant risks.*

We rely on Accredo Health Group, Inc. (Accredo) and CVS Health Corporation (CVS) to distribute and sell Remodulin, Tyvaso and Orenitram in the United States. These distributors are also partially responsible for negotiating reimbursements from third-party payers for the cost of our therapies. From time-to-time, we increase the price of products sold to our U.S.-based and international distributors. Our price increases may not be fully reimbursed by third-party payers. If our distributors do not achieve acceptable profit margins on our products, they may reduce or discontinue the sale of our products. Furthermore, if our distributors devote fewer resources to sell our products or are unsuccessful in their sales efforts, our revenues may decline materially. Outside the U.S. we are substantially reliant on our international distributors to maintain regulatory approvals for our products and to market and sell our products in compliance with applicable laws and regulations.

We rely on Lilly to manufacture and supply Adcirca for us, and we use Lilly's pharmaceutical wholesaler network to distribute Adcirca in the United States and Puerto Rico. If Lilly is unable to manufacture or supply Adcirca or its distribution network is disrupted, it could delay, disrupt or prevent us from selling Adcirca, which would slow the growth of our business. In addition, Lilly has the right to determine the wholesale price of Adcirca, which generally moves in parity with the wholesale price Lilly sets for Cialis ® (both of these products contain the same active ingredient). Changes in Lilly's wholesale prices could adversely impact demand or reimbursement for Adcirca, particularly in light of the commercial availability of generic sildenafil, the active ingredient in Revatio, which could be prescribed in lieu of Adcirca.

In addition, any change in service providers could interrupt the distribution of our commercial products and our other products and services, and impede the progress of our clinical trials, commercial launch plans and related revenues.

We rely heavily on third-party contract research organizations, contract laboratories, clinical investigative sites and other third-parties to conduct our clinical trials, preclinical studies and other research and development activities. In addition, the success of certain products we are developing will depend on clinical trials sponsored by third parties. Failure by any third party to conduct or assist us in conducting clinical trials in accordance with study protocols, quality controls and GCP, or other applicable U.S. or international requirements or to submit associated regulatory filings, could limit or prevent our ability to rely on results of those trials in seeking regulatory approvals.

We rely heavily on Medtronic for the success of our program to develop an implantable pump to deliver intravenous Remodulin (the Remodulin Implantable System). Medtronic has completed a clinical study in this regard, and submitted a premarket approval application (PMA) seeking FDA approval for the Remodulin Implantable System. We rely on Medtronic to respond to FDA requests for additional information with respect to its PMA, and following approval we will rely on Medtronic to manufacture the Remodulin Implantable System and to maintain appropriate quality controls relating to the system. As such, we can provide no assurances as to the timing or likelihood of the Remodulin implantable pump program's success.

We are reliant on third parties to supply pumps and other supplies necessary to deliver Remodulin. There are a limited number of pumps available in the market, and the discontinuation of any particular pump could have a material, adverse impact on our Remodulin revenues.

Our operations must comply with extensive laws and regulations in the United States and other countries, including FDA regulations. Failure to obtain approvals on a timely basis or to achieve continued compliance could delay, disrupt or prevent the commercialization of our products.

The products we develop must be approved for marketing and sale by regulatory agencies and, once approved, are subject to extensive regulation. Our research and development efforts must comply with extensive regulations, including those promulgated by the FDA and the United States Department of Agriculture. The process of obtaining and maintaining regulatory approvals for new drugs is lengthy, expensive and uncertain. The regulatory approval process is particularly uncertain for our lung transplantation programs, which include the development of xenotransplantation, regenerative medicine and cell-based products. The manufacture, distribution, advertising and marketing of our products are also subject to extensive regulation, including strict pharmacovigilance and adverse event and medical device reporting requirements. Any future product approvals we receive could be accompanied by significant restrictions on the use or marketing of a given product. Furthermore, our product candidates may fail to receive marketing approval on a timely basis, or at all. If granted, product approvals can be withdrawn for failure to comply with regulatory requirements, such as post-marketing requirements and post-marketing commitments, or upon the occurrence of adverse events subsequent to commercial introduction.

Discovery of previously unknown problems with our marketed products or problems with our manufacturing, regulatory, compliance, research and development, pharmacovigilance and adverse event reporting, marketing or sales activities could result in regulatory restrictions on our products up to and including withdrawal of our products from the market. If we fail to comply with applicable regulatory requirements, we could be subject to penalties that may consist of fines, suspension of regulatory approvals, product recalls, seizure of our products and/or criminal prosecution. In addition, our reputation could be harmed as a result of any such regulatory restrictions or actions, and patients and physicians may avoid the use of our products even after we have resolved the issues that led to such regulatory action.

For example, in December 2013 we received a subpoena from the OIG in connection with a civil investigation by the United States Department of Justice, principally represented by the United States Attorney's Office for the District of Maryland. The subpoena requests documents regarding Remodulin,

Tyvaso and Adcirca, including our marketing practices relating to these products. We are cooperating with the investigation, which has and will continue to increase our legal expenses, and will require significant management time and attention. We are not aware that a claim, litigation or assessment has been asserted in connection with the subpoena. However, such subpoenas are often associated with previously filed qui tam actions brought under the federal and state false claims acts. Qui tam actions are lawsuits brought by private plaintiffs on behalf of the federal government, and often state governments, for alleged federal or state false claims act violations, with potential liability including mandatory treble damages and significant per-claim penalties, currently set at $5,500 to $11,000 per false claim. We may currently be subject to investigation in connection with qui tam actions filed under seal. We also cannot predict what actions, if any, may be taken against us or our employees by the OIG, the Department of Justice, other governmental entities, or any third parties in connection with such investigation, nor can we predict or determine the outcome of the government's investigation or reasonably estimate the amount or range of amounts of fines, damages, restitutions or penalties that might result from a settlement or an adverse outcome. As a result of the investigation we may also be subject to exclusion of our products from reimbursement under the federal healthcare programs, debarment, or a corporate integrity agreement, and certain of our employees may also be subject to exclusion or debarment. Any of these risks and uncertainties, including the conduct of the investigation itself, could adversely affect our revenues, results of operations, cash flows and financial condition.

We are subject to ongoing regulatory review of our currently marketed products.

After our products receive regulatory approval, they remain subject to ongoing regulatory requirements, which can impact, among other things, product labeling, manufacturing practices, pharmacovigilance and adverse event and medical device reporting, complaint processing, storage, distribution, advertising and promotion, and record keeping. If we do not comply with applicable regulations, the range of possible sanctions may include: (1) adverse publicity, (2) product recalls or seizures, (3) fines, (4) total or partial suspensions of production and/or distribution, (5) suspension of marketing applications, and (6) enforcement actions, including injunctions and civil suits or criminal prosecution. Further, the FDA often requires post-marketing testing and surveillance to monitor the effects of approved products. The FDA and comparable international regulatory agencies may condition approval of our product candidates on the completion of such post-marketing clinical studies. These post-marketing studies may suggest that a product causes undesirable side effects or may present a risk to the patient. If data we collect from post-marketing studies suggest that one of our approved products may present an unacceptable safety risk, regulatory authorities could withdraw the product's approval, suspend production or place other marketing restrictions on that product. If regulatory sanctions are applied or if regulatory approval is delayed or withdrawn, our operating results and the value of our company may be adversely affected.

Regulatory approval for our currently marketed products is limited by the FDA and other regulators to those specific indications and conditions for which clinical safety and efficacy have been demonstrated.

Any regulatory approval of our products is limited to specific diseases and indications for which our products have been deemed safe and effective by the FDA. In addition to the FDA approval required for new formulations, any new indication for an approved product also requires FDA approval. If we are not able to obtain FDA approval for any desired future indications for our products, our ability to effectively market and sell our products may be reduced.

While physicians may choose to prescribe drugs for uses that are not described in the product's labeling and for uses that differ from those approved by regulatory authorities (called "off-label" uses), our ability to promote the products is limited to those indications that are specifically approved by the FDA. Although U.S. regulatory authorities generally do not regulate the behavior of physicians, they do restrict communications by companies on the subject of off-label use. If our promotional activities fail

to comply with these regulations or guidelines, we may be subject to warnings from, or enforcement action by, these authorities. In addition, failure to follow FDA rules and guidelines relating to promotion and advertising can result in the FDA's refusal to approve a product, suspension or withdrawal of an approved product from the market, product recalls, fines, disgorgement of money, operating restrictions, civil lawsuits, injunctions or criminal prosecution.

We must comply with various laws in jurisdictions around the world that restrict certain marketing practices in the pharmaceutical and medical device industries. Failure to comply with such laws could result in penalties and have a material adverse effect on our business, financial condition and results of operations.

There are various laws in jurisdictions around the world that restrict particular marketing practices in the pharmaceutical and medical device industries. These laws include, but are not limited to, anti-kickback and false claims statutes, the Foreign Corrupt Practices Act and the UK Bribery Act. Our business activities may be subject to challenge under these laws, and any penalties imposed upon us could have a material adverse effect on our business and financial condition. Furthermore, we have significantly expanded our sales and marketing staff. Any expansion of sales and marketing efforts can increase the risks of noncompliance with these laws. Finally, the growth in our operations outside the United States, both directly and through third-party distributors, also has increased these risks.

In the United States, the federal health care program anti-kickback statute prohibits, among other activities, knowingly and willfully offering, paying, soliciting, or receiving compensation to induce, or in return for, the purchase, lease, order or arranging the purchase, lease or order of any health care product or service reimbursable under any federally financed health-care program. This statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on the one hand and prescribers, purchasers, and formulary managers on the other. The exemptions and safe harbors for this statute are narrow, and practices that involve compensation intended to induce prescriptions, purchases, or recommendations may be subject to scrutiny if they do not qualify for an exemption or safe harbor. Our practices may not always meet all of the criteria for safe harbor protection.

The federal False Claims Act prohibits any person from knowingly presenting or causing to be presented a false claim or knowingly making or causing a false statement material to a false claim. Several pharmaceutical and health care companies have been prosecuted under these laws for allegedly providing free product to customers with the expectation that the customers would bill federal programs for the free product. Other companies have been prosecuted for causing false claims to be submitted because of these companies' marketing of a product for unapproved and non-reimbursable uses. Potential liability under the federal False Claims Act includes mandatory treble damages and significant per-claim penalties, currently set at $5,500 to $11,000 per false claim. The majority of states also have statutes or regulations similar to the federal anti-kickback statute and False Claims Act, which apply to items and services reimbursed under Medicaid and other state programs; furthermore, in several states, these statutes and regulations apply regardless of the payer. Sanctions under these federal and state laws may include civil monetary penalties, exclusion of a manufacturer's product from reimbursement under government programs, debarment, criminal fines, and imprisonment.

In December 2013 we received a subpoena from the OIG reflecting a civil investigation by the United States Department of Justice, principally represented by the United States Attorney's Office for the District of Maryland. The subpoena requests documents regarding Remodulin, Tyvaso and Adcirca, including our marketing practices relating to these products. For further details, see *Part I, Item 3.—Legal Proceedings.*

The Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010 (PPACA), also imposed new reporting requirements for pharmaceutical, biologic and device manufacturers with regard to payments or other transfers of value made to

physicians and teaching hospitals. In addition, pharmaceutical, biologic and device manufacturers, with certain exceptions, are required to report and disclose investment interests held by physicians and their immediate family members during the preceding calendar year. Failure to submit required information may result in civil monetary penalties of up to $150,000 per year (and up to $1.0 million per year for "knowing failures") for all payments, transfers of value or ownership or investment interests not reported in an annual submission.

Further, the PPACA amends the intent requirement of the federal anti-kickback and criminal health care fraud statutes. This amendment provides that a person or entity no longer needs to have knowledge of these statutes or specific intent to violate them. In addition, the government may assert that a claim including items or services resulting from a violation of the federal anti-kickback statute constitutes a false or fraudulent claim for purposes of the False Claims Act.

If not preempted by this federal law, several states currently require pharmaceutical companies to report expenses relating to the marketing and promotion of pharmaceutical products and to report gifts and payments to individual physicians in those states. Depending on the state, legislation may prohibit various other marketing related activities, or require the posting of information relating to clinical studies and their outcomes. In addition, certain states, such as California, Nevada, Connecticut and Massachusetts, require pharmaceutical companies to implement compliance programs or marketing codes and several other states are considering similar proposals. Compliance with these laws is difficult and time consuming, and companies that do not comply with these state laws will face civil penalties.

Government health care reform could increase our costs, which would adversely affect our revenue and results of operations.

Our industry is highly regulated and changes in law may adversely impact our business, operations or financial results. The PPACA is a broad measure intended to expand health care coverage within the United States, primarily through the imposition of health insurance mandates on employers and individuals and expansion of the Medicaid program. The reforms imposed by the law will significantly impact the pharmaceutical industry; however, the full effects of the PPACA will be unknown until all of these provisions are implemented and the Centers for Medicare and Medicaid Services and other federal and state agencies issue applicable regulations or guidance. Moreover, in the coming years, additional changes could be made to governmental health care programs that could significantly impact the success of our products or product candidates.

Reports of actual or perceived side effects and adverse events associated with our products, such as sepsis, could cause physicians and patients to avoid or discontinue use of our products in favor of alternative treatments.

Reports of side effects and adverse events associated with our products could have a significant adverse impact on the sale of our products. An example of a known risk associated with intravenous Remodulin is sepsis, which is a serious and potentially life-threatening infection of the bloodstream caused by a wide variety of bacteria. Intravenous prostacyclin analogues, such as intravenous Remodulin, are infused continuously through a catheter placed in a large vein in the patient's chest, and sepsis is a known risk associated with this type of delivery. As a result, sepsis is included as a risk in the Remodulin package insert, and the occurrence of sepsis is familiar to physicians who prescribe intravenously administered therapies. Concerns about bloodstream infections may affect a physician's decision to prescribe or a patient's willingness to use intravenous Remodulin.

Negative attention from special interest groups may impair our business.

As is common with pharmaceutical and biotechnology companies, our early-stage research and development involves animal testing, which we conduct both directly and through contracts with third

parties. Notwithstanding the vital role of animal research in the drug discovery and development process, certain special interest groups categorically object to the use of animals for research purposes. Historically, our research and development activities have not been the subject of significant animal rights media attention. However, research activities with animals have been the subject of adverse attention, generally including demonstrations near facilities operated by other companies in our industry. Any negative attention, threats or acts of vandalism directed against our animal research activities in the future could impede the operation of our business.

If any of the license or other agreements under which intellectual property rights are licensed to, or were acquired by us, are breached or terminated, our right to continue to develop, produce and sell the products covered by such agreements could be impaired or lost.

Our business depends upon our continuing ability to exploit our intellectual property rights in the drugs and other products that have been discovered and initially developed by others and those which we have commercialized and are developing further. These intellectual property rights have either been licensed to us or have been acquired by us. Under each of our product license agreements, we are granted a license to intellectual property owned by others that covers a drug or other product. Under each of our purchase agreements, we have rights to certain intellectual property. We may be required to license other intellectual property owned by third parties to continue to develop and commercialize our products.

This dependence on intellectual property developed by others involves the following risks:

- We may be unable to obtain rights to intellectual property that we determine we need for our business at a reasonable cost or at all;
- If any of our product licenses or purchase agreements are terminated, we may lose our rights to develop, make and sell the products to which such licenses or agreements relate;
- Our license and purchase agreements generally provide the licensor or seller with the right to terminate the agreement in the event of a breach; for example, if we fail to pay royalties and other fees timely and do not cure the failure within a stated time period; and
- If a licensor of intellectual property that we have rights to breaches its obligation or otherwise fails to maintain the intellectual property licensed, we may lose any ability to prevent others from developing or marketing similar products that are covered by such intellectual property. In addition, we may be forced to incur substantial costs to maintain the intellectual property ourselves or take legal action seeking to force the licensor to do so.

Certain agreements under which we acquired or licensed intellectual property rights may restrict our ability to develop related products in certain countries or for particular diseases and may impose other restrictions that affect our ability to develop and market related products in the most effective manner.

When we acquire or license intellectual property rights to drugs and other products that have been discovered and initially developed by others, these rights are frequently limited. For instance, our rights to market Adcirca are geographically limited to the United States and Puerto Rico. Furthermore, we cannot undertake any additional investigational work with respect to Adcirca in other indications of pulmonary hypertension without Lilly's prior approval. Provisions in our license and purchase agreements may impose other restrictions that affect our ability to develop and market products to which the intellectual property relates. For example, Lilly also has authority over all regulatory activities and has the right to determine the net wholesale price for Adcirca.

Our intellectual property rights may not effectively deter competitors from developing competing products that, if successful, could have a material adverse effect on our revenues and profits.

The period under which our commercial and developmental therapies are protected by our patent rights is limited. Three of our U.S. patents covering our current methods of synthesizing and producing treprostinil expire in October 2017, and a fourth will expire in 2028. We also have been granted one patent in the European Union and one patent in Japan, each of which covers our treprostinil synthesis and production methods and will expire in October 2018. Our three U.S. patents covering an improved diluent for Remodulin will expire in 2028 and 2029. Our patents for Tyvaso covering methods of treating PAH by inhaled delivery will expire in the United States and in various countries throughout the world in 2018 and 2020, respectively. Our patents for Orenitram covering methods of use for treating PAH, orally administered formulations, controlled moisture storage and production methods and controlled release formulations will expire in the United States between 2024 and 2031 and in various countries throughout the world in 2024. The U.S. patent for Adcirca for the treatment of pulmonary hypertension will expire in November 2017.

We continue to conduct research into new methods to synthesize treprostinil and have pending U.S. and international patent applications and patents relating to such methods. However, we cannot be sure that these additional patents will effectively deter or delay competitors' efforts to bring new products to market, or that additional patent applications will result in new patents. Upon the expiration of any of our patents, competitors may develop generic versions of our products and may market those generic versions at a lower price to compete with our products. Competitors may also seek to design around our patents prior to their expiration in an effort to develop competing products that do not infringe our patents. Prior to the expiration of our patents, third parties may challenge the validity of our patents, through patent litigation, proceedings before the U.S. Patent and Trademark Office or other applicable patent filing office, or other means.

The scope of any patent we hold may not deter competitors from developing a product that competes with the product we sell that is covered by the patent. Patent laws of foreign jurisdictions may not protect our patent rights to the same extent as the patent laws of the United States. In addition, we may be forced to incur substantial costs to defend the intellectual property rights conferred by our patents. Furthermore, our suppliers who have granted us exclusive rights may have inadequate intellectual property protections. Competitors also may attempt to invalidate our existing patents before they expire.

In addition to patent protection, we also rely on trade secrets to protect our proprietary know-how and other technological advances that we do not disclose to the public. We enter into confidentiality agreements with our employees and others to whom we disclose trade secrets and other confidential information. These agreements may not necessarily prevent our trade secrets from being used or disclosed without our authorization and confidentiality agreements may be difficult, time-consuming and expensive to enforce or may not provide an adequate remedy in the event of unauthorized disclosure. In addition, if any of our trade secrets were to be lawfully obtained or independently developed by a competitor, we would have no right to prevent such third party, or those to whom they communicate such technology or information, from using that technology or information to compete with us. If any of our trade secrets were to be disclosed to or independently developed by a competitor, our business and competitive position could be harmed.

The validity, enforceability and scope of certain of our patents covering Remodulin are currently being challenged as a result of abbreviated new drug application (ANDA) filings by two generic drug companies. The outcome of current or future challenges with respect to the validity, enforceability or scope of our patents could significantly reduce revenues from Remodulin.

Both Sandoz and Teva have filed ANDAs seeking FDA approval to market generic versions of Remodulin. We have filed lawsuits against Sandoz and Teva in the U.S. District Court for the District of New Jersey alleging patent infringement. For details on the status of these proceedings, please see *Part I, Item 3.—Legal Proceedings* , included in this Annual Report on Form 10-K.

There can be no assurance that we will prevail in our defense of our patent rights, or that additional challenges from other ANDA filers will not surface with respect to Remodulin or our other treprostinil-based products. Our existing patents could be invalidated, found unenforceable or found not to cover one or more generic forms of Remodulin, Tyvaso or Orenitram. If any ANDA filer were to receive approval to sell a generic version of Remodulin, Tyvaso or Orenitram and/or prevail in any patent litigation, the affected product would become subject to increased competition and our revenue would decrease.

Third parties may allege that our patents are invalid, or that our products or services infringe their patents and other intellectual property rights, which could result in the payment of royalties. Payment of royalties would negatively affect our profits; furthermore, if we chose to contest these allegations, we could be subject to costly and time-consuming litigation or could lose the ability to continue to sell the related products.

Third parties may seek to invalidate or otherwise challenge our patents, through patent litigation and/or initiating proceedings, including re-examinations, *inter partes* reviews, post-grant reviews and interference proceedings, before the U.S. Patent and Trademark Office. We may initiate litigation to enforce or defend our patents or intellectual property rights; however, litigation can be time consuming, distracting to our operations, costly and may conclude unfavorably for us. In addition, the outcome of patent infringement litigation often is difficult to predict. If we are unsuccessful with respect to any future legal action in the defense of our patents and our patents are invalidated or determined to be unenforceable, our business could be negatively impacted. Even if our patents are determined to be valid or enforceable, it is possible that a competitor could circumvent our patents by effectively designing around the claims of our patents. Accordingly, our patents may not provide us with any competitive advantage.

To the extent third-party patents to which we currently do not hold licenses are necessary for us to manufacture, use or sell our products, we would need to obtain necessary licenses to prevent infringement. In the case of products or services that utilize intellectual property of strategic collaborators or other suppliers, such suppliers may have an obligation to secure the needed license to these patents at their cost. Otherwise, we would be responsible for the cost of these licenses. Royalty payments and other fees under these licenses would erode our profits from the sale of related products and services. Moreover, we may be unable to obtain these licenses on acceptable terms or at all. If we fail to obtain a required license or are unable to alter the design of the product to avoid infringing a third-party patent, we would be unable to continue to manufacture or sell related products.

If a third party commences legal action against us for infringement, or institutes proceedings challenging the validity of our patents, we could be compelled to incur significant costs to defend the action and our management's attention could be diverted, whether or not the action were to have any merit. We cannot be certain that we could prevail in the action, and an adverse judgment or settlement resulting from the action could require us to pay substantial amounts in damages for infringement or substantial amounts to obtain a license to continue to use the intellectual property that is the subject of the infringement claim.

We may not maintain adequate insurance coverage to protect us against significant product liability claims.

The testing, manufacturing, marketing, and sale of drugs and diagnostics involve product liability risks. We may not be able to maintain our current product liability insurance at an acceptable cost, if at all. In addition, our insurance coverage may not be adequate for all potential claims. If claims or losses significantly exceed our liability insurance coverage, we may experience financial hardship or potentially be forced out of business.

If we fail to attract and retain key management and qualified scientific and technical personnel, we may not be able to achieve our business objectives.

Members of our management team, including our founder, Chairman and Co-Chief Executive Officer, Dr. Martine Rothblatt, and our President and Co-Chief Executive Officer, Dr. Roger Jeffs, play a critical role in defining our business strategy and maintaining our corporate culture. The loss of the services and leadership of Dr. Rothblatt, Dr. Jeffs or any other members of our senior management team could have an adverse effect on our business. We do not maintain key person life insurance on our senior management team members. In addition, effective succession planning is important to our long-term success. Failure to identify and retain adequate replacements for members of our senior management team and to transfer knowledge effectively could impede the achievement of our business objectives. Our future success also depends on our ability to attract and retain qualified scientific and technical personnel. Competition for skilled scientific and technical personnel in the biotechnology and pharmaceutical industries is intense. Furthermore, our compensation arrangements may not be sufficient to attract new qualified scientific and technical employees or retain such core employees. If we fail to attract and retain such employees, we may not be successful in developing and commercializing new therapies for PAH and other diseases.

Improper handling of hazardous materials used in our activities could expose us to significant remediation liabilities.

Our research and development and manufacturing activities involve the controlled use of chemicals and hazardous substances and we are expanding these activities in both scale and location. In addition, patients may dispose of our products using means we do not control. Such activities subject us to numerous federal, state, and local environmental and safety laws and regulations that govern the management, storage and disposal of hazardous materials. Compliance with current and future environmental laws and regulations can require significant costs; furthermore, we can be subject to substantial fines and penalties in the event of noncompliance. The risk of accidental contamination or injury from these materials cannot be completely eliminated. Furthermore, once chemical and hazardous materials leave our facilities, we cannot control the manner in which such hazardous waste is disposed of by our contractors. In the event of an accident, we could be liable for substantial civil damages or costs associated with the cleanup of the release of hazardous materials. Any related liability could have a material adverse effect on our business.

We may encounter substantial difficulties managing our growth relative to product demand.

We have spent considerable resources building and expanding our offices, laboratories and production facilities, and we are currently seeking regulatory approvals for certain facilities. However, our facilities could be insufficient to meet future demand for our products. Conversely, we may have excess capacity at our facilities if future demand falls short of our projections, or if we do not receive regulatory approvals for the products we intend to produce at our facilities. Constructing our facilities is expensive and our ability to satisfactorily recover our investment will depend on sales of the products manufactured at these facilities in sufficient volume. If we do experience substantial sales growth, we may have difficulty managing inventory levels as marketing new therapies is complicated and gauging future demand can be difficult and uncertain until we possess sufficient post-launch sales experience.

If we need additional financing and cannot obtain it, our product development and sales efforts may be limited.

We may be required to seek additional sources of financing to meet unplanned or planned expenditures. Unplanned expenditures could be significant and may result from necessary modifications to product development plans or product offerings in response to difficulties encountered with clinical trials. We may also face unexpected costs in preparing products for commercial sale, or in maintaining sales levels of our currently marketed therapeutic products. If we are unable to obtain additional funding on commercially reasonable terms or at all, we may be compelled to delay clinical studies, curtail operations or obtain funds through collaborative arrangements that may require us to relinquish rights to certain products or potential markets.

We may require additional financing to meet significant future obligations. For instance, upon maturity or conversion of our 1.0 percent Convertible Senior Notes due September 15, 2016 (Convertible Notes), subject to certain provisions, we must repay our investors in cash up to the remaining principal balance of $138.8 million. Further, in certain circumstances constituting a fundamental change under the Convertible Notes, we may be required to repurchase the Convertible Notes for cash.

Awards granted under our Share Tracking Award Plans (which we collectively refer to as the STAP) entitle participants to receive in cash an amount equal to the appreciation in the price of our common stock, which is calculated as the positive difference between the closing price of our common stock on the date of exercise and the date of grant. Consequently, our STAP may require significant future cash payments to participants to the extent the price of our common stock appreciates and the number of vested STAP awards increases over time. If we do not have sufficient funds to meet such obligations or the ability to secure alternative sources of financing, we could be in default, face litigation and/or lose key employees, which could have a material adverse effect on our business.

Information technology security breaches and other disruptions could compromise our information and expose us to legal responsibility which would cause our business and reputation to suffer.

In the ordinary course of our business, we collect and store sensitive data, including intellectual property, our proprietary business information and that of our suppliers, customers and business partners, and personally identifiable information. The secure maintenance of this information is critical to our operations and business strategy. Despite our security measures, our information technology and infrastructure may be vulnerable to attacks by hackers or breached due to employee error, malfeasance or other disruptions. Such breaches could compromise sensitive and confidential information stored on our networks and expose such information to public disclosure, loss or theft. Any access, disclosure or other loss of information could result in legal claims or proceedings, liability under laws that protect the privacy of personal information, disruption of our operations, and damage to our reputation which could adversely affect our business.

Risks Related to Our Common Stock

The price of our common stock can be highly volatile and may decline.

The price of common stock can be highly volatile within the pharmaceutical and biotechnology sector. Consequently, there can be significant price and volume fluctuations in the market that may not relate to operating performance. The following table sets forth the high and low closing prices of our common stock for the periods indicated:

	High	Low
January 1, 2014—December 31, 2014	$ 136.16	$ 86.14
January 1, 2013—December 31, 2013	$ 114.51	$ 51.64
January 1, 2012—December 31, 2012	$ 58.91	$ 40.42

The price of our common stock could decline sharply due to the following factors, among others:

- Failure to meet estimates or expectations of securities analysts;
- Quarterly and annual financial results;
- Timing of enrollment and results of our clinical trials;
- Announcements by us or others regarding generic or other challenges to the intellectual property relating to our products, including developments with respect to the ANDAs filed by Sandoz and Teva relating to certain of our Remodulin patents and to our pending lawsuits defending our patent rights;
- The outcome of the ongoing OIG investigation related to Remodulin, Tyvaso and Adcirca;
- Physician, patient, investor or public concerns regarding the efficacy and/or safety of products marketed or being developed by us or by others;
- Changes in, or new legislation and regulations affecting reimbursement of, our therapeutic products by Medicare, Medicaid or other government payers, and changes in reimbursement policies of private health insurance companies;
- Announcements by us or others of technological innovations or new products or announcements regarding our existing products, including in particular, the development of new, competing PAH therapies;
- Substantial sales of our common stock by us or our existing shareholders;
- Future issuances of common stock by us or any other activity which could be viewed as being dilutive to our shareholders;
- Rumors among, or incorrect statements by, investors and/or analysts concerning our company, our products, or our operations;
- Failure to obtain or maintain regulatory approvals from the FDA or international regulatory agencies;
- Discovery of previously unknown problems with our marketed products, or problems with our production, regulatory, compliance, promotional, marketing or sales activities that result in regulatory penalties or restrictions on our products, up to the withdrawal of our products from the market;
- Accumulation of significant short positions in our common stock by hedge funds or other investors or the significant accumulation of our common stock by hedge funds or other institutional investors with investment strategies that may lead to short-term holdings; and

- General market conditions.

We may fail to meet third-party projections for our revenues or profits.

Many securities analysts publish quarterly and annual projections of our revenues and profits. Such projections are inherently subject to uncertainty. As a result, actual revenues and profits may fail to meet these projections. Even minor variations in reported revenues and profits compared to securities analysts' expectations could have a significant adverse impact on the price of our common stock.

Sales or issuances of our common stock may depress our stock price.

The price of our common stock could decline if: (1) we issue common stock to raise capital or to acquire a license or business; (2) our shareholders transfer ownership of our common stock, or sell substantial amounts in the public market; (3) our investors become concerned that substantial sales of our common stock may occur; or (4) we issue shares upon the settlement of warrants relating to the hedging transaction relating to our Convertible Notes. A decrease in the price of our common stock could make it difficult for us to raise capital or fund acquisitions through the issuance of our stock.

Any sales of common stock issued to holders of our Convertible Notes could adversely affect the prevailing market price of our common stock or result in short selling by market participants in expectation of a decline in the price of our common stock.

Our share repurchases may affect the value of our common stock.

In recent years, our Board of Directors has authorized several programs to repurchase our common stock, including a $500.0 million share repurchase program effective during the one-year period that began on August 1, 2014. The price of our common stock may, in part, reflect expectations that our repurchase program will be fully consummated. Our share repurchase program does not obligate us to acquire any specific number of shares. If we fail to meet analyst or investor expectations regarding our repurchase program, our stock price may decline.

We are subject to counterparty risk with respect to the convertible note hedge transaction.

The counterparty to the convertible note hedge transaction we entered into in connection with the issuance of our Convertible Notes (call options) will subject us to counterparty risk in that the counterparty may default on fulfilling its obligations under the call options. Our exposure to the credit risk of the counterparty will not be secured by any collateral. Recent global economic conditions have resulted in the actual or perceived failure or financial difficulties of many financial institutions. If such counterparty becomes subject to insolvency proceedings, we will become an unsecured creditor in those proceedings with a claim based on our exposure at that time under the call options. Our exposure will depend on many factors but, generally, the increase in our exposure will be correlated to the increase in the market price and in the volatility of our common stock. In addition, upon a default by the counterparty, we may suffer adverse tax consequences and dilution with respect to our stock due to our obligation to deliver shares subsequent to the conversion of the notes. We cannot provide any assurances as to the future financial stability or viability of the counterparty to our convertible note hedge transaction.

Provisions of Delaware law and our amended and restated certificate of incorporation, second amended and restated by-laws, shareholder rights plan, Convertible Notes, convertible note hedge transaction and employment and license agreements, among other things, could prevent or delay a change of control or change in management that may be beneficial to our public shareholders.

Certain provisions of Delaware law and our amended and restated certificate of incorporation, second amended and restated by-laws and shareholder rights plan may prevent, delay or discourage:

- A merger, tender offer or proxy contest;
- The assumption of control by a holder of a large block of our securities; and/or
- The replacement or removal of current management by our shareholders.

For example, our amended and restated certificate of incorporation divides our Board of Directors into three classes. Members of each class are elected for staggered three-year terms. This provision may make it more difficult for shareholders to replace the majority of directors. It may also deter the accumulation of large blocks of our common stock by limiting the voting power of such blocks.

Non-competition and all other restrictive covenants in most of our employment agreements will terminate upon a change of control that is not approved by our Board.

We may be required to repurchase the outstanding Convertible Notes from their holders in the event of a fundamental change and increase the conversion rate in connection with a make whole adjustment event in certain circumstances, including a change of control of our company. This may delay or prevent a change in control of our company that would otherwise be beneficial to our shareholders.

Terminating or unwinding the convertible note hedge transaction could require us to make substantial payments to the counterparty or may increase the price of our common stock. The costs or any increase in stock price that may arise from terminating or unwinding the transaction could make an acquisition of our company significantly more expensive to the purchaser.

Similarly, a change of control, under certain circumstances, could also result in an acceleration of the vesting of outstanding STAP awards. This, together with any increase in our stock price resulting from the announcement of a change of control, could make an acquisition of our company significantly more expensive to the purchaser. We also have a broad-based change of control severance program, under which employees may be entitled to severance benefits in the event they are terminated without cause (or they terminate their employment for good reason) following a change of control. This program could also increase the cost of acquiring our company.

We enter into certain license agreements that generally prohibit our counterparties or their affiliates from taking necessary steps to acquire or merge with us, directly or indirectly throughout the term of these agreements, plus a specified period thereafter. We are also party to certain license agreements that restrict our ability to assign or transfer the rights licensed to us to third parties, including parties with whom we wish to merge, or those attempting to acquire us. These agreements often require that we obtain prior consent of the counterparties to these agreements if we are contemplating a change of control. If these counterparties withhold consent, related agreements could be terminated and we would lose related license rights. For example, both Lilly and Toray have the right to terminate our license agreements relating to Adcirca and beraprost, respectively, in the event of certain change of control transactions. These restrictive change of control provisions could impede or prevent mergers that could benefit our shareholders.

Because we do not intend to pay cash dividends, our shareholders must rely on stock appreciation for any return on their investment in us.

We have never declared or paid cash dividends on our common stock. Furthermore, we do not intend to pay cash dividends in the future. As a result, the return on an investment in our common stock will depend entirely upon the future appreciation in the price of our common stock. There can be no assurances that our common stock will provide a return to investors.

ITEM 1B. UNRESOLVED STAFF COMMENTS

None.

ITEM 2. PROPERTIES

Maryland—We own a 232,000 square foot combination laboratory and office building complex in Silver Spring, Maryland that serves as our co-headquarters and is used for the synthesis of treprostinil, the active ingredient in Remodulin and Tyvaso, and treprostinil diolamine, the active ingredient in Orenitram, as well as the production of Remodulin and Tyvaso and our ch14.18 monoclonal antibody. We also own several other buildings in Silver Spring used principally for office and laboratory space and we lease warehouse space near Silver Spring.

North Carolina—We own a 380,000 square foot combination manufacturing facility and office building in Research Triangle Park, North Carolina (RTP facility), which serves as our co-headquarters and is occupied by our clinical research and development, commercialization and our logistics and manufacturing personnel. We warehouse and distribute Remodulin, Tyvaso and Orenitram and produce Orenitram at this location. In 2012, we acquired a 132-acre property containing approximately 312,000 square feet of building space adjacent to our RTP facility, which we use for our research, development and production facilities relating to our lung regeneration program, office space and for future expansion.

Europe—We own an office building near London, England which serves as our European headquarters. In Germany, we lease a warehouse where we maintain inventory of components for our Tyvaso Inhalation System.

District of Columbia—We own two adjacent buildings in Washington, D.C., which serve as office space.

Florida—We own office buildings in Satellite Beach and Melbourne, Florida.

We believe that these facilities, along with various other owned and leased facilities, are adequate for our current operations and that additional land and facilities for future expansion are reasonably available.

ITEM 3. LEGAL PROCEEDINGS

Department of Health and Human Services Subpoena

In December 2013, we received a subpoena from the Office of the Inspector General (OIG) of the Department of Health and Human Services in connection with a civil investigation by the United States Department of Justice, principally represented by the United States Attorney's Office for the District of Maryland. The subpoena requests documents regarding Remodulin, Tyvaso and Adcirca, including our marketing practices relating to these products. We are cooperating with the investigation. We are not aware that a claim, litigation or assessment has been asserted in connection with the subpoena. However, we cannot predict what actions, if any, may be taken by the OIG, the Department of Justice, other governmental entities, or any third parties in connection with this investigation.

Sandoz Inc.

In February 2012, we received a Paragraph IV certification letter (the Original Notice Letter) from Sandoz Inc. (Sandoz) advising that Sandoz had submitted an abbreviated new drug application (ANDA) to the FDA requesting approval to market a generic version of the 10 mg/mL strength of Remodulin. In December 2012, we received notice (the Second Notice Letter) that Sandoz had amended its previously filed ANDA to request additional approval to market generic versions of the 1 mg/mL, 2.5 mg/mL, and 5 mg/mL strengths of Remodulin. In the Original Notice Letter and the Second Notice Letter, Sandoz stated that it intends to market a generic version of Remodulin before the expiration of the following patents relating to Remodulin: U.S. Patent No. 5,153,222, which expires in October 2014; U.S. Patent No. 6,765,117, which expires in October 2017; and U.S. Patent No. 7,999,007, which expires in March 2029. Each of these patents is listed in the Orange Book.

We responded to the Original Notice Letter by filing a lawsuit in March 2012 against Sandoz in the U.S. District Court for the District of New Jersey alleging patent infringement. We responded to the Second Notice Letter by filing an additional lawsuit in January 2013 for patent infringement in the U.S. District Court for the District of New Jersey. Sandoz filed counterclaims in each action alleging that the patents at issue in the litigation are invalid or will not be infringed by the commercial manufacture, use or sale of the proposed product described in Sandoz's ANDA submission. Shortly before trial, Sandoz withdrew its request to market a generic version of Remodulin before the expiration of U.S. Patent No. 5,153,222, but maintained its request to market a generic version of Remodulin before the expiration of the other two patents. The trial for both lawsuits, limited to U.S. Patent Nos. 6,765,117 and 7,999,007, occurred in May and June 2014 and we received the Court's decision in August 2014. In that decision, with respect to U.S. Patent No. 6,765,117 the Court both ruled that the patent is valid and enforceable against Sandoz, and enjoined Sandoz from marketing its generic product until the expiration of that patent in October 2017. With respect to U.S. Patent No. 7,999,007, the Court ruled that the patent is valid, but that it would not be infringed by Sandoz' generic product.

Sandoz has appealed the ruling that U.S. Patent No. 6,765,117 is valid and would be infringed, and that U.S. Patent No. 7,999,007 is valid. We have filed a cross-appeal challenging the Court's ruling that U.S. Patent No. 7,999,007 would not be infringed by Sandoz's generic version of Remodulin.

In July 2014, we received an additional Paragraph IV certification letter (Third Notice Letter) from Sandoz, seeking permission to market and sell its generic version of Remodulin before the expiration of U.S. Patent No. 8,497,393, which expires in December 2028 and is also listed in the Orange Book. We responded to Sandoz's Third Notice Letter by filing a lawsuit in September 2014 in the U.S. District Court for the District of New Jersey for patent infringement with respect to U.S. Patent No. 8,497,393.

We intend to vigorously enforce our intellectual property rights relating to Remodulin.

Teva Pharmaceuticals USA, Inc.

On July 21, 2014, we received a Paragraph IV certification letter (Teva's Notice Letter) from Teva Pharmaceuticals USA, Inc. (Teva) advising that Teva had submitted an ANDA to the FDA requesting approval to market a generic version of Remodulin.

In Teva's Notice Letter, Teva states that it intends to market a generic version of Remodulin before the expiration of U.S. Patent Nos. 6,765,117 and 8,497,393, both of which are also the subject of Paragraph IV certifications by Sandoz, as discussed above. Teva's Notice Letter states that the ANDA contains a Paragraph IV certification alleging that these patents are not valid, not enforceable and/or will not be infringed by the commercial manufacture, use or sale of the proposed product described in Teva's ANDA submission.

We responded to Teva's Notice Letter by filing a lawsuit in September 2014 against Teva in the U.S. District Court for the District of New Jersey alleging infringement of U.S. Patent Nos. 6,765,117, 7,999,007 and 8,497,393, as well as infringement of U.S. Patent Nos. 8,653,137 and 8,658,694, both of which expire in September 2028. Teva has filed its answer to our complaint, and has also filed a counterclaim alleging that the patents at issue in the litigation are invalid or will not be infringed by the commercial manufacture, use or sale of the proposed product described in Teva's ANDA submission. We have filed an answer to the counterclaim.

Under the Hatch-Waxman Act, the FDA is automatically precluded from approving Teva's ANDA for up to 30 months from receipt of Teva's Notice Letter or until the issuance of a U.S. District Court decision that is adverse to us, whichever occurs first. We intend to vigorously enforce our intellectual property rights relating to Remodulin.

ITEM 4. MINE SAFETY DISCLOSURES

Not applicable.

PART II

ITEM 5. MARKET FOR REGISTRANT'S COMMON EQUITY, RELATED STOCKHOLDER MATTERS AND ISSUER PURCHASES OF EQUITY SECURITIES

Market Information

Our common stock (and associated preferred stock purchase rights) trades on the NASDAQ Global Select Market under the symbol "UTHR". The table below sets forth the high and low closing prices for our common stock for the periods indicated:

	2014		2013	
	High	Low	High	Low
January 1—March 31	$ 113.39	$ 90.67	$ 62.57	$ 51.64
April 1—June 30	$ 107.81	$ 86.14	$ 69.31	$ 59.64
July 1—September 30	$ 136.16	$ 86.44	$ 79.58	$ 66.10
October 1—December 31	$ 134.80	$ 122.11	$ 114.51	$ 80.03

Number of Holders

As of February 17, 2015, there were 39 holders of record of our common stock.

Dividend Policy

We have never paid and have no present intention to pay cash dividends on our common stock in the foreseeable future. We intend to retain any earnings for use in our business operations.

Issuer Purchases of Equity Securities

Period	Total Number of Shares (or Units) Purchased	Average Price Paid Per Share (or Unit)(1)	Total Number of Shares (or Units) Purchased as Part of Publicly Announced Plans or Programs	Maximum Number (or Approximate Dollar Value) of Shares (or Units) That May Yet Be Purchased Under the Plans or Programs(2)
Beginning repurchase authority				$ 474,403,291
October 1, 2014—October 31, 2014	—	$ —	—	474,403,291
November 1, 2014—November 30, 2014	193,819	128.93	193,819	449,414,691
December 1, 2014—December 31, 2014	419,059	131.08	419,059	394,484,011
Total	612,878	$ 130.40	612,878	$ 394,484,011

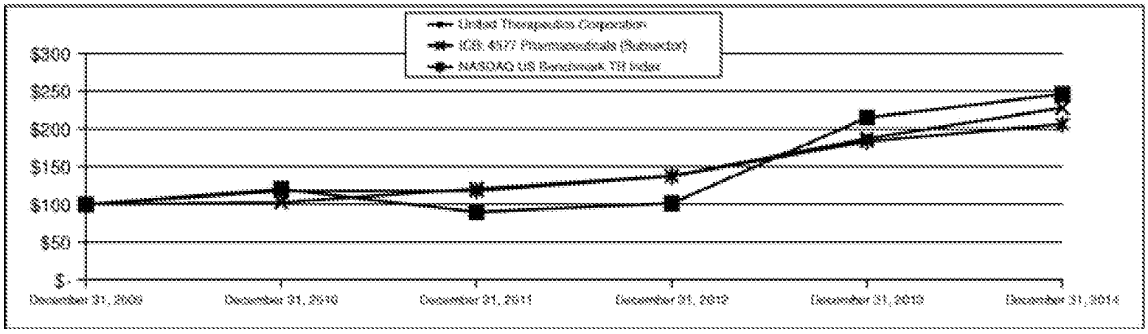
(1) Average price paid per share calculated at settlement, including commission.

(2) On June 27, 2014, we announced that our Board of Directors authorized a share repurchase program for up to $500.0 million in aggregate repurchases, which became effective August 1, 2014 and will remain open for up to one year.

(3) From January 1, 2015 through February 19, 2015 we have acquired 586,709 shares of our common stock at an aggregate cost of $82.5 million.

Comparison of Five-Year Total Cumulative Shareholder Return

The following chart shows the performance from December 31, 2009 through December 31, 2014 of United Therapeutics' common stock, compared with an investment in the stocks represented in each of the NASDAQ U.S. Benchmark TR Index and the NASDAQ ICB: 4577 Pharmaceutical Stock Index, assuming the investment of $100 at the beginning of the period and the reinvestment of dividends, if any.



ITEM 6. SELECTED FINANCIAL DATA

The following selected consolidated financial data should be read in conjunction with our consolidated financial statements and the notes accompanying the consolidated financial statements and *Item 7—Management's Discussion and Analysis of Financial Condition and Results of Operations* included in this Annual Report on Form 10-K. The historical results are not necessarily indicative of results to

be expected for future periods. The following information is presented in thousands, except per share data.

	Year Ended December 31,				
	2014	2013	2012	2011	2010
Consolidated Statements of Operations Data:					
Revenues	$ 1,288,519	$ 1,116,984	$ 916,076	$ 743,183	$ 592,899
Operating expenses:					
Research and development	242,549	299,348	173,387	180,015	165,306
Selling, general and administrative	381,287	394,010	201,746	156,482	188,606
Cost of product sales	125,883	131,127	119,297	88,904	67,674
Total operating expenses	749,719	824,485	494,430	425,401	421,586
Operating income	538,800	292,499	421,646	317,782	171,313
Total other (expense) income, net	(13,620)	(13,596)	19,025	(18,665)	(16,162)
Income from continuing operations before income tax	525,180	278,903	440,671	299,117	155,151
Income tax expense	(185,106)	(104,343)	(136,229)	(81,874)	(43,945)
Income from continuing operations	340,074	174,560	304,442	217,243	111,206
Income (loss) from discontinued operations, net of tax(1)	—	—	—	625	(5,290)
Net income	$ 340,074	$ 174,560	$ 304,442	$ 217,868	$ 105,916
Net income per common share:					
Basic(2)	$ 7.06	$ 3.49	$ 5.84	$ 3.81	$ 1.89
Diluted(2)	$ 6.28	$ 3.28	$ 5.71	$ 3.67	$ 1.78
Weighted average number of common shares outstanding:					
Basic(2)	48,176	50,076	52,093	57,163	56,142
Diluted(2)	54,155	53,231	53,280	59,395	59,516

	Year Ended December 31,				
	2014	2013	2012	2011	2010
Consolidated Balance Sheet Data:					
Cash, cash equivalents and marketable investments (3)	$ 812,944	$ 1,136,668	$ 784,931	$ 747,378	$ 759,932
Total assets	1,884,410	2,087,567	1,626,595	1,518,079	1,431,635
Debt	130,224	286,182	276,323	266,835	305,968
Retained earnings	1,068,114	728,040	553,480	249,038	31,170
Total stockholders' equity	1,242,356	1,259,274	1,083,981	948,488	883,886

(1) In March 2011, we sold Medicomp, Inc., our former telemedicine subsidiary and subsequently discontinued all of our continuing telemedicine-related activities. Accordingly, the results of Medicomp, Inc. have been included within discontinued operations for each of the years presented prior to the sale of the subsidiary.

(2) Refer to Note 11— *Stockholders' Equity—Earnings per Share* to our consolidated financial statements contained in this Annual Report on Form 10-K for the computation of basic and diluted net income per share.

(3) Excludes restricted marketable investments and cash.

ITEM 7. MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

The following discussion should be read in conjunction with our consolidated financial statements and related notes to the consolidated financial statements included in this Annual Report on Form 10-K. The following discussion contains forward-looking statements made pursuant to the safe harbor provisions of Section 21E of the Securities Exchange Act of 1934 and the Private Securities Litigation Reform Act of 1995. These statements are based on our expectations about future outcomes and are subject to risks and uncertainties that could cause actual results to differ materially from anticipated results. Factors that could cause or contribute to such differences include those described under *Part I, Item 1A—Risk Factors* included in this Annual Report on Form 10-K and factors described in other cautionary statements, cautionary language and risk factors set forth in other documents filed with the Securities and Exchange Commission. We undertake no obligation to publicly update forward-looking statements, whether as a result of new information, future events or otherwise.

Overview

Our key therapeutic products and product candidates include:

- *Prostacyclin analogues (Remodulin ®, Tyvaso ®, Orenitram ® and esuberaprost, formally known as 314d):* stable synthetic forms of prostacyclin, an important molecule produced by the body that has powerful effects on blood vessel health and function;
- *Phosphodiesterase type 5 (PDE-5) inhibitor (Adcirca ®):* a molecule that acts to inhibit the degradation of cyclic guanosine monophosphate (cyclic GMP) in cells. Cyclic GMP is activated by nitric oxide (NO), a naturally occurring substance in the body that mediates the relaxation of vascular smooth muscle;
- *Monoclonal antibody for oncologic applications (ch14.18 MAb):* an antibody that treats cancer by activating the immune system;
- *Glycobiology antiviral agents:* a novel class of small, sugar-like molecules that have shown antiviral activity in a range of preclinical settings;
- *Cell-based therapy:* a cell-based product known as PLacental eXpanded (PLX) cells we are developing for the treatment of pulmonary hypertension; and
- *Lung transplantation:* engineered lungs and lung tissue, which we are developing using xenotransplantation and regenerative medicine technologies, for transplantation in patients suffering from pulmonary arterial hypertension (PAH) and other lung diseases. We are also developing technologies aimed at improving outcomes for lung transplant recipients and increasing the supply of donor lungs through ex-vivo lung perfusion.

We concentrate substantially all of our research and development efforts on the preceding key therapeutic programs. We currently market and sell the following commercial products:

- *Remodulin (treprostinil) Injection (Remodulin).* Remodulin, a continuously-infused formulation of the prostacyclin analogue treprostinil, is approved by the United States Food and Drug Administration (FDA) for subcutaneous (under the skin) and intravenous (in the vein) administration. Remodulin is indicated to diminish symptoms associated with exercise in World Health Organization (WHO) Group 1 PAH patients. Remodulin is also approved for the treatment of patients requiring transition from Flolan ® (epoprostenol sodium) for Injection. Remodulin has also been approved in various countries outside of the United States. In the second and third quarters of 2014, we commenced sales of Remodulin to distributors in China and Japan, respectively. Remodulin is sold in Japan under the brand name Treprost™.

- *Tyvaso (treprostinil) Inhalation Solution (Tyvaso).* Tyvaso, an inhaled formulation of treprostinil, is approved by the FDA to improve exercise ability in WHO Group 1 PAH patients.

- *Orenitram (treprostinil) Extended-Release Tablets (Orenitram).* In December 2013, the FDA approved Orenitram, a tablet dosage form of treprostinil, for the treatment of PAH in WHO Group 1 PAH patients to improve exercise capacity. Orenitram's label provides for dosing either twice per day (BID) or three times per day (TID), and we anticipate that TID dosing may lead to a more favorable pharmacokinetic profile than BID, although TID dosing was not studied in our pivotal trial. We commenced sales of Orenitram during the second quarter of 2014.

- *Adcirca (tadalafil) Tablets (Adcirca).* We acquired exclusive commercialization rights to Adcirca, an oral PAH therapy, in the United States and Puerto Rico from Eli Lilly and Company (Lilly). Adcirca is approved by the FDA to improve exercise ability in WHO Group 1 PAH patients.

Revenues

Sales of Remodulin, Tyvaso and Adcirca comprise substantially all of our revenues. Despite commencing Orenitram sales during the second quarter of 2014, we remain substantially reliant on sales of Remodulin, Tyvaso and Adcirca for the next several years as our principal sources of revenue.

We have entered into separate, non-exclusive distribution agreements with Accredo Health Group, Inc. (Accredo) and CVS Caremark (Caremark) in the United States, to distribute Remodulin, Tyvaso and Orenitram. In April 2012, Express Scripts, Inc., the parent company of CuraScript Inc. (CuraScript), then one of our specialty pharmaceutical distributors, completed its acquisition of Medco Health Solutions, Inc., the parent company of Accredo. As a result, CuraScript's operations have been integrated into Accredo's, and in December 2013 we consolidated our distribution agreements with the two organizations into one contract for each product. We also sell Remodulin to distributors internationally. We sell Adcirca through Lilly's pharmaceutical wholesaler network at a wholesale price determined by Lilly, which Lilly generally increases two or three times per year. Most recently, Lilly increased the wholesale price of Adcirca by 9.9 percent effective December 4, 2014.

Under our distribution agreements, we sell each of our treprostinil-based products to these distributors at a transfer price that we establish. We have generally increased the price of Tyvaso by 4.9 percent annually, and the last price increase became effective on January 1, 2015. We have not increased the price of Remodulin since 2010.

We require our specialty pharmaceutical distributors to maintain reasonable levels of inventory reserves as the interruption of Remodulin, Tyvaso or Orenitram therapy can be life threatening. Our specialty pharmaceutical distributors typically place monthly orders based on estimates of future demand and contractual minimum inventory requirements. As a result, sales of Remodulin and Tyvaso, our most significant sources of revenue, can vary depending on the timing and magnitude of these orders and may not precisely reflect patient demand.

We recognize revenues net of: (1) estimated rebates; (2) prompt pay discounts; (3) allowances for sales returns; and (4) distributor fees. We estimate our liability for rebates based on an analysis of historical levels of rebates to both Medicaid and commercial third-party payers and considering the impact of sales trends, changes in government and commercial rebate programs and any anticipated changes in our products' pricing. In addition, we determine our obligation for prescription drug discounts required for Medicare Part D patients within the coverage gap based on estimates of the number of Medicare Part D patients and the period such patients will remain within the coverage gap. We provide prompt pay discounts to customers that pay amounts due within a specific time period and base related estimates on observed historical customer payment behavior. Prior to 2013, we derived estimates relating to our allowance for returns of Adcirca from published industry data specific to

specialty pharmaceuticals and, beginning in 2013, from actual return data accumulated since the drug's launch in 2009. This change in the methodology for estimating returns of Adcirca resulted in a $3.1 million reduction of our allowance for returns associated with Adcirca for the twelve-month period ending December 31, 2013. We also compare patient prescription data for Adcirca to sales on a quarterly basis to ensure a reasonable relationship between prescription and sales trends. To date, we have not identified any unusual patterns in the volume of prescriptions relative to sales that would warrant reconsideration of our methodology for estimating Adcirca returns. Remodulin, Tyvaso and Orenitram are distributed under separate contracts with substantially similar terms, which include exchange rights in the event that product is damaged during shipment or expires. The allowance for exchanges for Remodulin and Tyvaso is based on the historical rate of product exchanges, which has been negligible and immaterial. Furthermore, we anticipate minimal exchange activity in the future for Tyvaso, Remodulin and Orenitram since we typically sell these products with a remaining shelf life in excess of one year and our distributors generally carry a thirty- to sixty-day supply of our products at any given time. As a result, we do not record reserves for exchanges for Tyvaso, Remodulin and Orenitram at the time of sale. Lastly, we pay our distributors for contractual services rendered and accrue for related fees based on contractual rates applied to the estimated units of service provided by distributors for a given financial reporting period.

Generic Competition

We disclose in *Part I, Item 3.—Legal Proceedings* of this Annual Report on Form 10-K that we are engaged in litigation with Sandoz Inc. (Sandoz) and Teva Pharmaceuticals USA, Inc. (Teva), contesting their abbreviated new drug applications (ANDAs) seeking FDA approval to market generic versions of Remodulin before the expiration of certain of our U.S. patents in October 2017, December 2028, March 2029 and (in the case of Sandoz's ANDA) September 2028.

We intend to vigorously enforce our intellectual property rights relating to Remodulin. However, there can be no assurance that we will prevail in defending our patent rights, or that additional challenges from other ANDA filers or other challengers will not surface with respect to Remodulin or our other treprostinil-based products. Our existing patents could be invalidated, found unenforceable or found not to cover one or more generic forms of Remodulin, Tyvaso or Orenitram. If any ANDA filer were to receive approval to sell a generic version of Remodulin, Tyvaso or Orenitram and/or prevail in any patent litigation, the affected product(s) would become subject to increased competition which could reduce our sales.

Certain patents for Revatio ®, a PDE-5 inhibitor marketed by Pfizer, Inc. for the treatment of PAH, expired in 2012, leading several manufacturers to launch generic formulations of sildenafil citrate, the active ingredient in Revatio. Generic sildenafil's lower price relative to Adcirca could lead to an erosion of Adcirca's market share and limit its potential sales. Although we believe Adcirca's once-daily dosing regimen provides an appealing alternative to generic sildenafil's multiple dosing regimen, we believe that government payers and private insurance companies may favor the use of less expensive generic sildenafil over Adcirca. Thus far, we have not observed any measurable impact of generic sildenafil on sales of Adcirca; however, circumstances could change over time and our revenues could be adversely impacted. The U.S. patent for Adcirca for the treatment of pulmonary hypertension will expire in November 2017.

Patent expiration and generic competition for any of our commercial products could have a significant, adverse impact on our revenues, the magnitude of which is inherently difficult to predict. For additional discussion, please refer to the risk factor entitled, *Our intellectual property rights may not effectively deter competitors from developing competing products that, if successful, could have a material adverse effect on our revenues and profits* , contained in *Part I* , *Item 1A—Risk Factors* included in this Annual Report on Form 10-K.

Cost of Product Sales

Cost of product sales comprise: (1) costs to produce and acquire products sold to customers; (2) royalty payments under license agreements granting us rights to sell related products; and (3) direct and indirect distribution costs incurred in the sale of products. We acquired the rights to sell our commercial products through license and assignment agreements with the original developers of these products. These agreements obligate us to pay royalties based on specified percentages of our net revenues from related products. We paid GlaxoSmithKline PLC (Glaxo) a royalty of ten percent of net sales of our treprostinil-based products (Remodulin, Tyvaso and Orenitram) until October 2014, when the patents we acquired from Glaxo expired. We no longer have any royalty obligations for Remodulin or Tyvaso, and our only remaining royalty obligation on Orenitram sales will be a single-digit royalty relating to technology used in its formulation. We pay a five percent royalty to Lilly on net sales of Adcirca.

We synthesize treprostinil, the active ingredient in Remodulin and Tyvaso, and treprostinil diolamine, the active ingredient in Orenitram, and produce Remodulin and Tyvaso, at our facility in Silver Spring, Maryland. We produce Orenitram in our Research Triangle Park, North Carolina facility (RTP facility). We intend to use our own facilities to produce our primary supply of Remodulin, Tyvaso and Orenitram. We utilize third-party contract manufacturers to supplement our Remodulin and Tyvaso production capacity and mitigate the risk of shortages and we are working to obtain FDA approval of a third party to serve as an additional producer of Orenitram. We engage a third-party contract manufacturer to produce the Tyvaso Inhalation System.

We began selling Orenitram during the second quarter of 2014. Typical of the initial commercial activities of a newly-launched product, Orenitram's cost of product sales as a percentage of its net revenue is significantly higher than that of our other commercial products. We expect that as Orenitram's revenues increase, its cost of product sales as a percentage of net revenue will decrease to levels more comparable to our other treprostinil-based commercial products.

Lilly manufactures Adcirca. We take title to Adcirca upon its manufacture and bear any losses related to the storage, distribution and sale of Adcirca.

Operating Expenses

Since our inception, we have devoted substantial resources to our various clinical trials and other research and development efforts, which are conducted both internally and through third parties. From time to time, we also license or acquire additional technologies and compounds to be incorporated into our development pipeline.

Share-Based Compensation

Our operating expenses and net income are often materially impacted by the recognition of share-based compensation expense (benefit) associated with awards granted under our share tracking award plans (STAP) and potential stock option grants containing a market or performance condition, as the fair value of these awards varies with the changes in our stock price. The fair values of STAP awards and potential stock option grants are measured using inputs and assumptions under the Black-Scholes-Merton model that can materially impact the amount of compensation expense (benefit) for a given period.

We account for STAP awards as liabilities because they are settled in cash. As such, we must re-measure the fair value of outstanding STAP awards at the end of each financial reporting period until the awards are no longer outstanding. Changes in our STAP-related liability resulting from such re-measurements are recorded as adjustments to share-based compensation expense (benefit) and can create substantial volatility within our operating expenses from financial reporting period to period. The

following factors, among others, have a significant impact on the amount of share-based compensation expense (benefit) recognized in connection with the STAP from period to period: (1) volatility in the price of our common stock (specifically, increases in the price of our common stock will generally result in an increase in our STAP liability and related compensation expense, while decreases in our stock price will generally result in a reduction in our STAP liability and related compensation expense); (2) changes in the number of outstanding awards; (3) changes in the number of vested and partially vested awards; and (4) the probability of meeting the relevant performance criteria.

Through December 31, 2014, we were contractually obligated to award stock options each year to our Chairman and Co-Chief Executive Officer, Dr. Rothblatt, based on a formula tied to the growth (if any) in our market capitalization. These awards were granted at year-end, and vested immediately upon grant. We accrued compensation expense for Dr. Rothblatt's estimated stock option grant when we determined that it was probable that the performance criteria would be met. Beginning in 2015, Dr. Rothblatt's long term incentive compensation will be similar to other employees in that she will be eligible for an annual grant of performance-based STAP awards based on the achievement of our annual corporate milestones, which will vest over a four year period from the grant date.

Major Research and Development Projects

Our major research and development projects focus on: (1) the use of prostacyclin analogues and other therapies, as well as lung transplantation technologies, to treat cardiopulmonary diseases; (2) monoclonal antibodies to treat a variety of cancers; and (3) glycobiology antiviral agents to treat infectious diseases.

Cardiopulmonary Disease Projects

Remodulin

Intravenous Remodulin Administered via Implantable Pump

In 2009, we entered into an agreement with exclusive rights in the United States, United Kingdom, France, Germany, Italy and Japan, with Medtronic, Inc. (Medtronic) to develop its proprietary intravascular infusion catheter to be used with Medtronic's SynchroMed ® II implantable infusion pump and related infusion system components (together referred to as the Remodulin Implantable System) in order to deliver Remodulin for the treatment of PAH. If the Remodulin Implantable System is successful, it could reduce many of the patient burdens and other complications associated with infused prostacyclin analogues. With our funding, Medtronic completed the *DelIVery* clinical trial, in order to study the safety of the Remodulin Implantable System while administering Remodulin. The primary objective was to demonstrate a rate of catheter-related complications below 2.5 per 1,000 patient-days while using the Remodulin Implantable System to deliver Remodulin. In September 2013, Medtronic informed us that this primary objective was met ($p<0.0001$). In December 2014, Medtronic completed other stability, compatibility and technical assessments of the Remodulin Implantable System, including modifications to its hardware and software, and filed a premarket approval application (PMA) seeking FDA approval for the catheter and labeling changes. Medtronic is responsible for responding to any FDA requests for additional information concerning the use of the Remodulin Implantable System with Remodulin. In January 2015, we submitted new labeling requesting FDA approval to allow the use of Remodulin with the Remodulin Implantable System. The FDA has indicated that our submission will be treated as a new NDA.

Subcutaneous Remodulin Administered via Pre-Filled, Semi-Disposable Pump

In December 2014, we entered into an exclusive agreement with DEKA Research & Development Corp. (DEKA) to develop a pre-filled, semi-disposable pump system for subcutaneous delivery of Remodulin. Under the terms of the agreement, we will fund the development costs related to the

semi-disposable pump system and will pay product fees and a single-digit royalty to DEKA based on commercial sales of the system and the Remodulin sold for use with the system. Our goal is to be in a position to receive FDA approval for this delivery system by the end of 2018.

Tyvaso

In connection with Tyvaso's approval by the FDA, we agreed to a post-marketing requirement (PMR) obligating us to conduct an additional study to continue to assess the safety of Tyvaso. In accordance with our PMR, we are required to complete a long-term observational study in the United States that includes 1,000 patient years of follow-up in patients treated with Tyvaso and 1,000 patient years of follow-up in control patients receiving other PAH treatments, to evaluate the potential association between Tyvaso and oropharyngeal and pulmonary toxicity. We have completed this study and are preparing to submit the results of the study by the FDA's deadline of June 30, 2015.

Orenitram

In December 2013, the FDA approved Orenitram for the treatment of PAH in WHO Group 1 patients to improve exercise capacity. The primary study that supported efficacy of Orenitram was a 12-week monotherapy study (FREEDOM-M) in which PAH patients were not on any approved background therapy. Analysis of the FREEDOM-M results demonstrated that patients receiving Orenitram improved their six-minute walk distance by a median of approximately 23 meters (p=0.0125) compared to patients receiving placebo. The median change from baseline at week 12 was 25 meters for patients receiving Orenitram and –5 meters for patients receiving placebo.

Orenitram's label notes that Orenitram has not been shown to improve exercise capacity in patients on background vasodilator therapy, and that Orenitram is probably most useful to replace subcutaneous, intravenous, or inhaled treprostinil, but use of these forms has not been studied.

We believe that in order for Orenitram to reach its full commercial potential, we need to complete further studies to support an amendment to Orenitram's label to indicate that Orenitram delays morbidity and mortality in patients who are on an approved oral background therapy. As such, we are enrolling up to 610 patients in a phase IV clinical trial called FREEDOM-EV, which began in 2012. FREEDOM-EV is a placebo-controlled study of patients who enter the study on an approved background therapy, and one of the two primary endpoints of the study is the time to clinical worsening.

We expect to seek approval of Orenitram in Europe upon completion of the FREEDOM-EV study. In 2005, the European Medicines Agency (EMA) announced that Orenitram had been designated an orphan medicinal product for the treatment of PAH. A request for orphan drug designation for Orenitram is pending before the FDA.

Esuberaprost (formally known as 314d)

We have been studying various formulations of beraprost since 2000. We completed a phase I safety trial of esuberaprost, a reformulated, single-isomer version of beraprost in July 2012, and the data suggested that dosing esuberaprost four times a day was safe. We believe that esuberaprost and treprostinil have differing prostacyclin receptor-binding profiles and thus could provide benefits to certain groups of patients with differing sets of safety and efficacy profiles. We also believe that inhaled treprostinil and esuberaprost have complimentary pharmacokinetic and pharmacodynamic profiles, which indicate that they should provide greater efficacy in combination. As a result, in 2013 we began enrolling a phase III study called BEAT (***BE*** raprost 314d ***A*** dd-on to ***T*** yvaso) to evaluate the clinical benefit and safety of esuberaprost in combination with Tyvaso for patients with PAH who show signs of deterioration on inhaled treprostinil or have a less than optimal response to inhaled treprostinil

treatment. We intend to enroll 240 patients in the study, which will have a primary endpoint of time to clinical worsening.

Cell-Based Therapy

In 2011, we entered into a license agreement with Pluristem Ltd. (Pluristem) to develop and commercialize a cell-based product for the treatment of PAH using Pluristem's proprietary cell technology known as PLacental eXpanded (PLX) cells. We commenced a phase I clinical study in Australia in 2013.

Lung Transplantation

The only reported cure for PAH is a lung transplant. We believe that fewer than 100 PAH patients receive a lung transplant each year due to the shortage of available lungs for transplant and the demand for transplantable lungs in patients with other end-stage pulmonary diseases, such as chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis.

In 2011, we acquired all of the outstanding stock of Revivicor, Inc., a company focused on developing genetic biotechnology platforms to provide alternative tissue sources for the treatment of human degenerative disease through tissue and organ xenotransplantation. We are focused on this platform with the goal of providing transplantable lungs for human patients.

In May 2014, we completed a $50.0 million preferred stock investment in Synthetic Genomics Inc. (SGI). We also entered into a separate multi-year research and development collaboration agreement whereby SGI will develop engineered primary pig cells with modified genomes for use in our xenotransplantation program, which is principally focused on lungs. Under this agreement, each party will assume its own research and development costs and SGI may receive royalties and milestone payments from development and commercialization of organs.

We are also engaged in preclinical development of several regenerative technologies for creating transplantable lung tissue and whole lungs for patients with end-stage lung disease, as well as other technologies intended to improve outcomes for lung transplant recipients. We are preparing to commence a clinical trial in the United States to study the use of ex-vivo lung perfusion technology originally developed in Canada (where it is already used commercially) to provide extended preservation and assessment of donated lungs that are initially rejected for transplantation. In 2014, we completed the construction of the only laboratory facility in the United States devoted to performing ex-vivo lung perfusion on a fee-for-service basis.

From inception to December 31, 2014, we have spent $1.1 billion on all of our current and former cardiopulmonary disease programs.

Cancer-Related Projects

Ch14.18 Antibody

In 2010, we entered into a Cooperative Research and Development Agreement (CRADA) with the National Cancer Institute (NCI) of the United States National Institutes for Health (NIH) to collaborate on the late-stage development and regulatory approval process for Chimeric Monoclonal Antibody 14.18 (ch14.18) for children with high-risk neuroblastoma and patients with other forms of cancer. Ch14.18 is an antibody that has shown potential in the treatment of neuroblastoma by targeting GD2, a glycolipid on the surface of tumor cells. Under the terms of the CRADA, the NCI has completed necessary studies and we have developed the ability to produce ch14.18 on a commercial scale. Collectively, related NCI-supported studies and our production data were used as the foundation for our marketing authorization application, which the EMA accepted for review in December 2013, and a biologics license application, which the FDA accepted for review in June 2014. We previously

received orphan drug designation for ch14.18 from both the FDA and the EMA. In lieu of a royalty payment to the NCI, we have an ongoing obligation to provide the NCI with ch14.18 for its studies free of charge.

From inception to December 31, 2014, we have spent $124.2 million on all of our current and former cancer programs.

Infectious Disease Projects

Pursuant to our research agreement with the University of Oxford (Oxford), we have the exclusive right to commercialize a platform of glycobiology antiviral drug candidates in various preclinical stages of testing for the treatment of a wide variety of viruses. Through our research agreement with Oxford, we are also supporting the research of new glycobiology antiviral drug candidates and technologies. We are currently testing many of these compounds in preclinical studies and Oxford continues to synthesize new agents that we may elect to test.

In 2011, we were awarded a cost plus fixed fee contract with an aggregate value of up to $45.0 million under a Broad Agency Announcement from the National Institute of Allergy and Infectious Diseases (NIAID) of the NIH for studies directed toward the development of a broad spectrum antiviral drug with a primary indication for dengue and a secondary indication for influenza, based on our glycobiology antiviral platform. There are eight milestone-based options to expand the project and funding under the contract. To date, we have received contract modifications exercising five of these options, increasing total committed contract funding to $28.1 million. We recognize revenue under this contract to the extent of allowable costs incurred, plus a proportionate amount of fees earned. Related revenues are included under the caption *Other Revenues* on our consolidated statements of operations.

We began enrolling a phase I clinical trial of our lead antiviral candidate, an alpha-glucosidase inhibitor called UV-4B, for the treatment of dengue in the third quarter of 2014. In November 2014, the FDA granted orphan drug designation for UV-4B for the treatment of acute dengue illness. We are also performing preclinical studies of UV-4B for the treatment of patients with ebola.

From inception to December 31, 2014, we have spent $86.6 million on all of our current and former infectious disease programs.

Future Prospects

The extent of our future success is dependent on, among other things, how well we achieve the following objectives: (1) in the near term, continued sales growth of our current commercial products by increasing our market share and launching enhancements designed to improve patient care, such as implantable pumps for Remodulin, and growing sales of our recently-launched product, Orenitram; (2) in the medium term, augmenting our near-term product growth through: (a) the successful launch of Orenitram for use in combination with other oral therapies following positive FREEDOM-EV results, and (b) the launch of esuberaprost following positive results of the BEAT study; and (3) in the long term, supplementing our oral, inhaled and infused PAH therapy revenues by introducing transplantable cells, tissues and organs that may prove effective in treating PAH and other end-stage lung diseases.

Our ability to achieve these objectives and sustain our growth and profitability will depend on many factors, including among others: (1) the timing and outcome of clinical trials and regulatory approvals for products we develop; (2) the timing of, and the degree of success related to, the commercial launch of new products; (3) the demand for our products; (4) pricing and reimbursement of our products by public and private health insurance organizations; (5) the competition we face within our industry; (6) our ability to effectively manage our business in an increasingly complex legal

and regulatory environment; (7) our ability to defend against generic competition and challenges to our patents, including the ongoing challenge to our Remodulin patents by two generic drug companies; and (8) the risks identified in *Part I, Item 1A—Risk Factors* , included in this Annual Report on Form 10-K.

We may need to construct additional facilities to support the development and commercialization of our products. For example, the development of broad-spectrum anti-viral drugs, cell therapies and transplantable lungs and lung tissues will require the design and construction of sophisticated facilities that will need to comply with stringent regulatory requirements related to these programs, some of which have not yet been developed or adopted by the relevant government agencies. The extent to which we fully develop any of these facilities will depend on the progress of our preclinical and clinical development in various earlier stage programs.

We operate in a highly competitive market in which a small number of pharmaceutical companies control a majority of the available PAH therapies. These pharmaceutical companies are well established in the market and possess greater financial, technical and marketing resources than we do. In addition, there are a number of investigational products in late-stage development that, if approved, may erode the market share of our existing commercial therapies and make market acceptance more difficult to achieve for any therapies we attempt to market in the future.

Financial Position

Cash and cash equivalents and current and non-current marketable investments (excluding restricted amounts of $5.4 million) at December 31, 2014 were $812.9 million, compared to approximately $1,136.7 million as of December 31, 2013. The decrease in cash and cash equivalents of $323.7 million resulted largely from the use of (1) $483.1 million to repurchase shares of our common stock; (2) $111.3 million relating to principal payments for early conversions of our 1.0 percent Convertible Senior Notes due September 15, 2016 (Convertible Notes); (3) $66.5 million for the payoff of the remaining principal balance of our 2010 Credit Agreement with Wells Fargo Bank, National Association and Bank of America, N.A. (Wells mortgage loan) in December 2014; (4) $144.1 million related to the exercise of cash-settled STAP awards; and (5) $195.6 million for estimated tax payments during the year ended December 31, 2014. These payments were offset by an estimated $693.4 million of cash generated from operations for the year ended December 31, 2014.

Accounts receivable at December 31, 2014, was $162.3 million, compared to $126.3 million at December 31, 2013. The $36.0 million increase reflects an approximately 20 percent increase in sales during the quarter ended December 31, 2014, compared to the quarter ended December 31, 2013, and the timing of invoicing and cash collections.

Other assets increased by $44.6 million at December 31, 2014 to $97.8 million compared to $53.3 million at December 31, 2013, primarily as a result of our $50.0 million investment in SGI, offset in part by our sale at par of $5.0 million of stock we held in another private company.

Current convertible notes decreased by $89.4 million, from $126.4 million at December 31, 2014 compared to $215.8 million at December 31, 2013, as a result of the early conversions of $111.3 million of principal of our Convertible Notes during the fourth quarter 2014, net of amortization of $11.0 million and $10.8 million for the write off of the unamortized discount for the early conversions of our Convertible Notes. Refer to Note 8— *Debt—Convertible Notes Due 2016* to the consolidated financial statements contained in this Annual Report on Form 10-K for details.

Line of credit and mortgages payable—current decreased by $66.5 million to $67,000 at December 31, 2014, compared to $66.6 million at December 31, 2013, as a result of the December 2014 maturity of our Wells mortgage loan. Refer to Note 8— *Mortgage Financing—Wells Fargo Bank* to the consolidated financial statements contained in this Annual Report on Form 10-K for details.

Temporary equity at December 31, 2014 was $23.2 million, compared to $45.0 million at December 31, 2013. The $21.8 million decrease in temporary equity corresponded to (1) $11.1 million for the reclassification of the equity component related to the amortization of the Convertible Notes' discount during the year from additional paid-in capital, since our Convertible Notes were convertible at the election of their holders throughout 2014 and (2) $10.8 million for the write off of the unamortized discount related to the early conversions of our Convertible Notes. For further details refer to Note 10— *Temporary Equity* and Note 8— *Debt—Convertible Notes Due 2016* to the consolidated financial statements contained in this Annual Report on Form 10-K for further details.

Additional paid-in capital increased by $318.9 million from $1,057.2 million at December 31, 2013, to $1,376.1 million at December 31, 2014. The increase was comprised of the following elements: (1) $81.0 million in proceeds and related tax benefits from stock option exercises; (2) $30.6 million of share-based compensation, primarily related to our Co-Chief Executive Officer's year-end stock option award based on the terms of her employment agreement; (3) $193.0 million related to the fair value of the common stock issued in connection with the early conversion of our Convertible Notes based on the closing price of our common stock on the date the shares were issued; and (4) $11.1 million from the amortization of the discount related to our Convertible Notes. Refer to Note 11— *Stockholders' Equity—Equity Incentive Plan* and Note 8— *Debt—Convertible Notes Due 2016* to the consolidated financial statements contained in this Annual Report on Form 10-K for further details.

Treasury stock was $1,185.8 million at December 31, 2014, compared to $513.4 million at December 31, 2013. The increase of $672.4 million corresponded to our repurchase of approximately 4.8 million shares of our common stock for $483.1 million and $189.3 million for the receipt of 1.5 million shares from our note hedge in connection with early conversion of $111.3 million of our Convertible Notes based on the closing price of our common stock on the date the shares were received. Refer to Note 11— *Stockholders' Equity—Share Repurchases* and Note 8— *Debt—Convertible Notes Due 2016* to the consolidated financial statements contained in this Annual Report on Form 10-K for further details.

Results of Operations

Years ended December 31, 2014 and 2013

Revenues

The following table presents the components of net revenues (dollars in thousands):

	Year Ended December 31,		Percentage Change
	2014	2013	
Cardiopulmonary products:			
Remodulin	$ 553,728	$ 491,179	12.7%
Tyvaso	463,067	438,793	5.5%
Adcirca	221,471	176,972	25.1%
Orenitram	41,267	—	100.0%
Other	8,986	10,040	(10.5)%
Total net revenues	$ 1,288,519	$ 1,116,984	15.4%

The growth in revenues for the year ended December 31, 2014, compared to the year ended December 31, 2013, corresponded primarily to the continued increase in the number of patients being treated with our products and the commencement of Orenitram sales.

For the years ended December 31, 2014 and 2013, approximately 74 percent and 76 percent, respectively, of total net revenues were derived from sales to our U.S.-based specialty pharmaceutical distributors. Remaining revenues were derived primarily from sales of Adcirca and sales of Remodulin to our international distributors.

The tables below include a reconciliation of the accounts associated with estimated rebates, prompt-pay discounts, sales allowances and distributor fees (in thousands):

	Year Ended December 31, 2014				
	Rebates	Prompt Pay Discounts	Allowance for Sales Returns	Distributor Fees	Total
Balance, January 1, 2014	$ 22,475	$ 2,500	$ 2,862	$ 1,092	$ 28,929
Provisions attributed to sales in:					
Current period	116,813	27,096	1,671	7,854	153,434
Prior periods	6,622	—	429	278	7,329
Payments or credits attributed to sales in:					
Current period	(85,833)	(23,998)	—	(7,139)	(116,970)
Prior periods	(28,461)	(2,313)	(934)	(1,528)	(33,236)
Balance, December 31, 2014	$ 31,616	$ 3,285	$ 4,028	$ 557	$ 39,486

	Year Ended December 31, 2013				
	Rebates	Prompt Pay Discounts	Allowance for Sales Returns	Distributor Fees	Total
Balance, January 1, 2013	$ 15,207	$ 2,115	$ 3,350	1,281	$ 21,953
Provisions attributed to sales in:					
Current period	81,938	24,154	1,254	7,008	114,354
Prior periods	997	—	(1,530)	3	(530)
Payments or credits attributed to sales in:					
Current period	(59,225)	(21,654)	—	(5,916)	(86,795)
Prior periods	(16,442)	(2,115)	(212)	(1,284)	(20,053)
Balance, December 31, 2013	$ 22,475	$ 2,500	$ 2,862	$ 1,092	$ 28,929

Research and Development Expense

The table below summarizes research and development expense by major project and non-project component (dollars in thousands):

	Year Ended December 31,		Percentage Change
	2014	2013	
Project and non-project:			
Cardiopulmonary	$ 131,843	$ 116,137	13.5%
Share-based compensation expense	72,714	134,706	(46.0)%
Other	37,991	48,505	(21.7)%
Total research and development expense	$ 242,549	$ 299,348	(19.0)%

Cardiopulmonary. The increase in cardiopulmonary program expenses of $15.7 million for the year ended December 31, 2014, compared to the year ended December 31, 2013, resulted from a $20.1 million increase in expenses related to our esuberaprost program offset by a $7.9 million decrease of our sustained-release, self-injectable product development which we terminated during 2014.

Share-based compensation. The decrease in share-based compensation of $62.0 million for the year ended December 31, 2014, compared to the year ended December 31, 2013, resulted from the approximately 15 percent appreciation in the price of our common stock during the year ended

December 31, 2014, compared to the approximately 112 percent increase in the price of our common stock price during the year ended December 31, 2013.

Other. The decrease in other research and development expenses of $10.5 million for the year ended December 31, 2014, compared to the year ended December 31, 2013, was primarily attributable to a $1.6 million decrease in expenditures for our development of ch14.18 and a $7.5 million decrease in research and development expenditures not allocated to specific projects.

Selling, General and Administrative Expense

The table below summarizes selling, general and administrative expense by major category (dollars in thousands):

	Year Ended December 31,		Percentage Change
	2014	2013	
Category:			
General and administrative	$ 186,312	$ 140,235	32.9%
Sales and marketing	82,000	73,871	11.0%
Share-based compensation expense	112,975	179,904	(37.2)%
Total selling, general and administrative expense	$ 381,287	$ 394,010	(3.2)%

General and administrative. The increase in general and administrative expenses of $46.1 million for the year ended December 31, 2014, compared to the year ended December 31, 2013, resulted primarily from the following: (1) an $8.7 million increase in grants to non-affiliated, non-profit organizations that provide financial assistance to patients with PAH; (2) $5.4 million and $7.5 million increases in operating expenses and salaries and other compensation-related expenses, respectively, associated with the general expansion of our business and the reclassification of certain staff from research and development to a general and administrative classification; and (3) an $18.2 million increase in consulting and professional fees primarily driven by our ongoing patent litigation and our response to a subpoena issued by the Office of Inspector General (OIG) of the Department of Health and Human Services relating to our marketing practices.

Sales and marketing. The increase in sales and marketing expenses of $8.1 million reflects the following: (1) a $2.8 million increase in marketing activities; and (2) a $5.3 million increase in salaries and other compensation-related expenses as we expanded our sales personnel during 2014.

Share-based compensation. The decrease in share-based compensation of $66.9 million for the year ended December 31, 2014, compared to the year ended December 31, 2013, corresponded to the approximately 15 percent appreciation in the price of our common stock during the year ended December 31, 2014, compared to the approximately 112 percent appreciation in our stock price during the year ended December 31, 2013.

Cost of Product Sales

Cost of product sales as a percentage of product revenues decreased to 9.8 percent for the year ended December 31, 2014 compared to 11.8 percent for the year ended December 31, 2013. In October 2014, our royalty payment obligation to Glaxo on sales of our treprostinil-based products expired.

Income Tax Expense

The provision for income taxes was $185.1 million for the year ended December 31, 2014 compared to $104.3 million for the year ended December 31, 2013. The increase in the provision for income taxes corresponded to the increase in pre-tax earnings. For the years ended December 31, 2014 and December 31, 2013, the effective tax rates were approximately 35 percent and 37 percent, respectively. For complete details refer to Note 13— *Income Taxes* to the consolidated financial statements contained in this Annual Report on 10-K.

Years ended December 31, 2013 and 2012

Revenues

The following table presents the components of net revenues (dollars in thousands):

	Year Ended December 31,		Percentage Change
	2013	2012	
Cardiopulmonary products:			
Remodulin	$ 491,179	$ 457,969	7.3%
Tyvaso	438,793	325,614	34.8%
Adcirca	176,972	122,540	44.4%
Other	10,040	9,953	0.9%
Total revenues	$ 1,116,984	$ 916,076	21.9%

The growth in revenues for the year ended December 31, 2013, compared to the year ended December 31, 2012, corresponded to the continued increase in the number of patients being treated with our products.

For the years ended December 31, 2013 and 2012, approximately 76 percent and 78 percent, respectively, of net revenues were derived from sales of Remodulin and Tyvaso to U.S.-based specialty pharmacy distributors. Remaining revenues were derived primarily from sales of Adcirca and sales of Remodulin to our international distributors.

The table below includes a reconciliation of the accounts associated with estimated rebates, prompt-pay discounts, allowances for sales returns and distributor fees (in thousands):

	Year Ended December 31, 2013				
	Rebates	Prompt Pay Discounts	Allowance for Sales Returns	Distributor Fees	Total
Balance, January 1, 2013	$ 15,207	$ 2,115	$ 3,350	$ 1,281	$ 21,953
Provisions attributed to sales in:					
Current period	81,938	24,154	1,254	7,008	114,354
Prior periods	997	—	(1,530)	3	(530)
Payments or credits attributed to sales in:					
Current period	(59,225)	(21,654)	—	(5,916)	(86,795)
Prior periods	(16,442)	(2,115)	(212)	(1,284)	(20,053)
Balance, December 31, 2013	$ 22,475	$ 2,500	$ 2,862	$ 1,092	$ 28,929

	Year Ended December 31, 2012				
	Rebates	Prompt Pay Discounts	Allowance for Sales Returns	Distributor Fees	Total
Balance, January 1, 2012	$ 13,993	$ 1,679	$ 1,402	$ 732	$ 17,806
Provisions attributed to sales in:					
Current period	53,674	18,682	1,717	6,089	80,162
Prior periods	(949)	6	381	31	(531)
Payments or credits attributed to sales in:					
Current period	(39,559)	(16,567)	—	(4,808)	(60,934)
Prior periods	(11,952)	(1,685)	(150)	(763)	(14,550)
Balance, December 31, 2012	$ 15,207	$ 2,115	$ 3,350	$ 1,281	$ 21,953

Cost of Product Sales

The cost of product sales as a percentage of product revenues decreased to 11.8 percent for the year ended December 31, 2013, compared to 13.0 percent for the year ended December 31, 2012. During the year ended December 31, 2012, we increased our reserves for inventory obsolescence by $8.9 million, representing the cost of the inhalation devices incorporated into our Tyvaso Inhalation System that were expected to be rendered obsolete based on the then pending commercial release of our improved inhalation device, the TD-100.

Research and Development Expense

The table below summarizes research and development expense by major project and non-project components (dollars in thousands):

	Year Ended December 31,		Percentage Change
	2013	2012	
Project and non-project:			
Cardiopulmonary	$ 116,137	$ 122,350	(5.1)%
Share-based compensation (benefit) expense	134,706	11,237	1,098.8%
Other	48,505	39,800	21.9%
Total research and development expense	$ 299,348	$ 173,387	72.6%

Cardiopulmonary. The decrease in cardiopulmonary program expenses of $6.2 million for the year ended December 31, 2013, compared to the year ended December 31, 2012, resulted from a $6.1 million decrease in expenses relating to the development of once-daily injectable prostacyclin analogues.

Share-based compensation. The increase in share-based compensation of $123.5 million for the year ended December 31, 2013, compared to the year ended December 31, 2012, resulted from the approximately 112 percent appreciation in the price of our common stock during the year ended December 31, 2013, compared to the approximately 13 percent appreciation in the price of our common stock price during the year ended December 31, 2012.

Other. The increase in other research and development expenses of $8.7 million for the year ended December 31, 2013, compared to the year ended December 31, 2012, was attributable to a $5.1 million increase in expenditures for our development of ch14.18 and $2.5 million in support expenses not allocated to specific projects.

Selling, General and Administrative Expense

The table below summarizes selling, general and administrative expense by major category (dollars in thousands):

	Year Ended December 31, 2013	Year Ended December 31, 2012	Percentage Change
Category:			
General and administrative	$ 140,235	$ 116,899	20.0%
Sales and marketing	73,871	67,220	9.9%
Share-based compensation (benefit) expense	179,904	17,627	920.6%
Total selling, general and administrative expense	$ 394,010	$ 201,746	95.3%

General and administrative. The increase in general and administrative expenses of $23.3 million for the year ended December 31, 2013, compared to the year ended December 31, 2012, was driven by the following: (1) a $9.2 million increase in grants to non-affiliated, non-profit organizations that provide financial assistance to patients with PAH; (2) $6.9 million and $5.8 million increases in operating expenses and salaries and other compensation-related expenses, respectively, associated with the general expansion of our business, including headcount; and (3) a $6.3 million increase in consulting and professional fees related to ongoing legal matters. These increases were offset in part by a one-time $6.8 million impairment charge on an acquired contract-based intangible asset we recognized during the year ended December 31, 2012.

Sales and marketing. The increase in sales and marketing expenses of $6.7 million reflects the following increases: (1)a $4.2 million increase in marketing activities; and (2) $2.4 million in salaries and other compensation-related expenses as we expanded our sales personnel during 2013.

Share-based compensation. The increase in share-based compensation of $162.3 million for the year ended December 31, 2013, compared to the year ended December 31, 2012, corresponded to the approximately 112 percent appreciation in the price of our common stock during the year ended December 31, 2013, compared to the approximately 13 percent appreciation in our stock price during the year ended December 31, 2012.

Other (expense) Income—Other, net

Other, net income was $4.5 million for the year ended December 31, 2013, compared to other, net income of $35.7 million for the year ended December 31, 2012. The $31.2 million decrease was the result of the recognition of an approximately $31.0 million gain from insurance proceeds received during the year ended December 31, 2012, for which there was no corresponding transaction during the year ended December 31, 2013.

Income Tax Expense

The provision for income taxes was $104.3 million for the year ended December 31, 2013 compared to $136.2 million for the year ended December 31, 2012. For the years ended December 31, 2013 and December 31, 2012, the effective tax rates were approximately 37 percent and 31 percent, respectively. The increase in the effective tax rate for the year ended December 31, 2013, resulted from certain non-deductible executive compensation expenses, driven primarily by the increase in our STAP liability as a result of the appreciation in our stock price. For complete details refer to Note 13— *Income Taxes* to the consolidated financial statements contained in this Annual Report on 10-K.

Liquidity and Capital Resources

We have funded our operations principally through sales of our commercial products and, from time-to-time, third-party financing arrangements. We believe that our current liquidity is sufficient to fund ongoing operations and future business plans as we expect continued growth in demand for our commercial products. Furthermore, our customer base remains stable and we believe presents minimal credit risk. However, any projections of future cash flows are inherently subject to uncertainty and we may seek other forms of financing.

Cash Flows and Working Capital

2014 Compared to 2013

Operating

Net cash provided by operating activities declined by $70.0 million during the year ended December 31, 2014 to $355.3 million, compared to net cash provided by operating activities of

$425.3 million for the year ended December 31, 2013. The significant components of the decline in net cash provided by operating activities were (amounts in millions):

	Year Ended December 31, 2014	2013	Dollar change	Explanation
Significant Components:				
Net income	$ 340.1	$ 174.6	$ 165.5	Due to a 15.4 percent increase in revenues and a decrease in share-based compensation expense during 2014 as compared to 2013 (1)
Adjustments to reconcile net income to net cash provided by operating activities:				
Current and deferred tax expense	185.1	104.3	$ 80.8	Primarily due to the increase in taxable income
Share-based compensation expense	190.1	320.8	$ (130.7)	Due to a smaller increase in the price of our common stock during 2014 as compared to 2013(1)
Excess tax benefits from share-based compensation	(30.8)	(9.3)	$ (21.5)	As a result of a 69 percent increase in the number of stock options exercised during 2014 as compared to 2013, coupled with a higher average stock price during 2014 than during 2013
Accounts receivable	(35.7)	(10.0)	$ (25.7)	Due to a 22 percent increase in sales during the fourth quarter of 2014 as compared to the same period in 2013
Accounts payable and accrued expenses	(6.8)	7.5	$ (14.3)	Primarily the result of lower accrued royalty expense at December 31, 2014 as compared to December 31, 2013 as a result of the cessation of our royalty obligation to Glaxo in October 2014
Other liabilities	(315.5)	(196.6)	(118.9)	Primarily due to an $88.2 million increase in STAP exercises and a $35.5 million increase in cash tax payments made during 2014 as compared to 2013, as a result of a higher average stock price during 2014 as compared to 2013 and an increase in taxable income, respectively
Total	$ 326.5	$ 391.3	$ (64.8)	

(1) The price of our common stock increased 15 percent during 2014 compared to a 120 percent increase in 2013.

Investing

Net cash provided by investing activities was $338.5 million for the year ended December 31, 2014, compared to $295.0 million used in investing activities for the year ended December 31, 2013. The $633.4 million increase in net cash provided by investing activities reflects $430.9 million of cash provided from the net maturities of held-to-maturity investments during the year ended December 31, 2014, compared to $232.3 million in net purchases of held-to-maturity investments during the same period in 2013. Due to the funding requirements in 2014 for our ongoing share repurchase programs and the conversions of our Convertible Notes, we have not been reinvesting the proceeds from our maturing investments. This increase in cash from maturing investments was partially offset by a $15.5 million increase in capital expenditures relating primarily to the completion of facilities used in our lung transplantation programs.

Financing

Net cash used in financing activities was $576.5 million for the year ended December 31, 2014 compared to $5.1 million for the year ended December 31, 2013. The $571.4 million increase reflects an increase of $440.6 million in repurchases of our common stock and an increase of $176.5 million in principal payments of debt, offset by a $45.1 million increase in proceeds and tax benefits from the exercise of stock options during the year ended December 31, 2014, compared to the year ended December 31, 2013.

2013 Compared to 2012

Operating

Net cash provided by operating activities was $425.3 million for the year ended December 31, 2013, compared to $323.6 million for the year ended December 31, 2012. The increase in net operating cash flows of $101.6 million was driven by a $290.7 million increase in share-based compensation primarily as a result of the 112 percent increase of our stock price during the year ended December 31, 2013. This increase in non-cash expense was partially offset by decreases of $129.9 million in net income and a $50.9 million decrease in other liabilities, consisting primarily of $40.6 million and $24.1 million increases in cash paid relating to income taxes and STAP award exercises, respectively, during the year ended December 31, 2013 compared to 2012.

Investing

Net cash used in investing activities was $295.0 million for the year ended December 31, 2013, compared to $163.4 million for the year ended December 31, 2012. The increase of $131.6 million in cash used in investing activities reflects an increase in cash used to purchase $180.8 million of held-to-maturity investments, net of maturities and $30.8 million used to purchase investments in privately-held investments. These increases in cash used for investing were offset by a $72.3 million decrease in construction related expenditures in 2013 as compared to 2012, as we had completed our major construction projects in Silver Spring, Maryland and Research Triangle Park, North Carolina in early 2012. Our ability to invest an additional $180.8 million in to held-to-maturity investments was also due in part to the $145.6 million reduction in repurchases of our common stock during 2013 as compared to 2012.

Financing

Net cash used in financing activities for the year ended December 31, 2013 was $5.1 million, compared to $169.1 million for the year ended December 31, 2012. The $164.0 million decrease in cash used in financing activities comprised in large part the following: (1) a $145.6 million decrease in repurchases of our common stock; (2) a $16.1 million increase in stock-option exercises and related tax

benefits; and (3) $2.7 million in proceeds related to our employee stock purchase plan during 2013, compared to none in 2012. The increase in stock option exercises and related tax benefits and the decrease in repurchases of our common stock were all attributable to the 112 percent appreciation in the price of our common stock during 2013.

Working Capital

At December 31, 2014, we had working capital of $469.9 million, compared to $226.7 million at December 31, 2013. The increase in working capital at December 31, 2014 of $243.2 million resulted from (1) the repayment of the $66.5 million upon maturity of an outstanding mortgage loan; (2) $111.3 million principal payments for early conversions of our 1.0 percent Convertible Senior Notes due September 15, 2016; and (3) a $36.0 million increase in accounts receivable corresponding to a 20 percent increase in revenues when comparing sales for the quarter ended December 31, 2014 to the same quarter in 2013.

In addition, at December 31, 2014, we had approximately $122.7 million of long-term marketable securities that could be liquidated or used to collateralize borrowings against our line of credit facility, if necessary, to fund our operations.

Line of Credit

In September 2013, we entered into a one-year Credit Agreement with Wells Fargo Bank, National Association (Wells Fargo) providing for a $75.0 million revolving loan facility, which may be increased by up to an additional $75.0 million provided certain conditions are met (the 2013 Credit Agreement). In July 2014, we amended the Credit Agreement solely to extend its maturity to September 30, 2015. We use this facility for general corporate purposes. At our option, amounts borrowed under the 2013 Credit Agreement bear interest at either the one-month LIBOR rate plus a 0.50 percent margin, or a fluctuating base rate excluding any margin. In addition, we are subject to a monthly commitment fee at a rate of 0.06 percent per annum based on the average daily unused balance of the facility. Amounts borrowed under the 2013 Credit Agreement are secured by certain of our marketable investments. As of December 31, 2014, we had no outstanding balance on the line of credit.

Convertible Senior Notes

In October 2011, we issued the Convertible Notes with an aggregate principal value of $250.0 million. The Convertible Notes are unsecured, unsubordinated debt obligations that rank equally with all of our other unsecured and unsubordinated indebtedness. We pay interest at 1.0 percent per annum semi-annually on March 15 and September 15 of each year. The initial conversion price is $47.69 per share. As of December 31, 2014, the outstanding principal balance of our Convertible Notes was $138.8 million.

Conversion can occur: (1) any time after June 15, 2016; (2) during any calendar quarter that follows a calendar quarter in which the price of our common stock exceeds 130 percent of the conversion price for at least 20 days during the 30 consecutive trading-day period ending on the last trading day of the quarter; (3) during the ten consecutive trading-day period following any five consecutive trading-day period in which the trading price of the Convertible Notes is less than 95 percent of the closing price of our common stock multiplied by the then-current number of shares underlying the Convertible Notes; (4) upon specified distributions to our shareholders; (5) in connection with certain corporate transactions; or (6) in the event that our common stock ceases to be listed on the NASDAQ Global Select Market, the NASDAQ Global Market or the New York Stock Exchange, or any of their respective successors.

The closing price of our common stock exceeded 130 percent of the conversion price of the Convertible Notes for more than 20 trading days during the 30 consecutive trading day period ended

December 31, 2014. Consequently, the Convertible Notes are convertible at the election of their holders. As this conversion right is not within our control, the Convertible Notes have been classified as a current liability on our consolidated balance sheet at December 31, 2014. We are required to calculate this contingent conversion criteria at the end of each quarterly reporting period. Therefore, the convertibility and classification of our Convertible Notes may change depending on the price of our common stock.

Upon conversion, holders of our Convertible Notes are entitled to receive: (1) cash equal to the lesser of the principal amount of the notes or the conversion value (the number of shares underlying the Convertible Notes multiplied by the then-current conversion price per share); and (2) to the extent the conversion value exceeds the principal amount of the notes, shares of our common stock. In the event of a change in control, as defined in the indenture under which the Convertible Notes have been issued, holders can require us to purchase all or a portion of their Convertible Notes for 100 percent of the principal amount plus any accrued and unpaid interest. We currently have sufficient cash and cash equivalents and borrowing capacity to fund any conversions.

During the period from January 1, 2015 through February 11, 2015, we settled conversion requests representing $14.0 million in principal value of the Convertible Notes. We paid out $14.0 million for the principal value of the notes and issued 193,000 shares of our common stock during the settlement of these conversions. We also received 193,000 shares from our convertible note hedge with Deutsche Bank AG London at the settlement dates. As of February 11, 2015, there are 2.6 million underlying shares representing the aggregate consideration upon future conversions of our Convertible Notes.

Mortgage Financing

In December 2010, we entered into a Credit Agreement with Wells Fargo and Bank of America, N.A., pursuant to which we obtained a $70.0 million mortgage loan (the 2010 Credit Agreement). The 2010 Credit Agreement matured in December 2014 and we repaid in full the outstanding $66.5 million principal balance.

Share Tracking Award Plans

Awards granted under our STAP entitle participants to receive in cash the appreciation in our common stock, which is calculated as the increase in the closing price of our common stock between the date of grant and the date of exercise. Depending on the future price movements of our common stock, cash requirements associated with the exercise of awards could be significant. At December 31, 2014, the fair value of STAP awards that could potentially be exercised during 2015 was $205.1 million. We review the potential future cash requirements of the STAP program annually. Based on our review, we can modify our operating budgets, the metrics used in determining the number of awards to be granted, or both. We currently have sufficient cash and cash equivalents and borrowing capacity to fund any STAP awards which could be exercised during 2015 and beyond. In addition, in January 2014 our Board of Directors approved a 3.0 million increase in the number of available STAP awards to accommodate anticipated future grants of STAP awards under our long-term incentive bonus and compensation programs through 2015.

Share Repurchases

From time to time, our Board of Directors may authorize plans to repurchase shares of our common stock. In June 2014, our Board of Directors authorized the repurchase of up to $500.0 million of our common stock. This program became effective on August 1, 2014, and will remain open for up to one year. From the effective date of the program through December 31, 2014, we acquired approximately 887,100 shares of our common stock at an aggregate cost of $105.5 million under this program.

We currently have sufficient cash and cash equivalents, borrowing capacity and, if needed, marketable investments, to fund repurchases of our common stock under this program.

Toray License Obligations

Pursuant to a March 2007 amendment to our license agreement for the development of beraprost, we issued 400,000 shares of our common stock to Toray. Toray has the right to request that we repurchase these shares at their issuance price of $27.21 per share upon 30 days prior written notice. To date, Toray has not notified us that it intends to require us to repurchase these shares. As part of the July 2011 amendment to our license, we agreed to pay Toray $50.0 million in equal, non-refundable payments over a five-year period ending in 2015 in exchange for a reduction in royalty rates. As of December 31, 2014, the undiscounted outstanding balance of this obligation was $10.0 million.

Obligations Under License and Assignment Agreements

We pay Lilly a five percent royalty on net sales of Adcirca and we pay Supernus Pharmaceuticals Inc. a single-digit percentage royalty based on net sales of Orenitram. We have entered into other license rights arrangements under which we are required to make milestone payments upon the achievement of certain developmental and commercialization objectives and royalty payments upon the commercialization of related licensed technology.

Off-Balance Sheet Arrangements

We do not have any off-balance sheet arrangements within the meaning of Item 303(a)(4) of Regulation S-K.

Contractual Obligations

At December 31, 2014, we had the following contractual obligations (in thousands):

	Payments Due by Period				
	Total	Less than 1 year	2-3 Years	4-5 Years	More than 5 Years
Convertible Notes(1)	$ 138,750	$ 13,975	$ 124,775	$ —	$ —
Mortgage and other loans	3,811	102	3,627	82	—
Operating lease obligations	13,985	3,839	6,680	3,338	128
Obligations under the STAP(2)	485,371	282,864	103,955	98,552	—
Obligations under the SERP(3)	61,910	20,875	—	4,430	36,605
Purchase commitments	14,500	14,500	—	—	—
Milestone payments under license and acquisition agreements(4)	29,165	3,171	3,158	15,059	7,777
Total(5)	$ 747,492	$ 339,326	$ 242,195	$ 121,461	$ 44,510

(1) Assumes no early conversions other than those settled or pending as of February 11, 2015 and that the price of our common stock will exceed the conversion value so that the full principal balance of our Convertible Notes is paid at their contractual maturity date.

(2) Estimated based on the intrinsic value of outstanding STAP awards expected to vest, assuming that awards will be exercised immediately upon vesting. Refer to Note 7 —*Share Tracking Award Plans* to our consolidated financial statements included in this Annual Report on Form 10-K for further details.

(3) Consists of actuarially derived, estimated future payouts of benefits. Refer to Note 14— *Employee Benefit Plans—Supplemental Executive Retirement Plan* to our consolidated financial statements included in this Annual Report on Form 10-K for further details.

(4) Based on our estimates of the timing and probability of achieving milestones specified under our various license and acquisition agreements.

(5) As of December 31, 2014, we had $1.4 million in unrecognized tax benefits. The contractual obligations disclosed above exclude these amounts due to the uncertainty surrounding the amounts and timing of future payments.

Summary of Critical Accounting Policies and Estimates

We prepare our consolidated financial statements in conformity with generally accepted accounting principles in the United States (GAAP). GAAP requires that we make estimates and assumptions that affect the amounts and timing reported in our consolidated financial statements. As we become aware of updated information or new developments, these estimates and assumptions may change and materially impact reported amounts. We consider the following accounting policies to be critical to our consolidated financial statements because they require the use of our judgment and estimates (including those that are forward-looking) in their application.

Revenue Recognition

Remodulin, Tyvaso and Orenitram

We market Remodulin, Tyvaso and Orenitram to specialty pharmaceutical distributors under materially similar contractual arrangements. Sales of Remodulin, Tyvaso and Orenitram are recognized when title and risk of ownership pass to our distributors upon satisfactory delivery to our distributors' facilities—i.e., when all of our performance obligations under these distributor arrangements have been satisfied. We record sales of Remodulin, Tyvaso and Orenitram net of: (1) estimated rebates; (2) prompt payment discounts; and (3) service fees we pay to distributors. Determining sales allowances involves the use of significant estimates and judgment and may involve the use of information from external sources.

We derive our provisions for rebates from an analysis of historical levels of rebates to both state Medicaid agencies and commercial third-party payers by product, relative to sales of each product. In addition, we determine our obligation for prescription drug discounts required for Medicare Part D Orenitram patients within the coverage gap based on estimations of the number of Medicare Part D Orenitram patients and the period that such patients will remain within the coverage gap. In formulating our estimates, we also consider the impact of anticipated changes in product prices, sales trends and changes to government rebate programs, particularly as they relate to eligibility requirements and/or rebate pricing. We analyze rebate data separately for Remodulin, Tyvaso and Orenitram, as these therapies have different routes of administration to treat PAH patients at different stages in the disease continuum and therefore, rebate eligibility and pricing requirements can differ for each therapy.

We estimate prompt pay discounts based on observed payment behavior. Our distributors have routinely taken advantage of these discounts and we expect them to continue to do so.

We pay our distributors for contractual services rendered and accrue for related fees based on contractual rates applied to the estimated units of service provided by distributors for a given financial reporting period.

Our distributors do not have return rights; however, we provide exchange rights in the event that product is damaged during shipment or expires. Exchanges for damaged product are rare. In the event

that Remodulin, Tyvaso or Orenitram has been damaged during shipment and we have been promptly notified as required under our distributor arrangements, we do not recognize revenue on that shipment until damaged product has been satisfactorily replaced. Replacement generally occurs within several days after we are notified of the damage. The number of product exchanges due to expiration has been negligible because we sell Remodulin, Tyvaso and Orenitram with expiration dates in excess of one year and our distributors typically carry a thirty- to sixty-day supply of related inventories. In addition, we do not require, nor do we provide incentives for our distributors to assume, inventory levels of Remodulin, Tyvaso or Orenitram beyond that which would be considered reasonable and customary in the ordinary course of business. In addition, we monitor inventory levels closely in the distribution channels.

The financial effects of exchange rights for Remodulin, Tyvaso and Orenitram have been immaterial and we expect the future volume of exchanges to be consistent with historical levels. Specifically, exchanges for Remodulin, Tyvaso and Orenitram have comprised significantly less than one percent of the volume of units sold. Since exchanges of Remodulin, Tyvaso and Orenitram have been, and are expected to be, insignificant, we do not recognize a reserve for estimated exchange rights in the period of sale. Lastly, we regularly monitor exchange data for both of these therapies to ensure that our assumptions continue to be reasonable, appropriate and current.

Adcirca

Adcirca is manufactured for us by Lilly and distributed through Lilly's pharmaceutical wholesaler network. Specifically, Lilly handles all of the administrative functions associated with the sale of Adcirca on our behalf, including the receipt and processing of customer purchase orders, shipment of Adcirca to customers and the invoicing and collection of customer payments. In addition, sales terms for Adcirca include return rights that extend throughout the distribution channel. We recognize sales of Adcirca on a gross basis (net of allowances) upon delivery to customers due to the following factors: (1) we are responsible for the acceptability of the product sold; (2) we bear all inventory risk, as title and risk of loss pass to us at the shipping point from Lilly's manufacturing facility; (3) we assume credit risk if Lilly is unable to collect amounts due from customers; (4) we bear the return of product risk; and (5) we assume the risk and cost of a product recall, if required.

We recognize sales of Adcirca net of: (1) estimated rebates; (2) prompt pay discounts; (3) allowances for product returns; and (4) wholesaler fees. We estimate our liability for rebates based on an analysis of historical levels of rebates to both Medicaid and commercial third-party payers and we consider the impact of sales trends, changes in government and commercial rebate programs and anticipated changes in Adcirca's pricing. In addition, we determine our obligation for prescription drug discounts required for Medicare Part D patients within the coverage gap based on estimations of the number of Medicare Part D patients and the period that such patients will remain within the coverage gap. We base our estimates for prompt pay discounts on observed customer payment behavior and expectations regarding the future utilization of such discounts. Prior to 2013, we derived estimates relating to our allowance for returns of Adcirca from published industry data specific to specialty pharmaceuticals and, beginning in 2013, from actual return data accumulated since launch. This change in the methodology for estimating returns of Adcirca resulted in a $3.1 million reduction of our allowance for returns for the twelve-month period ending December 31, 2013. In addition, we quarterly compare patient prescription data for Adcirca to sales of Adcirca to ensure a reasonable relationship between prescription and sales trends. To date, we have not identified any unusual patterns in the volume of prescriptions relative to sales that would warrant reconsideration of, or adjustment to, the methodology we currently employ to estimate our allowance for returns. Lastly, wholesaler fees are based on contractual percentages of wholesalers' sales.

Share-Based Compensation

Our share-based awards are classified as either equity (stock options and our employee stock purchase plan) or as liabilities (STAP awards). We recognize related share-based compensation expense based on the fair value of the options granted to purchase stock and on outstanding STAP awards. We estimate the fair value of all share-based awards using the Black-Scholes-Merton valuation model. Valuation models, like the Black-Scholes-Merton model, require the use of subjective assumptions that could materially impact the estimation of fair value and related compensation expense to be recognized. These assumptions include, among others, the expected volatility of our stock price, the expected term of awards and the expected forfeiture rate. Developing these assumptions requires the use of judgment.

Marketable Investments

Substantially all of our marketable securities are classified as held-to-maturity. For marketable investments in which the fair value is lower than the carrying value, we periodically review these securities to determine whether the related impairments are other than temporary. This review requires us to make judgments, particularly as they relate to: (1) the extent and duration of a decline in the fair value of a security; (2) the probability, extent and timing of a recovery of a security's value; (3) our assessment as to whether it is more likely than not that we will be required to sell a security prior to recovery of its amortized cost; and (4) our estimation of the present value of the cash flows we would expect to collect that are attributable to an impaired debt security to determine whether a credit loss exists. The scope of this evaluation requires forward-looking assessments pertaining to a security and the relevant financial markets, an issuer's financial condition and business outlook, and our estimation of the value of cash flows we would expect to collect from an issuer upon maturity of an impaired security. Accordingly, we must make assessments regarding current conditions and future events, which involve a considerable degree of uncertainty and judgment. When we determine that the decline in value of a security is other than temporary, we are required to recognize the credit loss portion as an impairment charge to our consolidated statement of operations.

In addition, we classify substantially all of our marketable investments as held-to-maturity because we believe we have the positive intent and ability to hold related securities until they mature. This assertion requires us to make forward-looking judgments regarding our future cash flow requirements relative to the maturity dates of such securities.

Fair Value Measurements

We are required to disclose assets and liabilities subject to fair value measurements within a specified fair value hierarchy. The fair value hierarchy gives the highest priority to fair value measurements based on unadjusted quoted prices in active markets for identical assets or liabilities (Level 1 measurements) and the lowest priority to fair value measurements derived through the use of unobservable inputs (Level 3 measurements). Assets and liabilities are classified within the fair value hierarchy, in their entirety, based on the lowest level input that is significant to the related fair value measurement. Determining where a particular asset or liability should be disclosed within the hierarchy involves judgment regarding the significance of inputs relative to a fair value measurement and where such inputs lie within the hierarchy. Furthermore, assets and liabilities that are not actively traded may have little or no price transparency. As such, estimating the fair value of Level 3 assets and liabilities involves the use of significant subjective assumptions that we believe market participants would consider in pricing. We often employ a discounted cash flow model to help us estimate the fair value of our Level 3 assets and liabilities. Inputs to the model that involve a significant degree of judgment include estimating the amounts and timing of expected cash flows and determining a suitable discount rate.

Income Taxes

Income taxes are accounted for in accordance with the asset and liability method. Accordingly, deferred tax assets and liabilities are recognized for the future tax consequences attributable to differences between the financial statement carrying amounts of existing assets and liabilities and their tax bases. Deferred tax assets and liabilities are measured using the enacted tax rates that are expected to apply to taxable income in the years in which those temporary differences are expected to be recovered or settled. Deferred tax assets are reduced by a valuation allowance when, in our opinion, it is more likely than not that some or all of the deferred tax assets will not be realized. Evaluating whether deferred assets will be realized requires us to review forecasts of earnings and taxable income, among other considerations. Accordingly, the evaluation of deferred tax assets requires us to make significant judgments and forward-looking assessments regarding the amounts and availability of future taxable income.

Financial statement recognition of a tax position taken or expected to be taken in a tax return is determined based on a more likely than not threshold of that position being sustained. If the tax position meets this threshold, the benefit to be recognized is measured as the largest amount that is more than 50 percent likely to be realized upon ultimate settlement. Accounting for uncertain tax positions involves considerable judgment in assessing the future tax consequences of amounts that have been recognized in our financial statements or tax returns. The ultimate resolution of uncertain tax positions could result in amounts different from those recognized in our consolidated financial statements.

Intangible Assets and Goodwill

In connection with transactions that we account for as business combinations, we typically recognize intangible assets, based on their acquisition-date fair value, and goodwill, representing the excess of the fair value of the consideration transferred, over the estimated fair value of assets acquired and liabilities assumed. Measuring the acquisition-date fair value of intangible assets involves the use of significant judgment and estimates with respect to determining, among other inputs: (1) the timing and amounts of cash flows and operating profits for potential product candidates; (2) the timing and probability of regulatory approvals for product candidates under development; (3) the useful lives of potential product candidates; and (4) appropriate discount rates.

We are required to test goodwill for impairment annually or more frequently if impairment indicators exist. Evaluating goodwill for impairment requires judgment, particularly as it relates to determining the fair value of a reporting unit to which goodwill has been assigned. When required, we often use a discounted cash flow model to test goodwill for impairment, which involves the use of significant and subjective inputs. Inputs requiring our judgment include, among others, the estimation of the amounts and timing of future cash flows, future growth rates and profitability of a reporting unit. Changes in our business strategy or adverse changes in market conditions could impact impairment analyses and require the recognition of an impairment charge equal to the excess of the carrying value of goodwill over its implied fair value.

We test our finite-lived intangible assets for impairment when conditions suggest that their carrying values may not be recoverable. Evaluating intangible assets for impairment requires judgment, particularly when determining amounts of undiscounted cash flows used in assessing recoverability and measuring the fair value of such assets, if necessary. These projections require forward-looking assumptions that may include, among others, estimates of future growth, discount rates and future business or industry conditions. Changes in our business strategy or adverse changes in market conditions could indicate one or more finite-lived intangible assets have been impaired. Therefore, we would be initially required to test such assets for recoverability. If determined unrecoverable, we would

recognize an impairment charge equal to the extent the carrying value of such assets exceed their fair value.

Pension Benefit Obligation

Accounting for our Supplemental Executive Retirement Plan (SERP) requires that we recognize in our consolidated balance sheet a liability equal to the unfunded status of the SERP (the total estimated projected benefit obligation, as we do not fund the SERP) and measure our projected benefit obligation as of the end of our fiscal year. Estimating the SERP obligation involves the use of judgment and estimates. The SERP obligation and related pension expense are derived from actuarial valuations that are developed using a number of assumptions. A key assumption underlying the valuation is the discount rate. The discount rate should be representative of the rate associated with high-quality, fixed-income debt securities. We must consider prevailing economic conditions and outlook, the state of the credit markets and other economic factors when determining an appropriate discount rate to employ. Changes in the discount rate can significantly increase or decrease our SERP obligation. For instance, a reduction in the discount rate would increase our projected benefit obligation and result in an actuarial loss. Consequently, we could be required to recognize additional pension expense in our consolidated statements of operations related to the actuarial loss in future periods if certain thresholds are met. Other actuarial assumptions include participant demographics such as the expected date of retirement, rate of salary increases and withdrawal rates, among other factors. Not only can actual experience differ from actuarial assumptions, but changes in any of these assumptions can also materially affect the measurement of the SERP obligation.

Recently Issued Accounting Standards

In May 2014, the Financial Accounting Standards Board (FASB) issued Accounting Standards Update No. 2014-09 (ASU 2014-09), *Revenue from Contracts with Customers.* ASU 2014-09 will eliminate transaction-specific and industry-specific revenue recognition guidance under current GAAP and replace it with a principle-based approach for determining revenue recognition. ASU 2014-09 will require that companies recognize revenue based on the value of transferred goods or services as they occur in the contract. ASU 2014-09 also will require additional disclosure about the nature, amount, timing and uncertainty of revenue and cash flows arising from customer contracts, including significant judgments and changes in judgments and assets recognized from costs incurred to obtain or fulfill a contract. ASU 2014-09 is effective for annual reporting periods beginning after December 15, 2016. Early application is not permitted. Entities can transition to the standard either retrospectively or as a cumulative-effect adjustment as of the date of adoption. Presently, we are assessing what effect the adoption of ASU 2014-09 will have on our consolidated financial statements and accompanying notes.

ITEM 7A. QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK

As of December 31, 2014, we have invested $420.5 million in corporate-debt securities and federally-sponsored agencies. The market value of these investments varies inversely with changes in prevailing market interest rates. In general, as interest rates increase, the market value of a debt investment would be expected to decrease. Conversely, as interest rates decrease, the market value of a debt investment would be expected to increase. To date, we have not experienced significant volatility in the value of these investments. However, to address market risk, we invest in debt securities with terms no longer than three years and hold these investments to maturity so that they can be redeemed at their stated or face value. At December 31, 2014, our investments in debt securities issued by corporations and federally-sponsored agencies had a weighted average stated interest rate of approximately 0.54 percent and a weighted average maturity of 1.0 years. Many of our investments may be called by their respective issuers prior to maturity.

During sustained periods of instability and uncertainty in the financial markets, we may be subjected to additional investment-related risks that could materially affect the value and liquidity of our investments. In light of these risks, we actively monitor market conditions and developments specific to the securities and security classes in which we invest. In addition, we believe that we maintain a conservative investment approach in that we invest exclusively in unstructured, highly-rated securities with relatively short maturities that we believe reduce our exposure to undue risks. While we believe we take prudent measures to mitigate investment related risks, such risks cannot be fully eliminated, as circumstances can occur that are beyond our control.

ITEM 8. FINANCIAL STATEMENTS AND SUPPLEMENTARY DATA

UNITED THERAPEUTICS CORPORATION
INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

Report of Independent Registered Public Accounting Firm

The Board of Directors and Shareholders
United Therapeutics Corporation

We have audited the accompanying consolidated balance sheets of United Therapeutics Corporation as of December 31, 2014 and 2013, and the related consolidated statements of operations, comprehensive income, stockholders' equity, and cash flows for each of the three years in the period ended December 31, 2014. Our audits also included the financial statement schedule listed in the Index at Item 15(a)(2). These financial statements and schedule are the responsibility of the Company's management. Our responsibility is to express an opinion on these financial statements and schedule based on our audits.

We conducted our audits in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement. An audit includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements. An audit also includes assessing the accounting principles used and significant estimates made by management, as well as evaluating the overall financial statement presentation. We believe that our audits provide a reasonable basis for our opinion.

In our opinion, the financial statements referred to above present fairly, in all material respects, the consolidated financial position of United Therapeutics Corporation at December 31, 2014 and 2013, and the consolidated results of its operations and its cash flows for each of the three years in the period ended December 31, 2014, in conformity with U.S. generally accepted accounting principles. Also, in our opinion, the related financial statement schedule, when considered in relation to the basic financial statements taken as a whole, presents fairly in all material respects the information set forth therein.

We also have audited, in accordance with the Standards of the Public Company Accounting Oversight Board (United States), United Therapeutics Corporation's internal control over financial reporting as of December 31, 2014, based on criteria established in Internal Control—Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework) and our report dated February 24, 2015 expressed an unqualified opinion thereon.

/s/ Ernst & Young LLP

McLean, Virginia
February 24, 2015

Report of Independent Registered Public Accounting Firm on Internal Control over Financial Reporting

The Board of Directors and Shareholders
United Therapeutics Corporation

We have audited United Therapeutics Corporation's internal control over financial reporting as of December 31, 2014, based on criteria established in Internal Control—Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework) (the COSO criteria). United Therapeutics Corporation's management is responsible for maintaining effective internal control over financial reporting and for its assessment of the effectiveness of internal control over financial reporting included in the accompanying *Management's Report on Internal Control Over Financial Reporting* . Our responsibility is to express an opinion on the Company's internal control over financial reporting based on our audit.

We conducted our audit in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audit to obtain reasonable assurance about whether effective internal control over financial reporting was maintained in all material respects. Our audit included obtaining an understanding of internal control over financial reporting, assessing the risk that a material weakness exists, testing and evaluating the design and operating effectiveness of internal control based on the assessed risk, and performing such other procedures as we considered necessary in the circumstances. We believe that our audit provides a reasonable basis for our opinion.

A company's internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. A company's internal control over financial reporting includes those policies and procedures that: (1) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company; (2) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of the company are being made only in accordance with authorizations of management and directors of the company; and (3) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of the company's assets that could have a material effect on the financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

In our opinion United Therapeutics Corporation maintained, in all material respects, effective internal control over financial reporting as of December 31, 2014, based on the COSO criteria.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States), the consolidated balance sheets of United Therapeutics Corporation as of December 31, 2014 and 2013 and the related consolidated statements of operations, comprehensive income, stockholders' equity and cash flows for each of the three years in the period ended December 31, 2014 and our report dated February 24, 2015, expressed an unqualified opinion thereon.

/s/ Ernst & Young LLP

McLean, Virginia
February 24, 2015

UNITED THERAPEUTICS CORPORATION

Consolidated Balance Sheets

(In thousands, except share and per share data)

	December 31, 2014	December 31, 2013
Assets		
Current assets:		
Cash and cash equivalents	$ 397,697	$ 284,258
Marketable investments	297,842	409,645
Accounts receivable, net of allowance of none for 2014 and 2013	162,287	126,297
Inventories, net	66,927	47,758
Other current assets	49,444	46,424
Total current assets	974,197	914,382
Marketable investments	122,787	448,134
Goodwill and other intangible assets, net	29,465	14,115
Property, plant, and equipment, net	478,421	464,950
Deferred tax assets, net	181,721	192,718
Other assets	97,819	53,268
Total assets	$ 1,884,410	$ 2,087,567
Liabilities and Stockholders' Equity		
Current liabilities:		
Accounts payable and accrued expenses	$ 85,382	$ 92,244
Convertible notes	126,414	215,845
Share tracking awards plan	282,101	287,956
Line of credit and mortgages payable—current	67	66,614
Other current liabilities	10,346	25,015
Total current liabilities	504,310	687,674
Other liabilities	114,526	95,582
Total liabilities	618,836	783,256
Commitments and contingencies:		
Temporary equity	23,218	45,037
Stockholders' equity:		
Preferred stock, par value $.01, 10,000,000 shares authorized, no shares issued	—	—
Series A junior participating preferred stock, par value $.01, 100,000 shares authorized, no shares issued	—	—
Common stock, par value $.01, 245,000,000 shares authorized, 65,988,561 and 63,013,192 shares issued, and 47,107,709 and 50,388,140 shares outstanding at December 31, 2014 and 2013, respectively	660	630
Additional paid-in capital	1,376,141	1,057,224
Accumulated other comprehensive loss	(16,734)	(13,183)
Treasury stock, 18,880,852 and 12,625,052 shares at December 31, 2014 and 2013, respectively	(1,185,825)	(513,437)
Retained earnings	1,068,114	728,040
Total stockholders' equity	1,242,356	1,259,274
Total liabilities and stockholders' equity	$ 1,884,410	$ 2,087,567

See accompanying notes to consolidated financial statements.

UNITED THERAPEUTICS CORPORATION

Consolidated Statements of Operations

(In thousands, except per share data)

	Year Ended December 31,		
	2014	2013	2012
Revenues:			
Net product sales	$ 1,279,533	$ 1,106,944	$ 906,123
Other	8,986	10,040	9,953
Total revenues	1,288,519	1,116,984	916,076
Operating expenses:			
Research and development	242,549	299,348	173,387
Selling, general and administrative	381,287	394,010	201,746
Cost of product sales	125,883	131,127	119,297
Total operating expenses	749,719	824,485	494,430
Operating income	538,800	292,499	421,646
Other (expense) income:			
Interest expense	(17,592)	(18,058)	(16,639)
Other, net	3,972	4,462	35,664
Total other (expense) income, net	(13,620)	(13,596)	19,025
Income before income taxes	525,180	278,903	440,671
Income tax expense	(185,106)	(104,343)	(136,229)
Net income	$ 340,074	$ 174,560	$ 304,442
Net income per common share:			
Basic	$ 7.06	$ 3.49	$ 5.84
Diluted	$ 6.28	$ 3.28	$ 5.71
Weighted average number of common shares outstanding:			
Basic	48,176	50,076	52,093
Diluted	54,155	53,231	53,280

See accompanying notes to consolidated financial statements.

UNITED THERAPEUTICS CORPORATION

CONSOLIDATED STATEMENTS OF COMPREHENSIVE INCOME

(In thousands)

	Year Ended December 31,		
	2014	2013	2012
Net income	$ 340,074	$ 174,560	$ 304,442
Other comprehensive (loss) income:			
Foreign currency translation (loss) gain	(4,789)	(1,193)	691
Defined benefit pension plan:			
Prior service cost arising during period, net of tax	(2,415)	—	—
Actuarial gain (loss) arising during period, net of tax	2,999	2,075	(5,352)
Less: amortization of actuarial gain and prior service cost included in net periodic pension cost, net of tax	904	1,020	522
Defined benefit pension plan, net	1,488	3,095	(4,830)
Unrealized (loss) gain on available-for-sale securities, net of tax	(250)	(128)	67
Other comprehensive (loss) gain, net of tax	(3,551)	1,774	(4,072)
Comprehensive income	$ 336,523	$ 176,334	$ 300,370

See accompanying notes to consolidated financial statements.

UNITED THERAPEUTICS CORPORATION

Consolidated Statements of Stockholders' Equity

(In thousands, except share data)

	Common Stock		Additional Paid-in Capital	Accumulated Other Comprehensive Income/(Loss)	Treasury Stock	Retained Earnings	Stockholders' Equity
	Shares	Amount					
Balance, December 31, 2011	61,506,063	$ 615	$ 992,718	$ (10,885)	$ (282,998)	$ 249,038	$ 948,488
Net income	—	—	—	—	—	304,442	304,442
Foreign currency translation adjustment	—	—	—	691	—	—	691
Unrealized gain on available-for-sale securities	—	—	—	67	—	—	67
Defined benefit pension plan	—	—	—	(4,830)	—	—	(4,830)
Repurchase of shares	—	—	—	—	(188,000)	—	(188,000)
Exercise of stock options	575,944	6	16,799	—	—	—	16,805
Tax benefit from exercises of non-qualified stock options	—	—	3,054	—	—	—	3,054
Share-based compensati	—	—	3,264	—	—	—	3,264
Balance, December 2012	62,082,007	621	1,015,835	(14,957)	(470,998)	553,480	1,083,981
Net income	—	—	—	—	—	174,560	174,560
Foreign currency translation adjustment	—	—	—	(1,193)	—	—	(1,193)
Unrealized (loss) on available-for-sale securities	—	—	—	(128)	—	—	(128)
Defined benefit pension plan	—	—	—	3,095	—	—	3,095
Shares issued under employee stock purchase plan	55,070	1	2,734	—	—	—	2,735
Equity component 2016 convertible notes (Note 10)	—	—	(34,155)	—	—	—	(34,155)
Repurchase of shares	—	—	—	—	(42,439)	—	(42,439)
Exercise of stock options	876,115	8	26,611	—	—	—	26,619
Tax benefit from exercises of non-qualified stock options	—	—	9,299	—	—	—	9,299
Share-based							

compensation	—	—	36,900	—	—	—	36,900
Balance, December 31, 2013	63,013,192	630	1,057,224	(13,183)	(513,437)	728,040	1,259,274
Net income	—	—	—	—	—	340,074	340,074
Foreign currency translation adjustment	—	—	—	(4,789)	—	—	(4,789)
Unrealized (loss) on available-for-sale securities	—	—	—	(250)	—	—	(250)
Defined benefit pension plan	—	—	—	1,488	—	—	1,488
Shares issued under employee stock purchase plan	45,657	1	3,329	—	—	—	3,330
Conversion of 2016 convertible notes (Note 10)	1,467,343	15	192,966	—	(189,311)	—	3,670
Equity component 2016 convertible notes (Note 10)	—	—	11,056	—	—	—	11,056
Repurchase of shares	—	—	—	—	(483,077)	—	(483,077)
Exercise of stock options	1,462,369	14	50,154	—	—	—	50,168
Tax benefit from exercises of non-qualified stock options	—	—	30,845	—	—	—	30,845
Share-based compensati	—	—	30,567	—	—	—	30,567
Balance, December 31, 2014	65,988,561	$ 660	$ 1,376,141	$ (16,734)	$ (1,185,825)	$ 1,068,114	$ 1,242,356

See accompanying notes to consolidated financial statements.

UNITED THERAPEUTICS CORPORATION

Consolidated Statements of Cash Flows

(In thousands)

	Year Ended December 31,		
	2014	2013	2012
Cash flows from operating activities:			
Net income	$ 340,074	$ 174,560	$ 304,442
Adjustments to reconcile net income to net cash provided by operating activities:			
Depreciation and amortization	32,245	31,259	27,145
Current and deferred tax expense	185,106	104,343	136,229
Share-based compensation expense	190,054	320,786	30,115
Impairment write downs	—	—	6,804
Amortization of debt discount and debt issue costs	12,456	12,601	11,064
Amortization of discount or premium on investments	5,231	4,501	4,604
Other	6,493	3,182	14,471
Excess tax benefits from share-based compensation	(30,845)	(9,299)	(3,054)
Changes in assets and liabilities:			
Accounts receivable	(35,689)	(10,027)	(23,991)
Inventories	(21,032)	(12,394)	(5,933)
Other assets	(6,619)	(5,112)	(9,705)
Accounts payable and accrued expenses	(6,753)	7,507	(22,804)
Other liabilities	(315,462)	(196,640)	(145,759)
Net cash provided by operating activities	355,259	425,267	323,628
Cash flows from investing activities:			
Purchases of property, plant and equipment, net	(47,439)	(31,910)	(111,905)
Purchases of held-to-maturity investments	(118,672)	(762,198)	(579,316)
Maturities of held-to-maturity investments	549,576	529,900	527,858
Purchase of investments under the cost method, net	(45,000)	(30,766)	—
Net cash provided by (used in) investing activities	338,465	(294,974)	(163,363)
Cash flows from financing activities:			
Principal payments of debt	(177,800)	(1,320)	(999)
Payments to repurchase common stock	(483,077)	(42,439)	(188,000)
Proceeds from line of credit	140,000	—	—
Payments on the line of credit	(140,000)	—	—
Proceeds from exercise of stock options	50,168	26,611	16,805
Issuance of stock under employee stock purchase plan	3,329	2,734	—
Excess tax benefits from share-based compensation	30,845	9,299	3,054
Net cash used in financing activities	(576,535)	(5,115)	(169,140)
Effect of exchange rate changes on cash and cash equivalents	(3,750)	(319)	229
Net increase (decrease) in cash and cash equivalents	113,439	124,859	(8,646)
Cash and cash equivalents, beginning of year	284,258	159,399	168,045
Cash and cash equivalents, end of year	$ 397,697	$ 284,258	$ 159,399
Supplemental cash flow information :			
Cash paid for interest	$ 5,453	$ 5,518	$ 5,302
Cash paid for income taxes	$ 195,564	$ 142,140	$ 101,505
Non-cash investing and financing activities:			
Acquisitions—non-cash consideration	$ 5,200	$ —	$ —
Non-cash additions to property, plant and equipment	$ 3,150	$ 9,018	$ 1,820
Issuance of common stock upon conversion of convertible notes	$ 189,311	$ —	$ —

See accompanying notes to consolidated financial statements.

UNITED THERAPEUTICS CORPORATION

Notes to Consolidated Financial Statements

1. Organization and Business Description

United Therapeutics Corporation is a biotechnology company focused on the development and commercialization of innovative products to address the unmet medical needs of patients with chronic and life-threatening conditions. As used in these notes to the consolidated financial statements, unless the context otherwise requires, the terms "we", "us", "our," and similar terms refer to United Therapeutics Corporation and its consolidated subsidiaries.

We have approval from the United States Food and Drug Administration (FDA) to market the following therapies: Remodulin ® (treprostinil) Injection (Remodulin), Tyvaso ® (treprostinil) Inhalation Solution (Tyvaso), Adcirca ® (tadalafil) Tablets (Adcirca) and Orenitram ® (treprostinil) Extended-Release Tablets (Orenitram). We commenced commercial sales of Orenitram during the second quarter of 2014. Remodulin has also been approved in various countries outside the United States.

2. Summary of Significant Accounting Policies

Basis of Presentation and Principles of Consolidation

The accompanying consolidated financial statements of United Therapeutics and its wholly owned subsidiaries have been prepared in accordance with accounting principles generally accepted in the United States (GAAP). All intercompany balances and transactions have been eliminated in consolidation.

Use of Estimates

The preparation of the consolidated financial statements in accordance with GAAP requires our management to make estimates and assumptions that affect reported amounts of assets and liabilities at the date of the consolidated financial statements and the reported amounts of revenues and expenses during the reporting period. We base our estimates on assumptions regarding historical experience, currently available information and anticipated developments that we believe are reasonable and appropriate. However, because the use of estimates involves an inherent degree of uncertainty, actual results could differ from those estimates. Our significant accounting policies that require use of subjective and/or complex judgment and estimates impact the following financial statement areas: revenue recognition, share-based compensation, marketable investments, fair value measurements (including those relating to our acquisitions), income taxes, goodwill and other intangible assets, and obligations related to our Supplemental Executive Retirement Plan.

Fair Value of Financial Instruments

The carrying amounts of cash and cash equivalents, accounts receivables, accounts payable, and accrued expenses approximate fair value because of their short maturities. The fair values of our marketable investments and 1.0 percent Convertible Senior Notes due September 15, 2016 (Convertible Notes) are reported in Note 4 —*Investments* and Note 5 —*Fair Value Measurements* , respectively. The recorded value of our 2010 Wells Fargo Bank mortgage financing as of December 31, 2013 approximated its fair value as it bore a variable rate of interest that we believe approximated the market rate of interest for debt with similar credit risk profiles, terms and maturities. Refer to Note 8— *Debt—Mortgage Financing—Wells Fargo Bank* .

UNITED THERAPEUTICS CORPORATION

Notes to Consolidated Financial Statements (Continued)

2. Summary of Significant Accounting Policies (Continued)

Fair Value Measurements

Fair value is a market-based measurement, not an entity-specific measurement. The objective of a fair value measurement is to estimate the price to sell an asset or transfer a liability in an orderly transaction between market participants at the measurement date under current market conditions. Such transactions to sell an asset or transfer a liability are assumed to occur in the principal market for that asset or liability, or in the absence of the principal market, the most advantageous market for the asset or liability.

Assets and liabilities subject to fair value measurement disclosures are required to be classified according to a three-level fair value hierarchy with respect to the inputs (or assumptions) used to determine fair value. Observable inputs such as unadjusted quoted market prices for identical assets or liabilities are given the highest priority within the hierarchy (Level 1). When observable inputs are unavailable, fair value is measured using unobservable inputs—i.e., inputs that a reporting entity believes market participants would use in pricing that are developed based on the best information available. Unobservable inputs are given the lowest priority within the hierarchy (Level 3). The level in which an asset or liability is disclosed within the fair value hierarchy is based on the lowest level input that is significant to the related fair value measurement in its entirety. The guidance under the fair value measurement framework applies to other existing accounting guidance in the Financial Accounting Standard Board (FASB) codification that requires or permits fair value measurements. Refer to related disclosures at Note 5— *Fair Value Measurements* to these consolidated financial statements.

Cash Equivalents

Cash equivalents consist of highly liquid investments with maturities of three months or less from the date of acquisition and include money market funds, commercial paper, and certificates of deposit.

Marketable Investments

Substantially all of our marketable investments are debt securities that we classify as held-to-maturity because of our positive intent and ability to hold the securities until maturity. Held-to-maturity securities are classified as either current or non-current assets on our consolidated balance sheets based on their contractual maturity dates and are recorded at amortized cost, adjusted for the amortization of discounts or premiums. Related discounts and premiums are amortized over the term of these securities as an adjustment to yield using the effective interest method.

We monitor our investment portfolio for impairment quarterly or more frequently if circumstances warrant. In the event that the carrying value of an investment exceeds its fair value and the decline in value is determined to be other-than-temporary, we record an impairment charge within earnings attributable to the estimated credit loss. In determining whether a decline in the value of an investment is other-than-temporary, we evaluate currently available factors that may include, among others: (1) general market conditions; (2) the duration and extent to which fair value has been less than the carrying value; (3) the investment issuer's financial condition and business outlook; and (4) our assessment as to whether it is more likely than not that we will be required to sell a security prior to recovery of its amortized cost basis.

UNITED THERAPEUTICS CORPORATION

Notes to Consolidated Financial Statements (Continued)

2. Summary of Significant Accounting Policies (Continued)

Trade Receivables

Trade receivables consist of short-term amounts due from customers and are stated at the amount we expect to collect. We establish an allowance for doubtful accounts, if any, based on our assessment of the collectability of specific customer accounts.

Inventories

Inventories are stated at the lower of cost (first-in, first-out method) or market (current replacement cost) and consist of the following, net of reserves (in thousands):

	As of December 31,	
	2014	2013
Raw materials	$ 21,317	$ 18,377
Work-in-progress	15,994	11,802
Finished goods	29,616	17,579
Total inventories	$ 66,927	$ 47,758

Goodwill and Other Intangible Assets

The carrying amount of goodwill is not amortized but is subject to annual impairment testing. We conduct our impairment testing of goodwill annually during the fourth quarter, or more frequently, if impairment indicators exist. Initially, we evaluate various pertinent qualitative factors to assess whether it is more likely than not that the fair value of a reporting unit to which goodwill has been assigned is less than its carrying value. Such qualitative factors can include, among others: (1) industry and market conditions; (2) present and anticipated sales and cost factors; and (3) overall financial performance. If we conclude based on our qualitative assessment that it is more likely than not that the fair value of a reporting unit is less than its carrying value, we then measure the fair value of the reporting unit and compare its fair value to its carrying value (Step 1 of the goodwill impairment test). If the carrying amount of the reporting unit exceeds its fair value, then the amount of an impairment loss, if any, is measured as the excess of the recorded amount of goodwill over its implied fair value (Step 2 of the goodwill impairment test).

Intangible assets subject to amortization are reviewed for impairment whenever events or changes in circumstances indicate that the carrying amount of an intangible asset may not be recoverable. Impairment losses are measured and recognized to the extent the carrying value of such assets exceeds their fair value.

UNITED THERAPEUTICS CORPORATION

Notes to Consolidated Financial Statements (Continued)

2. Summary of Significant Accounting Policies (Continued)

Goodwill and other intangible assets comprise the following (in thousands):

	As of December 31, 2014			As of December 31, 2013		
	Gross	Accumulated Amortization	Net	Gross	Accumulated Amortization	Net
Goodwill(1)	$ 10,264	$ —	$ 10,264	$ 10,703	$ —	$ 10,703
Other intangible assets (1):						
Technology, patents and trade names	6,494	(4,100)	2,394	5,049	(3,730)	1,319
In-process, research and development	15,500	—	15,500	—	—	—
Customer relationships and non-compete agreements	4,369	(3,062)	1,307	4,947	(2,886)	2,061
Contract-based	1,270	(1,270)	—	2,020	(1,988)	32
Total	$ 37,897	$ (8,432)	$ 29,465	$ 22,719	$ (8,604)	$ 14,115

(1) Includes foreign currency translation adjustments.

We are amortizing other intangible assets over an estimated weighted average life of 8.7 years. Related amortization expense for the years ended December 31, 2014, 2013 and 2012, was $1.4 million, $2.6 million and $2.1 million, respectively. As of December 31, 2014, aggregate amortization expense relating to intangible assets for each of the five succeeding years and thereafter is estimated as follows (in thousands):

Year Ended December 31,	
2015	$ 1,081
2016	615
2017	452
2018	125
2019	125
Thereafter	1,303
	$ 3,701

Property, Plant and Equipment

Property, plant and equipment is recorded at cost and depreciated over its estimated useful life using the straight-line method. The estimated useful lives of property, plant and equipment by major category are as follows:

Buildings	25-39 Years
Building improvements	10-39 Years
Furniture, equipment and vehicles	3-20 Years
Leasehold improvements	Remaining lease term, or the estimated useful life of the improvement, whichever is shorter

UNITED THERAPEUTICS CORPORATION

Notes to Consolidated Financial Statements (Continued)

2. Summary of Significant Accounting Policies (Continued)

Property, plant and equipment consists of the following (in thousands):

	As of December 31,	
	2014	2013
Land	$ 46,141	$ 47,677
Buildings, building improvements and leasehold improvements	413,066	381,577
Buildings under construction	17,379	32,609
Furniture, equipment and vehicles	136,805	109,295
	613,391	571,158
Less—accumulated depreciation	(134,970)	(106,208)
Property, plant and equipment, net	$ 478,421	$ 464,950

Depreciation expense for the years ended December 31, 2014, 2013 and 2012 was $30.8 million, $28.6 million and $25.0 million, respectively.

Buildings under construction consists of direct costs relating to our construction projects and includes capitalized interest.

Treasury Stock

Repurchased treasury stock is recorded at cost, including commissions and fees. Treasury stock acquired from the convertible note hedge on our Convertible Notes is recorded at the fair value on the acquisition date closing price of our common stock. The cost of treasury shares sold is determined using the first-in, first-out method. Related gains and losses on sales of treasury stock are recognized as adjustments to stockholders' equity.

Revenue Recognition

Remodulin, Tyvaso and Orenitram

We sell Remodulin, Tyvaso and Orenitram to our specialty pharmaceutical distributors under similar contractual arrangements. Sales of Remodulin, Tyvaso and Orenitram are recognized when title and risk of ownership pass to our distributors upon satisfactory delivery— *i.e.,* when all of our performance obligations under our distribution agreements have been satisfied. We record sales of Remodulin, Tyvaso and Orenitram net of various product sales allowances in the period that associated revenues are recognized. These sales allowances include estimated rebates, prompt payment discounts and service fees paid to our distributors. Calculating these sales allowances involves the use of significant estimates and judgments and information obtained from external sources.

We derive our provisions for rebates from an analysis of historical levels of rebates to both state Medicaid agencies and commercial third-party payers by product, relative to sales of each product. In addition, for Orenitram patients, we determine our obligation for prescription drug discounts required by Medicare Part D for patients within the coverage gap based on estimations of the number of patients and the period that such patients will remain within the coverage gap. In formulating our estimates, we also consider the impact of anticipated changes in our product pricing, if any, sales trends

UNITED THERAPEUTICS CORPORATION

Notes to Consolidated Financial Statements (Continued)

2. Summary of Significant Accounting Policies (Continued)

and government rebate programs, particularly as they relate to eligibility requirements and/or rebate pricing.

We estimate prompt pay discounts based on observed payment behavior. Our distributors have routinely taken advantage of these discounts and we expect them to continue to do so.

We pay our distributors for contractual services rendered and accrue for related fees based on contractual rates applied to the estimated units of service provided by distributors for a given financial reporting period.

Our distributors do not possess return rights; however, we provide exchange rights in the event that product is damaged during shipment or expires. Exchanges for damaged product are highly infrequent. In the event that Remodulin, Tyvaso or Orenitram has been damaged during shipment and we have been promptly notified as required under our distribution agreements, we do not recognize revenue on that shipment until damaged product has been replaced. Replacement of damaged product generally occurs within several days after notification of the damage. Furthermore, the number of product exchanges due to expiration has been minimal because we sell Remodulin, Tyvaso and Orenitram with a remaining shelf life in excess of one year and our distributors typically carry a thirty- to sixty-day supply of our products at any given time. In addition, we closely track inventory levels held by our distributors. Except for contractual minimum inventory levels to prevent shortages of drug supply, we do not require, nor do we provide incentives for our distributors to assume, inventory levels of Remodulin, Tyvaso or Orenitram beyond what would be considered reasonable and customary in the ordinary course of business.

The financial effects of exchange rights for Remodulin, Tyvaso and Orenitram have been immaterial and we expect the volume of exchanges to be consistent with historical levels. Specifically, exchanges of Remodulin, Tyvaso and Orenitram have comprised substantially less than one percent of the volume of the units that we sell. Because historical and anticipated future exchanges of Remodulin, Tyvaso and Orenitram have been and are expected to be immaterial, we do not record a reserve for estimated exchange rights in the period of sale. Lastly, we closely monitor product exchange data for all of these therapies to ensure that our assumptions continue to be reasonable, appropriate and current.

Adcirca

Adcirca is manufactured for us by Eli Lilly and Company (Lilly) and distributed through Lilly's pharmaceutical wholesaler network. Specifically, Lilly handles all of the administrative functions associated with the sale of Adcirca on our behalf, including the receipt and processing of customer purchase orders, shipment to customers, and invoicing and collection of customer payments. In addition, the sales terms for Adcirca include return rights that extend throughout the distribution channel. We recognize sales of Adcirca on a gross basis (net of allowances) upon delivery to customers due to the following factors: (1) we are responsible for the acceptability of the product purchased by wholesalers; (2) we bear all inventory risk, as title and risk of loss pass to us at the shipping point from Lilly's manufacturing facility; (3) we assume credit risk if Lilly is unable to collect amounts due from customers; and (4) we assume the risk and cost of a product recall, if required.

We recognize sales of Adcirca net of: (1) estimated government-based and commercial payer rebates; (2) prompt pay discounts; (3) allowances for product returns; and (4) wholesaler fees. We estimate our liability for rebates based on an analysis of historical levels of rebates to both Medicaid

UNITED THERAPEUTICS CORPORATION

Notes to Consolidated Financial Statements (Continued)

2. Summary of Significant Accounting Policies (Continued)

and commercial third-party payers and we consider the impact of sales trends, changes in government and commercial rebate programs and anticipated changes in Adcirca's pricing. In addition, for Adcirca patients, we determine our obligation for prescription drug discounts required by Medicare Part D for patients within the coverage gap based on estimations of the number of patients and the period that such patients will remain within the coverage gap. We base our estimates for prompt pay discounts on observed customer payment behavior and expectations regarding the future utilization of such discounts. Prior to 2013, we derived estimates relating to our allowance for returns of Adcirca from published industry data specific to specialty pharmaceuticals. Beginning in 2013, we derive these estimates based on actual return data accumulated since the commercial launch of Adcirca in 2009. This change in the methodology for estimating returns resulted in a $3.1 million reduction of our allowance for returns for the twelve-month period ending December 31, 2013. In addition, we compare patient prescription data for Adcirca to sales of Adcirca on a quarterly basis to ensure a reasonable relationship between prescription and sales trends. To date, we have not identified any unusual patterns in the volume of prescriptions relative to sales that would warrant reconsideration of, or adjustment to, the methodology we currently employ to estimate our allowance for returns. Lastly, wholesaler fees are based on contractual percentages of sales to wholesalers.

Research and Development

Research and development costs are expensed as incurred except for refundable payments made in advance of services to be provided to us. Related expenses consist of internal labor and overhead, costs to acquire pharmaceutical products and product rights for development, materials used in clinical trials and amounts paid to third parties for services and materials relating to drug development and clinical trials.

We recognize the following as research and development expense in the period related costs are incurred:

- Costs associated with in-house or contracted production activities prior to receiving FDA approval for such facilities, or for major unproven changes to our production processes;
- Costs incurred in licensing the rights to technologies in the research and development stage that have no alternative future uses; and
- Up-front payments made in connection with arrangements to obtain license and distribution rights to pharmaceutical product candidates prior to regulatory approval, absent any alternative future uses.

Share-Based Compensation

Our share tracking award plans require cash settlement upon exercise and are classified as a liability. Accordingly, the fair value of related cash-settled awards is re-measured at each reporting date until awards are exercised or are otherwise no longer outstanding. Related changes in the fair value of outstanding cash-settled awards at each financial reporting date are recognized as adjustments to share-based compensation expense.

Generally, the fair value of a stock option grant is measured on its grant date and related compensation expense is recognized ratably over the requisite service period. For stock option awards that vest immediately upon issuance, compensation expense is recognized in its entirety based on the

UNITED THERAPEUTICS CORPORATION

Notes to Consolidated Financial Statements (Continued)

2. Summary of Significant Accounting Policies (Continued)

grant-date fair value. Compensation expense is accrued for performance-based stock option grants when we determine it is probable that the performance criteria will be met. We issue new shares of our common stock upon the exercise of stock options.

We measure the fair value of stock to be purchased through our employee stock purchase plan at the beginning of an offering period, or grant date, and recognize related compensation expense ratably over the requisite service period (the offering period). We issue new shares of our common stock upon the end of each offering period, or exercise date.

Income Taxes

Income taxes are accounted for in accordance with the asset and liability method. Accordingly, deferred tax assets and liabilities are recognized for the future tax consequences attributable to differences between the financial statement carrying amounts of existing assets and liabilities and their tax bases. Deferred tax assets and liabilities are measured using the enacted tax rates that are expected to apply to taxable income in the years in which those temporary differences are expected to be recovered or settled. The effect of a change in tax rates on deferred tax assets and liabilities is recognized in the period that includes the enactment date. Deferred tax assets are reduced by a valuation allowance when, in our judgment, it is more likely than not that some or all of the deferred tax assets will not be realized.

Financial statement recognition of a tax position taken or expected to be taken in a tax return is determined based on a more likely than not threshold of that position being sustained. If the tax position meets this threshold, the benefit to be recognized is measured as the largest amount that is more than 50 percent likely to be realized upon ultimate settlement. It is our policy to record interest and penalties related to uncertain tax positions as a component of income tax expense.

Earnings (Loss) per Share

Basic earnings per share is computed by dividing net income by the weighted average number of shares of common stock outstanding during the period. Diluted earnings per common share is computed by dividing net income by the weighted average number of shares of common stock outstanding during the period, plus the potential dilutive effect of other securities if such securities were converted or exercised. During periods in which we incur net losses, both basic and diluted loss per share is calculated by dividing the net loss by the weighted average shares outstanding—potentially dilutive securities are excluded from the calculation because their effect would be anti-dilutive.

Concentrations of Credit Risk, Products, Revenues and Customers

Concentration of credit risk

Financial instruments that are exposed to credit risk consist of cash, money market funds, commercial paper, marketable investments, and trade receivables. We maintain our cash and money market funds with financial institutions that are federally insured. While balances deposited in these institutions often exceed Federal Deposit Insurance Corporation limits, we have not experienced any losses on related accounts to date. Furthermore, we limit our risk exposure by maintaining funds in financial institutions that we believe are creditworthy and financially sound. Our investments in marketable debt securities have been issued by corporate entities and federally-sponsored enterprises

UNITED THERAPEUTICS CORPORATION

Notes to Consolidated Financial Statements (Continued)

2. Summary of Significant Accounting Policies (Continued)

with high credit ratings. We mitigate investment risks by investing in highly-rated securities with relatively short maturities that we believe do not subject us to undue investment or credit risk. In addition, our investment policy does not provide for investments in complex or structured financial instruments. At any given time, our trade receivables are concentrated among a small number of principal customers. If any of these financial institutions, issuers or customers fail to perform their obligations under the terms of these financial instruments, our maximum exposure to potential losses would be equal to amounts reported on our consolidated balance sheets.

Concentration of products, revenues, and customers

In the United States, through 2013 we sold Remodulin, Tyvaso, and Orenitram to three specialty pharmaceutical distributors: Accredo Health Group Inc. (Accredo), CuraScript Inc. (CuraScript) and CVS Caremark (Caremark). In December 2013, the operations of CuraScript have been integrated into Accredo's operations as a result of the 2012 acquisition of Medco Health Solutions, Inc., the parent company of Accredo, by Express Scripts, Inc., the parent company of CuraScript, and we have consolidated our distribution agreements with CuraScript and Accredo into one contract for each product. During the years ended December 31, 2014, 2013 and 2012, net sales of Remodulin, Tyvaso and Orenitram to these distributors accounted for 74 percent, 76 percent and 78 percent, respectively, of our total net revenues. During the years ended December 31, 2014, 2013 and 2012, net sales of Remodulin accounted for 43 percent, 44 percent and 50 percent, respectively, of our total net revenues, while net sales of Tyvaso during this period comprised 36 percent, 39 percent and 36 percent, respectively of our total net revenues. Orenitram accounted for 3 percent of our net revenues for the year ended December 31, 2014, the year of Orenitram's commercial launch.

At December 31, 2014 and 2013, 52 percent and 59 percent, respectively, of our accounts receivable was due from U.S.-based specialty pharmaceutical distributors.

During the years ended December 31, 2014, 2013 and 2012, we derived 58 percent, 57 percent and 56 percent of our total net revenues from one customer. Estimated net revenues from that customer were as follows (in thousands):

	Year Ended December 31,		
	2014	2013	2012
Accredo Health Group, Inc.(1)	$ 744,765	$ 632,599	$ 514,095

(1) CuraScript's operations were merged with Accredo's beginning in 2014.

UNITED THERAPEUTICS CORPORATION

Notes to Consolidated Financial Statements (Continued)

3. Recently Issued Accounting Standards

In May 2014, the Financial Accounting Standards Board (FASB) issued Accounting Standards Update No. 2014-09 (ASU 2014-09), *Revenue from Contracts with Customers.* ASU 2014-09 will eliminate transaction-specific and industry-specific revenue recognition guidance under current GAAP and replace it with a principle-based approach for determining revenue recognition. ASU 2014-09 will require that companies recognize revenue based on the value of transferred goods or services as they occur in the contract. ASU 2014-09 also will require additional disclosure about the nature, amount, timing and uncertainty of revenue and cash flows arising from customer contracts, including significant judgments and changes in judgments and assets recognized from costs incurred to obtain or fulfill a contract. ASU 2014-09 is effective for annual reporting periods beginning after December 15, 2016. Early application is not permitted. Entities can transition to the standard either retrospectively or as a cumulative-effect adjustment as of the date of adoption. Presently, we are assessing what effect the adoption of ASU 2014-09 will have on our consolidated financial statements and accompanying notes.

4. Investments

Marketable Investments

Held-to-Maturity Investments

Marketable investments classified as held-to-maturity consist of the following (in thousands):

As of December 31, 2014	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
Government-sponsored enterprises	$ 127,212	$ 118	$ (39)	$ 127,291
Corporate notes and bonds	293,288	260	(108)	293,440
Total	$ 420,500	$ 378	$ (147)	$ 420,731
Reported under the following captions on the consolidated balance sheet:				
Current marketable investments	$ 297,842			
Noncurrent marketable investments	122,658			
	$ 420,500			

As of December 31, 2013	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
Government-sponsored enterprises	$ 445,939	$ 257	$ (77)	$ 446,119
Corporate notes and bonds	411,455	300	(163)	411,592
Total	$ 857,394	$ 557	$ (240)	$ 857,711
Reported under the following captions on the consolidated balance sheet:				
Current marketable investments	$ 409,645			
Noncurrent marketable investments	447,749			
	$ 857,394			

UNITED THERAPEUTICS CORPORATION

Notes to Consolidated Financial Statements (Continued)

4. Investments (Continued)

The following table summarizes gross unrealized losses and the length of time marketable investments have been in a continuous unrealized loss position (in thousands):

	As of December 31,			
	2014		2013	
	Fair Value	Gross Unrealized Loss	Fair Value	Gross Unrealized Loss
Government-sponsored enterprises:				
Continuous unrealized loss position less than one year	$ 15,293	$ (39)	$ 76,651	$ (77)
Continuous unrealized loss position greater than one year	—	—	—	—
	15,293	(39)	76,651	(77)
Corporate notes and bonds:				
Continuous unrealized loss position less than one year	86,824	(97)	168,669	(163)
Continuous unrealized loss position greater than one year	3,443	(11)	—	—
	90,267	(108)	168,669	(163)
Total	$ 105,560	$ (147)	$ 245,320	$ (240)

We attribute the unrealized losses on held-to-maturity securities as of December 31, 2014 and 2013, to the variability in related market interest rates. We do not intend to sell these securities, nor is it more likely than not that we will be required to sell them prior to the end of their contractual terms. Furthermore, we do not believe that these securities expose us to undue market risk or counterparty credit risk. As such, we do not consider these securities to be other than temporarily impaired.

The following table summarizes the contractual maturities of held-to-maturity marketable investments (in thousands):

	As of December 31, 2014	
	Amortized Cost	Fair Value
Due in less than one year	$ 297,842	$ 297,969
Due in one to two years	107,405	107,522
Due in three to five years	15,253	15,240
Due after five years	—	—
Total	$ 420,500	$ 420,731

Investments Held at Cost

As of December 31, 2014, we maintain in the aggregate, non-controlling equity investments of approximately $83.0 million in privately-held corporations, including a $50.0 million investment in the preferred stock of Synthetic Genomics Inc. (SGI), which we purchased in May 2014. We account for these investments under the cost method since we do not have the ability to exercise significant influence over these companies and their fair values are not readily determinable. The fair values of

UNITED THERAPEUTICS CORPORATION

Notes to Consolidated Financial Statements (Continued)

4. Investments (Continued)

these investments have not been estimated at December 31, 2014, as we did not identify any events or developments indicating that their carrying amounts may be impaired. We include these investments within other assets on our accompanying consolidated balance sheets.

In addition to the SGI investment noted above, we entered into a separate multi-year research and development collaboration agreement whereby SGI will develop engineered primary pig cells with modified genomes for use in our xenotransplantation program, which is primarily focused on lungs. Under this agreement, each party will assume its own research and development costs and SGI may receive royalties and milestone payments from the development and commercialization of organs.

5. Fair Value Measurements

Assets and liabilities subject to fair value measurements are required to be disclosed within a fair value hierarchy. The fair value hierarchy ranks the quality and reliability of inputs used to determine fair value. Accordingly, assets and liabilities carried at, or permitted to be carried at, fair value are classified within the fair value hierarchy in one of the following categories based on the lowest level input that is significant in measuring fair value:

Level 1—Fair value is determined by using unadjusted quoted prices that are available in active markets for identical assets and liabilities.

Level 2—Fair value is determined by using inputs other than Level 1 quoted prices that are directly or indirectly observable. Inputs can include quoted prices for similar assets and liabilities in active markets or quoted prices for identical assets and liabilities in inactive markets. Related inputs can also include those used in valuation or other pricing models such as interest rates and yield curves that can be corroborated by observable market data.

Level 3—Fair value is determined by using inputs that are unobservable and not corroborated by market data. Use of these inputs involves significant and subjective judgment.

Assets and liabilities subject to fair value measurements are as follows (in thousands):

	As of December 31, 2014			
	Level 1	Level 2	Level 3	Balance
Assets				
Money market funds(1)	$ 298,416	$ —	$ —	$ 298,416
Federally-sponsored and corporate debt securities(2)		420,731	—	420,731
Total assets	$ 298,416	$ 420,731	$ —	$ 719,147
Liabilities				
Convertible notes due 2016(3)	$ 388,153	$ —	$ —	$ 388,153
Contingent consideration(4)	—	—	11,502	11,502
Total liabilities	$ 388,153	$ —	$ 11,502	$ 399,655

UNITED THERAPEUTICS CORPORATION

Notes to Consolidated Financial Statements (Continued)

5. Fair Value Measurements (Continued)

	As of December 31, 2013			
	Level 1	Level 2	Level 3	Balance
Assets				
Money market funds(1)	$ 145,194	$ —	$ —	$ 145,194
Federally-sponsored and corporate debt securities(2)	—	857,711	—	857,711
Total assets	$ 145,194	$ 857,711	$ —	$ 1,002,905
Liabilities				
Convertible notes due 2016(3)	$ 593,750	$ —	$ —	$ 593,750
Contingent consideration(4)	—	—	6,616	6,616
Total liabilities	$ 593,750	$ —	$ 6,616	$ 600,366

(1) Included in cash and cash equivalents on the accompanying consolidated balance sheets.

(2) Included in current and non-current marketable investments on the accompanying consolidated balance sheets. The fair value of these securities is principally measured or corroborated by trade data for identical securities in which related trading activity is not sufficiently frequent to be considered a Level 1 input or comparable securities that are more actively traded. See also Note 4— *Investments—Marketable Investments—Held-to-Maturity Investments* to these consolidated financial statements.

(3) Included in convertible notes on the accompanying consolidated balance sheets. The fair value of our Convertible Notes is estimated using Level 1 observable inputs since our Convertible Notes are trading with sufficient frequency such that we believe related pricing can be used as the primary basis for measuring their fair value. As of December 31, 2014 and December 31, 2013, the fair value of the Convertible Notes was substantially higher than their book value. This was primarily due to the excess conversion value of the notes compared to the notes' par value, and the fact that any such excess would be paid in shares of our common stock.

(4) Included in other liabilities on the accompanying consolidated balance sheets. The fair value of contingent consideration has been estimated using probability weighted discounted cash flow (DCF) models. The DCF models incorporate Level 3 inputs including estimated discount rates that we believe market participants would consider relevant in pricing and the projected timing and amount of cash flows, which are estimated and developed, in part, based on the requirements specific to each acquisition agreement. We analyze and evaluate these fair value measurements quarterly to determine whether valuation inputs continue to be relevant and appropriate or whether current period developments warrant adjustments to valuation inputs and related measurements. Any increases or decreases in discount rates would have an inverse impact on the corresponding fair value, while increases or decreases in expected cash flows would result in corresponding increases or decreases in fair value. As of the years ending December 31, 2014 and 2013, the cost of debt and weighted average cost of capital used to discount projected cash flows relating to our contingent consideration ranged from 6.1 percent to 15.5 percent and 8.7 percent to 16.5 percent, respectively.

UNITED THERAPEUTICS CORPORATION

Notes to Consolidated Financial Statements (Continued)

5. Fair Value Measurements (Continued)

The tables below provide a reconciliation of the beginning and ending balances of Level 3 assets and liabilities for the years ended December 31, 2014 and 2013 (in thousands):

	Contingent Consideration
Balance January 1, 2014—Asset (Liability)	$ (6,616)
Transfers into Level 3	—
Transfers out of Level 3	—
Total gains/(losses) realized/unrealized:	
Included in earnings	(1,090)
Included in other comprehensive income	112
Purchases	(5,200)
Sales	—
Issuances	—
Settlements	1,292
Balance December 31, 2014—Asset (Liability)	$ (11,502)
Amount of total gains/(losses) for the year ended December 31, 2014 included in earnings that are attributable to the change in unrealized gains or losses related to outstanding liabilities	$ (1,090)

	Contingent Consideration
Balance January 1, 2013—Asset (Liability)	$ (6,730)
Transfers into Level 3	—
Transfers out of Level 3	—
Total gains/(losses) realized/unrealized:	
Included in earnings	210
Included in other comprehensive income	(96)
Purchases	—
Sales	—
Issuances	—
Settlements	—
Balance December 31, 2013—Asset (Liability)	$ (6,616)
Amount of total gains/(losses) for the year ended December 31, 2013 included in earnings that are attributable to the change in unrealized gains related to outstanding liabilities	$ 210

UNITED THERAPEUTICS CORPORATION

Notes to Consolidated Financial Statements (Continued)

6. Accounts Payable and Accrued Expenses

Accounts payable and accrued expenses consist of the following by major categories (in thousands):

	As of December 31, 2014	
	2014	2013
Accounts payable	$ 6,995	$ 6,708
Accrued expenses:		
Sales related (royalties, rebates and fees)	38,095	48,213
Payroll related	28,019	26,930
Research related	7,500	5,780
Other	4,773	4,613
Total accrued expenses	78,387	85,536
Total accounts payable and accrued expenses	$ 85,382	$ 92,244

7. Share Tracking Award Plans

We maintain the United Therapeutics Corporation Share Tracking Awards Plan, adopted in June 2008 (2008 STAP) and the United Therapeutics Corporation 2011 Share Tracking Awards Plan, adopted in March 2011 (2011 STAP). In 2012, we amended the 2008 STAP to prohibit future grants from the plan. Since both plans otherwise contain similar terms and conditions, we refer to these plans collectively as the "STAP" and awards granted and/or outstanding under either of these plans as "STAP Awards." STAP Awards convey the right to receive in cash an amount equal to the appreciation of our common stock, which is calculated as the positive difference between the closing price of our common stock on the date of exercise and the date of grant. Awards generally vest in equal increments on each anniversary of the date of grant over a four-year period and expire ten years from the grant date. The aggregate balance of the STAP liability at December 31, 2014 was $322.7 million, of which $40.6 million has been classified as non-current liabilities under the caption "Other Liabilities" on our consolidated balance sheets as these STAP Awards will vest in excess of one year. At December 31, 2014, 2.7 million STAP awards remained available for grant under the 2011 STAP. On January 30, 2014 our Board of Directors approved an additional 3.0 million increase in the number of available STAP awards under the 2011 STAP.

We estimate the fair value of STAP awards using the Black-Scholes-Merton valuation model. In estimating the fair value of STAP awards, we are required to use inputs that can materially impact the determination of fair value and the amount of compensation expense (benefit) to be recognized. These inputs include the price of our common stock, the expected volatility of the price of our common stock, the risk-free interest rate, the expected term of STAP awards, the expected forfeiture rate and the expected dividend yield.

A description of the key inputs, requiring estimates, used in determining the fair value of the awards is provided below:

Expected volatility —Volatility is a measure of the amount the price of our common stock has fluctuated (historical volatility) or is expected to fluctuate (expected volatility) during a period. We use historical volatility based on weekly price observations of our common stock during the period immediately preceding an award that is equal to its expected term up to a maximum period of five

UNITED THERAPEUTICS CORPORATION

Notes to Consolidated Financial Statements (Continued)

7. Share Tracking Award Plans (Continued)

years. We believe the volatility in the price of our common stock over the preceding five years generally provides a reliable projection of future long-term volatility.

Risk-free interest rate —The risk-free interest rate is the average interest rate consistent with the yield available on a U.S. Treasury note with a term equal to the expected term of an award.

Expected term —The expected term reflects the estimated time period we expect an award to remain outstanding. For the year ended December 31, 2014, we used historical data to develop this input. Prior to 2014, we applied the simplified method to develop an estimate of the expected term. The change in methodologies for calculating the expected term of an award did not have a significant impact to our consolidated financial statements.

Expected forfeiture rate —The expected forfeiture rate is an estimated percentage of awards granted that are expected to be forfeited or canceled on an annual basis prior to becoming fully vested. We derive our estimate based on historical forfeiture experience for similar classes of employees.

Expected dividend yield —We do not pay cash dividends on our common stock and do not expect to do so in the future. Therefore, the dividend yield is zero.

The table below presents the assumptions used to measure the fair value of STAP Awards:

	As of December 31, 2014		
	2014	2013	2012
Expected volatility	34.0%	32.7%	32.8%
Risk-free interest rate	1.3%	1.1%	0.5%
Expected term of awards (in years)	4.0	3.9	3.7
Expected forfeiture rate	9.3%	10.1%	8.7%
Expected dividend yield	0.0%	0.0%	0.0%

A summary of the status and activity of the STAP is presented below:

	Number of Awards	Weighted-Average Exercise Price	Weighted Average Remaining Contractual Term (Years)	Aggregate Intrinsic Value (in 000s)
Outstanding at January 1, 2014	8,734,901	$ 52.75		
Granted	1,604,525	95.39		
Exercised	(2,315,093)	48.01		
Forfeited	(307,909)	63.96		
Outstanding at December 31, 2014	7,716,424	$ 62.59	7.4	$ 516,222
Exercisable at December 31, 2014	2,618,117	$ 52.69	5.9	$ 201,075
Expected to vest at December 31, 2014	4,615,370	$ 67.89	8.2	$ 284,296

The weighted average grant-date fair value of STAP awards granted during the years ended December 31, 2014, 2013 and 2012 was $33.82, $24.78 and $21.28, respectively.

UNITED THERAPEUTICS CORPORATION

Notes to Consolidated Financial Statements (Continued)

7. Share Tracking Award Plans (Continued)

Share-based compensation expense recognized in connection with the STAP is as follows (in thousands):

	Year Ended December 31,		
	2014	2013	2012
Research and development	$ 72,269	$ 134,355	$ 11,130
Selling, general and administrative	82,937	143,407	14,490
Cost of product sales	4,283	6,124	1,230
Share-based compensation expense before taxes	159,489	283,886	26,850
Related income tax benefit	(56,560)	(106,693)	(9,902)
Share-based compensation expense, net of taxes	$ 102,929	$ 177,193	$ 16,948
Share-based compensation capitalized as part of inventory	$ 2,027	$ 1,593	$ 275

Cash paid to settle STAP exercises during the years ended December 31, 2014, 2013 and 2012 was $144.1 million, $55.9 million, and $31.8 million, respectively.

8. Debt

Line of Credit

In September 2013, we entered into a Credit Agreement with Wells Fargo Bank, National Association (Wells Fargo) providing us a $75.0 million revolving loan facility, which may be increased by up to an additional $75.0 million provided certain conditions are met (the 2013 Credit Agreement). At our option, amounts borrowed under the 2013 Credit Agreement bear interest at either the one-month LIBOR rate plus a 0.50 percent margin, or a fluctuating base rate excluding any margin. In addition, we are subject to a monthly commitment fee of 0.06 percent per annum on the average daily unused balance of the facility. In July 2014, we extended the term of the 2013 Credit Agreement to September 30, 2015. Amounts borrowed under the 2013 Credit Agreement are secured by certain of our marketable investments. As of December 31, 2014, we had no outstanding balance on the facility. The 2013 Credit Agreement does not subject us to any financial covenants.

Convertible Notes Due 2016

In October 2011, we issued $250.0 million in aggregate principal value 1.0 percent Convertible Senior Notes due September 15, 2016 (Convertible Notes). The Convertible Notes are unsecured, unsubordinated debt obligations that rank equally with all of our other unsecured and unsubordinated indebtedness. We pay interest semi-annually on March 15 and September 15 of each year. The initial conversion price is $47.69 per share.

Conversion can occur: (1) any time after June 15, 2016; (2) during any calendar quarter that follows a calendar quarter in which the price of our common stock exceeds 130 percent of the conversion price for at least 20 days during the 30 consecutive trading-day period ending on the last trading day of the quarter; (3) during the ten consecutive trading-day period following any five consecutive trading-day period in which the trading price of the Convertible Notes is less than 95 percent of the closing price of our common stock multiplied by the then-current number of shares underlying the Convertible Notes; (4) upon specified distributions to our shareholders; (5) in

UNITED THERAPEUTICS CORPORATION

Notes to Consolidated Financial Statements (Continued)

8. Debt (Continued)

connection with certain corporate transactions; or (6) in the event that our common stock ceases to be listed on the NASDAQ Global Select Market, the NASDAQ Global Market or the New York Stock Exchange, or any of their respective successors.

The closing price of our common stock exceeded 130 percent of the conversion price of the Convertible Notes for more than 20 trading days during the 30 consecutive trading day period ended December 31, 2014. Consequently, the Convertible Notes are convertible at the election of their holders. As we do not control this conversion right, the Convertible Notes have been classified as a current liability on our consolidated balance sheet at December 31, 2014. We are required to calculate this contingent conversion provision at the end of each quarterly reporting period. Therefore, the convertibility and classification of our Convertible Notes may change depending on the price of our common stock.

At December 31, 2014, the aggregate conversion value of the Convertible Notes exceeded their par value by $238.0 million using a conversion price of $129.49, which was the closing price of our common stock on December 31, 2014.

Upon conversion, holders of our Convertible Notes are entitled to receive: (1) cash equal to the lesser of the par value of the notes or the conversion value (the number of shares underlying the Convertible Notes multiplied by the then current conversion price per share); and (2) to the extent the conversion value exceeds the par value of the notes, shares of our common stock. In the event of a change in control, as defined in the indenture under which the Convertible Notes have been issued, holders can require us to purchase all or a portion of their Convertible Notes for 100 percent of the notes' par value plus any accrued and unpaid interest.

During the three-month period ended December 31, 2014, we settled conversion requests representing $111.3 million in principal value of our Convertible Notes. We paid $111.3 million in principal and issued 1.5 million shares of our common stock during the settlement process. We received 1.5 million shares of our common stock under our convertible note hedge (discussed below under *Convertible Note Hedge and Warrant Transactions*) from Deutsche Bank AG London (DB London) which we placed into our treasury stock account. We recognized a $4.6 million extinguishment loss with the settlement of these conversions. As of December 31, 2014, there are 2.9 million underlying shares representing the aggregate consideration upon future conversions on the outstanding Convertible Notes.

During the period from January 1, 2015 through February 11, 2015, we settled conversion requests representing $14.0 million in principal value of the Convertible Notes. We paid $14.0 million for the principal value of the notes and issued 193,000 shares of our common stock during the settlement of these conversions. We also received 193,000 shares from our convertible note hedge with DB London at the settlement dates which we placed into our treasury stock account. We expect to recognize a $513,000 extinguishment loss with the settlement of these conversions. As of February 11, 2015, there are 2.6 million underlying shares representing the aggregate consideration upon future conversions on the $124.8 million outstanding principal of the Convertible Notes.

The terms of the Convertible Notes provide for settlement wholly or partially in cash. Consequently, we are required to account for their liability and equity components separately so that the subsequent recognition of interest expense reflects our non-convertible borrowing rate. Accordingly, as of the date of issuance, we estimated the fair value of the Convertible Notes without consideration of the conversion option (Liability Component). The excess of the proceeds received over the estimated

UNITED THERAPEUTICS CORPORATION

Notes to Consolidated Financial Statements (Continued)

8. Debt (Continued)

fair value of the Liability Component totaling $57.9 million has been recorded as the conversion option (Equity Component) and a corresponding offset has been recognized as a discount to the Convertible Notes to reduce their net carrying value. A portion of the Equity Component equal to the unamortized discount as of December 31, 2014 has been reclassified to temporary equity because one of the contingent conversion criteria had been met at December 31, 2014, as disclosed above. Refer to Note 10— *Temporary Equity* . We are amortizing the discount over the five-year period ending September 15, 2016 (the expected life of the Liability Component) using the effective interest method and an effective rate of interest of 6.7 percent, which corresponded to our estimated non-convertible borrowing rate at the date of issuance.

Interest expense incurred in connection with our convertible notes consisted of the following (in thousands):

	Year Ended December 31,		
	2014	2013	2012
Contractual coupon rate of interest	$ 2,151	$ 2,500	$ 2,500
Discount amortization	11,057	11,178	10,487
Interest expense—convertible notes	$ 13,208	$ 13,678	$ 12,987

The carrying value of our convertible notes consisted of the following (in thousands):

	As of December 31,	
	2014	2013
Principal balance	$ 138,750	$ 250,000
Discount, net of accumulated amortization of $19,819 and $23,783	(12,336)	(34,155)
Carrying amount	$ 126,414	$ 215,845

Convertible Note Hedge and Warrant Transactions

In connection with the issuance of our Convertible Notes, we entered into separate convertible note hedge and warrant transactions with DB London to reduce the potentially dilutive impact of the conversion of our convertible notes. Pursuant to the convertible note hedge, we purchased call options to acquire up to approximately 5.2 million shares of our common stock with a strike price of $47.69. The call options become exercisable upon any conversions and the maturity of the Convertible Notes, and will terminate upon the maturity of the Convertible Notes or the first day the Convertible Notes are no longer outstanding, whichever occurs first. The call options will offset on a share for share basis, any shares of our common stock that we issue upon any conversion or at the maturity of our Convertible Notes. As of December 31, 2014, we had approximately 2.9 million shares of our common stock remaining under the call options after the settlement of $111.3 million of conversion requests during the fourth quarter of 2014. We also sold DB London warrants to acquire up to approximately 5.2 million shares of our common stock with a strike price of $67.56. The warrants will expire incrementally on a series of expiration dates subsequent to the maturity date of our Convertible Notes. Both the convertible note hedge and warrant transactions will be settled on a net-share basis. To the extent that the price of our common stock exceeds the strike price of the warrants on any or all of the

UNITED THERAPEUTICS CORPORATION

Notes to Consolidated Financial Statements (Continued)

8. Debt (Continued)

series of related incremental expiration dates, we will be required to issue shares of our common stock to DB London.

Mortgage Financing—Wells Fargo Bank

In December 2010, we entered into a Credit Agreement with Wells Fargo and Bank of America, N.A., pursuant to which we obtained a $70.0 million mortgage loan (the 2010 Credit Agreement). The 2010 Credit Agreement matured in December 2014 and we repaid the outstanding $66.5 million principal balance in full. The 2010 Credit Agreement was secured by certain of our facilities in Research Triangle Park, North Carolina and Silver Spring, Maryland. Annual principal payments were based on a twenty-five year amortization schedule using a fixed rate of interest of 7.0 percent and the outstanding debt bore a floating rate of interest per annum based on the one-month LIBOR, plus a credit spread of 3.75 percent.

Interest Expense

Details of interest expense presented on our consolidated statements of operations are as follows (in thousands)

	Year Ended December 31,		
	2014	2013	2012
Interest expense	$ 17,592	$ 18,117	$ 17,544
Less: interest capitalized	—	(59)	(905)
Total interest expense	$ 17,592	$ 18,058	$ 16,639

9. Commitments and Contingencies

Operating Leases

We lease facilities space and equipment under operating lease arrangements that have terms expiring at various dates through 2020. Certain lease arrangements include renewal options and escalation clauses. In addition, various lease agreements to which we are party require that we comply with certain customary covenants throughout the term of these leases. If we are unable to comply with these covenants and cannot reach a satisfactory resolution in the event of noncompliance, these agreements could terminate.

Future minimum lease payments under non-cancelable operating leases are as follows (in thousands):

Year Ending December 31,	
2015	$ 3,839
2016	3,409
2017	3,271
2018	2,695
2019	643
Thereafter	128
Total	$ 13,985

UNITED THERAPEUTICS CORPORATION

Notes to Consolidated Financial Statements (Continued)

9. Commitments and Contingencies (Continued)

Total rent expense was $3.6 million, $3.5 million and $3.6 million for the years ended December 31, 2014, 2013 and 2012, respectively.

Milestone Payments

We are party to certain license agreements as described in Note 15— *Assignment and License Agreements* and acquisition agreements. Generally, these agreements require that we make milestone payments in cash upon the achievement of certain product development and commercialization goals and payments of royalties upon commercial sales.

Future milestone payments based on our estimates of the timing and probability of achieving milestones specified under these arrangements are as follows (in thousands):

Year Ending December 31,	(1)
2015	$ 2,311
2016	1,383
2017	1,339
2018	12,491
2019	2,568
Thereafter	7,777
Total	$ 27,869

(1) The amounts and timing of future milestone payments may vary depending on when related milestones will be attained, if at all.

Research Agreement

We maintain a research agreement with the University of Oxford (Oxford) to develop antiviral compounds. Research under this agreement is performed by Oxford Glycobiology Institute, which is headed by a member of our Board of Directors and our scientific advisory board. Under the terms of the agreement, we are required to fund related research activities and make milestone payments for the successful completion of clinical trials. We are also obligated to pay royalties to Oxford equal to a percentage of our net sales from any discoveries and products developed by Oxford. Milestone payments and royalties are subject to reduction depending upon third-party contributions to discoveries and/or third-party licenses necessary to develop products. In 2010, the term of the research agreement was extended through September 2016. In connection with the extension of the term, we agreed to pay Oxford a total of $2.9 million (using the then-prevailing exchange rate) in 60 equal monthly installments. As of December 31, 2014, approximately $1.1 million remains outstanding under this 2010 agreement. In addition, in December 2012, we amended our agreement with Oxford, under which we agreed to pay Oxford an additional $871,000 in the aggregate (using the exchange rate as of the amendment date) in 36 equal monthly installments beginning in January 2013 for additional work supporting the development of our virology platform. As of December 31, 2014, approximately $290,000 remains outstanding under this 2012 amendment. During the years ended December 31, 2014, 2013 and 2012, we incurred approximately $937,000, $890,000 and $577,000, respectively, in expenses under the terms of the agreement.

UNITED THERAPEUTICS CORPORATION

Notes to Consolidated Financial Statements (Continued)

9. Commitments and Contingencies (Continued)

From time to time, we may enter into other service agreements with Oxford relating to specific development activities that are outside the scope of our research agreement described above. We incurred expenses of approximately none, $55,000 and $336,000 relating to these additional services during the years ended December 31, 2014, 2013 and 2012, respectively.

10. Temporary Equity

Temporary equity includes securities that: (1) have redemption features that are outside our control; (2) are not classified as an asset or liability; (3) are excluded from permanent stockholders' equity; and (4) are not mandatorily redeemable. Amounts included in temporary equity relate to securities that are redeemable at a fixed or determinable price.

Components comprising the carrying value of temporary equity include the following (in thousands):

	As of December 31, 2014	As of December 31, 2013
Reclassification of Equity Component(1)	$ 12,336	$ 34,155
Common stock subject to repurchase(2)	10,882	10,882
Total	$ 23,218	$ 45,037

(1) Represents the reclassification of the Equity Component equal to the unamortized discount of our Convertible Notes as of December 31, 2014 from additional paid-in capital to temporary equity. As of December 31, 2014, our Convertible Notes were convertible at the election of their holders as disclosed above in Note 8— *Debt — Convertible Notes Due 2016* .

(2) In connection with our amended 2007 agreement with Toray Industries Inc. (Toray), we issued 400,000 shares of our common stock and provided Toray the right to request that we repurchase the shares at a price of $27.21 per share.

11. Stockholders' Equity

Equity Incentive Plan

We maintain an equity incentive plan (EIP) under which we may grant stock options to employees and non-employees. The EIP provides for the issuance of up to 29.9 million shares of our common stock. As of December 31, 2014, there were 9.3 million shares remaining for issuance under the EIP, of which approximately 9.2 million were reserved for issuance in connection with options granted to our Chairman and Co-Chief Executive Officer, Dr. Rothblatt. If granted, options awarded under the EIP are nontransferable, carry a maximum contractual term of ten years and typically vest in equal annual increments over a maximum period of three years, except for options granted to Dr. Rothblatt, which vest immediately upon grant in accordance with the terms of her employment agreement. The exercise price of stock options granted under the EIP can be no less than the fair market value of our common stock on the date of grant. We issue new shares of our common stock upon the exercise of options.

UNITED THERAPEUTICS CORPORATION

Notes to Consolidated Financial Statements (Continued)

11. Stockholders' Equity (Continued)

Employee Stock Options

We estimate the fair value of stock options using the Black-Scholes-Merton valuation model. Option-pricing models, including the Black-Scholes-Merton model, require the use of judgment and subjective assumptions that can materially impact the estimation of fair value and share-based compensation.

Inputs included in estimating the fair value of a stock option include the price of our common stock, the expected volatility of our common stock, risk-free interest rate, the expected term of stock option awards, expected forfeiture rate and the expected dividend yield.

A description of the key inputs, requiring estimates, used in determining the fair value of stock options is provided below:

Expected volatility —Volatility is a measure of the amount the price of our common stock has fluctuated (historical volatility) or is expected to fluctuate (expected volatility) during a period. We use historical volatility based on weekly price observations of our common stock during the period immediately preceding a stock option grant that is equal to the expected term of the grant (up to a maximum of five years). We believe the volatility of the price of our common stock measured over the preceding five years provides a reliable projection of future long-term volatility.

Risk-free interest rate —The risk-free interest rate is the average interest rate consistent with the yield available on a U.S. Treasury note with a term equal to the expected term of a given stock option grant.

Expected term —The expected term reflects the estimated time period we expect an option grant to remain outstanding. We use historical data to develop this input.

Expected forfeiture rate —The expected forfeiture rate is the estimated percentage of options granted that are expected to be forfeited or canceled on an annual basis prior to becoming fully vested. We derive our estimate based on historical forfeiture experience for similar classes of employees.

Expected dividend yield —We do not pay dividends on our common stock and do not expect to do so in the future. Therefore, the dividend yield is assumed to be zero.

The following weighted-average assumptions were used in estimating the fair value of stock options granted to employees:

	Year Ended December 31,	
	2014	2013
Expected volatility	32.6%	33.0%
Risk-free interest rate	1.7%	1.8%
Expected term of options (in years)	5.0	5.0
Expected forfeiture rate	0.0%	0.0%
Expected dividend yield	0.0%	0.0%

UNITED THERAPEUTICS CORPORATION

Notes to Consolidated Financial Statements (Continued)

11. Stockholders' Equity (Continued)

A summary of the status and activity of employee stock options is presented below:

	Options	Weighted-Average Exercise Price	Weighted Average Remaining Contractual Term (in Years)	Aggregate Intrinsic Value (in 000s)
Outstanding at January 1, 2014	4,749,449	$ 56.06		
Granted	723,869	129.49		
Exercised	(1,414,369)	34.16		
Forfeited	(4,178)	34.35		
Outstanding and exercisable at December 31, 2014	4,054,771	$ 76.83	6.4	$ 213,505

The weighted average fair value of an employee stock option granted during each of the years in the three-year period ended December 31, 2014, was $40.70, $36.10 and $19.74, respectively. The total fair value of vested employee stock options for each of the years in the three-year period ended December 31, 2014 was $29.5 million, $36.1 million and $3.0 million, respectively.

Total share-based compensation expense relating to employee stock options is as follows (in thousands):

	Year Ended December 31,		
	2014	2013	2012
Selling, general and administrative	$ 29,460	$ 36,097	$ 3,024
Related income tax benefit	(10,429)	(13,566)	(1,115)
Share-based compensation expense, net of taxes	$ 19,031	$ 22,531	$ 1,909

As of December 31, 2014, all employee stock options were fully vested; consequently, there were no amounts of unrecognized compensation cost remaining.

Employee and non-employee stock option exercise data is summarized below (dollars in thousands):

	Year Ended December 31,		
	2014	2013	2012
Number of options exercised	1,462,369	876,115	575,944
Cash received from options exercised	$ 50,168	$ 26,620	$ 14,290
Total intrinsic value of options exercised	$ 108,425	$ 37,530	$ 15,508
Tax benefits realized from options exercised	$ 30,845	$ 9,299	$ 3,054

Employee Stock Purchase Plan

In June 2012, our shareholders approved the United Therapeutics Corporation Employee Stock Purchase Plan (ESPP), which has been structured to comply with Section 423 of the Internal Revenue Code. The ESPP provides eligible employees the right to purchase shares of our common stock at a discount through elective accumulated payroll deductions at the end of each offering period. Offering periods, which began in September 2012, occur in consecutive six-month periods commencing on

UNITED THERAPEUTICS CORPORATION

Notes to Consolidated Financial Statements (Continued)

11. Stockholders' Equity (Continued)

September 5th and March 5th of each year. During the year ended December 31, 2014, we issued 45,657 shares of our common stock in exchange for $3.3 million in employee contributions. Eligible employees may contribute up to 15 percent of their base salary, subject to certain annual limitations as defined in the ESPP. The purchase price of the shares is equal to the lower of 85 percent of the closing price of our common stock on either the first or last trading day of a given offering period. In addition, the ESPP provides that no eligible employee may purchase more than 4,000 shares during any offering period. The ESPP has a 20-year term and limits the aggregate number of shares that can be issued to 3.0 million.

Related share-based compensation expense for years ended December 31, 2014, 2013 and 2012 was $1.1 million, $803,000 and $240,000, respectively. We estimate the fair value of the option to purchase shares of our common stock under the ESPP using the same methodology that we employ in valuing our stock options and STAP awards.

Earnings per Share

The components of basic and diluted earnings per share are as follows (in thousands, except per share amounts):

	Year Ended December 31,		
	2014	2013	2012
Numerator:			
Net income	$ 340,074	$ 174,560	$ 304,442
Denominator:			
Weighted average outstanding shares—basic	48,176	50,076	52,093
Effect of dilutive securities(1):			
Convertible notes	2,630	1,736	218
Warrants	1,910	276	—
Stock options and employee stock purchase plan	1,439	1,143	969
Weighted average shares—diluted	54,155	53,231	53,280
Earnings per common share:			
Basic	$ 7.06	$ 3.49	$ 5.84
Diluted	$ 6.28	$ 3.28	$ 5.71
Stock options and warrants excluded from calculation(2)	9,273	11,210	11,862

(1) Calculated using the treasury stock method.

(2) Certain stock options and warrants have been excluded from the computation of diluted earnings per share because their impact would be anti-dilutive.

Share Repurchases

During the year ended December 31, 2012, we repurchased approximately 4.0 million shares of our common stock for $188.0 million.

UNITED THERAPEUTICS CORPORATION

Notes to Consolidated Financial Statements (Continued)

11. Stockholders' Equity (Continued)

In February 2013, our Board of Directors authorized a share repurchase program for up to $420.0 million in aggregate repurchases of our common stock. We completed this repurchase program during the quarter ended June 30, 2014 and acquired 4.6 million shares of our common stock in the aggregate under the program.

In June 2014, our Board of Directors authorized the repurchase of up to an additional $500.0 million of our common stock in open market or privately negotiated transactions, at our discretion (the 2014 Repurchase Program). This program became effective on August 1, 2014, and will remain open for up to one year. During the year ended December 31, 2014, we acquired 887,114 shares of our common stock at an aggregate cost of $105.5 million under the 2014 Repurchase Program.

Shareholder Rights Plan

In June 2008, we entered into an Amended and Restated Rights Agreement with The Bank of New York as Rights Agent (the Plan), which amended and restated our original Rights Agreement dated December 17, 2000. The Plan, as amended and restated, extended the expiration date of the Preferred Share Purchase Rights (Rights) from December 29, 2010 to June 26, 2018, and increased the purchase price of each Right from $64.75 to $400.00, respectively. Each Right entitles holders to purchase one one-thousandth of a share of our Series A Junior Participating Preferred Stock. Rights are exercisable only upon our acquisition by another company, or commencement of a tender offer that would result in ownership of 15 percent or more of the outstanding shares of our voting stock by a person or group (as defined under the Plan) without our prior express written consent. As of December 31, 2014, we have not issued any shares of our Series A Preferred Stock.

12. Accumulated Other Comprehensive Loss

The following table includes changes in accumulated other comprehensive (loss) income by component, net of tax (in thousands):

	Defined Benefit Pension Plan(1)	Foreign Currency Translation Losses	Unrealized Gains and (Losses) on Available-for-Sale Securities	Total
Balance, January 1, 2014	$ (8,445)	$ (5,069)	$ 331	$ (13,183)
Other comprehensive income (loss) before reclassifications	584	(4,789)	(250)	(4,455)
Amounts reclassified from accumulated other comprehensive gain	904	—	—	904
Net current-period other comprehensive income (loss)	1,488	(4,789)	(250)	(3,551)
Balance, December 31, 2014	$ (6,957)	$ (9,858)	$ 81	$ (16,734)

(1) Refer to Note 14— *Employee Benefit Plans — Supplemental Executive Retirement Plan* which identifies the captions within our consolidated statement of operations where reclassification adjustments were recognized and their associated tax impact.

UNITED THERAPEUTICS CORPORATION

Notes to Consolidated Financial Statements (Continued)

13. Income Taxes

Components of income tax expense (benefit) consist of the following (in thousands):

	Year Ended December 31,		
	2014	2013	2012
Current:			
Federal	$ 137,993	$ 120,030	$ 83,905
State	19,051	20,099	13,949
Foreign	1,252	2,164	659
Total current	158,296	142,293	98,513
Deferred			
Federal	(2,945)	(37,713)	37,259
State	463	(9,059)	(415)
Foreign	(225)	(1,055)	182
Total deferred	(2,707)	(47,827)	37,026
Other non-current			
Federal	27,115	7,797	573
State	2,383	1,907	114
Foreign	19	173	3
Total other	29,517	9,877	690
Total income tax expense	$ 185,106	$ 104,343	$ 136,229

Presented below is a reconciliation of income taxes computed at the statutory federal tax rate to income tax expense as reported (in thousands):

	Year Ended December 31,		
	2014	2013	2012
Federal tax provision computed at 35%	$ 183,813	$ 97,616	$ 154,235
State tax provision, net of federal tax provision	12,865	8,320	9,149
General business credits	(12,195)	(13,346)	(10,980)
Incentive stock option expense	(181)	(304)	(479)
Section 199 deduction	(11,735)	(10,861)	(15,629)
Nondeductible compensation expense	13,000	22,813	2,609
Nondeductible expenses	(461)	105	(2,676)
Total income tax expense	$ 185,106	$ 104,343	$ 136,229

UNITED THERAPEUTICS CORPORATION

Notes to Consolidated Financial Statements (Continued)

13. Income Taxes (Continued)

Components of the net deferred tax asset are as follows (in thousands):

	As of December 31,	
	2014	2013
Deferred tax assets:		
General business credits	$ 2,186	$ 277
Impairment losses on investments	291	318
License fees capitalized for tax purposes	61,770	75,181
Nonqualified stock options	42,697	40,808
SERP	17,478	14,059
STAP awards	86,414	84,274
Other	29,086	28,118
Total deferred tax assets	239,922	243,035
Deferred tax liabilities:		
Plant and equipment principally due to differences in depreciation	(30,758)	(32,725)
Other	(7,854)	(1,351)
Net deferred tax asset before valuation allowance	201,310	208,959
Valuation allowance	(2,981)	(2,507)
Net deferred tax assets	$ 198,329	$ 206,452

Deferred tax assets are reduced by a valuation allowance when, in our judgment, it is more likely than not that a portion or all of the deferred tax assets will not be realized. In evaluating our ability to realize deferred tax assets, we consider all available positive and negative evidence. Accordingly, we consider past operating results, forecasts of earnings and taxable income, the reversal of temporary differences and any prudent and feasible tax planning strategies. Future increases in the valuation allowance would result in a corresponding charge to earnings in the period such a determination is made. Conversely, future reductions to the valuation allowance would result in the recognition of a tax benefit in the period we conclude a reduction is warranted.

We expect to utilize all of our federal general business tax credits in tax year 2014.

UNITED THERAPEUTICS CORPORATION

Notes to Consolidated Financial Statements (Continued)

13. Income Taxes (Continued)

A reconciliation of the beginning and ending balances of unrecognized tax benefits for the years indicated is as follows (in thousands):

Unrecognized tax benefits at January 1, 2014	$ 2,836
Gross increases—tax positions in prior period	28
Gross decreases—tax positions in prior period	(1,419)
Gross increases—tax positions in the current period	—
Gross decreases—tax positions in current period	—
Settlements	—
Lapse of statute of limitations	—
Unrecognized tax benefits at December 31, 2014	$ 1,445
Unrecognized tax benefits at January 1, 2013	$ 1,511
Gross increases—tax positions in prior period	1,325
Gross decreases—tax positions in prior period	—
Gross increases—tax positions in the current period	—
Gross decreases—tax positions in the current period	—
Settlements	—
Lapse of statute of limitations	—
Unrecognized tax benefits at December 31, 2013	$ 2,836
Unrecognized tax benefits at January 1, 2012	$ 1,733
Gross increases—tax positions in prior period	146
Gross decreases—tax positions in prior period	(368)
Gross increases—tax positions in the current period	—
Gross decreases—tax positions in the current period	—
Settlements	—
Lapse of statute of limitations	—
Unrecognized tax benefits at December 31, 2012	$ 1,511

Included in unrecognized tax benefits at December 31, 2014, 2013 and 2012, is $1.0 million, $2.4 million, and $1.0 million, respectively, of tax benefits that, if recognized, would impact the effective tax rate. As of December 31, 2014 and 2013, we accrued $28,000 and $249,000, respectively, in interest expense relating to uncertain state tax positions.

We are subject to federal and state taxation in the United States and various foreign jurisdictions. Currently, our 2013, 2012, 2011 and 2010 tax years are subject to examination by the IRS and by state taxing authorities. We are unaware of any positions for which it is reasonably possible that the total amounts of unrecognized tax benefits will significantly increase or decrease within the next twelve months.

14. Employee Benefit Plans

Supplemental Executive Retirement Plan

We maintain the United Therapeutics Corporation Supplemental Executive Retirement Plan (SERP) to provide retirement benefits to certain senior members of our management team.

UNITED THERAPEUTICS CORPORATION

Notes to Consolidated Financial Statements (Continued)

14. Employee Benefit Plans (Continued)

Participants who retire at age 60 or older are eligible to receive either monthly payments or a lump sum payment based on an average of their total gross base salary over the last 36 months of active employment, subject to certain adjustments. Related benefit payments commence on the first day of the sixth month after retirement. Participants who elect to receive monthly payments will continue payments through the remainder of their life. Alternatively, participants who elected to receive a lump sum distribution will receive a payment equal to the present value of the estimated monthly payments that would have been received upon retirement. As of December 31, 2014 and 2013, all SERP participants had elected to receive a lump sum distribution. Participants who terminate employment for any reason other than death, disability, or change in control prior to age 60 will not be entitled to receive any benefits under the SERP.

To help fund our obligations under the SERP, we maintain the United Therapeutics Corporation Supplemental Executive Retirement Plan Rabbi Trust Document (Rabbi Trust). Participants of the SERP will have no preferred claim on, nor any beneficial ownership interest in, any assets of the Rabbi Trust. The balance in the Rabbi Trust was $5.1 million as of December 31, 2014 and 2013 and are included under "Cash and cash equivalents" on our consolidated balance sheets.

We recognize the unfunded balance of the SERP as a liability on our consolidated balance sheets. Since we do not fund the SERP, the liability is equal to the projected benefit obligation as measured at the end of each fiscal year. Expenses related to the SERP are reported under the captions, "research and development expense" and "selling, general and administrative expense" in the accompanying consolidated statements of operations.

A reconciliation of the beginning and ending balances of the projected benefit obligation is presented below (in thousands):

	Year Ended December 31,	
	2014	2013
Projected benefit obligation at the beginning of the year	$ 51,034	$ 47,206
Service cost	5,517	5,406
Interest cost	2,367	1,584
Plan amendments	3,862	—
Actuarial gain	(4,825)	(3,162)
Projected benefit obligation at the end of the year	$ 57,955	$ 51,034
Fair value of plan assets at the end of the year	—	—
Unfunded at end of the year(1)	$ 57,955	$ 51,034

(1) At December 31, 2014, the aggregate balance of the SERP liability was $58.0 million, of which $20.9 million, representing the benefit obligation due for participants who are currently eligible to retire, has been classified as current liabilities under the caption "Other current liabilities" on our consolidated balance sheets.

The accumulated benefit obligation, a measure that does not consider future increases in participants' salaries, was $43.5 million and $37.2 million at December 31, 2014 and 2013, respectively.

UNITED THERAPEUTICS CORPORATION

Notes to Consolidated Financial Statements (Continued)

14. Employee Benefit Plans (Continued)

Future estimated benefit payments, based on current assumptions, including election of lump-sum distributions and expected future service, are as follows (in thousands):

Year Ended December 31,	
2015	$ 20,875
2016	—
2017	—
2018	—
2019	4,430
2020-2024	36,605
Total	$ 61,910

The following weighted-average assumptions were used to measure the SERP obligation:

	Year Ended December 31,	
	2014	2013
Discount Rate	3.64%	4.34%
Salary Increases	5.00%	5.00%

The components of net periodic pension cost recognized on our consolidated statement of operations consist of the following (in thousands):

	Year Ended December 31,		
	2014	2013	2012
Service cost	$ 5,517	$ 5,406	$ 4,315
Interest cost	2,367	1,584	1,475
Amortization of prior service cost	1,234	827	827
Amortization of net actuarial loss	210	794	—
Total	$ 9,328	$ 8,611	$ 6,617

UNITED THERAPEUTICS CORPORATION

Notes to Consolidated Financial Statements (Continued)

14. Employee Benefit Plans (Continued)

Reclassification adjustments related to the SERP from accumulated other comprehensive loss to the statement of operations by line item and the tax impact of these reclassifications is presented below (in thousands):

Components Reclassified from Accumulated Other Comprehensive Loss(1)	As of December 31, 2014	As of December 31, 2013
Prior service cost:		
Research and development	$ 408	$ 312
Selling, general and administrative	826	515
Total	1,234	827
Amortization of net actuarial loss:		
Research and development	69	300
Selling, general and administrative	141	494
Total	210	794
Total prior service cost and amortization of net actuarial loss	1,444	1,621
Tax benefit	(540)	(601)
Total, net of tax	$ 904	$ 1,020

(1) Refer to Note 12— *Accumulated Other Comprehensive Loss* .

Amounts relating to the SERP that have been recognized in other comprehensive gain (loss) are as follows (in thousands):

	Year Ended December 31, 2014	2013	2012
Net unrecognized actuarial gain (loss)	$ 5,035	$ 3,956	$ (8,464)
Net unrecognized prior service cost	(2,627)	827	827
Total	2,408	4,783	(7,637)
Tax	(920)	(1,688)	2,807
Total, net of tax	$ 1,488	$ 3,095	$ (4,830)

The table below presents amounts relating to the SERP included in accumulated other comprehensive loss that have not yet been recognized as a component of net periodic pension cost on our consolidated statements of operations (in thousands):

	Year Ended December 31, 2014	2013	2012
Net unrecognized actuarial loss	$ 2,767	$ 7,803	$ 11,758
Net unrecognized prior service cost	8,326	5,698	6,525
Total	11,093	13,501	18,283
Tax	(4,150)	(5,074)	(6,743)
Total, net of tax	$ 6,943	$ 8,427	$ 11,540

UNITED THERAPEUTICS CORPORATION

Notes to Consolidated Financial Statements (Continued)

14. Employee Benefit Plans (Continued)

Estimated amounts included in accumulated other comprehensive loss as of December 31, 2014 that are expected to be recognized as components of net periodic pension expense on our statement of operations for the year ended December 31, 2015 comprise the following (in thousands):

Amortization of prior service cost	$ 1,234
Amortization of net actuarial loss	—
Total	$ 1,234

Employee Retirement Plan

We maintain a Section 401(k) Salary Reduction Plan which is open to all eligible full-time employees. Under the 401(k) Plan, eligible employees can make pre-tax contributions up to statutory limits. Currently, we make discretionary matching contributions to the 401(k) Plan equal to 40 percent of a participant's elected salary deferral. Matching contributions vest immediately for participants who have been employed for three years; otherwise, matching contributions vest annually, in one-third increments over a three-year period until the three-year employment requirement has been met. Expenses related to the 401(k) Plan were $3.0 million, $2.5 million and $2.1 million for the years ended December 31, 2014, 2013 and 2012, respectively.

15. Assignment and License Agreements

GlaxoSmithKline PLC

In 1997, GlaxoSmithKline PLC (Glaxo) assigned to us patents and patent applications for use of the stable prostacyclin analogue UT-15 (now known as treprostinil) for the treatment of PAH and congestive heart failure. Under the agreement, Glaxo was entitled to receive royalties on sales exceeding a specified threshold for a minimum period of ten years (or until expiration of the licensed patents) following the date of the first commercial sale of any initial product containing treprostinil. Pursuant to these terms, our royalty obligation ended in October 2014.

Supernus Pharmaceuticals, Inc.

In June 2006, we entered into an exclusive license agreement with Supernus Pharmaceuticals, Inc. (Supernus) for the use of certain technologies developed by Supernus in our Orenitram tablet. The agreement required us to make milestone payments to Supernus in connection with the development of Orenitram and a $2.0 million payment upon its commercial launch, which occurred during the second quarter of 2014. Additionally, we will pay a single digit royalty to Supernus based on net sales of Orenitram. Royalties will be paid for approximately twelve years commencing with the first commercial sale subject to adjustments.

Eli Lilly and Company

In November 2008, we acquired from Lilly exclusive rights to develop, market, promote and commercialize Adcirca for the treatment of pulmonary hypertension in the United States and Puerto Rico. In exchange for these license rights, we agreed to pay Lilly, among other fees, royalties of five percent of our net sales of Adcirca as a pass through of Lilly's third-party royalty obligations for as long as Lilly is required to make such royalty payments. Pursuant to the terms of our license

UNITED THERAPEUTICS CORPORATION

Notes to Consolidated Financial Statements (Continued)

15. Assignment and License Agreements (Continued)

arrangement, Lilly manufactures Adcirca for us and distributes Adcirca via its wholesaler network in the same manner that it distributes its own pharmaceutical products. We purchase Adcirca from Lilly at a fixed manufacturing cost, which is adjusted by Lilly from time to time. The terms of this licensing arrangement will continue generally until the later of: (1) the expiration or lapse of the last to expire claim within a Lilly patent covering commercialization of Adcirca; or (2) the expiration of any government conferred exclusivity rights to Adcirca. In addition, at Lilly's discretion the license agreement may be terminated in the event that we undergo a change in control.

National Cancer Institute

In July 2010, we entered into a Cooperative Research and Development Agreement (CRADA) with the National Cancer Institute (NCI) of the United States National Institutes for Health (NIH) to collaborate on the late-stage development and regulatory approval process for Chimeric Monoclonal Antibody 14.18 (ch14.18) for children with high-risk neuroblastoma and patients with other forms of cancer. Ch14.18 is an antibody that has shown potential in the treatment of neuroblastoma by targeting GD2, a glycolipid on the surface of tumor cells. Under the terms of the CRADA, we have developed the capability to commercially produce the antibody. Collectively, related NCI-supported studies and our production data were used as the foundation for our marketing authorization application which was accepted by the European Medicines Agency (EMA) in December 2013, and a biologics license application which the FDA accepted in June 2014. We previously received orphan drug designation for ch14.18 from both the FDA and the EMA. In lieu of a royalty payment to the NCI, we have an ongoing obligation to provide the NCI with ch14.18 for its studies free of charge.

Toray Industries, Inc.

In 2000, we entered into an agreement with Toray to obtain exclusive rights to develop and market beraprost, a chemically stable oral prostacyclin analogue, in a sustained release formulation in the United States and Canada for the treatment of all cardiovascular indications. In 2007, we amended the agreement to expand our rights to commercialize a modified release formulation of beraprost (beraprost-MR). As part of the 2007 amendment, we issued 400,000 shares of our common stock to Toray with certain put rights. These put rights provide Toray the ability to request at its discretion that we repurchase these shares at a price of $27.21 per share upon 30 days' prior written notice. Accordingly, we classified the value of the shares within temporary equity on our consolidated balance sheets. In the event that Toray requests that we repurchase these shares, we will reclassify the repurchase value of the stock as a liability until settlement. The 2007 amendment also provided for certain milestone payments during the development period and upon receipt of regulatory approval in the United States or the European Union.

In July 2011, we amended our license agreement with Toray. The amendment did not materially change the terms of our license agreement, except for a reduction in royalty rates. In exchange for the reduction in royalty rates, we agreed to pay Toray $50.0 million in equal, non-refundable payments over the five-year period ending in 2015. As of December 31, 2014, our remaining obligation to Toray under this agreement is $10.0 million.

UNITED THERAPEUTICS CORPORATION

Notes to Consolidated Financial Statements (Continued)

15. Assignment and License Agreements (Continued)

Pluristem License Agreement

In June 2011, we entered into a license agreement with Pluristem Ltd. (Pluristem) for exclusive worldwide rights to develop and commercialize a cell-based product for the treatment of PAH using Pluristem's proprietary PLX cell technology. The agreement provides for additional milestone payments to Pluristem at various stages, as well as royalties on commercial sales.

Medtronic Inc.

In 2009, we entered into an exclusive agreement with Medtronic Inc. (Medtronic), which was amended in 2011, to collaborate on the development and commercialization of Medtronic's proprietary intravascular infusion catheter to be used with Medtronic's Synchromed II implantable infusion pump and related infusion system components (together referred to as the Remodulin Implantable System) in order to deliver Remodulin for the treatment of PAH in the U.S., UK, Canada, France, Germany, Italy and Japan. If this development program is successful, our agreement provides that, upon commercialization, we will purchase infusion pumps and supplies from Medtronic and will also pay a royalty to Medtronic based on net sales of Remodulin for use in the Remodulin Implantable System within the exclusive territories, subject to certain adjustments specified in the agreement. The Remodulin Implantable System will be exclusive to Remodulin so long as we purchase a minimum percentage of our annual requirement for implantable pump systems from Medtronic.

DEKA Research & Development Corp.

In December 2014, we entered into an exclusive agreement with DEKA Research & Development Corp. (DEKA) to develop a pre-filled, semi-disposable pump system for subcutaneous delivery of Remodulin. Under the terms of the agreement, we will fund the development costs related to the semi-disposable pump system and will pay product fees and a single-digit royalty to DEKA based on commercial sales of the system and the Remodulin sold for use with the system.

Other

We are party to various other license agreements relating to therapies under development. These license agreements require us to make payments based on a percentage of sales, if we are successful in commercially developing these therapies, and may require other payments upon the achievement of certain milestones.

16. Distribution Agreements

U.S.-Based Specialty Pharmaceutical Distributors

We are party to separate distribution agreements for Remodulin, Tyvaso and Orenitram with two U.S.-based specialty pharmaceutical distributors. The distribution agreements are similar to one another, and generally have one-year terms that renew automatically for additional one-year periods, unless terminated earlier. The agreements contain contractual responsibilities relating to ordering specifications, inventory requirements and exchange rights. We also have agreements with these distributors to perform certain services for us on a fee-for-service basis. If any of our distribution agreements expire or terminate, we may be required under certain circumstances to repurchase any unsold inventory held by our distributors.

UNITED THERAPEUTICS CORPORATION

Notes to Consolidated Financial Statements (Continued)

16. Distribution Agreements (Continued)

International Distributors

We currently sell Remodulin internationally through various distributors. The financial terms and conditions relating to these distributor arrangements are structured in a manner substantially similar to those of our U.S. distribution agreements described above.

17. Segment Information

We currently operate as one operating segment. However, our chief operating decision makers regularly review revenues, cost of product sales and gross profit data as a primary measure of performance for each of our four commercial products. We commenced sales of Orenitram during the second quarter of 2014.

Net revenues, cost of product sales and gross profit for each of our commercial products were as follows (in thousands):

	Remodulin	Tyvaso	Adcirca	Orenitram	Total
Year Ended December 31, 2014					
Net revenues	$ 553,728	$ 463,067	$ 221,471	$ 41,267	$ 1,279,533
Cost of product sales	47,327	57,442	13,495	7,619	125,883
Gross profit	$ 506,401	$ 405,625	$ 207,976	$ 33,648	$ 1,153,650
Year Ended December 31, 2013					
Net revenues	$ 491,179	$ 438,793	$ 176,972	$ —	$ 1,106,944
Cost of product sales	59,314	60,831	10,982	—	131,127
Gross profit	$ 431,865	$ 377,962	$ 165,990	$ —	$ 975,817
Year Ended December 31, 2012					
Net revenues	$ 457,969	$ 325,614	$ 122,540	$ —	$ 906,123
Cost of product sales	57,618	53,825	7,854	—	$ 119,297
Gross profit	$ 400,351	$ 271,789	$ 114,686	$ —	$ 786,826

Geographic revenues are determined based on the country in which our customers (distributors) are located. Net revenues from external customers by geographic area are as follows (in thousands):

Year Ended December 31,	2014	2013	2012
United States	$ 1,180,759	$ 1,032,435	$ 846,611
Rest-of-World(1)	107,760	84,549	69,465
Total	$ 1,288,519	$ 1,116,984	$ 916,076

(1) Primarily Europe.

For the years ended December 31, 2014, 2013 and 2012, sales to Accredo Health Group, Inc. comprised 58 percent, 57 percent and 56 percent, respectively, of total consolidated net revenues.

UNITED THERAPEUTICS CORPORATION

Notes to Consolidated Financial Statements (Continued)

17. Segment Information (Continued)

Long-lived assets (property, plant and equipment) located by geographic area are as follows (in thousands):

Year Ended December 31,	2014	2013	2012
United States	$ 462,377	$ 442,673	$ 425,585
Rest-of-World(1)	16,044	22,277	28,100
Total	$ 478,421	$ 464,950	$ 453,685

(1) Facilities principally located in the United Kingdom.

18. Quarterly Financial Information (Unaudited)

Summarized quarterly financial information for each of the years ended December 31, 2014 and 2013 are as follows (in thousands, except per share amounts):

	Quarter Ended			
	December 31, 2014	September 30, 2014	June 30, 2014	March 31, 2014
Net sales	$ 346,363	$ 329,950	$ 322,802	$ 289,403
Gross profit	329,611	287,466	282,620	253,953
Net income (loss)(1)	115,935	(25,237)	111,852	137,524
Net income (loss) per share—basic	$ 2.44	$ (0.53)	$ 2.35	$ 2.73
Net income (loss) per share—diluted	$ 2.17	$ (0.53)	$ 2.10	$ 2.43

	Quarter Ended			
	December 31, 2013	September 30, 2013	June 30, 2013	March 31, 2013
Net sales	$ 289,017	$ 302,225	$ 280,606	$ 245,136
Gross profit	247,519	269,290	245,175	213,833
Net (loss) income(2)	(30,314)	62,685	79,864	62,325
Net (loss) income per share—basic	$ (0.60)	$ 1.25	$ 1.60	$ 1.24
Net (loss) income per share—diluted	$ (0.60)	$ 1.17	$ 1.52	$ 1.19

(1) Operating results for the quarter ended September 30 2014, include $140.3 million, net of tax, charge to operating expenses related to share-based compensation expense.

(2) Operating results for the quarter ended December 31, 2013, include $111.2 million, net of tax, charge to operating expenses related to share-based compensation expense.

19. Litigation

Department of Health and Human Services Subpoena

In December 2013, we received a subpoena from the Office of the Inspector General (OIG) of the Department of Health and Human Services in connection with a civil investigation by the United States Department of Justice, principally represented by the United States Attorney's Office for the District of

UNITED THERAPEUTICS CORPORATION

Notes to Consolidated Financial Statements (Continued)

19. Litigation (Continued)

Maryland. The subpoena requests documents regarding Remodulin, Tyvaso and Adcirca, including our marketing practices relating to these products. We are cooperating with the investigation. We are not aware that a claim, litigation or assessment has been asserted in connection with the subpoena. However, we cannot predict what actions, if any, may be taken by the OIG, the Department of Justice, other governmental entities, or any third parties in connection with this investigation.

Sandoz Inc.

In February 2012, we received a Paragraph IV certification letter (the Original Notice Letter) from Sandoz Inc. (Sandoz) advising that Sandoz had submitted an abbreviated new drug application (ANDA) to the FDA requesting approval to market a generic version of the 10 mg/mL strength of Remodulin. In December 2012, we received notice (the Second Notice Letter) that Sandoz had amended its previously filed ANDA to request additional approval to market generic versions of the 1 mg/mL, 2.5 mg/mL, and 5 mg/mL strengths of Remodulin. In the Original Notice Letter and the Second Notice Letter, Sandoz stated that it intends to market a generic version of Remodulin before the expiration of the following patents relating to Remodulin: U.S. Patent No. 5,153,222, which expires in October 2014; U.S. Patent No. 6,765,117, which expires in October 2017; and U.S. Patent No. 7,999,007, which expires in March 2029. Each of these patents is listed in the Orange Book.

We responded to the Original Notice Letter by filing a lawsuit in March 2012 against Sandoz in the U.S. District Court for the District of New Jersey alleging patent infringement. We responded to the Second Notice Letter by filing an additional lawsuit in January 2013 for patent infringement in the U.S. District Court for the District of New Jersey. Sandoz filed counterclaims in each action alleging that the patents at issue in the litigation are invalid or will not be infringed by the commercial manufacture, use or sale of the proposed product described in Sandoz's ANDA submission. Shortly before trial, Sandoz withdrew its request to market a generic version of Remodulin before the expiration of U.S. Patent No. 5,153,222, but maintained its request to market a generic version of Remodulin before the expiration of the other two patents. The trial for both lawsuits, limited to U.S. Patent Nos. 6,765,117 and 7,999,007, occurred in May and June 2014 and we received the Court's decision in August 2014. In that decision, with respect to U.S. Patent No. 6,765,117 the Court both ruled that the patent is valid and enforceable against Sandoz, and enjoined Sandoz from marketing its generic product until the expiration of that patent in October 2017. With respect to U.S. Patent No. 7,999,007, the Court ruled that the patent is valid, but that it would not be infringed by Sandoz' generic product.

Sandoz has appealed the ruling that U.S. Patent No. 6,765,117 is valid and would be infringed, and that U.S. Patent No. 7,999,007 is valid. We have filed a cross-appeal challenging the Court's ruling that U.S. Patent No. 7,999,007 would not be infringed by Sandoz's generic version of Remodulin.

In July 2014, we received an additional Paragraph IV certification letter (Third Notice Letter) from Sandoz, seeking permission to market and sell its generic version of Remodulin before the expiration of U.S. Patent No. 8,497,393, which expires in December 2028 and is also listed in the Orange Book. We responded to Sandoz's Third Notice Letter by filing a lawsuit in September 2014 in the U.S. District Court for the District of New Jersey for patent infringement with respect to U.S. Patent No. 8,497,393.

We intend to vigorously enforce our intellectual property rights relating to Remodulin.

UNITED THERAPEUTICS CORPORATION

Notes to Consolidated Financial Statements (Continued)

19. Litigation (Continued)

Teva Pharmaceuticals USA, Inc.

On July 21, 2014, we received a Paragraph IV certification letter (Teva's Notice Letter) from Teva Pharmaceuticals USA, Inc. (Teva) advising that Teva had submitted an ANDA to the FDA requesting approval to market a generic version of Remodulin.

In Teva's Notice Letter, Teva states that it intends to market a generic version of Remodulin before the expiration of U.S. Patent Nos. 6,765,117 and 8,497,393, both of which are also the subject of Paragraph IV certifications by Sandoz, as discussed above. Teva's Notice Letter states that the ANDA contains a Paragraph IV certification alleging that these patents are not valid, not enforceable and/or will not be infringed by the commercial manufacture, use or sale of the proposed product described in Teva's ANDA submission.

We responded to Teva's Notice Letter by filing a lawsuit in September 2014 against Teva in the U.S. District Court for the District of New Jersey alleging infringement of U.S. Patent Nos. 6,765,117, 7,999,007 and 8,497,393, as well as infringement of U.S. Patent Nos. 8,653,137 and 8,658,694, both of which expire in September 2028. Teva has filed its answer to our complaint, and has also filed a counterclaim alleging that the patents at issue in the litigation are invalid or will not be infringed by the commercial manufacture, use or sale of the proposed product described in Teva's ANDA submission. We have filed an answer to the counterclaim.

Under the Hatch-Waxman Act, the FDA is automatically precluded from approving Teva's ANDA for up to 30 months from receipt of Teva's Notice Letter or until the issuance of a U.S. District Court decision that is adverse to us, whichever occurs first. We intend to vigorously enforce our intellectual property rights relating to Remodulin.

United Therapeutics Corporation
Schedule II—Valuation and Qualifying Accounts
Years Ended December 31, 2014, 2013, and 2012
(In thousands)

	Valuation Allowance on Deferred Tax Assets			
	Balance at Beginning of Year	Additions Charged to Expense	Deductions	Balance at End of Year
Year Ended December 31, 2014	$ 2,507	$ 474	$ —	$ 2,981
Year Ended December 31, 2013	$ 5,665	$ 169	$ (3,327)	$ 2,507
Year Ended December 31, 2012	$ 5,458	$ 207	$ —	$ 5,665

	Reserve for Inventory Obsolescence			
	Balance at Beginning of Year	Additions Charged to Expense	Deductions	Balance at End of Year
Year Ended December 31, 2014	$ 18,301	$ 3,431	$ (11,195)	$ 10,537
Year Ended December 31, 2013	$ 16,679	$ 3,341	$ (1,719)	$ 18,301
Year Ended December 31, 2012	$ 8,801	$ 12,136	$ (4,258)	$ 16,679

ITEM 9. CHANGES IN AND DISAGREEMENTS WITH ACCOUNTANTS ON ACCOUNTING AND FINANCIAL DISCLOSURE

None.

ITEM 9A. CONTROLS AND PROCEDURES

Evaluation of Disclosure Controls and Procedures

Our management, with participation of our Chairman and Co-Chief Executive Officer and Chief Financial Officer, has evaluated the effectiveness of our disclosure controls and procedures, as defined in Rules 13a-15(e) and 15d-15(e) of the Securities Exchange Act of 1934, as of December 31, 2014. Based on that evaluation, our Chairman and Co-Chief Executive Officer and Chief Financial Officer concluded that our disclosure controls and procedures were effective as of December 31, 2014.

Management's Report on Internal Control Over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over financial reporting (as defined in Rules 13a-15(f) and 15d-15(f) under the Securities Exchange Act of 1934, as amended). Our internal control over financial reporting was designed to provide reasonable assurance to our management and Board of Directors regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. All internal controls over financial reporting, no matter how well designed, have inherent limitations. As a result of these inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Therefore, even those internal controls determined to be effective can provide only reasonable assurance with respect to the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles.

Our management assessed the effectiveness of our internal control over financial reporting as of December 31, 2014, based on the criteria set forth by the Committee of Sponsoring Organizations of the Treadway Commission (COSO) in *Internal Control—Integrated Framework (2013)* . Management's assessment included an evaluation of the design of our internal control over financial reporting and testing of the operational effectiveness of our internal control over financial reporting. Based on this assessment, our management concluded that, as of December 31, 2014, our internal control over financial reporting was effective.

Ernst & Young LLP, an independent registered public accounting firm, has issued an attestation report on our internal control over financial reporting. The report of Ernst & Young LLP is contained in Item 8 of this Annual Report on Form 10-K.

Attestation of Independent Registered Public Accounting Firm

The attestation report of our independent registered public accounting firm regarding internal control over financial reporting is set forth in Item 8 of this Annual Report on Form 10-K under the caption "Report of Independent Registered Public Accounting Firm" and incorporated herein by reference.

Changes in Internal Control over Financial Reporting

There were no changes in our internal control over financial reporting during the quarter ended December 31, 2014 that have materially affected, or are reasonably likely to materially affect, our internal controls over financial reporting.

ITEM 9B. OTHER INFORMATION

Chief Financial Officer Succession

On February 23, 2015, our Chief Financial Officer, John Ferrari, announced his decision to retire effective March 13, 2015. Following his retirement, Mr. Ferrari has elected to serve as a "senior advisor" on a part-time basis, in accordance with the terms of his employment agreement.

On February 23, 2015, our Board of Directors, acting on the recommendation of the Nominating and Governance Committee and the Audit Committee, appointed James Edgemond to succeed Mr. Ferrari and assume the role of Chief Financial Officer and Treasurer upon Mr. Ferrari's retirement.

Mr. Edgemond, age 47, has served as Treasurer and Vice President, Strategic Financial Planning since January 2013. He is an alumnus of the Harvard Business School, Virginia Tech and James Madison University. Prior to joining United Therapeutics, he was Vice President, Corporate Controller and Treasurer of Clark Construction Group from November 2008 through January 2013. He also served in a variety of roles at The Corporate Executive Board Company from 1998 to 2008, including most recently as Executive Director, Finance from 2005 to 2008. He began his career as a public accountant at KPMG Peat Marwick LLP, where he served in a variety of roles from 1990 through 1998, including most recently as a Senior Manager.

The Compensation Committee of the Board of Directors approved changes to the compensation program for Mr. Edgemond in connection with his promotion to Chief Financial Officer and Treasurer. The changes, which become effective upon Mr. Ferrari's retirement, are as follows:

- Mr. Edgemond's salary will increase to $400,000;
- Mr. Edgemond's annual cash incentive bonus opportunity for 2015 will increase to 50% of his salary; and
- Mr. Edgemond's long-term incentive bonus award opportunity will be 50,000 STAP awards.

The foregoing 2015 contingent cash incentive bonus target opportunities and long-term inventive opportunities will be assessed pursuant to the Company-Wide Milestone Program criteria applicable for 2015, and a subjective evaluation of individual performance. In addition, the Compensation Committee may exercise its discretion to increase or decrease the award percentage earned.

Mr. Edgemond will receive a one-time grant of 25,000 STAP awards upon his promotion, to be issued on March 13, 2015 at an exercise price equal to the NASDAQ closing price for the Company's common stock on that date. The award will vest in equal installments on each of the first four anniversaries of the date of grant, and will expire ten years from the date of grant.

In connection with his promotion to Chief Financial Officer and Treasurer, the Company also entered into an employment agreement with Mr. Edgemond, which will become effective March 13, 2015. Mr. Edgemond's employment agreement has an initial term of three years, and is automatically extended by one additional year periods at the end of the then-current term unless at least 60 days prior to the end of the then-current term, either party delivers notice not to extend the agreement. The agreement provides for an annual base salary of $400,000, which will be subject to review and annual increase by the Company at its discretion.

The agreement provides that if Mr. Edgemond is terminated by the Company after a change of control of the Company, he is entitled to an acceleration of all unvested stock options and STAP awards. The agreement prohibits Mr. Edgemond from accepting employment, consultancy or other business relationships with an entity that directly competes with the Company for a period of one year following his last receipt of compensation from the Company.

Mr. Edgemond and the Company are also parties to a Change in Control Severance Agreement, dated November 12, 2014, providing benefits to Mr. Edgemond in the event of his termination following a change of control of the Company. In particular, these benefits include a cash severance payment equal to two times his base salary, plus two times his annual target cash bonus. This cash severance would become payable is in lieu of any severance payment under Mr. Edgemond's employment agreement, unless severance under the employment agreement would result in a greater benefit. The Change in Control Severance Agreement also provides for continuation of medical benefits for 24 months following termination, and outplacement benefits with a value of $10,000.

The foregoing summary is qualified in its entirety by reference to the full text of (a) Mr. Edgemond's Employment Agreement, a copy of which is filed as Exhibit 10.55 to this Annual Report on Form 10-K; and (b) Mr. Edgemond's Change in Control Severance Agreement, a copy of which is filed herewith as Exhibit 10.56 to this Annual Report on Form 10-K.

A detailed discussion of our executive compensation program will be provided in our definitive proxy statement in connection with our 2015 annual meeting of shareholders, which we expect to file with the Securities and Exchange Commission on or about April 30, 2015.

PART III

ITEM 10. DIRECTORS, EXECUTIVE OFFICERS AND CORPORATE GOVERNANCE

Information as to the individuals serving on our board of directors is set forth below under the heading *Board of Directors* . Additional information required by Item 10 regarding nominees and directors appearing under Proposal No. 1: *Election of Directors* in our definitive proxy statement for our 2015 annual meeting of shareholders scheduled for June 26, 2015 (the 2015 Proxy Statement) is hereby incorporated herein by this reference. Information regarding our executive officers appears in Part I, Item I of this Annual Report on Form 10-K under the heading *Executive Officers of the Registrant* . Information regarding the Audit Committee and the Audit Committee's financial expert appearing under the heading *Committees of our Board of Directors—Audit Committee* in our 2015 Proxy Statement is hereby incorporated herein by this reference.

Information appearing under the heading *Section 16(a) Beneficial Ownership Reporting Compliance* in our 2015 Proxy Statement is hereby incorporated herein by this reference.

We have a written Code of Conduct and Business Ethics that applies to our principal executive officer, principal financial officer and our principal accounting officer and every other director, officer and employee of United Therapeutics. The Code of Conduct and Business Ethics is available on our Internet website at *http://ir.unither.com/corporate-governance.cfm* . A copy of the Code of Conduct and Business Ethics will be provided free of charge by making a written request and mailing it to our corporate headquarters offices to the attention of the Investor Relations Department. If any amendment to, or a waiver from, a provision of the Code of Conduct and Business Ethics that applies to the principal executive officer, principal financial officer and principal accounting officer is made, such information will be posted on our Internet website within four business days at *www.unither.com* .

Board of Directors

Christopher Causey, M.B.A.

Principal, Causey Consortium

Raymond Dwek, F.R.S.

Director of the Glycobiology Institute and Professor Emeritus, University of Oxford

Richard Giltner

Private Investor

Roger Jeffs, Ph.D.

President and Co-Chief Executive Officer of United Therapeutics

Katherine Klein, Ph.D.

Vice-Dean and Professor, The Wharton School of the University of Pennsylvania

Ray Kurzweil

Director of Engineering, Google Inc.

Christopher Patusky, J.D., M.G.A.

Founding Principal, Patusky Associates, LLC

Martine Rothblatt, Ph.D., J.D., M.B.A.

Chairman and Co-Chief Executive Officer of United Therapeutics

Louis Sullivan, M.D.

Former Secretary, U.S. Department of Health and Human Services

Tommy Thompson, J.D.

Former Secretary, U.S. Department of Health and Human Services

ITEM 11. EXECUTIVE COMPENSATION

Information concerning executive compensation required by Item 11 will appear under the headings *Director Compensation* , *Compensation Discussion and Analysis, Summary Compensation Table and Grants of Plan-Based Awards in 2014, Narratives to Summary Compensation Table and Grants of Plan-Based Awards Table, Summary of Terms of Plan-Based Awards, Supplemental Executive Retirement Plan, Rabbi Trust, Potential Payments Upon Termination or Change in Control, and Director Compensation* in our 2015 Proxy Statement and is incorporated herein by reference.

Information concerning the Compensation Committee required by Item 11 will appear under the heading *Compensation Committee Report* in our 2015 Proxy Statement and is incorporated herein by reference.

ITEM 12. SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT AND RELATED STOCKHOLDER MATTERS

The information regarding beneficial ownership of our common stock required by Item 12 will appear under *Beneficial Ownership of Common Stock* in our 2015 Proxy Statement and is incorporated herein by reference.

Securities Authorized for Issuance Under Equity Compensation Plans

The following table presents information as of December 31, 2014, regarding our securities authorized for issuance under equity compensation plans:

Plan category	Number of securities to be issued upon exercise of outstanding options (a)	Weighted average exercise price of outstanding options (b)	Number of securities remaining available for future issuance under equity compensation plans (excluding securities reflected in column (a) (c)
Equity compensation plan approved by security holders	4,060,771	$ 76.78	9,256,016
Equity compensation plans not approved by security holders	—	0.00	N/A
Total	4,060,771	$ 76.78	9,256,016

All outstanding stock options were issued under our equity incentive plan approved by security holders in 1997 (the EIP). Information regarding this plan is contained in Note 11 —*Stockholders' Equity* to the consolidated financial statements included in this Annual Report on Form 10-K. Aside from stock options issued under the EIP, we do not have any outstanding stock options, warrants or rights that are outstanding or available for issuance as described in Regulation S-K Item 201(d).

ITEM 13. CERTAIN RELATIONSHIPS AND RELATED TRANSACTIONS, AND DIRECTOR INDEPENDENCE

Information concerning related party transactions and director independence required by Item 13 will appear under the headings *Other Matters—Certain Relationships and Related Party Transactions, Board of Directors, Committees, Corporate Governance—Director Independence and Committees of our Board of Directors* in our 2015 Proxy Statement and is incorporated herein by reference.

ITEM 14. PRINCIPAL ACCOUNTING FEES AND SERVICES

Information required by Item 14 concerning the principal accounting fees paid by the Registrant and the Audit Committee's pre-approval policies and procedures, will appear under the heading *Report of the Audit Committee and Information on our Independent Auditors* in our 2015 Proxy Statement and is incorporated herein by reference.

PART IV

ITEM 15. EXHIBITS, FINANCIAL STATEMENT SCHEDULES

In reviewing the agreements included or incorporated by reference as exhibits to this Annual Report on Form 10-K, it is important to note that they are included to provide investors with information regarding their terms, and are not intended to provide any other factual or disclosure information about United Therapeutics or the other parties to the agreements. The agreements contain representations and warranties made by each of the parties to the applicable agreement. These representations and warranties have been made solely for the benefit of the other parties to the applicable agreement, and: (1) should not be treated as categorical statements of fact, but rather as a way of allocating risk between the parties; (2) have in some cases been qualified by disclosures that were made to the other party in connection with the negotiation of the applicable agreement, which disclosures are not necessarily reflected in the agreement; (3) may apply standards of materiality in a way that is different from what may be material to investors; and (4) were made only as of the date of the applicable agreement or such other date or dates as may be specified in the agreement and are subject to more recent developments.

Accordingly, these representations and warranties may not describe the actual state of affairs as of the date they were made or at any other time. Additional information about United Therapeutics may be found elsewhere in this Annual Report on Form 10-K and our other public filings, which are available without charge through the SEC's website at *http://www.sec.gov* .

(a)(1) Our financial statements filed as part of this report on Form 10-K are set forth in the Index to Consolidated Financial Statements under Part II, Item 8 of this Form 10-K.

(a)(2) The Schedule II—Valuation and Qualifying Accounts is filed as part of this Form 10-K. All other schedules are omitted because they are not applicable or not required, or because the required information is included in the consolidated statements or notes thereto.

(a)(3) Exhibits filed as a part of this Form 10-K are listed on the Exhibit Index, which is incorporated by reference herein.

Certain exhibits to this report have been included only with the copies of this report filed with the Securities and Exchange Commission. Copies of individual exhibits will be furnished to shareholders upon written request to United Therapeutics and payment of a reasonable fee (covering the expense of furnishing copies). Shareholders may request exhibit copies by contacting: United Therapeutics Corporation, Attn: Investor Relations, 1040 Spring Street, Silver Spring, Maryland 20910.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereto duly authorized.

UNITED THERAPEUTICS CORPORATION

By: /s/ MARTINE A. ROTHBLATT

Martine A. Rothblatt, Ph.D.
Chairman of the Board and Co-Chief Executive Officer

February 24, 2015

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the registrant and in the capacities and on the dates indicated.

Signatures	Title	Date
/s/ MARTINE A. ROTHBLATT Martine A. Rothblatt	Chairman of the Board and Co-Chief Executive Officer (Principal Executive Officer)	February 24, 2015
/s/ JOHN M. FERRARI John M. Ferrari	Chief Financial Officer (Principal Financial Officer and Principal Accounting Officer)	February 24, 2015
/s/ ROGER A. JEFFS Roger A. Jeffs	President, Co-Chief Executive Officer and Director	February 24, 2015
/s/ CHRISTOPHER CAUSEY Christopher Causey	Director	February 24, 2015
/s/ RAYMOND DWEK Raymond Dwek	Director	February 24, 2015
/s/ RICHARD GILTNER Richard Giltner	Director	February 24, 2015
/s/ KATHERINE KLEIN Katherine Klein	Director	February 24, 2015
/s/ RAYMOND KURZWEIL Raymond Kurzweil	Director	February 24, 2015

Signatures	Title	Date
/s/ CHRISTOPHER PATUSKY Christopher Patusky	Director	February 24, 2015
/s/ LOUIS W. SULLIVAN Louis W. Sullivan	Director	February 24, 2015
/s/ TOMMY THOMPSON Tommy Thompson	Director	February 24, 2015

EXHIBIT INDEX

Exhibit No.	Description
3.1	Amended and Restated Certificate of Incorporation of the Registrant, incorporated by reference to Exhibit 3.1 of the Registrant's Registration Statement on Form S-1 (Registration No. 333-76409).
3.2	Certificate of Amendment to Amended and Restated Certificate of Incorporation of the Registrant, incorporated by reference to Exhibit 3.1 of the Registrant's Current Report on Form 8-K, filed on June 28, 2010.
3.3	Third Amended and Restated By-laws of the Registrant, incorporated by reference to Exhibit 3.1 of the Registrant's Current Report on Form 8-K filed on June 27, 2014.
3.4	Form of Certificate of Designation, Preferences and Rights of Series A Junior Participating Preferred Stock of the Registrant, incorporated by reference to Exhibit A to Exhibit 4 to the Registrant's Current Report on Form 8-K, filed December 18, 2000.
4.1	Reference is made to Exhibits 3.1, 3.2, 3.3 and 3.4.
4.2	First Amended and Restated Rights Agreement, incorporated by reference to Exhibit 4.1 of the Registrant's Current Report on Form 8-K filed on July 3, 2008.
4.3	Indenture, dated as of October 17, 2011, between the Registrant and The Bank of New York Mellon Trust Company, N.A., as trustee (including form of 1.0% Convertible Senior Note due September 15, 2016), incorporated by reference to Exhibit 4.1 of the Registrant's Current Report on Form 8-K filed October 17, 2011.
4.4	Form of 1.0% Convertible Senior Note due September 15, 2016, incorporated by reference to Exhibit 4.2 of the Registrant's Current Report on Form 8-K filed October 17, 2011.
10.1**	United Therapeutics Corporation Amended and Restated Equity Incentive Plan, as amended effective as of September 24, 2004, incorporated by reference to Exhibit 10.1 of the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2004.
10.2**	Amended and Restated Executive Employment Agreement dated as of January 1, 2009, between the Registrant and Martine A. Rothblatt, incorporated by reference to Exhibit 10.2 of the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2009.
10.3**	Employment Agreement dated as of June 16, 2001 between the Registrant and Paul A. Mahon, incorporated by reference to Exhibit 10.4 of the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2002.
10.4**	Employment Agreement dated November 29, 2000 between the Registrant and Roger Jeffs, incorporated by reference to Exhibit 10.9 of the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2002.
10.5	Form of Indemnification Agreement between the Registrant and each of its Directors and Executive Officers, incorporated by reference to Exhibit 10.1 of the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2009.
10.6**	Amendment dated December 11, 2002 to Employment Agreement between the Registrant and Roger Jeffs, incorporated by reference to Exhibit 10.40 of the Registrant's Annual Report on Form 10-K for the fiscal year ended December 31, 2002.
10.7**	Amendment dated December 11, 2002 to Employment Agreement between the Registrant and Paul Mahon, incorporated by reference to Exhibit 10.43 of the Registrant's Annual Report on Form 10-K for the fiscal year ended December 31, 2002.
10.8**	Amendment dated December 29, 2004 to Employment Agreement between Roger Jeffs and the Registrant dated November 29, 2000, as previously amended, incorporated by reference to Exhibit 10.2 of the Registrant's Current Report on Form 8-K filed on December 29, 2004.

Exhibit No.	Description
10.9**	Amendment dated December 29, 2004 to Employment Agreement between Paul A. Mahon and the Registrant dated June 16, 2001, as previously amended, incorporated by reference to Exhibit 10.4 of the Registrant's Current Report on Form 8-K filed on December 29, 2004.
10.10**	Form of terms and conditions for awards granted to Employees by the Registrant under the Amended and Restated Equity Incentive Plan, incorporated by reference to Exhibit 10.1 of the Registrant's Current Report on Form 8-K filed on December 17, 2004.
10.11**	Form of Terms and Conditions for Awards granted to Non-Employees by the Registrant under the Amended and Restated Equity Incentive Plan, incorporated by reference to Exhibit 10.2 of the Registrant's Current Report on Form 8-K filed on December 17, 2004.
10.12**	United Therapeutics Corporation Supplemental Executive Retirement Plan, effective as of July 1, 2006, incorporated by reference to Exhibit 10.1 of the Registrant's Current Report on Form 8-K filed on May 4, 2006.
10.13**	Employment Agreement, dated as of August 2, 2006, between John Ferrari and the Registrant, incorporated by reference to Exhibit 10.1 of the Registrant's Current Report on Form 8-K filed on August 4, 2006.
10.14**	Amendment, dated as of July 31, 2006, to amended Employment Agreement, dated November 29, 2000, between Roger Jeffs and the Registrant, incorporated by reference to Exhibit 10.2 of the Registrant's Current Report on Form 8-K filed on August 4, 2006.
10.15**	Amendment, dated as of July 31, 2006, to amended Employment Agreement, dated June 16, 2001, between Paul A. Mahon and the Registrant, incorporated by reference to Exhibit 10.3 of the Registrant's Current Report on Form 8-K filed on August 4, 2006.
10.16**	Amendment, dated as of December 28, 2006, to Employment Agreement, dated August 2, 2006, between John Ferrari and the Registrant, incorporated by reference to Exhibit 10.1 of the Registrant's Current Report on Form 8-K filed on December 29, 2006.
10.17	United Therapeutics Corporation Supplemental Executive Retirement Plan Rabbi Trust Document entered into on December 28, 2007, by and between the Registrant and Wilmington Trust Company, as trustee, incorporated by reference to Exhibit 10.1 of the Registrant's Current Report on Form 8-K filed on December 28, 2007.
10.18**	United Therapeutics Corporation Share Tracking Awards Plan, incorporated by reference to Exhibit 10.1 of the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2008.
10.19**	First Amendment to the United Therapeutics Corporation Share Tracking Awards Plan, incorporated by reference to Exhibit 10.1 of the Registrant's Current Report on Form 8-K filed on September 18, 2009.
10.20**	Second Amendment to the United Therapeutics Corporation Share Tracking Awards Plan, incorporated by reference to Exhibit 10.1 of the Registrant's Current Report on Form 8-K filed on February 6, 2012.
10.21**	Form of terms and conditions for awards granted to non-employees by the Registrant under the United Therapeutics Corporation Share Tracking Awards Plan, incorporated by reference to Exhibit 10.2 of the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2008.
10.22**	Form of terms and conditions for awards granted to employees by the Registrant prior to January 1, 2010, under the United Therapeutics Corporation Share Tracking Awards Plan, incorporated by reference to Exhibit 10.3 of the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2008.
10.23**	Form of terms and conditions for awards granted to employees by the Registrant on or after January 1, 2010, under the United Therapeutics Corporation Share Tracking Awards Plan, incorporated by reference to Exhibit 10.48 of the Registrant's Annual Report on Form 10-K for the year ended December 31, 2009.

Exhibit No.	Description
10.24**	Form of terms and conditions for awards granted to employees on or after March 15, 2011 under the United Therapeutics Corporation 2011 Share Tracking Awards Plan and the United Therapeutics Corporation 2008 Share Tracking Awards Plan, incorporated by reference to Exhibit 10.2 of Registrant's Registration Statement on Form S-8 (Registration No. 333-173858) filed on May 2, 2011.
10.25**	Form of grant letter used by Registrant under the United Therapeutics Corporation Share Tracking Awards Plan, incorporated by reference to Exhibit 10.4 of the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2008.
10.26**	United Therapeutics Corporation 2011 Share Tracking Awards Plan, incorporated by reference to Exhibit 10.1 of the Registrant's Current Report on Form 8-K filed on March 18, 2011.
10.27**	First Amendment to the United Therapeutics Corporation 2011 Share Tracking Awards Plan, incorporated by reference to Exhibit 10.2 of the Registrant's Current Report on Form 8-K filed on February 6, 2012.
10.28**	Second Amendment to the United Therapeutics Corporation 2011 Share Tracking Awards Plan, incorporated by reference to Exhibit 10.1 of the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2012.
10.29**	Third Amendment to the United Therapeutics Corporation 2011 Share Tracking Awards Plan, incorporated by reference to Exhibit 10.1 of the Registrant's Current Report on Form 8-K filed on February 4, 2013.
10.30**	Fourth Amendment to the United Therapeutics Corporation 2011 Share Tracking Awards Plan, incorporated by reference to Exhibit 10.1 of the Registrant's Current Report on Form 8-K filed on January 31, 2014.
10.31**	Form of terms and conditions for awards granted to employees by the Registrant on or after March 15, 2011 under the United Therapeutics Corporation Share Tracking Awards Plan or the United Therapeutics Corporation 2011 Share Tracking Awards Plan, incorporated by reference to Exhibit 10.2 of the Registrant's Current Report on Form 8-K filed on March 18, 2011.
10.32**	Form of terms and conditions for awards granted to non-employees by the Registrant on or after March 15, 2011 under the United Therapeutics Corporation Share Tracking Awards Plan or the United Therapeutics Corporation 2011 Share Tracking Awards Plan, incorporated by reference to Exhibit 10.3 of the Registrant's Current Report on Form 8-K filed on March 18, 2011.
10.33**	Form of grant letter used by Registrant under the United Therapeutics Corporation 2011 Share Tracking Awards Plan, incorporated by reference to Exhibit 10.4 of the Registrant's Current Report on Form 8-K filed on March 18, 2011.
10.34**	United Therapeutics Corporation Employee Stock Purchase Plan, incorporated by reference to Exhibit 10.1 of the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2012.
10.35*	License Agreement, dated as of November 14, 2008, by and between Eli Lilly and Company and the Registrant, incorporated by reference to Exhibit 10.2 of the Registrant's Current Report on Form 8-K filed on December 24, 2008.
10.36*	Manufacturing and Supply Agreement, dated as of November 14, 2008, by and between Eli Lilly and Company, Lilly del Caribe, Inc. and the Registrant incorporated by reference to Exhibit 10.3 of the Registrant's Current Report on Form 8-K filed on December 24, 2008.
10.37**	Form of Amendment to Employment Agreement between the Registrant and each of Roger Jeffs, Paul Mahon and John Ferrari, each dated as of January 1, 2009, incorporated by reference to Exhibit 10.3 of the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2009.

Exhibit No.	Description
10.38**	Form of Amendment to Employment Agreements between the Registrant and each of Roger Jeffs, Paul Mahon and John Ferrari, each dated as of February 22, 2010, incorporated by reference to Exhibit 10.46 of the Registrant's Annual Report on Form 10-K for the year ended December 31, 2009.
10.39	Distribution Agreement relating to Tyvaso, dated as of August 17, 2009 between the Registrant and Accredo Health Group, Inc., incorporated by reference to Exhibit 10.47 of the Registrant's Annual Report on Form 10-K for the year ended December 31, 2009.
10.40	First Amendment to Distribution Agreement relating to Tyvaso, dated as of September 1, 2011, between the Registrant and Accredo Health Group, Inc., incorporated by reference to Exhibit 10.44 of the Registrant's Annual Report on Form 10-K for the year ended December 31, 2013.
10.41	Second Amendment to Distribution Agreement relating to Tyvaso, dated as of December 18, 2013, between the Registrant, Accredo Health Group, Inc., CuraScript, Inc. and Priority Healthcare Distribution, Inc.., incorporated by reference to Exhibit 10.45 of the Registrant's Annual Report on Form 10-K for the year ended December 31, 2013.
10.42	Stipulation of Settlement, dated October 25, 2010, among the parties to a derivative lawsuit against the directors and officers of the Registrant identified therein, incorporated by reference to Exhibit 10.1 to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2010.
10.43*	Amended and Restated Distribution Agreement relating to Remodulin, dated as of February 21, 2011, between the Registrant and Accredo Health Group, Inc., incorporated by reference to Exhibit 10.38 to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2010.
10.44	First Amendment to Amended and Restated Distribution Agreement relating to Remodulin, dated as of December 18, 2013, between the Registrant, Accredo Health Group, Inc., CuraScript, Inc. and Priority Healthcare Distribution, Inc.
10.45*	Confirmation, dated October 11, 2011, of a note hedging transaction between the Registrant and Deutsche Bank AG, London Branch, incorporated by reference to Exhibit 10.3 to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2011.
10.46*	Confirmation, dated October 11, 2011, of a warrant transaction between the Registrant and Deutsche Bank AG, London Branch, incorporated by reference to Exhibit 10.2 to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2011.
10.47*	Confirmation, dated October 11, 2011, of an accelerated share repurchase transaction between the Registrant and Deutsche Bank AG, London Branch, incorporated by reference to Exhibit 10.4 to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2011.
10.48	Credit Agreement dated as of September 26, 2013, by and among the Registrant, the lenders party thereto from time to time, Wells Fargo Bank, National Association, as the Administrative Agent, and a subsidiary of the Registrant, as guarantor, incorporated by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K filed September 27, 2013.
10.49**	Amendment to Amended and Restated Executive Employment Agreement between the Registrant and Martine Rothblatt, Ph.D., dated as of January 1, 2015, incorporated by reference to Exhibit 10.1 to Registrant's Current Report on Form 8-K filed December 17, 2014.
10.50**	Employment Agreement, dated as of June 26, 2006, between the Company and David Zaccardelli, Pharm.D., together with three amendments thereto, dated January 26, 2007, September 23, 2009 and February 24, 2010, respectively, incorporated by reference to Exhibit 10.2 to Registrant's Current Report on Form 8-K filed December 17, 2014.

Exhibit No.	Description
10.51**	Change in Control Severance Agreement between the Company and David Zaccardelli, Pharm.D., dated as of February 14, 2012, incorporated by reference to Exhibit 10.3 to Registrant's Current Report on Form 8-K filed December 17, 2014.
10.52	Amendment No. 1 to Credit Agreement, dated as of July 24, 2014, by and among the Registrant, the lenders party thereto from time to time, Wells Fargo Bank, National Association, as the Administrative Agent, and a subsidiary of the Registrant, as guarantor, incorporated by reference to Exhibit 10.1 to Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2014.
10.53**	United Therapeutics Corporation Section 162(m) Bonus Plan, incorporated by reference to Exhibit 10.1 of the Registrant's Current Report on Form 8-K filed June 27, 2014.
10.54†	Third Amendment to Distribution Agreement relating to Tyvaso, dated October 20, 2014, by and among the Registrant, Accredo Health Group, Inc., CuraScript, Inc., and Priority Healthcare Distribution, Inc.
10.55**	Employment Agreement, dated as of March 13, 2015, between the Company and James Edgemond.
10.56**	Change in Control Severance Agreement between the Company and James Edgemond, dated as of November 12, 2014.
21	Subsidiaries of the Registrant.
23.1	Consent of Ernst & Young LLP, Independent Registered Public Accounting Firm
31.1	Certification of Principal Executive Officer pursuant to Rule 13a-14(a) of the Securities Exchange Act of 1934.
31.2	Certification of Principal Financial Officer pursuant to Rule 13a-14(a) of the Securities Exchange Act of 1934.
32.1	Certification of Principal Executive Officer pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
32.2	Certification of Principal Financial Officer pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
101	The following financial information from our Annual Report on Form 10-K for the year ended December 31, 2014, filed with the SEC on February 24, 2015, formatted in Extensible Business Reporting Language (XBRL): (i) Consolidated Balance Sheets as of December 31, 2014 and 2013, (ii) Consolidated Statements of Operations for each of three years in the period ended December 31, 2014, (iii) Consolidated Statements of Comprehensive Income for each of the three years in the period ended December 31, 2014, (iv) Consolidated Statements of Stockholders' Equity for each of the three years in the period ended December 31, 2014, (v) Consolidated Statements of Cash Flows for each of the three years in the period ended December 31, 2014, and (vi) Notes to Consolidated Financial Statements.

* Confidential treatment has been granted with respect to certain portions of this exhibit pursuant to Rule 406 of the Securities Act of 1933, as amended or Rule 246-2 of the Securities Act of 1934, as amended. The omitted portions of this document have been filed with the Securities and Exchange Commission.

** Designates management contracts and compensation plans.

† Confidential treatment has been requested with respect to certain portions of this exhibit pursuant to Rule 406 of the Securities Act of 1933, as amended, or Rule 246-2 of the Securities Act of 1934, as amended. The omitted portions of this document have been filed with the Securities and Exchange Commission.

CONFIDENTIAL

Pursuant to 17 C.F.R §240.24b-2, confidential information (indicated as [***]) has been omitted and has been filed separately with the Securities and Exchange Commission pursuant to a Confidential Treatment Application filed with the Commission.

Third Amendment to Distribution Agreement
(*TYVASO* ®)

THIS THIRD AMENDMENT TO DISTRIBUTION AGREEMENT (this " **Third Amendment** ") is made and effective this 20 th Day of October, 2014 (the " **Third Amendment Effective Date** ") by and among, **United Therapeutics Corporation** , a Delaware corporation having offices at 1040 Spring Street, Silver Spring, Maryland (" **UT** "), **Accredo Health Group, Inc.** , a Delaware corporation having offices at 6272 Lee Vista Boulevard, Orlando FL, 32822 (" **Accredo** "), **CuraScript, Inc.** , a Delaware corporation having offices at 6272 Lee Vista Boulevard, Orlando FL, 32822 (" **SP** ") and **Priority Healthcare Distribution, Inc** ., doing business as CuraScript SD Specialty Distribution, a Florida corporation with offices at 255 Technology Park, Lake Mary, Florida, 32746 (" **SD** "). SP, SD and Accredo are collectively referred to herein as the " **Distributor** ".

WHEREAS , UT and Accredo entered into a Distribution Agreement on August 17, 2009 (as amended from time to time, the " **Agreement** ") relating to the distribution of Tyvaso ® (treprostinil) Inhalation Solution; and

WHEREAS , the parties desire to amend the Agreement as provided herein, in order to make the Institutional Starter Kit and Supplemental Refill Kit referenced in Attachment A available for purchase by Distributor.

NOW, THEREFORE , in consideration of the mutual agreements and covenants contained herein, and for other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, the parties hereto, intending to be legally bound, agree as follows:

1. **AMENDMENT.** The Agreement is hereby amended by deleting Attachment A in its entirety, and replacing it with Attachment A to this Amendment.

2. **COUNTERPARTS** . This Amendment may be executed in any number of counterparts and via facsimile, email or other electronic form of transmission, and each of such counterparts shall for all purposes be deemed original, and all such counterparts shall together constitute one and the same instrument.

3. **EFFECT OF AMENDMENT.** Except as specifically amended hereby or by any previous amendments duly executed in accordance with the Agreement, all other terms and conditions of the Agreement remain in full force and effect. To the extent that any of the terms in the underlying agreement are inconsistent with the terms of this Amendment, the terms of this Amendment shall control.

[Signature page follows]

IN WITNESS WHEREOF, the parties hereto have caused this Third Amendment to be executed by their duly authorized representatives.

UNITED THERAPEUTICS CORPORATION

/s/ Jay A. Watson

Name: Jay A. Watson, Pharm.D.

Title: Executive Vice President, Strategic Operations and Logistics

Date: 20/Nov/2014

ACCREDO HEALTH GROUP, INC.

/s/ David A. Norton

Name: David A. Norton

Title: Senior Vice President

Date: December 10, 2014

CURASCRIPT, INC.

/s/ David A. Norton

Name: David A. Norton

Title: Senior Vice President

Date: December 10, 2014

PRIORITY HEALTHCARE DISTRIBUTION, INC.

/s/ Gayle C. Johnston

Name: Gayle C. Johnston

Title: President

Date: 12-4-14

Attachment A

Product Name	NDC Code	Price
Tyvaso Patient Starter Kit (PSK)	66302-206-01	$ [***]
Tyvaso Patient Resupply Kit (RSK)	66302-206-02	$ [***]
Tyvaso Supplemental Refill 4 ct	66302-206-03	$ [***]
Tyvaso Institutional Starter Kit (ISK)	66302-206-04	$ [***]

NDC 66302-206-01 Tyvaso Starter Kit includes:

- 28 ampoules of Tyvaso
- 2 Sets of Autoclavable Parts
- 2 Tyvaso Inhalation Devices
- 2 AC Power Adapters
- 1 Rechargeable Battery Pack
- 1 Car Power Cord
- 1 Leather Carrying Case
- 32 Medicine Cups
- 64 Filter Membranes
- 1 Nose Clip
- 1 Measuring Cup
- 1 Safety Box
- 2 Sets of Safety Plugs

NDC 66303-206-02 Tyvaso Re-Supply Kit includes

- 28 ampoules of Tyvaso
- 1 Set of Autoclavable Parts
- 32 Medicine Cups
- 64 Filter Membranes

NDC 66302-206-03 Tyvaso Supplemental Refill includes

- 4 ampoules of Tyvaso

NDC 66302-206-04 Tyvaso Institutional Starter Kit (ISK)

- 4 ampoules of Tyvaso
- 2 Sets of Autoclavable Parts
- 2 Tyvaso Inhalation Devices
- 2 AC Power Adapters
- 1 Rechargeable Battery Pack
- 1 Car Power Cord
- 1 Leather Carrying Case
- 32 Medicine Cups
- 64 Filter Membranes
- 1 Nose Clip
- 1 Measuring Cup
- 1 Safety Box
- 2 Sets of Safety Plugs

UT shall notify the DISTRIBUTOR in writing of any change (and the amount of the change) in the Price of any respective UT Product during the term of this Agreement in the same time and manner as it notifies other similarly situated distributors.

UT shall provide DISTRIBUTOR with a current list of Tyvaso prices to Discounted Entities, including FSS prices, Federal Ceiling Prices, and prices to section 340B entities, and shall promptly notify Distributor of any and all changes in such prices as well as the effective dates of such changes.

Exhibit 10.55

EMPLOYMENT AGREEMENT

THIS EMPLOYMENT AGREEMENT (this "Agreement") is entered into as of March 13, 2015 (the "Effective Date") by and between United Therapeutics Corporation (the "Company") and James Edgemond (the "Executive").

WHEREAS, the Company has employed Executive since January 14, 2013 ("Initial Start Date") and desires to continue to employ Executive as Chief Financial Officer and Treasurer, subject to the terms and conditions herein set forth; and

WHEREAS, the parties desire this Agreement to supersede and replace on a going-forward basis all previous or existing agreements between the Company and Executive relating to the subject matter covered by this Agreement;

NOW, THEREFORE, in consideration of the promises and mutual covenants contained herein, and for other good and valuable consideration, the receipt and sufficiency of which is hereby acknowledged, the parties hereto agree as follows.

1. Employment. Upon the other terms and conditions hereinafter stated, the Company agrees to employ the Executive and the Executive agrees to accept employment by the Company for the term set forth in Section 2 hereof and in the position and with the duties and responsibilities set forth in Section 3 hereof. Executive warrants that he is under no restriction that would prevent him from entering into this Agreement and from complying with all of its provisions to their fullest extent.

2. Term. The term of the Executive's employment under this Agreement will commence on the Effective Date, and end on the third anniversary of the Effective Date (the "Initial Term"), and thereafter shall continue from year to year for additional one-year terms (the "Additional Terms"), unless and until either party shall give notice of such party's intent to terminate not less than 60 days prior to the end of the then-current Initial Term or Additional Term, which termination shall be effective at the expiration of said term, or until sooner terminated as hereinafter set forth.

3. Position and Duties.

(a) Executive shall serve as Chief Financial Officer and Treasurer, with such duties and responsibilities (i) as are normally performed by such an executive of a biotechnology company and (ii) as may be assigned to Executive from time to time by the Company's Chairman and Co-CEO. The Executive shall report to the Company's Chairman and Co-CEO. The Executive shall at all times exert his best efforts and loyalty on behalf of the Company and shall devote full time and attention to such employment.

(b) Executive shall perform his duties from the Company's Silver Spring, Maryland offices, although Executive will travel as necessary or desirable to fulfill his duties and responsibilities to the Company.

(c) The Executive agrees to abide by all employment guidelines and policies as may be developed from time to time by the Company and applicable to all employees of the Company, including, without limitation, the United Therapeutics Corporation Company Manual, the United Therapeutics Corporation Securities Trades by Company Personnel Policy and the United Therapeutics Corporation Media & Analyst Communication Policy.

4. Compensation and Related Matters. The Company shall provide the following compensation and benefits to the Executive:

(a) The Company shall pay to the Executive an annual base salary of $400,000 (the "Base Salary") such annual base salary to be subject to review and increase annually by the Company at the Company's discretion. The Base Salary shall be payable semi-monthly or in such other installments as shall be consistent with the Company's payroll procedures. The Company shall deduct and withhold all necessary social security and withholding taxes and any other similar sums required by law or authorized by the Executive with respect to payment of the Base Salary and all other amounts and benefits payable under this Agreement.

(b) Executive is eligible to participate in the standard health, dental, vision care, short and long-term disability, life insurance and 401(k) benefits provided to the Company's employees. Detailed benefits information including employee costs will be included in annual enrollment information as provided to Company employees . Additionally, in Executive has received a copy of the Employee Handbook that explains many of United Therapeutics' policies and procedures, which Handbook is updated from time to time and is available on the Company's intranet.

5. Expenses. The Executive shall be reimbursed by the Company for reasonable travel and other expenses that are incurred and accounted for in accordance with the Company's normal practices.

6. Vacation. For Executive's first year of employment (beginning with the Original Start Date) he will be entitled to 19 days paid time off, earned on a pro-rated basis depending on Executive's date of hire. Additional paid time off will be accrued after each completed year of service based on the Executive's hire date in accordance with the Employee Handbook.

7. Termination of Employment.

(a) The Executive's employment hereunder shall terminate upon the Executive's death.

(b) The Company may terminate the Executive's employment hereunder as set forth in Section 2 above, and under the following circumstances:

(i) If, as a result of the Executive's incapacity or other disability owing to physical or mental illness, the Executive shall have been unable to perform all of the

Executive's material duties hereunder by reason of illness, or physical or mental disability or other similar capacity, which inability shall continue for more than two (2) consecutive months, the Company may terminate the Executive's employment hereunder.

(ii) The Company may terminate the Executive's employment hereunder for "Cause." For purposes of this Agreement, the Company shall have "Cause" to terminate the Executive's employment hereunder upon the (A) failure of the Executive (other than for reasons described in Sections 7(a) and 7(b)(i) hereof) to perform or observe any of the material terms or provisions of this Agreement; (B) negligent or unsatisfactory performance of the Executive's duties under this Agreement and the failure of the Executive, within 10 days after receipt of notice from the Company setting forth in reasonable detail the nature of the Executive's negligent or unsatisfactory performance, (i) to provide the Company with a reasonably satisfactory explanation of the Executive's actions (or inaction) and (ii) to correct to the satisfaction of the Company any reasonably identified deficiencies; (C) employment- or profession-related misconduct or other employment- or profession-related similar action on the part of the Executive; (D) conviction of the Executive of a crime involving a felony, fraud, embezzlement or the like; or (E) misappropriation of the Company funds or misuse of the Company's assets by Executive, or other act of dishonesty by Executive.

(c) Any termination of the Executive's employment by the Company or by the Executive (other than pursuant to Section 7(a) hereof) shall be communicated by written "Notice of Termination" to the other party hereto in accordance with Section 11 (c) hereof, which shall indicate the specific termination provision in this Agreement relied upon, if any, and shall set forth in reasonable detail the facts and circumstances claimed to provide a basis for termination of the Executive's employment under the provision so indicated.

(d) For purposes of this Agreement, the "Date of Termination" shall mean (i) if the Executive's employment is terminated by the Executive's death, the date of the Executive's death; (ii) if the Executive's employment is terminated pursuant to Section 7(b) (i) hereof, thirty (30) days after the Notice of Termination; provided , however , that the Executive shall not have returned to the performance of the Executive's duties on a full-time basis during such thirty (30) day period; (iii) if the Executive's employment is terminated pursuant to Section 7(b)(ii) hereof, the date specified in the Notice of Termination (which date, in the case of termination of Executive's employment solely pursuant to clause (B) of Section 7(b)(ii) by reason of inadequate performance, shall not be sooner than thirty (30) days from the date of the Notice of Termination); and (iv) if the Executive's employment is terminated for any other reason, the date on which the Notice of Termination is given.

(e) Following termination of this Agreement, Executive shall promptly make himself reasonably available to assist the Company with any information or other requests.

8. Compensation Upon Termination .

(a) If the Executive's employment is terminated by the Executive's death, the Company shall pay to the Executive's estate or as may be directed by the legal

representatives of such estate, the Executive's full Base Salary through the Date of Termination at the rate in effect at the time of the Executive's death.

(b) During any period that the Executive fails to perform the Executive's duties hereunder solely as a result of incapacity due to physical or mental illness ("disability period"), the Executive shall continue to receive the Executive's full base salary through the Date of Termination at the rate in effect at the time the Notice of Termination is given and all other unpaid amounts, if any, to which the Executive is entitled as of the Date of Termination in connection with any fringe benefits or under any incentive compensation plan or program of the Company hereof, at the time such payments are due; provided that payments so made to the Executive during the disability period shall be reduced by the sum of the amounts, if any, payable to the Executive at or prior to the time of any such payment under disability benefit plans of the Company and which amounts were not previously applied to reduce any such payment.

(c) If the Executive shall terminate the Executive's employment or the Company terminates the Executive's employment for Cause as provided in Section 7(b)(ii) hereof, the Company shall pay the Executive the Executive's full Base Salary through the Date of Termination at the rate in effect at the time the Notice of Termination is given, and the Company shall have no further obligations to the Executive under this Agreement.

(d) Subject to Section 8(e) below, if the Company terminates Executive's employment without Cause, the Company shall pay to Executive a lump-sum amount equal to Executive's Base Salary for the time remaining in the then-current Initial Term or Additional Term, payable in a manner consistent with the Company's payroll procedures. Such payments are subject to Executive executing (and not revoking) a release of claims acceptable to the Company within twenty-one (21) days following the Date of Termination (and not revoking such release).

(e) Company and Executive are parties to that certain Change in Control Severance Agreement, dated as of November 12, 2014 (the "CiC Agreement"). Capitalized terms used but not defined in this Section 8(e) shall have the meanings ascribed to such terms in the CiC Agreement. If Executive's employment with the Company and its Affiliates (i) is involuntarily terminated by the Company and its Affiliates within one year following a Change in Control other than due to Cause (as defined in the CiC Agreement), Total Disability or death, or (ii) is Terminated by Executive for Good Reason within one year following a Change in Control, subject to Executive executing a release of claims acceptable to the Company within twenty-one (21) days following the Date of Termination (and not revoking such release), Executive shall be entitled to the following (in addition to any benefits to which Executive is entitled under the CiC Agreement):

(i) (A) all unvested share tracking awards; (B) all unvested options to purchase shares of the Company's Common Stock; and (C) all other awards subject to vesting, in each case granted by the Company to Executive prior to Executive's Date of Termination, shall immediately vest in Executive as of the date of such termination, and the exercise period for each such previously-granted share tracking award, option or other award,

including those awards previously vested but unexercised, shall be the full remaining duration of the term of each such share tracking award, option or other award.

(f) Compensation to Executive upon termination described in this Section 8 shall be and is hereby made expressly contingent upon Executive's ongoing compliance with non-competition, confidentiality, non-solicitation, continuing cooperation and all other obligations of Executive that survive termination of this Agreement.

9. Intellectual Property Rights. As used in this Agreement, "Intellectual Property" means the following and any and all rights, title, and interest, including but not limited to domestic and foreign patents, copyrights, trademarks, trade-secret rights and Confidential Information (as defined below) in or relating to any of the following: all inventions, processes, computer programs, formulae, original works of authorship and other subject matter that Employee makes, conceives, reduces to practice or develops, in whole or in part, solely or jointly with others, either (i) during the Term or (ii) after termination of Employee's employment with the Company if based upon or derived from the Company's Confidential Information. Because of the highly specialized and technical nature of the business of the Company and the nature and scope of Executive's employment, Executive agrees that as between Executive and Company any and all rights, title, and interest in all of the Intellectual Property are and shall be the sole and exclusive property of the Company, and its respective successors, licensees, and assigns. In full consideration of the compensation provided to Executive by the Company, Executive agrees to each and all of the following:

(a) Assignment. Executive hereby irrevocably assigns, conveys and otherwise transfers to the Company or its designee, all Executive's rights, title and interests in and to the Intellectual Property, worldwide, including, without limitation, all copyrights, trademarks, patents, design patents, trade-secret and other proprietary rights therein, and all claims and causes of action with respect to any of the foregoing, whether now known or hereafter to become known. In the event that Executive has any right in the Intellectual Property that cannot be assigned, Executive hereby waives and agrees to waive enforcement worldwide of such right against the Company, its distributors, licensees and other designees and hereby licenses and agrees to license such right exclusively, worldwide to the Company with the right to grant and authorize sublicenses. These rights are assignable by the Company.

(b) Work Made for Hire. Executive acknowledges and agrees that all original works of authorship within the Intellectual Property are "works made for hire" within the meaning of United States copyright law which, as between Executive and Company, are and will be owned solely and exclusively by the Company. If the work is determined not to be a "work for hire" or such doctrine is not effective, Executive hereby irrevocably assigns, conveys and otherwise transfers to the Company, and its respective successors, licensees, and assigns, all right, title and interest worldwide in and to the work and all proprietary rights therein, including, without limitation, all copyrights, trademarks, patents, design patents, and trade-secret rights, and all claims and causes of action with

respect to any of the foregoing, whether now known or hereafter to become known, under Section 9(a) above.

(c) Original Work. Executive agrees that Executive will not include any copyrighted or patented material owned by a third party in any written, copyrightable or patentable material furnished or delivered by Executive under this Agreement without the unconditional written consent of the copyright or patent owner unless specific written approval of the Company for inclusions of such copyrighted or patented material is secured in advance. Executive also agrees that all work (or tangible expression of an idea) that Executive creates or contributes to the Company in the course of Executive's employment hereunder will be created solely by Executive, will be original to Executive, and will be free of any third party claims or interests.

(d) Applications for Patent, Copyrights and Trademarks. Executive shall, if the Company so decides at its sole discretion and expense, apply for United States and foreign letters patent, copyrights, and/or trademarks, either in Executive's name or as the Company in its sole discretion may direct. Executive hereby grants the Company the exclusive right, and appoints the Company as Executive's attorney-in-fact, to execute and prosecute an application for domestic and/or foreign patent or other statutory protection, and Executive shall execute and deliver to the Company, without charge to the Company but at the Company's expense, such other documents of registration and recordation, and do such other acts, such as give testimony in support of Executive's inventorship, as may be necessary in the opinion of the Company to vest in the Company or any other party nominated by the Company, or otherwise to protect, the exclusive rights conveyed and/or granted to the Company pursuant to this Agreement. Executive's duty to support the Company's claim of rights in patents, copyrights, or trademarks claimed by the Company, and resulting from Executive's service to the Company as its employee, shall continue for the life of any such patent, copyright or trademark.

(e) Use. The Company and its respective successors, licensees, and assigns, shall have the sole and exclusive right to practice, or to make, use or sell products, processes or services derived from any discoveries or creations within the scope of this Agreement, whether or not patentable or copyrightable under the laws of any jurisdiction, or protected by the trade secret laws of any jurisdiction.

(f) Trade Secret Protection. In the event that the Company decides not to pursue patent, copyright or trademark protection for any discovery or creation made by Executive, and instead decides to protect the discovery or creation pursuant to the trade secret laws of any jurisdiction, such decision shall not be construed as a waiver of the Company's rights pursuant to this Agreement. At the Company's expense, Executive shall also take whatever steps are necessary to sustain the Company's claim to such trade secrets, including but not limited to: (i) maintaining the confidential nature of any such discoveries or creations; and (ii) testifying and providing other support and substantiation for the Company's claims with regard to the discovery or creation.

(g) Reports. With respect to discoveries made by Executive, Executive shall maintain notebooks and other records adequate to describe such discovery to others conversant in the subject of the technology and to establish the date and circumstances of Executive's discovery. Executive shall notify the Company's Chairman and Co-Chief Executive Officer of any such discoveries and shall make copies of all documents or reports relating to such discoveries available to the Company. Any discovery shall be reported to the Company's Chairman and Co-Chief Executive Officer regardless of whether, in Executive's opinion, a given discovery is of value to the Company, or is protectable under patent, copyright or the laws of any jurisdiction.

(h) Infringement Actions. In the event that the Company shall bring an infringement suit against any third parties or shall be sued by any third parties as a result of Executive's authorship or creation, including any addition and/or modification of the aforementioned items of Confidential Information, Executive agrees to cooperate reasonably without charge to the Company, but at its request and expense, in defending against or prosecuting any such suit. This right shall be cumulative to any other rights of the Company hereunder.

(i) Covenant of Further Assurances. Upon the request of the Company, Executive shall execute and deliver such documents and take such actions as may be reasonably requested in order to carry out the intent and purposes of this Agreement, including but not limited to executing all documents necessary or desirable to protect the Company's rights in and title to any work (or tangible expression of an idea) that Executive creates or contributes to the Company in the course of Executive's employment hereunder.

10. Obligation of Confidentiality and Non-Competition.

(a) Executive agrees that Executive has a fiduciary duty to the Company and that Executive shall hold in confidence and shall not, except in the course of performing Executive's employment obligations or pursuant to written authorization from the Company, at any time during or for three years after termination of Executive's relationship with the Company knowingly (a) directly or indirectly reveal, report, publish, disclose or transfer the Confidential Information or any part thereof to any person or entity; (b) use any of the Confidential Information or any part thereof for any purpose other than for the benefit of the Company; (c) assist any person or entity other than the Company to secure any benefit from the Confidential Information or any part thereof or (d) solicit (on Executive's behalf or on behalf of any third party) any employee of the Company for the purpose of providing services or products which Executive is prohibited from providing hereunder.

(b) Executive agrees that all Confidential Information, as defined below, shall belong exclusively and without any additional compensation to the Company. For the purposes of this Agreement, "Confidential Information" shall mean each of the following: (a) any information or material proprietary to the Company or designated as confidential either orally or in writing by the Company; and (b) any information not generally known by non- Company personnel; and (c) any information which Executive should know the Company would not care to have revealed to others or used in competition with the Company; and (d) any information which Executive made or makes, conceived or conceives,

developed or develops or obtained or obtains knowledge or access through or as a result of Executive's relationship with the Company (including information received, originated, discovered or developed in whole or in part by Executive) from the initial date of Executive's employment with the Company.

(c) Executive agrees not to accept employment from, nor render services in any capacity for, nor have any other business relationships with, nor engage in any business activity in which it would be useful or helpful to Executive or others with whom he is associated for Executive to use or disclose Confidential Information of the Company, with a "Competing Organization", meaning any person or organization which is engaged in, or about to become engaged in, research on, or development, production, marketing, leasing, selling, licensing or servicing of, a Competing Product. Competing Organizations may include, but are not necessarily limited to, Gilead Sciences, Inc., GlaxoSmithKline PLC, Teva Pharmaceuticals USA, Inc., Sandoz Inc., Bayer AG, Actelion Ltd and Pfizer, Inc. and any other company that develops or markets any subsequently approved therapy for the treatment of pulmonary arterial hypertension, for a period of one (1) year following Executive's last receipt of compensation from the Company, whether the termination of Executive's employment by either party was with or without Cause. As used in this Agreement, a "Competing Product" means any product, system or service, in existence or under development, of any person or organization other than United Therapeutics which is the same as or similar to, and competes with, a product, process, system or service upon which Executive worked (in either a sales or a non-sales capacity) during the last three years of his or her employment by United Therapeutics or about which Executive acquired Confidential Information in the course of his or her employment with United Therapeutics. Competing Products may include, but are not necessarily limited to, Flolan, Veletri, Ventavis, Tracleer, Revatio, Opsumit, Adempas and Letairis, and other subsequently approved therapies for the treatment of pulmonary arterial hypertension. The parties acknowledge that the Company's business after the date of this Agreement may evolve into other or additional areas and activities. Executive and the Company agree that the terms of this Section 10(c) relating to non-competition are reasonable in scope and length and are necessary for the protection of the Company. In the event that a court finds the scope of this provision to be unreasonably broad or if the length of time of this provision is found to be unreasonably long, an arbitrator or court, as applicable, shall narrow the scope or shorten the length of time to the extent required to render the provision reasonable and enforceable and shall enforce the provision as so narrowed.

(d) While employed by the Company and for a period of one (1) year following Executive's last receipt of compensation from the Company, whether the termination of Executive's employment by either party was with or without Cause, the Executive will not (i) hire, induce, attempt to hire, assist in hiring, or cause to be hired, directly or indirectly, by another person or organization, any person who was an employee of the Company, and (ii) identify, or furnish any information about, any other employee of the Company to any other person or organization for the purpose of assisting or facilitating the hiring efforts of such other person or organization.

11. Miscellaneous.

(a) Entire Agreement. This Agreement contains the entire agreement between the parties hereto relating to the subject matter hereof, and this Agreement supersedes all prior understandings and agreements, whether oral or written, relating to the employment of the Executive by the Company.

(b) Assignment. This Agreement shall not be assignable or otherwise transferable by either party hereto, but any amounts owing to Executive upon the Executive's death shall inure to the benefit of the Executive's heirs, legatees, legal representatives, executor or administrator. Notwithstanding the foregoing, this Agreement applies with the prior written consent of the Executive, which consent shall not be unreasonably withheld. This Agreement shall be binding upon and shall inure to the benefit of the parties hereto and any such respective heirs, legatees, executors, administrators, representatives, successors and assigns.

(c) Notices. All notices, demands, requests or other communications which may be, or are required to be given, served or sent by any party to any party pursuant to this Agreement shall be in writing and shall be mailed by first class, registered or certified mail, return receipt requested, postage prepaid, or transmitted by hand delivery, telegram or telex and addressed as follows:

If to the Executive: James Edgemond
[Address on file with Human Resources Dept.]

If to the Company: United Therapeutics Corporation
1040 Spring Street
Silver Spring, Maryland 20910
Attn: General Counsel

(d) Amendment; Waiver. This Agreement shall not be amended, altered, modified or discharged except by an instrument in writing duly executed by the Executive and the Company. Neither the waiver by the parties hereto of a breach of, or default under, any of the provisions of this Agreement, nor the failure of either of the parties, on one or more occasions, to enforce any of the provisions of this Agreement or to exercise any right or privilege hereunder, shall thereafter be construed as a waiver of any such provisions, rights or privileges hereunder.

(e) Severability. The invalidity or unenforceabilty of any provision or provisions of this Agreement shall not affect the validity or enforceability of any other provisions of this Agreement, which shall remain in full force and effect.

(f) Applicable Law. This Agreement and the rights and obligations of the parties under this Agreement shall be construed, interpreted and enforced in accordance with the laws of the State of Maryland, exclusive of the choice-of-laws rules thereunder. The parties hereby irrevocably consent and submit to the exclusive jurisdiction of the courts located in the State of Maryland in connection with any suit, action or other proceeding concerning the interpretation or enforcement of this Agreement. Each party waives and

agrees not to assert any defense that such courts lack jurisdiction, venue is improper, inconvenient forum or otherwise.

(g) Survival. It is the express intention and agreement of the parties hereto that the provisions of Sections 7(e), 8, 9, 10 and 11 hereof shall survive the termination of employment of the Executive. In addition, all obligations of the Company to make payments hereunder shall survive any termination of this Agreement on the terms and conditions set forth.

(h) Execution. To facilitate execution, this Agreement may be executed in as many counterparts as may be required; and it shall not be necessary that the signatures of, or on behalf of, each party, or that the signatures of all persons required to bind any party, appear on each counterpart; but it shall be sufficient that the signature of, or on behalf of, each party, or that the signatures of the persons required to bind any party, appear on one or more of the counterparts. All counterparts shall collectively constitute a single agreement. It shall not be necessary in making proof of this Agreement to produce or account for more than a number of counterparts containing the respective signatures of, or on behalf of, all of the parties hereto.

IN WITNESS WHEREOF, the undersigned have duly executed this Agreement, or have caused this Agreement to be duly executed on their behalf, as of the date first above written.

UNITED THERAPEUTICS CORPORATION

/s/ James Edgemond	/s/ Martine Rothblatt
James Edgemond	By: Martine Rothblatt, PhD

SSN: [on file with HR]

Exhibit 10.56

CHANGE IN CONTROL SEVERANCE AGREEMENT

This Change in Control Severance Agreement (the "Agreement") is made and entered into by and between James Edgemond (the "Employee") and United Therapeutics Corporation, a Delaware corporation (the "Company"), effective as of November 12, 2014 (the "Effective Date").

RECITALS

A. Employee is a key member of the executive and management team of the Company or an Affiliate.

B. The Company's Board of Directors has approved a Change in Control Severance Program, consisting of the Change in Control Severance Plan and agreements such as this Agreement with certain individual employees, in order to provide severance protection to Employee in the event Employee's employment terminates in specified circumstances within one year following a Change in Control in order to (i) motivate Employee to drive business success independent of the possible occurrence of a Change in Control and (ii) reduce distractions associated with a potential Change in Control, and maximize shareholder value by retaining Employee through the closing of a Change in Control.

In consideration of the mutual covenants herein contained, and in consideration of the continuing employment of Employee by the Company, and for other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, the parties agree as follows.

Section 1. Severance Benefits. If Employee's employment with the Company and its Affiliates (i) is involuntarily Terminated by the Company and its Affiliates within one year following a Change in Control other than due to Cause, Total Disability or death, or (ii) is Terminated by Employee for Good Reason within one year following a Change in Control, subject to Employee executing a release of claims substantially in the form attached as Exhibit A within forty-five (45) days following such Termination (and not revoking such release), Employee shall be entitled to the following:

(a) Cash Severance Pay. Employee shall receive a lump sum cash payment equal to two (2) times the sum of (A) the Base Salary and (B) the Bonus Amount

(b) Medical Continuation. Employee and Employee's spouse and dependents (each as defined under the applicable plan) shall receive Company-paid medical and dental insurance coverages for twenty-four (24) months at the same benefit level as provided to Employee immediately prior to the Change in Control (which such period shall be treated as "alternative coverage" for purposes of COBRA).

(c) Outplacement Benefits. Employee shall be entitled to receive outplacement benefits with a value of $10,000, to be used over the six months following Employee's Termination (which such benefits shall be administered in compliance with Treasury Regulation section 1.409A-1(b)(9)(v)).

(d) Accrued Benefits. Employee shall receive any unpaid Base Salary through the date of Termination and any bonus unpaid as of the date of Employee's Termination for any previously completed fiscal year of the Company. In addition, Employee shall be entitled to prompt reimbursement of any unreimbursed expenses properly incurred by Employee in accordance with Company policies prior to the date of Employee's Termination. Employee shall also receive such other compensation (including any stock options or other equity-related payments (including, without limitation, any share tracking awards)) and benefits, if any, to which Employee may be entitled from time to time pursuant to the terms and conditions of Employee compensation, incentive, equity, benefit or fringe benefit plans, policies or programs of the Company, other than any Company severance policy.

Section 2. Form and Time of Payment; Payment in Lieu of Other Severance Benefits. The cash severance pay benefits payable to Employee under Section 1(a) shall be paid to Employee in a single lump sum less applicable withholdings within the later of (i) 15 business days after Employee's date of Termination or (ii) the expiration of the revocation period, if applicable, under the Release, but in all events no later than March 15 of the year following the year in which Employee's Termination of Employment occurs. The cash severance benefits provided pursuant to Section 1(a) hereof are in lieu of any cash severance benefits (but, not for the avoidance of doubt, in lieu of any equity-related payments (including, without limitation, share tracking awards) or payments under any tax-qualified or nonqualified retirement plan) that may be payable to Employee pursuant to any agreement between Employee and the Company or any other plan, program or arrangement of the Company and its Affiliates (unless the cash severance benefits under such agreement, plan, program or arrangement are more favorable in the aggregate to Employee, in which case such benefits shall be provided in lieu of the benefits hereunder). Notwithstanding the foregoing, to the extent the cash severance benefits under Section 1(a) would constitute an impermissible substitution within the meaning of Treasury Regulation section 1.409A-3(f) and payment of such benefits in the manner described herein would result in a violation of Section 409A of the Code, such benefits shall be paid on the same schedule as the benefits for which they are deemed to substitute.

Section 3. Definitions. Unless the context clearly indicates otherwise, when used in this Agreement:

(a) "Affiliate" means, with respect to any entity, any other corporation, organization, association, partnership, sole proprietorship or other type of entity, whether incorporated or unincorporated, directly or indirectly controlling or controlled by or under direct or indirect common control with such entity.

(b) "Base Salary" means Employee's annual rate of base salary in effect on the date of Employee's Termination of Employment (or, if higher, on the date of the Change in Control), determined in each case prior to reduction for any employee-elected salary reduction contributions made to a Company-sponsored non-qualified deferred compensation plan or a Company-sponsored plan pursuant to Section 401(k) or 125 of the Code, and excluding bonuses, overtime, allowances, commissions, deferred compensation payments and any other extraordinary remuneration.

(c) " Board " means the board of directors of the Company.

(d) " Bonus Amount " means the highest of (i) the cash bonus payable to Employee for the year immediately preceding the year in which the Change in Control occurs, (ii) the cash bonus payable to Employee for the year immediately preceding the year in which Employee's employment Terminates, or (iii) Employee's Target Bonus.

(e) " Cause " means (i) any act of personal dishonesty taken by Employee in connection with his or her responsibilities as an employee and intended to result in substantial personal enrichment of Employee; (ii) Employee's conviction of a felony; (iii) an act by Employee which constitutes willful or gross misconduct and which is demonstrably and materially injurious to the Company; or (iv) continued substantial willful violations by Employee of Employee's employment duties after there has been delivered to Employee a written demand for performance from the Company which specifically sets forth the factual basis for the Company's belief that Employee has not substantially performed his or her duties.

(f) " Change in Control " means, and shall be deemed to have occurred:

(i) if any person or group (as used in Section 13(d) of the Exchange Act) (other than the Company, any trustee or other fiduciary holding securities under an employee benefit plan of the Company, or any company owned, directly or indirectly, by the stockholders of the Company in substantially the same proportions as their ownership of stock of the Company) becomes the "beneficial owner" (as defined in Rule 13d-3 under the Exchange Act) of securities of the Company representing more than 30% of (a) the shares of the Company's common stock then outstanding or (b) the combined voting power (other than in the election of directors) of all voting securities of the Company then outstanding;

(ii) if, during any period of 24 consecutive months, individuals who at the beginning of such period constituted the Board, and any director whose election or nomination for election by the Company's stockholders was approved by a vote of at least two-thirds (2/3) of the directors then still in office who either were directors at the beginning of the period or whose election or nomination for election was previously so approved (the "Incumbent Board"), cease for any reason (other than death or disability) to constitute at least a majority thereof;

(iii) upon the consummation of a reorganization, merger, statutory share exchange or consolidation or similar transaction involving the Company or any of its subsidiaries unless, following such event, (A) all or substantially all of the individuals and entities that were the beneficial owners of the Company's common stock or the combined voting power of all voting securities of the Company immediately prior to such transaction beneficially own, directly or

indirectly, more than 50% of the then-outstanding shares of common stock (or, for a non-corporate entity, equivalent securities) and the combined voting power of the then-outstanding voting securities entitled to vote generally in the election of directors (or, for a non-corporate entity, equivalent governing body), as the case may be, of the entity resulting from such transaction (including, without limitation, an entity that, as a result of such transaction, owns the Company either directly or through one or more subsidiaries) in substantially the same proportions as their ownership immediately prior to such transaction of the Company's common stock or voting securities, as the case may be, (B) no person (excluding any corporation resulting from such transaction or any employee benefit plan (or related trust) of the Company or such corporation resulting from such transaction) beneficially owns, directly or indirectly, 30% or more of, respectively, the then-outstanding shares of common stock of the corporation resulting from such transaction or the combined voting power of the then-outstanding voting securities of such corporation, except to the extent that such ownership existed prior to the transaction, and (C) at least a majority of the members of the board of directors (or, for a non-corporate entity, equivalent governing body) of the entity resulting from such transaction were members of the Incumbent Board at the time of the execution of the initial agreement or of the action of the Board providing for such transaction; or

(iv) upon the complete liquidation of the Company or the sale or disposition by the Company of all or substantially all of the Company's assets, other than a liquidation of the Company into a wholly-owned subsidiary.

(g) " COBRA " means the Consolidated Omnibus Budget Reconciliation Act of 1985, as amended.

(h) " Code " means the Internal Revenue Code of 1986, as amended.

(i) " Exchange Act " means the Securities Exchange Act of 1934, as amended.

(j) " Good Reason " means any of the following actions upon or after a Change in Control, without Employee's express prior written approval, other than due to Employee's Total Disability or death: (i) (A) a material adverse change in Employee's status, title, position or responsibilities (including reporting responsibilities from Employee's status, title, position or responsibilities as in effect immediately prior to the Change in Control); (B) the assignment to Employee of any duties or responsibilities which are materially inconsistent with Employee's status, title, position or responsibilities as in effect immediately prior to the Change in Control; or (C) any removal of Employee from or failure to reappoint or reelect Employee to any of the offices or positions held by Employee immediately prior to the Change in Control, except in the case of (A), (B) or

(C), in connection with the Termination of Employee's employment for Cause, as a result of Employee's Total Disability or death, or by Employee other than for Good Reason; (ii) a reduction in Employee's Base Salary or any failure to pay Employee any compensation or benefits to which Employee is entitled within five days of the date due; (iii) a reduction in Employee's annual cash bonus opportunity or equity-type incentive opportunity; (iv) the Company requiring Employee to relocate to any place outside a 50 mile radius of the location serving as Employee's principal work site immediately prior to the Change in Control, except for reasonably required travel on the business of the Company or an Affiliate which is not materially greater than such travel requirements in effect immediately prior thereto; (v) the failure by the Company to continue in effect employee benefits for Employee no less favorable in the aggregate as in effect immediately prior to the Change in Control; (vi) any material breach by the Company of any provision of an agreement between the Company and Employee; or (vii) the failure of the Company to obtain an agreement from any successors and assigns to assume and agree to perform the obligations created under this Agreement. With respect to (i) through (vi) above, Good Reason shall not be deemed to have occurred unless Employee shall have notified the Company in writing of his or her intent to resign for Good Reason within thirty (30) days following occurrence of the event constituting Good Reason and the Company shall not have cured the grounds for Good Reason within ten (10) days following the provision of such notice.

(k) " Release " means a waiver and release to be signed by Employee substantially in the form attached hereto as Exhibit A (which Release is not revoked by Employee).

(l) " Target Bonus " means the greater of (i) Employee's annual cash target bonus in effect immediately prior to the date a Change in Control occurs, or (ii) Employee's annual cash target bonus in effect as of the date his or her employment Terminates, in either case assuming full attainment of companywide milestones,

(m) " Terminate " or " Termination of Employment " means Employee's "separation from service" from the Company and its Affiliates, as determined pursuant to Section 409A of the Code.

(n) " Total Disability " means that, in the Company's reasonable judgment, either (1) Employee has been unable to perform Employee's duties because of a physical or mental impairment for 80% or more of the normal working days during six consecutive calendar months or 50% or more of the normal working days during twelve consecutive calendar months, or (2) Employee has become totally and permanently incapable of performing the usual duties of his employment with the Company on account of a physical or mental impairment.

Section 4. Limitation of Certain Payments .

(a) In the event the Company reasonably determines, based upon the advice of the independent public accountants for the Company, that part or all of the consideration,

compensation or benefits to be paid to Employee under this Agreement constitute " parachute payments " under Section 280G(b)(2) of the Code, as amended, then, if the aggregate present value of such parachute payments, singularly or together with the aggregate present value of any consideration, compensation or benefits to be paid to Employee under any other plan, arrangement or agreement which constitute " parachute payments " (collectively, the " Parachute Amount ") exceeds 2.99 times Employee's " base amount ", as defined in Section 280G(b)(3) of the Code (the " Employee Base Amount "), the amounts constituting " parachute payments " which would otherwise be payable to or for the benefit of Employee shall be reduced to the extent necessary so that the Parachute Amount is equal to 2.99 times Employee Base Amount (the " Reduced Amount "); provided that such amounts shall not be so reduced if Employee determines, based upon the advice of an independent nationally recognized public accounting firm (which may, but need not be the independent public accountants of the Company), that without such reduction Employee would be entitled to receive and retain, on a net after tax basis (including, without limitation, any excise taxes payable under Section 4999 of the Code), an amount which is greater than the amount, on a net after tax basis, that Employee would be entitled to retain upon his receipt of the Reduced Amount. External accountants' advice contemplated by this Section 4(a), and fees and expenses incurred in connection therewith, shall be the sole responsibility of the Company.

(b) If the determination made pursuant to clause (a) of this Section 4 results in a reduction of the payments that would otherwise be paid to Employee except for the application of clause (a) of this Section 4, the amounts payable or benefits to be provided to Employee shall be reduced such that the reduction of compensation to be provided to Employee is minimized. In applying this principle, the reduction shall be made in a manner consistent with the requirements of Section 409A of the Code, and where two economically equivalent amounts are subject to reduction but payable at different times, such amounts shall be reduced on a pro rata basis (but not below zero).

(c) As a result of the uncertainty in the application of Section 280G of the Code at the time of a determination hereunder, it is possible that payments will be made by the Company which should not have been made under clause (a) of this Section 4 (" Overpayment ") or that additional payments which are not made by the Company pursuant to clause (a) of this Section 4 should have been made (" Underpayment "). In the event that there is a final determination by the Internal Revenue Service, or a final determination by a court of competent jurisdiction, that an Overpayment has been made, any such Overpayment shall be repaid by Employee to the Company together with interest at the applicable Federal rate provided for in Section 7872(f)(2) of the Code. In the event that there is a final determination by the Internal Revenue Service, a final determination by a court of competent jurisdiction or a change in the provisions of the Code or regulations pursuant to which an Underpayment arises under this Agreement, any such Underpayment shall be promptly (and in all events no later than December 31 of the year following the year in which the applicable tax is remitted) paid by the Company to or for the benefit of Employee, together with interest at the applicable Federal rate provided for in Section 7872(f)(2) of the Code.

Section 5. Successors. Any successor to the Company (whether direct or indirect and whether by purchase, lease, merger, consolidation, liquidation or otherwise) to all or substantially all of the Company's business and/or assets shall assume the obligations under this Agreement and agree expressly to perform the obligations under this Agreement in the same manner and to the same extent as the Company would be required to perform such obligations in the absence of a succession. The terms of this Agreement and all of Employee's rights hereunder shall inure to the benefit of, and be enforceable by, Employee's personal or legal representatives, executors, administrators, successors, heirs, distributees, devisees and legatees.

Section 6. Notice. Notices and all other communications contemplated by this Agreement shall be in writing and shall be deemed to have been duly given when personally delivered or when mailed by U.S. registered or certified mail, return receipt requested and postage prepaid. Mailed notices to Employee shall be addressed to Employee at the home address which Employee most recently communicated to the Company in writing. In the case of the Company, mailed notices shall be addressed to its corporate headquarters, and all notices shall be directed to the attention of its General Counsel.

Section 7. Miscellaneous Provisions.

(a) Waiver. No provision of this Agreement shall be modified, waived or discharged unless the modification, waiver or discharge is agreed to in writing and signed by Employee and by an authorized officer of the Company (other than Employee). No waiver by either party of any breach of, or of compliance with, any condition or provision of this Agreement by the other party shall be considered a waiver of any other condition or provision or of the same condition or provision at another time.

(b) Entire Agreement. This Agreement constitutes the entire understanding between the parties with respect to the matters addressed herein, superseding all negotiations, prior discussions and agreements, written or oral, concerning such matters (but excluding, for the avoidance of doubt, obligations to Employee under any stock option, stock award or agreements or obligations under any pension, deferred compensation or retention plan (including, without limitation, any share tracking awards)). In addition, any noncompetition and nonsolicitation covenants in any agreement between Employee and the Company shall continue to apply in accordance with their terms.

(c) Choice of Law. Except to the extent preempted by federal law, this Agreement shall be governed and construed in accordance the laws of the State of Delaware, without regard to principles of conflicts of laws.

(d) Severability. If any term or provision of this Agreement or the application thereof to any circumstance shall, in any jurisdiction and to any extent, be invalid or unenforceable, such term or provision shall be ineffective as to such jurisdiction to the extent of such invalidity or unenforceability without invalidating or rendering unenforceable the remaining terms and provisions of this Agreement or the application of such terms and provisions to circumstances other than those as to which it is held invalid or unenforceable, and a suitable and equitable term or provision shall be substituted

therefor to carry out, insofar as may be valid and enforceable, the intent and purpose of the invalid or unenforceable term or provision.

(e) No Assignment of Benefits. The rights of Employee to payments or benefits under this Agreement shall not be made subject to option or assignment, either by voluntary or involuntary assignment or by operation of law, including (without limitation) bankruptcy, garnishment, attachment or other creditor's process, and any action in violation of this subsection shall be void, provided Employee's estate shall be entitled to receive any benefits that have become payable, but which have not been paid in accordance with Section 2 above.

(f) Employment Taxes. Any payments made pursuant to this Agreement will be reported on Form W-2 and shall be subject to withholding of applicable income and employment taxes.

(g) Counterparts. This Agreement may be executed in counterparts, each of which shall be deemed an original, but all of which together will constitute one and the same instrument.

(h) Confidentiality of Agreement. Employee shall keep strictly confidential all the terms and conditions, including amounts, in this Agreement and shall not disclose them to any person other than Employee's immediate family members, Employee's legal or financial advisor, or governmental officials who seek such information in the course of their official duties, unless compelled by law to do so.

(i) Not An Employment Agreement. Nothing in this Agreement shall give Employee the right to be retained in the employ or other service of the Company or its Affiliates to interfere with the right of the Company and its Affiliates to discharge Employee in accordance with any employment agreement.

(j) No Duty to Mitigate. Employee shall not be required to mitigate the amount of any benefit contemplated by this Agreement (whether by seeking new employment or in any other manner), nor shall any such benefit be reduced by any earnings or benefits that Employee may receive from any other source.

(k) Waiver of Plan Benefits. Employee hereby waives participation in the United Therapeutics Corporation Change in Control Severance Plan and acknowledges that no benefits shall be paid to Employee pursuant to such Plan.

[Signature page follows]

IN WITNESS WHEREOF, each of the parties has executed this Agreement, in the case of the company by its duly authorized officer, as of the day and year first above written.

UNITED THERAPEUTICS CORPORATION	**EMPLOYEE**
By: /s/ Michael Benkowitz	/s/ James Edgemond
	Employee Signature
Title: EVP, Organizational Development	

EXHIBIT A

WAIVER AND RELEASE

For and in consideration of the payments and other benefits due to ("Employee") pursuant to the Change in Control Severance Agreement between Employee and United Therapeutics Corporation dated as of , 2012 (the "CIC Agreement"), and for other good and valuable consideration, Employee hereby agrees, for Employee, Employee's spouse and child or children (if any), Employee's heirs, beneficiaries, devisees, executors, administrators, attorneys, personal representatives, successors and assigns, to forever waive and release all known and unknown claims and causes of action, arising on or before the date of Employee's execution of this Waiver and Release, against United Therapeutics Corporation (the "Company") or any of its divisions, affiliates, subsidiaries, parents, branches, predecessors, successors, assigns, and, with respect to such entities, their officers, directors, trustees, employees, agents, shareholders, administrators, general or limited partners, representatives, attorneys, insurers and fiduciaries, past, present and future (the "Released Parties"), including, but not limited to, all such claims and causes of action which in any way pertain to Employee's employment with and/or termination of employment from the Company, all allegations of employment discrimination, and/or all other occurrences whatsoever, including but not limited to the Age Discrimination in Employment Act, Title VII of the Civil Rights Act of 1964, as amended, 42 U.S.C. Section 2000e et. seq., the Fair Labor Standards Act, as amended, 29 U.S.C. Section 201 et. seq., the Americans with Disabilities Act, as amended, 42 U.S.C. Section 12101 et. seq., the Reconstruction Era Civil Rights Act, as amended, 42 U.S.C. Section 1981 et. seq., the Rehabilitation Act of 1973, as amended, 29 U.S.C. Section 701 et. seq., the Family and Medical Leave Act of 1993, 29 U.S.C. Section 2601 et. seq., the False Claims Act, 31 U.S.C Section 3729 et. seq. and any and all state or local laws regarding employment discrimination and/or federal, state or local laws of any type or description regarding employment, including but not limited to any claims arising from or derivative of Employee's employment with the Company and its Affiliates, as well as any and all such claims under state contract or tort law.

Employee has read this Waiver and Release carefully, acknowledges that Employee has been given at least forty-five (45) days to consider all of its terms and has been advised to consult with an attorney and any other advisors of Employee's choice prior to executing this Waiver and Release, and Employee fully understands that by signing below Employee is voluntarily giving up any right which Employee may have to sue or bring any other claims against the Released Parties, including any rights and claims under the Age Discrimination in Employment Act. Employee also understands that Employee has a period of seven (7) days after signing this Waiver and Release within which to revoke his or her agreement, and that neither the Company nor any other person is obligated to make any payments or provide any other benefits to Employee pursuant to the CIC Agreement until eight (8) days have passed since Employee's signing of this Waiver and Release without Employee's signature having been revoked other than any accrued obligations or other benefits payable pursuant to the terms of the Company's normal payroll practices or employee benefit plans. Finally, Employee has not been forced or pressured in any manner whatsoever to sign this Waiver and Release, and Employee agrees to all of its terms voluntarily.

Notwithstanding anything else herein to the contrary, this Waiver and Release shall not affect: (i) the Company's obligations under any compensation or employee benefit plan, program or arrangement (including, without limitation, obligations to Employee under any stock option, stock award or agreements or obligations under any pension, deferred compensation or retention plan (including, without limitation, any share tracking awards)) provided by the Affiliated Entities where Employee's compensation or benefits are intended to continue or Employee is to be provided with compensation or benefits, in accordance with the express written terms of such plan, program or arrangement, beyond the date of Employee's termination; or (ii) rights to indemnification or liability insurance coverage Employee may have under the by-laws of the Company or applicable law.

In addition, excluded from this Waiver and Release are any claims which by law cannot be waived, including but not limited to the right to file a charge with or participate in an investigation by the Equal Employment Opportunity Commission ("EEOC"). Employee does, however, hereby waive all rights to recover any money, benefits or reinstatement should the EEOC or any other agency or individual pursue any claims on Employee's behalf.

This Waiver and Release is final and binding and may not be changed or modified except in a writing signed by both parties.

Date	Employee
Date	United Therapeutics Corporation

Exhibit 21

SUBSIDIARIES OF THE REGISTRANT

EvoLung Inc., a Delaware Corporation
Lung Bioengineering Inc., a Delaware Corporation
Lung Biotechnology Hong Kong Limited, a Hong Kong Company
Lung Biotechnology Inc., a Delaware Corporation
Lung Biotechnology (Nanjing) Co., Ltd., a Chinese Wholly Foreign-Owned Entity
Lung Rx Limited, a United Kingdom Company
PERFUSIX USA, Inc., a Delaware Corporation
Revivicor, Inc., a Delaware Corporation
United Therapeutics Europe, Ltd., a United Kingdom Company
Unither Biotech Inc., a Canadian Corporation
Unither Pharma, LLC, a Delaware Limited Liability Company
Unither Pharmaceuticals, LLC, a Delaware Limited Liability Company
Unither Telmed, Ltd., a Delaware Corporation
Unither Therapeutik GmbH, a German Company
Unither Virology, LLC, a Delaware Limited Liability Company
Unither.com, Inc., a Delaware Corporation
UTASIA Inc., a Delaware Corporation
1109 Spring Managing Holdings, LLC, a Delaware Limited Liability Company
1109 Spring Managing Member, LLC, a Delaware Limited Liability Company

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Exhibit 21

SUBSIDIARIES OF THE REGISTRANT

Exhibit 23.1

Consent of Independent Registered Public Accounting Firm

We consent to the incorporation by reference in the following Registration Statements:

(1) Registration Statement (Form S-8 No. 333-108169) pertaining to the United Therapeutics Corporation's Equity Incentive Plan,

(2) Registration Statement (Form S-8 No. 333-56922) pertaining to Employee Options and Consultant Options Granted Outside the United Therapeutics Corporation's Equity Incentive Plan,

(3) Registration Statement (Form S-8 No. 333-95419) pertaining to the United Therapeutics Corporation's Equity Incentive Plan,

(4) Registration Statement (Form S-8 No. 333-153695) pertaining to the United Therapeutics Corporation's Share Tracking Awards Plan,

(5) Registration Statement (Form S-8 No. 333-173858) pertaining to the United Therapeutics Corporation's 2011 Share Tracking Awards Plan,

(6) Registration Statement (Form S-4 No. 333-173857) pertaining United Therapeutics Corporation common stock,

(7) Registration Statement (Form S-8 No. 333-179746) pertaining to the United Therapeutics Corporation 2011 Share Tracking Awards Plan,

(8) Registration Statement (Form S-8 No. 333-182851) pertaining to the United Therapeutics Corporation Employee Stock Purchase Plan,

(9) Registration Statement (Form S-8 No. 333-188241) pertaining to the United Therapeutics Corporation 2011 Share Tracking Awards Plan, and

(10) Registration Statement (Form S-8 No. 333-197685) pertaining to the United Therapeutics Corporation's 2011 Share Tracking Awards Plan.

of our reports dated February 24, 2015, with respect to the consolidated financial statements and schedule of United Therapeutics Corporation and the effectiveness of United Therapeutics Corporation's internal control over financial reporting, included in this Annual Report (Form 10-K) for the year ended December 31, 2014.

/s/ Ernst & Young LLP

McLean, Virginia
February 24, 2015

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Exhibit 23.1

Consent of Independent Registered Public Accounting Firm

Exhibit 31.1

CERTIFICATION PURSUANT TO RULE 13a-14(a)
OF THE SECURITIES EXCHANGE ACT OF 1934

I, Martine A. Rothblatt, certify that:

1. I have reviewed this annual report on Form 10-K of United Therapeutics Corporation;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

   a. Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   b. Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

   c. Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   d. Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

   a. All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   b. Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: February 24, 2015

/s/ MARTINE A. ROTHBLATT

By: Martine A. Rothblatt, Ph.D.
Title: *Chairman and Co-Chief Executive Officer*
(Principal Executive Officer)

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Exhibit 31.1

CERTIFICATION PURSUANT TO RULE 13a-14(a) OF THE SECURITIES EXCHANGE ACT OF 1934

Exhibit 31.2

CERTIFICATION PURSUANT TO RULE 13a-14(a)
OF THE SECURITIES EXCHANGE ACT OF 1934

I, John M. Ferrari, certify that:

1. I have reviewed this annual report on Form 10-K of United Therapeutics Corporation;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

   a. Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   b. Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

   c. Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   d. Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

   a. All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   b. Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: February 24, 2015

/s/ JOHN M. FERRARI

By: John M. Ferrari
Title: *Chief Financial Officer (Principal Financial Officer)*

QuickLinks

Exhibit 31.2

CERTIFICATION PURSUANT TO RULE 13a-14(a) OF THE SECURITIES EXCHANGE ACT OF 1934

Exhibit 32.1

CERTIFICATION PURSUANT TO
18 U.S.C. SECTION 1350,
AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

In connection with the annual report of United Therapeutics Corporation (the "Company") on Form 10-K for the period ended December 31, 2014 as filed with the Securities and Exchange Commission (the "Report"), I, Martine A. Rothblatt, Chairman and Co-Chief Executive Officer of the Company, certify, to the best of my knowledge, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that:

1. The Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934; and

2. The information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

/s/ MARTINE A. ROTHBLATT

Martine A. Rothblatt
Chairman and Co-Chief Executive Officer
(Principal Executive Officer)

United Therapeutics Corporation

February 24, 2015

THE FOREGOING CERTIFICATION IS BEING FURNISHED SOLELY PURSUANT TO SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002 AND IS NOT BEING FILED AS PART OF THE FORM 10-K OR AS A SEPARATE DISCLOSURE DOCUMENT.

A SIGNED ORIGINAL OF THIS WRITTEN STATEMENT REQUIRED BY SECTION 906, OR OTHER DOCUMENT AUTHENTICATING, ACKNOWLEDGING, OR OTHERWISE ADOPTING THE SIGNATURE THAT APPEARS IN TYPED FORM WITHIN THE ELECTRONIC VERSION OF THIS WRITTEN STATEMENT REQUIRED BY SECTION 906, HAS BEEN PROVIDED TO UNITED THERAPEUTICS CORPORATION AND WILL BE RETAINED BY UNITED THERAPEUTICS CORPORATION AND FURNISHED TO THE SECURITIES AND EXCHANGE COMMISSION OR ITS STAFF UPON REQUEST.

QuickLinks

Exhibit 32.1

CERTIFICATION PURSUANT TO 18 U.S.C. SECTION 1350, AS ADOPTED PURSUANT TO SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

Exhibit 32.2

CERTIFICATION PURSUANT TO
18 U.S.C. SECTION 1350,
AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

In connection with the annual report of United Therapeutics Corporation (the "Company") on Form 10-K for the period ended December 31, 2014 as filed with the Securities and Exchange Commission (the "Report"), I, John M. Ferrari, Chief Financial Officer of the Company, certify, to the best of my knowledge, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that:

(1) The Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934; and

(2) The information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

/s/ JOHN M. FERRARI

John M. Ferrari
Chief Financial Officer (Principal Financial Officer)
United Therapeutics Corporation
February 24, 2015

THE FOREGOING CERTIFICATION IS BEING FURNISHED SOLELY PURSUANT TO SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002 AND IS NOT BEING FILED AS PART OF THE FORM 10-K OR AS A SEPARATE DISCLOSURE DOCUMENT.

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Exhibit 32.2

CERTIFICATION PURSUANT TO 18 U.S.C. SECTION 1350, AS ADOPTED PURSUANT TO SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

Electronic Acknowledgement Receipt	
EFS ID:	25046084
Application Number:	14849981
International Application Number:	
Confirmation Number:	6653
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First Named Inventor/Applicant Name:	Hitesh BATRA
Customer Number:	22428
Filer:	Stephen Bradford Maebius/Karen Strawderman
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Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Miscellaneous Incoming Letter	NotificationRltdProc.pdf	48752 69791c5bcd8643bb8dbcfb5ebfeb9148ae78c9ba	no	2

Warnings:
Information:

2	Miscellaneous Incoming Letter	POPrelRspandExhibits.pdf	21312387 011bfa814fe07ae561f11f5aabcd6da70f2e65d6	no	975
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			Total Files Size (in bytes):	21361139	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/08 (modified)

Substitute for form 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	14/849,981
Date Submitted: FEB 29 2016				**Filing Date**	9/10/2015
(use as many sheets as necessary)				**First Named Inventor**	Hitesh BATRA
Sheet	1	of	1	Art Unit	1672
				Examiner Name	Yevgeny Valenrod
				Attorney Docket Number	080618-1581

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	C1	2001/0038855 A1	11/08/2001	Desjardin et al.	
	C2	2001/0056095 A1	12/27/2001	Mylari	
	C3	4,434,164 A	02/28/1984	Lombardino	
	C4	5,466,713 A	11/14/1995	Blitstein-Willinger et al.	
	C5	5,506,265 A	04/09/1996	Blitstein-Willinger	
	C6	6,706,283 B1	03/16/2004	Appel et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Documents	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]
	C7	WO 98/18452 A1	05/07/1998	Shire Laboratories, Inc.		

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]
	C8	BIGHLEY et al., "Salt Forms of Drugs and Absorption," Encyclopedia of Pharmaceutical Technology, Swarbrick et al., Eds., 1995, 13:453-499.	
	C9	SIMONNEAU et al., "Continuous Subcutaneous Infusion of Treprostinil, a Prostacyclin Analogue, in Patients with Pulmonary Arterial Hypertension," Am. J. Respir. Crit. Care Med., 2002, 165:800-804.	

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VOLUME 13

PRESERVATION OF PHARMACEUTICAL PRODUCTS TO SALT FORMS OF DRUGS AND ABSORPTION

MARCEL DEKKER, INC., NEW YORK • BASEL • HONG KONG

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Salt Forms of Drugs and Absorption

Introduction

Salt formation is frequently performed on weak acidic or basic drugs because it is a relatively simple chemical manipulation which may alter the physicochemical, formulation, biopharmaceutical, and therapeutic properties of a drug without modifying the basic chemical structure. Salt selection has been largely semi-empirical, based on consideration of cost of raw materials, yield, ease of preparation and purification, etc. Although attempts have been made to apply "decision analysis" and "potential problem analysis" to select salts and help predict salt performance [1], the choice of which salt to use remains a difficult decision.

The ideal characteristics of a salt are that it is chemically stable, not hygroscopic, presents no processing problems, dissolves quickly from solid dosage forms (unless it is formed with the intent to delay dissolution), and exhibits good bioavailability.

The literature contains a large amount of information on salts; however, much of the early research addresses the use of salt formation to prolong the release of the active component, thereby eliminating various undesirable drug properties[2–6]. This article supplements an extensive review published in 1977 [7], providing a literature overview of approximately 40–45 years. Its objectives are to present potentially useful salts, their effect on the properties of the parent drug, and a decision tree for choosing the most desirable salt form(s) for development.

Potentially Useful Salts

Salt formation is one of the simplest chemical reactions, involving either a proton transfer or a neutralization reaction between an acid and a base. The relative strength of the acid or base, or the acidity and basicity constants of the species involved, significantly influences the occurrence of the reaction and provides a measure of the stability of the resulting salt. Theoretically, every compound possessing acidic and/or basic properties can participate in salt formation.

Salt forms that have been clinically evaluated in humans or were commercially marketed through 1993 are shown in Tables 1 and 2, compiled from the drug monographs listed in *Martindale, The Extra Pharmacopoeia*, 30th ed. [8]. Table 1 gives all anionic salt forms, Table 2 all cationic forms. The relative frequency (as a percentage) of use for each salt type was calculated based on the total number of anionic or cationic salts used through 1993.

The monoprotic hydrochlorides are by far the most frequent choice of an anionic salt-forming radical, probably for physiological reasons and simple availability. For similar reasons, sodium is the most predominate cation. These findings are identical to those reported in a similar survey [7] from 1977, even though they are based on twice the number of salts as the earlier study. Other comparisons between this and the previous review show an increase of approximately 40% in the types of anionic salts and approxi-

TABLE 1 Anionic Pharmaceutical Salt Forms Currently in Use

Anion	Percent[a]	Anion	Percent[a]	Anion	Percent[a]
Aceglumate	0.07	Formate	0.07	Nicotinate	0.13
Acephyllinate (7-Theophyllineacetate)	0.26	Fosfatex (Metaphosphate)	0.07	Nitrate	1.18
Acetamidobenzoate	0.07	Fumarate	0.92	Oleate	0.13
Acetate	2.09	Gluceptate (Glucoheptonate)	0.13	Orotate	0.26
Acetylasparaginate	0.07	Gluconate	0.52	Oxalate	0.26
Acetylaspartate	0.07	Glucuronate	0.13	Oxoglurate	0.13
Adipate	0.13	Glutamate	0.07	Pamoate (Embonate)	1.37
Aminosalicylate	0.13	Glycerophosphate	0.52	Pantothenate	0.07
Anhydromethylenecitrate	0.07	Glycinate	0.13	Pectinate	0.07
Ascorbate	0.13	Glycollylarsinilate (*p*-Glycollamidophenylarsonate)	0.07	Phenylethylbarbiturate	0.13
Aspartate	0.33	Glycyrrhizate	0.07	Phosphate	2.48
Benzoate	0.20	Hippurate	0.07	Picrate	0.07
Besylate (Benzenesulfonate)	0.26	Hemisulfate	0.13	Policrilix (Methacrylic acid polymer)	0.07
Bicarbonate	0.07	Hexylresorcinate	0.07	Polistirex[b]	0.85
Bisulfate	0.13	Hybenzate *o*-(4-Hydroxybenzyl)benzoate	0.20	Polygalacturonate	0.07
Biartrate	0.52	Hydrobromide	1.37	Propionate	0.20
Borate	0.26	Hydrochloride	43.99	Pyridoxylphosphate	0.13
Bromide	3.79	Hydroiodide	0.07	Saccharinate	0.20
Butylbromide	0.07	Hydroxybenzenesulfonate	0.07	Salicylate	0.78
Camphorate	0.01	Hydroxybenzoate	0.07	Stearate	0.20
Camsylate (Camphorsulfonate)	0.59	Hydroxynaphthoate	0.07	Stearylsulfate	0.07

Butylbromide	0.07	Hydroxyethanesulfonate	0.07	Stearate	0.20
Camphorate	0.01	Hydroxybenzoate	0.07	Stearylsulfate	0.07
Camsylate (Camphorsulfonate)	0.59,	Hydroxynaphthoate	0.07		
Carbonate	0.46	Iodide	1.11	Subacetate	0.07
Chloride	3.53	Isethionate (2-Hydroxyethanesulfonate)	0.52	Succinate	0.52
Chlorophenoxyacetate	0.07	Lactate	0.98	Sulfate	5.82
Citrate	2.81	Lactobionate	0.07	Sulfosalicylate	0.07
Closylate (4-Chlorobenzenesulfonate)	0.07	Lysine	0.65	Tannate	0.85
Cromesilate (6,7-Dihydroxycoumarin-4-methanesulfonate)	0.07	Malate	0.26	Tartrate	2.68
Cyclamate	0.13	Maleate	3.14	Teprosilate[c]	0.07
Dehydrocholate	0.07	Mandalate	0.13	Terephthalate	0.07
Dihydrochloride	1.37	Mesylate	3.20	Teoclate (8-Chlorotheophyllinate)	0.33
Dimalonate	0.07	Methylbromide	0.39	Thiocyanate	0.20
Edetate	0.07	Methyliodide	0.20	Tidiacicate (Thiazolidine-2,4-dicarboxylate)	0.07
Edisylate (1,2-Ethanedisulfonate)	0.20	Methylnitrate	0.13	Timonacicate (Thiazolidine-4-carboxylate)	0.07
Esolate (Lauryl sulfate)	0.13	Methylsulfate	0.98	Tosylate (Toluene-4-sulfonate)	0.39
Esylate (Ethanesulfonate)	0.13	Monophosadenine (Adenylic acid)	0.07	Triethiodide	0.07
Ethylbromide	0.07	Mucate	0.07	Undecanoate	0.13
Ethylsulfate	0.07	Napadisylate	0.13	Xinafoate	0.07
Fendizoate (Hydroxyphenylbenzoylbenzoate)	0.07	Napsylate (1,5-Naphthalenedisulfonate)	0.20	(1-Hydroxyl-naphthoate)	

[a]Percent is based on total number of anionic salts in use through 1993.
[b]Sulfonated diethenylbenzene-ethenylbenzene copolymer complex.
[c]1,2,3,6-Tetrahydro-1,3-dimethyl-2,6-dioxopurine-7-propanesulfate.

TABLE 2 Cationic Pharmaceutical Salt Forms Currently in Use

Organic Cation	Percent[a]	Metallic Cation	Percent[a]
Ammonium	1.95	Aluminum	1.35
Benethamine (*N*-Benzylphenethylamine)	0.15	Bismuth	0.30
Benzathine (*N,N'*-Dibenzylethylenediamine)	0.45	Calcium	12.18
Betaine ((Carboxymethyl)trimethylammonium hydroxide)	0.15	Lithium	0.90
Carnitine	0.15	Magnesium	4.51
Clemizole[b]	0.15	Neodymium	0.15
Chlorcyclizine 1-(4-Chorobenzyhydryl)-4-methylpiperazine)	0.15	Potassium	9.77
Choline	0.60	Rubidium	0.15
Dibenzylamine	0.15	Sodium	57.74
Diethanolamine	0.45	Strontium	0.30
Diethylamine	0.60	Zinc	1.05
Diethylammonium	0.15		
Eglumine (*N*-Ethylglucamine)	0.15		
Erbumine (*t*-Butylamine)	0.15		
Ethylenediamine	0.15		
Heptaminol (6-Amino-2-methylheptan-2-ol)	0.15		
Hydrabamine (*N,N'*-Di(dihydroabietyl)ethylenediamine	0.15		
Hydroxyethylpyrrolidone	0.15		
Imidazole	0.30		
Meglumine (*N*-Methylglucamine)	2.41		
Olamine	0.45		
Piperazine	0.90		
4-Phenylcyclohexylamine	0.51		
Procaine	0.15		
Pyridoxine	0.15		
Triethanolamine	0.15		
Tromethamine (Tris(hydroxymethyl)aminomethane)	0.90		

[a]Percent based on total number of cationic salts in use through 1993.
[b]1-*p*-Chlorobenzyl-2-pyrrolidin-1'-ylmethylbenzimidazole

mately 80% in the types of cationic salts in use. This may be indicative of a trend to modify or optimize the properties of a substance through salt formation as opposed to more complex molecular modifications. In addition, the interest in polymer–drug salts for controlling drug release is indicated by the appearance of polistirex and policrilix salts.

It is well documented that due to differences in physical, chemical, and thermodynamic properties imparted by the salt-forming species, various salts of the same com-

pound often behave differently. Knowledge that a particular salt form imparts enhanced water solubility, reduced toxicity, or slow dissolution rate to a drug molecule greatly benefits chemists and formulators. Although some generalizations such as the statement by Miller and Heller on water solubility associated with carboxylic acid salts [9] can be followed, drug use and history frequently dictate the salt form selected. For example, most contrast agents requiring water solubility are meglumine salts, whereas many of the newer therapeutic peptides (i.e., buserelin, nafarelin, octreotide) are acetates. Many of the antibiotics administered intravenously are sodium salts. This indicates that the drug class, history of use and local tolerance, and possibly regulatory acceptability influence the selection of the salt form.

Both pamoic acid and alginic acid have been shown to prolong action by forming slightly soluble salts with certain basic drugs. The incorporation of pamoate salts in sustained-release preparations has been reviewed by Saias et al. [10]; numerous examples can be found in the literature [11–16]. Alginic acid salts of streptomycin [17] and pilocarpine [18] have been prepared and shown to provide sustained action.

A unique way of prolonging action through salt formation was demonstrated by Malek and co-workers [19]. Utilizing the knowledge that macromolecules have an affinity for the lymphatic system, salts of four antibiotics were prepared with high-molecular-weight polyacrylic acids, sulfonic or phosphorylated polysaccharides, and polyuronic derivatives. Parenteral administration of these macromolecular salts produced low antibiotic blood levels for long periods while lymph levels were high. Since lymphatic circulation is slow, the preferential distribution of the antibiotics to the lymphatic system prolonged the passage through the body.

The lauric acid salt of propranolol was studied as an alternative to polymeric formulations for sustaining the release of propranolol HCl. The findings indicated that the laurate salt increased the bioavailability. This was attributed to micellar solubilization or ion-pairing which could lead to lymphatic absorption or lower efficiency of extraction by the liver [20].

Toxicity is reduced by choosing the appropriate salt form; two different strategies have been utilitzed to accomplish this. One is based on organic radicals that occur naturally and are readily excreted or metabolized. Using this approach, salts formed with choline [21–23], amino acids [24,25], and vitamins [24, 26–32] have been prepared that exhibit lower toxicity and fewer side effects than the parent molecule or other salts. The second strategy is to select a salt component that pharmacologically overcomes an unfavorable property or properties of the principal agent. Salts incorporating *N*-cyclohexylsulfamic acid, better known as cyclamates, can make bitter-tasting drugs acceptable because of their characteristic sweet taste. Cyclamate salts of dextromethorphan and chlorpheniramine [33] raise the bitterness thresholds compared to commonly occurring salts. The preparation and characterization of other cyclamic acid salts have been reported [34–37].

Other examples include the preparation of the benzhydralamine salt of penicillin [38] and the 8-substituted theophylline salts of several antihistamines [39–42]. Benzhydralamine is an antihistamine. The preparation of the benzhydralamine salt of penicillin was an attempt to produce a repository form of penicillin with antiallergic properties. The synthesis of the xanthine salts of several antihistamines was an attempt to counteract the drowsiness caused by the antihistamines with the stimulant properties of the xanthines. A number of other 8-substituted theophyllines have been prepared [21, 43–49].

A quinidine salt with reduced toxicity has been prepared from polygalacturonic acid, a derivative of pectin [50,51]. This substance possesses special demulcent properties and inhibits mucosal irritation. It is used to reduce the shock to the gastrointestinal (GI) mucosa resulting from the liberation of irritating ions caused by the rapid dissociation of the conventional inorganic quinidine salts. Quinidine polygalacturonate is one-fourth as toxic orally as the sulfate.

The *N*-(2-hydroxyethyl)pyrrolidine salt of diclofenac (DHEP) was prepared as part of a study to obtain salts with balanced hydrophilic and hydrophobic properties [52]. Of the 24 salts synthesized, DHEP had the greatest solubility in both water and octanol. In addition, it exhibited surfactant properties and the ability to solubilize lipid materials above its critical micelle concentrations. These properties suggest that this salt is preferable to topical administration since it could promote its own absorption by interacting with the membrane components. Other compounds reported to be potentially useful as pharmaceutical salt forms are shown in Table 3.

Physicochemical Studies

Although different salts of the same drug elicit similar biological responses, the intensities of response may differ markedly [96,97]. A knowledge of the physicochemical properties of a salt and its influence on pharmacokinetics is necessary to understand the onset, duration, and intensity of action, relative toxicity, and possible routes of administration [2]. The influence of salt form on volatility and hygroscopicity has been investigated in preformulation studies [98].

Solubility

Solubility is an important factor in chemical stability, the formation of dosage forms, and the overall drug-absorption process.

Common-Ion Effect

Hydrochloride salts are the most common anionic salt-forming species [7]. However, they do not necessarily enhance the solubility of poorly soluble basic drugs in a chloride-containing medium because of the common-ion effect which suppresses the solubility product equilibrium [99–105]. In some instances, the solubility of various hydrochlorides was less than that of the corresponding free base at gastric pH. The practical effect of reducing solubility could ultimately be a reduction of the dissolution rate in gastric juice. The Setschenow salting-out constants for chloride are highest for these slightly soluble hydrochlorides [106]. However, the relationship between the aqueous solubility of sparingly soluble salts and the empirical Setschenow salting-out constant is valid only at low concentrations of added salt [107].

Prazosin is an example of a drug with a strong chloride-ion dependence. The hydrochloride salt in water has a solubility of 1.4 mg/mL at 30°C, whereas in 0.1M HCl it is 0.037 mg/mL [108].

A common-ion effect on the sodium salt of an organic acid has also been reported [109]. The solubility and dissolution rates decreased with varying sodium ion concen-

TABLE 3 Potentially Useful Salt Forms of Pharmaceutical Agents

Salt-Forming Agent	Compound Modified	Property Modified	Reference
p-Acetamidobenzoic acid	Various amines	Hygroscopicity	53
Acetylaminoacetic acid	Doxycycline	Solubility	54
N-Acetyl-L-asparagine	Erythromycin	Solubility, activity, stability	55
N-Acetylcystine	Doxycycline	Combined effect useful in pneumonia	56
Adamantoic acid	Alkylbiguanides	Prolonged action	57
Adipic acid	Piperazine	Stability, toxicity, organoleptic properties	58
N-Alkylsulfamates	Ampicillin	Absorption (oral)	59
	Lincomycin	Solubility	60
Anthraquinone-1,5-disulfonic acid	Cephalexin	Stability, absorption	61
Arabogalactan sulfate (arabino)	Various alkaloids	Prolonged action	62,63
Arginine	Cephalosporin	Toxicity	64
	Sulfobenzylpenicillin	Stability, hygroscopicity, toxicity	65
Aspartate	Erthromycin	Solubility	66
Betaine	Tetracycline	Gastric absorption	67
Bis(2-carboxychromon-5-yloxy)alkanes	7-Aminoalkyltheophyllines	Activity, prolonged prophylactic effect	68
Carnitine	Metformin	Toxicity	69
4-Chloro-*m*-toluenesulfonic acid	Propoxyphene	Organoleptic properties	70
Decanoate	Heptaminol	Proplonged action	71
Diacetyl sulfate	Thiamine	Stability, hygroscopicity	72
Dibenzylethylenediamine	Ampicillin	Prolonged action	73,74
Diethylamine	Cephalosporins	Reduced pain on injection	75
Diguiacyl phosphate	Tetracycline	Activity	76
Dioctyl succinate	Vincamine	Organoleptic properties	77
Embonic (pamoic) acid	Kanamycin	Toxicity	78
	2-Phenyl-3-methylmorpholine	Toxicity	79
Fructose-1,6-diphosphoric acid	Tetracycline	Solubility	80
	Erthromycin	Solubility	80
Glucose-1-phosphoric acid,	Tetracycline	Solubility	80
Glucose-6-phosphoric acid	Erythromycin	Solubility	80
L-Glutamine	Erythromycin	Solubility, activity, stability	55
Hydroxynaphthoate	Bephenium	Toxicity	81
2-(4-Imidazolyl)ethylamine	Prostaglandin	Prolonged action	82
Isobutanolamine	Theophylline	Stability	83
Lauryl sulfate	Vincamine	Organoleptic properties	84
Lysine	Sulfobenzylpenicillin	Toxicity, stability, hygroscopicity	65
	Cephalosporin		64
Methanesulfonic acid	Pralidoxime (2-PAM)	Solubility	85
N-Methylglucamine	Sulfobenzylpenicillin	Toxicity, stability, hygroscopicity	65

TABLE 3 *(Continued)*

Salt-Forming Agent	Compound Modified	Property Modified	Reference
	Cephalosporins	Reduced pain on injection	75
N-Methylpiperazine	Phenylbutazone	Toxicity, faster onset of action	86
Morpholine	Cephalosporins	Reduced pain on injection	75
2-Naphthalenesulfonic acid	Propoxyphene	Organoleptic properties	87
Octanoate	Heptaminol	Prolonged action	71
Probenicid	Pivampicillin	Organoleptic properties	88
Tannic acid	Various amines	Prolonged action	89,90
Theobromine acetic acid	Propoxyphene	Activity	91
3,4,5-Trimethoxybenzoate	Tetracycline	Organoleptic properties	92
	Heptaminol	Prolonged action	71
Tromethamine	Aspirin	Absorption (oral)	93
	Dinoprost (prostaglandin F)	Physical state	94
Xinafoate	Salmeterol	Local tolerance	95

trations. The reduction in solubility product in the presence of NaCl was attributed to a decrease in the degree of self-association of the drug in aqueous media.

Formulation

The choice of salt can have significant benefits for the formulation of a drug as, for example, with the cytotoxic drug, coralyne sulfoacetate. The solubility of coralyne chloride in water is 4.5 mg/mL, and that of the sulfoacetate is 6.5 mg/mL; however, solutions containing 25 mg/mL were required for iv infusion [110,111]. The solubility of the chloride salt was no higher in weakly alkaline aqueous media than in distilled water since it is a salt of a quaternary ammonium ion and the conjugate base of a strong acid. Adding sodium hydroxide greatly enhanced the solubility of the sulfoacetate. The reason is that the sulfoacetate anion is an acid which is ionized by the added base, resulting in an increase in the concentration of coralynium ion in solution.

The solubility of a salt can influence the use of formulation adjuvants. In the presence of methanesulfonic, acetic, and hydrochloric acids, 2,3,4,5-tetrahydro-8-(methylsulfonyl)-1-H-3-benzazepin-7-ol had water solubilities of approximately 440, 320, and 1 mg/mL. Addition of sodium chloride to a saturated solution of the mesylate (methanesulfonic) salt, reduced the solubility to approximately 60 mg/mL, even with a sodium chloride concentration as low as 0.05 M. This was probably due to the rapid conversion of the mesylate to the hydrochloride salt and may preclude the use of sodium chloride as an isoosmotic agent or the use of saline as diluent [103].

In addition to its effect on solubility, the choice of salt is important to the usefulness and efficacy of the formulation. For example, hydrochloride salts in aqueous solution may lower the pH, which can adversely affect their use in parenteral dosage forms because of the incidence of pain and subsequent venous inflammation [112]. It could also lead to incompatibilities with metal aerosol containers [108].

Sciarra et al.[113], using epinephrine as a model compound in an aerosol delivery system, points out that the solubility of the salt form in various propellants is important in products intended for local action in the lungs or for systemic therapy; furthermore, the salt form should be soluble in extracellular fluids.

Complex Salt Formation

Organic acid salt forms of basic drugs, such as amines, frequently have higher aqueous solubilities than their corresponding inorganic salts. Hydrochloric, nitric, sulfuric, and phosphoric salts of triamterine form insoluble complex salts [114]. Acetic acid produced solubilities higher than those observed with any of the inorganic acids. Although acetic acid complexes with triamterine, an insoluble complex was not found. This is important in the synthesis and selection of a salt form that exhibits enhanced bioavailability and desirable formulation characteristics.

Studies have been conducted on the complexation of some drugs with sodium polyphosphate [115]. Insoluble complex salts formed with amethocaine, amitriptyline, propranolol, and verapamil, but not with atropine, ephedrine, and procaine. The complex salt formed with verapamil produced a prolonged dissolution profile in acid compared to pure verapamil, but because of hygroscopicity it was difficult to process and store.

The solubility also of organic carboxylic acids is also affected by salt formation, in some cases adversely. For example, *N*-[4-(1,4-benzodioxan-6-yl)-2-thiazolyl] oxamic acid was less soluble in the presence of sodium, potassium, and calcium ions. However, these ions increased the distribution coefficients significantly between water and 1-octanol, even at low concentrations. The lower solubility was attributed to the formation of less soluble salts, whereas the increase in distribution coefficients was explained by ion-pairing and/or complexation [116].

Solubility Predictions

The solubility of a salt can be influenced by the structure of the organic moiety or by the hydrophilic properties of the anion or cation. A higher crystal lattice energy (crystallinity) is generally reflected by a higher melting point. An increase in melting point, usually by maximizing or encouraging crystal symmetry, reduces solubility. Gould [108] reports that the solubility of a drug frequently decreases by an order of magnitude with an increase of 100°C in its melting point. Where solubility and resultant pH are major issues, a low melting salt of a drug produced from a soluble, fairly weak acid or base, probably made in situ, is usually preferred.

The increase or decrease in melting point of a series of salts of basic compounds depends on the controlling effect of crystallinity from the conjugate anion. This is exemplified by an experimental drug candidate, UK47880, which has a basic pKa of 8 [108]. Salts prepared from planar, high melting aromatic sulfonic or hydroxycarboxylic acids yield high melting crystalline salts. However, flexible aliphatic acids such as citric and dodecylbenzene sulfonic yielded oils. Gould [108] discussed how crystal lattice forces of drugs with good hydrogen bonding potential could be built up by considering the symmetry and hydrogen bonding potential of the conjugate acid. He used epinephrine as an example, which gives high melting salts with small, strongly hydrogen-bonding acids like malonic and maleic. The larger bitartrate and presumably symmetrically unfavored fumarate give lower melting salts.

Various salts of α-(2-piperidyl)-3,6-bis(trifluoromethyl)-9-phenanthrenemethanol [102], chlorhexidine [117], erythromycin [118], and the *N*-alkylsulfamates of lincomycin [60] show enhanced solubility which can be attributed to a lower melting point and the hydrophilic properties of the anion. Organic salts may increase aqueous solubility through decreased crystal lattice energy, lowered melting point, increased hydrogen bonding of the salt counterions with water, etc.

There are exceptions to the solubility–melting point and solubility–hydrophilicity relationship. For example, the THAM, tris(hydroxymethyl)aminomethane, salts of certain analgesic-anti-inflammatory agents showed no simple solubility–melting point relationship [119]. Anderson and Condradi, using organic amine salts of flurbiprofen to predict water solubility, found a strong dependence of the solubility product on melting point; however, there was no significant correlation between solubility product and counterion hydrophilicity [120]. The authors concluded that this is in conflict with the notion that higher salt solubilities can be achieved by selecting more hydrophilic counterions, since such arguments neglect the likelihood that interactions in the crystal become stronger as the salt-forming species are made increasingly polar.

Rubino [121] found that the logarithms of the molar solubilities of a number of sodium salts of drugs were inversely related to their melting points, but a good correlation was not evident. However, the logarithms of the molar solubilities were inversely related to both the melting points and stoichiometric amounts of water in the crystal hydrates, but unrelated to the polarity of the corresponding acid forms of the drugs. It was concluded therefore that the melting point and the degree of crystal hydration of the solid phase are most important in determining the solubilities of the sodium salts of some drugs.

The solubilities of the sodium salts of some weakly acid drugs have been determined in mixtures of propylene glycol and water. The solubility in the mixed solvent of compounds with low temperatures of desolvation had increased, whereas the solubility of compounds with high desolvation temperatures had decreased. These data indicate that crystal hydrate formation plays a significant role in determining if a cosolvent can be used to enhance the solubilities of certain sodium salts [122].

The hydrogen ion concentration can significantly affect salt solubility. Anderson [123] discussed the influence of pH on the solubility of therapeutically useful weak acids and bases and their salts. This was followed a few years later by an extensive study on the solubility interrelationships of the hydrochloride and free base of two amines [124]. Mathematical equations describing the total solubility at an arbitrary pH in terms of the independent solubilities of the hydrochloride and free base species and the dissociation constant of the salt were derived and fitted to experimental data with good results. This report made the point that, although the solubility of an amine hydrochloride generally sets the maximum obtainable concentration for a given amine, the solubility of the free base and the pKa determine the maximum pH at which formulation as a solution is possible. This assumes that the desired concentration exceeds the free base solubility. Shifting the pH–solubility profile to higher pH values for formulation purposes may require increasing the solubility of the free base with the help of an appropriate cosolvent. Because the dissociation characteristics of carboxylic acids and other organic species are similar to those of organic hydrochlorides, the pH–solubility profiles could be characterized theoretically by the same treatment.

Chowhan [125] studied the solubilities of three organic carboxylic acids (naproxen; 7-methylsulfinyl-2-xanthonecarboxylic acid; and 7-methythio-2-xanthonecarboxylic acid) and their sodium, potassium, calcium, and magnesium salts as a function of pH. The

data were fitted to mathematical relationships similar to those used by Kramer and Flynn [124]. The results on the solubility of naproxen and its salts were in excellent agreement with theory. The solubilities of the two xanthone carboxylic acids and their salts were higher at higher pH than the values calculated for complete dissociation in solution.

Surface Activity

The salts of some compounds are surface active [126–128]. If the saturation solubility enables the critical micelle concentration (CMC) to be reached, solubility is enhanced significantly via micellar solubilization. A study of the colloidal properties of some chlorhexidine salts showed that the counterion can affect the CMC which was usually associated with a change in micellar size [126]. For example, the diacetate displays a higher CMC than the digluconate [126].

The hydrochloride salt of 2-butyl-3-benzofuranyl-4-[2-(diethylamino)ethoxy]-3,5-diiodophenyl ketone is capable of forming micelles. Anions such as chloride, sulfate, acetate, tartrate, and citrate significantly affect the equilibrium solubility of the compound, which is partly related to the effect on the CMC by the anionic environment [127].

The nonopioid kappa agonist analgesic amine, DuP 747, as the hydrochloride salt, exerts surface activity in aqueous solutions; however, the critical micellar concentration is not reached at the saturation solubility [128]. On the other hand, the methanesulfonate salt formed a micellar solution and allowed for a solubility of 60 mg/mL as opposed to 3 mg/mL for the hydrochloride.

Zomepirac, an insoluble, carboxylic, non-narcotic analgesic, has a solubility in water of 0.02 mg/mL. In a developing zomepirac solution containing 100 mg/mL [129], THAM was found to be a satisfactory solubilizer at a concentration where equivalent concentrations of sodium or potassium hydroxide were not. The solubility was achieved by a micellar mechanism. It is interesting that potassium hydroxide was more effective in solubilizing zomepirac than sodium hydroxide. Walkling et al. attributed the difference in their performance as solubilizers to the difference in their charge densities [129]. Additional references on the relationship of salt form and solubility are listed in Table 4.

Dissolution Rate

In many cases, the dissolution rate can be a good indicator of bioavailability, especially of poorly soluble drugs. A salt form frequently exhibits a higher dissolution rate than the corresponding conjugate acid or base at the same pH, even though they may have the same equilibrium solubility. In a review article on the biopharmaceutical basis for drug design, Nelson [150,151], and later Benet [152], referred to the self-buffering action of the salt form in the diffusion layer. The dissolution rates are determined by the pH values of the diffusion layer and are independent of the pH_{bulk} of the media used. Therefore, the difference in diffusion-layer pH between a parent compound and its salt accounts for the difference in the dissolution rates in a particular medium.

Effect of Salt Form

Nelson, using theophylline salts, was the first to show the correlation between diffusion-layer pH and dissolution rate [150]. Salts with a high diffusion-layer pH had higher

TABLE 4 References on Salt Form and Solubility

Topic	Reference
Mineral acid salts of lidocaine	130
Nonionic surfactant effect on rate of release of drugs from suppositories	131
Influence of solubility of salicyclic acid on diffusion from ointment bases	132
Influence of solubility on rate of GI absorption of aspirin	133
Effect of dosage form on GI absorption rate of salicylates	134
Physical-chemical properties of polyene macrolide esters and their water-soluble salts	135
Isolation and reaction products of orotic acid and amines and their water solubility	136
Solubility and stability of erythromycin salts	137
Pharmaceutical preparations of orotic acid; water-soluble properties of orotic acid salts	138
Solubility of antibiotics in 24 solvents	139,140
Solubility of antibiotics in 26 solvents	141
Aqueous stability and solubility of CI-988, a novel dipeptoid cholecystokinin-B receptor antagonist	142
Quaternary ammonium salts of dantrolene and clodanolene	143
Acetylacroninium salts as soluble prodrugs of the antineoplastic agent acronine	144
In vitro release characteristics of a membrane-coated pellet formulation of metroprolol salts, influence of drug solubility and particle size	145
Physical properties and solubility of different salts of fenoprofen	146
pH-Solubility profile of papaverine hydrochloride and its relationship to the dissolution rate of sustained-release pellets	147
pH-Solubility profiles of organic bases and their hydrochloride salts	148
Synthesis and properties of benzathine and embonate salts of some beta-lactam antibiotics	149

in vitro dissolution rates than those with a lower diffusion-layer pH. These salts effectively act as their own buffer to alter the pH of the diffusion layer and increase the apparent solubility of the parent compound in that layer. The rank order of dissolution rates correlated well with blood levels for these salts. Similar findings have been reported for other compounds [151,153–157].

These studies lay to rest the misconception that absorption is related only to solubility in the appropriate medium. They show that solubility affects absorption only to the extent that it affects dissolution rate, since dissolution is the preceeding process.

Although salt formation generally increases the dissolution rate, formulations of some salts may actually slow dissolution and absorption due to the precipitation of insoluble particles or film on the surface of the tablet [158–163]. This reduces the effective surface area and prevents deaggregation of the particles.

The deaggregation behavior of a relatively insoluble benzoic acid derivative and its sodium salt was postulated to be a possible rate-limiting step in the absorption of the drug [164]. Although no direct comparisons of the two forms were made, inspection of the data shows that the deaggregation of the salt was considerably more rapid than that of the free acid in equivalent dosage forms. Therefore, if absorption is dependent on the dissolution rate, which in turn is dependent on the deaggregation rate, the salt should produce the highest and earliest blood levels. On the other hand, it is possible

that hygroscopic (and deliquescent) salts absorb atmospheric moisture, cause a sticky surface, and inhibit deaggregation.

Effect of Formulation

Tablet processing and formulation factors can reduce the dissolution rate of a salt more than that of the nonionized form in human gastric juice and 0.1N HCl [165]. Granulation and tableting lower the dissolution rate of phenobarbital sodium, but have the opposite effect on phenobarbital. This was attributed to the fact that sodium phenobarbital tablets do not disintegrate in acidic media, but swell and dissolve slowly from the surface. The phenobarbital tablets, however, disintegrate very rapidly in acidic media. In some instances, rapid dissolution may be a problem even with very soluble drugs.

Common-Ion Effect

The common-ion effect can significantly alter the dissolution rate of a drug. Hydrochloride salts frequently have a dissolution rate lower than the nonionized form in chloride-containing media [99,166,167]. This is due to the solubility product equilibria strongly affecting the dissolution of these salts. In these cases, an alternative salt form or a less soluble free base may improve dissolution and bioavailability [167]. Because of the common-ion effect, absorption following administration of salts of basic drugs, and especially the hydrochloride salt, is probably dependent on stomach emptying rather than in vivo dissolution. Additional references on the influence of salts and salt forms on dissolution rate are listed in Table 5.

Organoleptic Properties

With a drug administered as a tablet or capsule and swallowed as an intact unit, taste is less of a problem. Taste acceptability is a primary consideration in the formulation of a liquid, chewable tablet, or lozenge. The examples outlined below are approaches to make drugs organoleptically acceptable. The most recent applications of taste masking in oral pharmaceuticals are reviewed in Ref. 193.

Poorly Soluble Salts

An example of the preparation of poorly soluble salts to minimize undesirable organoleptic properties is the formulation of erythromycin estolate (lauryl sulfate) [194] in an oral suspension. The level of bitterness of various salts of erythromycin is related to the size of the alkyl group attached to the acid and to the stability of the salt which is a function of the strength of the acid used to prepare the salt [118].

A similar solution has been applied to bacitracin by using the relatively insoluble zinc salt [195], whose taste is easily masked by sucrose [196].

A different approach is to form water-insoluble salts with ion-exchange resins. The practical application has been described and tested by several investigators [198–201].

Common-Ion Effect

In another method a poorly water soluble salt is treated with a common ion to further reduce solubility. The taste of propoxyphene napsylate suspensions can be improved

TABLE 5 References on Salt Form and Dissolution Rate

Topic	Reference
Effect of dissolution rate on absorption, metabolism, and pharmacologic activity of drugs	168
Scientific principles in design of drug dosage formulations	169
Dissolution rate of mixtures of weak acids and tribasic sodium phosphate	170
Physiological availability and in vitro dissolution characteristics of some solid dosage formulations of aminosalicylic acid and its salts	171
Biopharmaceutics, rate of dissolution (chronological bibliography)	172
Biopharmaceutics, rate of dissolution in vitro and in vivo	173
Dissolution tests and interpretation of anomalies observed in the dissolution process of sulfaquinoxaline based on salt formation	174
Influence of the dissolution rate of lithium tablets on side effects	175
Dissolution kinetics of drugs in human gastric juice	176
Comparison of dissolution and absorption rates of different commercial aspirin tablets	177
In vitro dissolution rates of aminorex dosage forms and their correlation with in vitro availability	178
Polymer-drug salts as an approach to physicochemical design of dosage forms	179
Release of acidic drugs from anionic exchange resinate complexes	180
Sustained-release microcapsules containing ion exchange resin-dextromethorphan HBr complex	181
Ion exchange resins as matrices for controlled drug release	182
Influence of polymeric excipients on drug release from hydroxypropylmethylcellulose matrixes	183
Effect of surfactants on release of a highly water-soluble compound from an inert, heterogeneous matrix	184
Effect of diffusion-layer pH and solubility on the dissolution rate of pharmaceutical bases and their HCl salts	185
Preparation and in vitro evaluation of salts of an antihypertensive agent to obtain slow release	186
Some factors influencing in vitro release of phenytoin from formulations	187
Effect of diffusion-layer pH and solubility on the dissolution rate of pharmaceutical acids and their sodium salts	188
Dissolution behavior of diclofenac salts with hydrophilic bases	189
Dissolution studies on naproxen and its sodium and piperazine salts	190
Dissolution profiles of ibuprofen, fenbufen, and their sodium salts	191
Relationship between intrinsic dissolution rates and rates of water absorption	192

significantly by adding a common ion like sodium or calcium napsylate to depress solubility even more [197].

Soluble Salts

The taste of a drug may be improved by formation of a soluble salt. However, solubilization does not always improve the taste. For example, potassium salts frequently have

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an unpleasant taste and leave a metallic aftertaste. A study of inorganic potassium salts showed similar taste thresholds in water, but varying degrees of palatability at therapeutic potassium concentrations. Although flavored vehicles and sucrose improved palatability, all potassium salts exhibited poor taste [202]. Some success has been reported using cyclamate sodium and saccharin. *N*-Cyclohexylsulfamate salts of several drugs have improved taste and enhanced solubility properties [33,34]. Conventional quaternary ammonium compounds have a very bitter taste, but benzalkonium saccharinate and a series of saccharinates of other quaternary ammonium compounds are sweet [203]; water solubility of the saccharinate anlogs differs greatly.

Stability

The chemical and physical stability of a pharmaceutical can significantly affect the choice of dosage form, manufacturing technique, packaging, and therapeutic efficacy of the final preparation. In some cases the salt-forming radical itself may enhance stability of the parent compound or contribute to its instability.

Hygroscopicity

The stability of the drug in the dry state can be influenced by differences in hygroscopicity of the salts. Hydrochloride salts, as well as some sulfates, and especially dihydrochlorides or disulfates, are very polar in nature. The polar ionized groups exposed on the crystal surfaces result in a highly hydrophilic nature which favors wettability and can lead to hygroscopicity [108,204]. This may present processing difficulties or reduced stability if the drugs are easily hydrolyzed. To improve drug stability through salt formation, hygroscopicity has to be controlled and the strength of the conjugate acid used to form the salt considered, especially with compacted dosage forms [108]. This is very important where the available moisture is shared by the salt and excipient, and when most of the moisture comes from the excipient rather than the drug. Salts of mineral acids, which produce a low pH and a high solubility in the available moisture, produce a more hostile environment than a sulfonate or carboxylate salt. Obviously, a balance between hygroscopicity and wettability must be struck to avoid interference with the bioavailability of the compound.

Moisture associated with certain salts of weak bases can be very acidic and potentially cause stability problems related to hygroscopicity, aqueous solubility, and resulting pH. The mononitrate salts of thiamine and various vitamin B complex formulations are less hygroscopic and much less water soluble than the hydrochloride salts [205–209]. The stabilities of numerous thiamine salts were studied in aqueous solution and in dry powder preparations with various excipients [210,211]. In aqueous solution, the resulting pH was the chief factor controlling hydrolysis and oxidative decomposition. The stability of powder preparations was related to their aqueous solubility, with sparingly soluble salts being more stable and presumably less hygroscopic.

The THAM salt had superior hygroscopic properties compared to the sodium salt for naproxen, ketorolac, RS-7337, and RS-82917 [119]. With the exception of naproxen, THAM salts did not have lower aqueous solubility or intrinsic dissolution rate than the sodium salt. The less hygroscopic THAM salts offer handling advantages in formulation and storage.

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A study of the effect of moisture on the stability of penicillin salts found the calcium salt to be less hygroscopic than the sodium salt, and, therefore, more stable in moist atmospheres [212]. Penicillin G potassium is much less hygroscopic than penicillin G sodium and is the preferred form for marketing in the dry state [213].

Salt stability also depends on the hydrophobic portion of the conjugate acid [214]. The aryl sulfonic acids protect xilobam which is easily hydrolyzed. The aryl groups present a hydrophobic barrier to minimize hygroscopicity and dissolution in the surface moisture. The napsylate salt is the most stable.

Disproportionation

Dihydrohalide salts of pharmaceutical compounds may undergo facile dissociation/disproportionation of HCl or HBr, leading to release of hydrohalide gas or reaction with excipients or process-related chemicals. In one study [166], a difference in strength of the basic centers in a dihydrochloride salt led to a loss of one hydrogen chloride molecule by release of hydrogen chloride gas. Dihydrochloride or dihydrobromide salts of pharmaceuticals have been reported to cause in the reduction of dimethyl sulfoxide to dimethyl sulfide under mild conditions [215]. In this study, no reactions were observed with the monohydrohalide salts.

A hydrochloride salt was reported to cause in rusting of tooling material used for tablet manufacturing [216]; hydrogen chloride liberated from the salt was the cause.

Thermal Stability

Lincomycin cyclamate exhibits enhanced thermal stability over the hydrochloride salt [35]. Differential thermal and thermogravimetric analyses showed that the hydrochloride undergoes thermal degradation, whereas the cyclamate anion is considerably more stable [217].

Similar differences in thermal stability are seen with penicillin G salts. Penicillin G procaine is stable in aqueous vehicles, but has less thermal stability than the sodium or potassium salts, and decomposes about 60°C. The sodium and potassium salts withstand heating up to 100°C for four days with little loss in potency [218]. These discrepancies may be due to differences in melting points among the salts.

Crystallinity

As Guillory and Higuchi [219] point out, the stability of organic compounds in the solid state is intimately related to the strength of the crystal lattice. Because the intermolecular forces in a crystal are small compared with the energy necessary to break chemical bonds, liquifaction occurs before degradation begins. Therefore, the melting point of a compound may be an important factor in determining stability. In general, an increase in melting point, usually by maximizing or encouraging crystal symmetry, improves stability, particularly if salt formation results in a crystalline solid [108,219].

Degradation of solid drugs usually occurs in the surface film phase and is accomplished by the formation of a liquid phase at temperatures below the normal melting point of the solid. Guillory and Higuchi [219] investigated the stability of esters and determined the relationship between degradation rate and melting point. Gould [108]

has postulated that this approach may have utility as a a method of assessing the bulk stability of nonhygroscopic salt forms.

Solubility

Low solubility can contribute significantly to the stability of a salt since it reduces the amount of drug in solution and hence its degradation. Low solubility is especially important in developing a stable aqueous suspension of a hydrolytically unstable water-soluble drug. This has been extensively studied with penicillin G and its salts because of the drug's therapeutic importance and its characteristic instability [220–223]. The 8-chlorotheophylline salt of penicillin was reported to be water soluble, yet stable in solution [224]. Inasmuch as it is acidic, it has been postulated that its stability is due to a buffer effect.

Polymorphic Forms

A study of the physical and chemical stability of the free acid and the salts of novobiocin showed that the amorphous calcium salt is the choice for the formulation of a liquid preparation [225]. The sodium salt is unstable in liquid form and the crystalline free acid is not absorbed from the GI tract. Amorphous novobiocin is metastable in solution and slowly converts to the unabsorbed crystalline form.

Hydrate Formation

If a compound readily forms a hydrate, production of an amorphous solid does not necessarily increase the dissolution rate and stability may be impaired. This was illustrated with ethacrynic acid and sodium ethacrynate [226]. The stability of both the amorphous ethacrynic acid and amorphous sodium ethacrynate was lower than that of crystalline samples or hydrated sodium ethacrynate. As expected, dissolution of the amorphous ball-milled ethacrynic acid was more rapid than that of the crystalline material. Dissolution of the amorphous sodium ethacrynate, however, was slower than that of its crystalline counterpart. The explanation offered was that the amorphous sample of sodium ethacrynate crystallized as the hydrate in the presence of the dissolution medium.

Stability of the water of hydration is important since the stability of salt hydrates is known to change with the counterion. Hirsch et al. [227] found that the dihydrate of both the sodium and the calcium salt of fenoprofen had suitable physical characteristics with respect to crystallinity and appreciable water solubility. However, attempts to formulate fenoprofen sodium dihydrate with either propoxyphene salts (hydrochloride or napsylate) or codeine salts (sulfate or phosphate) failed. The combinations were chemically and physically incompatible since eutectic melts and/or acid–base reactions resulted in all instances. The fenoprofen calcium dihydrate, on the other hand, was compatible. These differences are postulated to be due to the integrity of the bound water of hydration of the calcium salt compared to that of the sodium salt.

The effect of counterion charge on crystal structure and the hydration–dehydration behavior of the potassium, sodium, calcium, and magnesium salts of *p*-aminosalicylic acid was studied [228]. Within the series, the propensity to form hydrates increased with increasing ionic potential of the cations. This was evident from the increase in the

number of moles of water associated with the salts as the ionic radius decreased and the charge on the cation increased. The divalent salts had higher threshold temperatures of water loss due to stronger ion–dipole interactions because of short bond distances. The sodium salt had a lower threshold temperature of water loss due to weak ion–dipole interactions because of larger bond lengths and its more open structure. Hydrate stability is important since processing operations such as drying or compaction could potentially remove water of crystallization or cause a mixture of hydrated and dehydrated forms to exist within formulations. Hydrate stability can also affect formulation and drug combination compatibility as the fenoprofen salts demonstrated.

Changes in crystal form may affect the physical and/or chemical stability of tableted dosage forms. For instance, Yamaoka et al. [229] observed cracking of tablets of carbochromen HCl as an anhydrate changed to a hydrate under high-humidity conditions.

Oral Absorption

Drugs that are administered orally and are sensitive to acid environments benefit from forming salts which are poorly soluble in acidic solution. Generally, they must pass intact through the acidic environment of the stomach in order to exhibit therapeutic effect. Erythromycin estolate, because of its low solubility in gastric juice, is more stable than the free base, therefore it can be administered with food [194].

An interesting example of selecting a proper salt of a compound (RS-82856) displaying both weak acid and weak base characteristics was presented by Gu et al.[230]. This compound has a very high pKa (11.2) as an acid and a very low pKa (3.5) as a base, which gives a solubility minimum between pH 4 and 10. Their goal was to maximize drug absorption while achieving good physical and chemical stability. Because of the weak acid-base properties of the parent compound, only very strong bases and acids could be used to make physically stable salts. The phosphate salt was not physically stable. The hydrogen sulfate and chloride salts were less hygroscopic and more soluble in water than the sodium and potassium salts. All salts studied showed only slightly better intrinsic dissolution rates (approximately twofold) than the parent drug at pH 3.1 and 7.0; only the hydrogen sulfate and potassium salts had better dissolution rates at pH 1.2. The dissolution behavior was explained as being due to the extremely low buffering effect of the salts in the dissolution medium. The hydrogen sulfate salt was recommended for development and was supported by a twofold increase in absorption over the parent drug in a dog study. Gu et al. [230], suggested that since the buffering effect of the sodium and potassium salts of a weak acid-base would be expected to increase the pH of the medium and thus reduce solubility, anion salts of weak acid-base drugs are preferred to be developed. Additional references on the influence of salts on stability are included in Table 6.

Pharmaceutical Technology

The salt form of a drug may have a pronounced effect on the formulation of the parent compound, inasmuch as it influences the melting point, hygroscopicity, and the strength of the conjugate acid used to form the salt.

TABLE 6 References on Salt Form and Stability

Topic	Reference
Stability of chlorhexidine solutions	231
Stability of autoclaved chlorhexidine	232
Anhydrotetracycline and 4-epianhydrotetracycline in commercial tetracycline and aged tetracycline products	233
Physicochemical studies of the stability of penicillin salts	234
Light sensitivity of tetracyclines	235
Hygroscopic properties, thermostability, and solubility of oleandomycin salts	236
Stability of orotic acid and its amine salts in aqueous solution	237
Factors influencing the stability of aspirin tablets	238
Stability of aqueous solutions of sodium aminosalicylate	239
Hygroscopic properties of various preparations of erythromycin	240
Physicochemical studies on the decomposition of aminosalicylic acid and its salts	241
Stabilities of aqueous solutions of 2-diethylaminoethyl-3-methyl-2-phenylvalerate HCl and methobromide	242
Investigation of properties of penicillin G salts	243
Stability of ferrous iron tablets on storage	244
Stability of aspirin aluminum compounded with antacids	245
Dissociation and stability of insulin zinc and sodium insulin oligomers by bile salt micelles	246
Thermal stability of various epinephrine formulations	247
Forms of *p*-aminosalicylic acid and its salts in pharmaceutical practice	248

Melting Point

The melting point plays a crucial role in the comminution and tableting of drugs [108]. Because low-melting compounds tend to be plastic rather than brittle, they comminute poorly and frictional heating causes melting and deposition of the drug on the screens and pins of the mill causing "blinding." Therefore it may be difficult to obtain a free-flowing powder.

The melting point can have important implications for particle bonding during tablet compression. On compression, bonding occurs by point welding at the deformed or fragmented particle surfaces. At a certain temperature and pressure, a low-melting material would be expected to have better bonding. The pressure on the powder and the eutectics formed with other excipients can depress the melting point further. Gould [108] lists the melting points and heats of fusion of salts of an experimental drug candidate and suggests that the low melting point and heat of fusion for the mesylate salt would make it the most suitable candidate for bonding reasons of the salts studied for a direct compression tablet. Since the melting points of compounds are reduced under pressure, the solubility of salt forms would be expected to increase with increasing pressure. This can potentially cause the formation of solutions of the salts in the film of adsorbed moisture on the surface of the drug and excipient particles which may have an effect on drug bonding [249].

Hygroscopicity and Strength of Conjugate Acid

The effect of hygroscopicity and the strength of the conjugate acid is especially important for compacted dosage forms where most of the available moisture comes from the excipient rather than the drug. Salts of mineral acids have a lower pH and higher solubility in the available moisture and have a tendency to be less stable than the sulfonate or carboxylate[108].

Other Properties

The salt form can influence other physicochemical properties of a drug substance. The effect of the salt-forming radical on surface tension, ion-pair extraction, solubility, and zwitterion flux have been studied.

Surface Activity

The influence of the anion on the absorption of dextromethorphan and tetracycline in the rat stomach was studied [250,251]. A linear relationship existed between the rate of absorption from buffer solutions of anions being investigated and their surface tensions. Therefore, the absorption process was attributed to the surface activity of the various salts and not to their lipid solubilities. These results are similar to those reported on the surface activity of various phenothiazine salts [252].

Ion Pairing

Higuchi and co-workers extensively studied the physicochemical basis of the ion-pair extraction of pharmaceutical amines [253,254]. They found that the distribution ratios between an organic layer and water were highly dependent on the concentration and nature of anion present. Less hydrophilic anions yielded more readily extractable ion pairs. The entropy change associated with transfer of the different anions between phases is the mean controlling factor in the extraction process [255].

Zwitterions

Salts of zwitterions increase the solubility in both polar and nonpolar media as well as the flux in skin and membranes [256,257]. The rules for counterion selection followed the covalency of the salt formed and the solubilities of the salt in both the solvent and the membrane.

Biopharmaceutical Studies

The amount of drug absorbed from a dosage form and the onset, duration, and intensity of action depend on the physicochemical properties of the drug. These differences are due primarily to differences in amount and rate of absorption. Administration of a drug in salt form can be frequently used to alter the solubility and dissolution rate in order to increase bioavailability.

Influences on Bioavailability

Disintegration

The effect of formulation on the bioavailability of warfarin sodium was compared with that of warfarin [160,258]. Absorption from a lactose-base tablet was no better with warfarin sodium than with warfarin free acid. With starch in place of lactose, salt absorption was even worse, in spite of the fact that the in vitro water dissolution rate for warfarin sodium is 350 times that of warfarin free acid; yet, the latter exhibited rapid and complete absorption in vivo. The primary factor accounting for this apparent anomaly is that a strongly acidic medium is necessary for tablet disintegration. Following initial exposure to 0.1N HCl, in vitro dissolution of the warfarin tablet in pH 7.4 buffer was 14 times faster than that of the sodium salt, a result that explained the otherwise contradictory in vivo blood level. Therefore, absorption was ultimately dependent upon gastric emptying rate and gastric pH, as long as the formulation distintegrated properly in the stomach.

Common-Ion Effect

Hydrochloride salt formation does not necessarily enhance the bioavailability of basic drugs due to the common-ion effect. This is illustrated in studies comparing the absorption of the tetracyclines with that of their salts [156,251,259–262] or salts of lincomycin [263]. Administration of the free base of several tetracyclines resulted in higher plasma levels than after administration of the hydrochloride salt. Similar to reports for the tetracyclines, the hydrochloride salt of lincomycin did not produce as great an area under the curve as the hexadecylsulfamate salt. It is likely that the differences in bioavailability are due to differences in solubility at gastric pH because of the common-ion effect. It can be postulated that stomach emptying rather than in vivo dissolution is the rate-limiting factor in absorption. This may be a plausible explanation, since subcutaneous administration of the various lincomycin salts did not produce significantly different fractions absorbed, regardless of which salt was administered.

Ion Pairing

The absorption of drugs across membranes is usually attributed to the unionized form [264]. Many drugs are only weakly acidic or basic and a large fraction of the drug exists in the unionized form at some pH found in the GI tract. However, some drugs are sufficiently strong acids or bases so as to be largely ionized throughout the GI tract. An example of this is proxicromil [265], which, however, is reported to be reasonably well absorbed. The authors indicate that proxicromil possesses intrinsic lipophilicity and requires only charge neutralization to partition into lipoidal phases. It was suggested that ion-pair formation with naturally abundant cations such as sodium plays a significant role in the absorption of proxicromil.

The increase in lipophilicity and the transport of various cationic drugs across an artificial lipid membrane [266], rabbit skin [267], or human skin [268] has been attributed to ion-pair formation with the carboxylate anion of oleic, lauric, or myristic acids.

The absorption characteristics of an ionized dianionic drug was claimed to be altered upon ion association with a quaternary ammonium salt [269]. Using a human

buccal absorption test, approximately a tenfold increase in the uptake of cromoglycate ion in the presence of alkylbenzyldimethylammonium chlorides was reported compared with uptake of the drug alone.

Propranolol laurate was investigated for the possibility of using a fatty acid salt as an alternative to polymeric formulations in a sustained-release preparation [20]. Studies in dogs showed an increase in bioavailability over the immediate release or sustained-release formulations of propranolol HCl. Explanations offered for the improved bioavailability include association of the drug with a fatty acid, micellar solubilization, or ion-pair association.

Ion-pair absorption of drugs has been reviewed [270]. The authors conclude that ion-pair absorption may occur, but that the literature on the subject is controversial.

Bioavailability

The bioavailability in rats of magnesium and calcium salts of indomethacin was compared with that of indomethacin [271]. The mean plasma levels after a single oral dose of the salts were significantly higher and the area under the plasma curve after multiple oral dosing of the salts was significantly larger than after administration of indomethacin free acid. There was no significant change in plasma protein binding between the two groups of rats. The increased absorption was attributed to enhanced lipid solubility and increased solubility in bile and intestinal juice.

Aerosolized pentamidine isoethionate is retained in the lung and appears to prevent *Pneumocystis carinii* pneumonia in many AIDS patients; in an attempt to find salts that would reduce the airway irritation, the gluconate and lactate salts were also prepared [272]. More than 50% of pentamidine, aerosolized as the three different salts, is retained in the lung for at least two weeks after a single dose, and each salt produced a high lung-to-extrapulmonary drug ratio. None of the three pentamidine salts produced histological evidence of organ toxicity even when aerosolized daily for two weeks at very high doses.

In a comparison study of ampicillin sodium and potassium with ampicillin trihydrate [273], the absorption rate constants were higher for the salt forms, but the overall bioavailability was unaffected. This indicates that the dissolution of the ampicillin trihydrate was the rate-limiting step in its absorption.

Salt forms of a compound may influence the kinetics of drugs which exhibit nonlinear pharmacokinetics. For example, the area under the plasma concentration–time curve of unmetabolized drug from aminosalicylic acid administration was smaller than for salts of this compound [171,274–276]. This was attributed to concentration-dependent metabolism during absorption. At a high rate of absorption, the metabolic processes become saturated and more unmetabolized drug remains in the blood. At a low absorption rate, as for the free acid, a higher percentage of drug is metabolized.

The relative bioavailability of the vasodilator naftidrofuryl as the oxalate or citrate salt was studied [277]. The relative rate of absorption, but not the extent, was higher for the citrate salt than for the oxalate salt. The degree of intersubject variability was similar after administration of either compound.

Blood levels in rabbits were significantly higher during the 30 min to 2 h post-administration period after rectal administration of suppositories containing amino acid and choline salts of phenobarbital compared with those from a suppository of phenobarbital [278].

A significant amount of work has been done on the salts of theophylline [150,279–281], the penicillins [153,282–291], and ampicillin [292].

Throughout the years numerous studies have been, and continue to be, published on erythromycin and its salts and esters [293–300]. The pharmacokinetics and bioavailability of various erythromycin salts and dosage forms have been discussed [301], including the effects of clinical protocol and formulation differences on drug serum levels.

Steady-state bioavailability and day-to-day variability of plasma levels of metoprolol were evaluated in 18 subjects in a crossover study of a multiple unit (CR) and a single unit (OROS) delivery system [302]. The CR contained metoprolol succinate and the OROS an equal dose of metropolol fumarate. Although there were minor dissimilarities in the in vitro dissolution profiles, perhaps the result of different salts or delivery systems, both formulations were bioequivalent for C_{max} and area under the curve (AUC); however, the day-to-day variability of AUC was significantly lower for the CR formulation. The authors concluded that salt forms did not influence the variability, which was rather due to formulation-related differences. Additional references on the influence of salts on bioavailability are given in Table 7.

General Pharmacy

Pharmacological Effect

Calcium pectinate, the insoluble salt of pectin, can potentially be used as a colon-specific drug-delivery system compressed into tablets with insoluble drug [350]. Like pectin, calcium pectinate can be decomposed by specific pectinolytic enzymes in the colon, but retains its integrity in the small intestine.

The effects of chlorpromazine hydrochloride and quaternary chlorpromazine chloride on the central nervous system were examined [351]. The quaternized compound was less potent and more toxic to rodents than the parent tertiary compound.

A series of salts of 9-aminoacridine and its derivatives were screened for antifungal and antibacterial activity [352–354]. The antifungal action paralleled the length of the carbon chain of the anion. These results were attributed to the lipid solubility of the salts which would allow them to pass through the cell wall of the microorganism more readily, possibly as an ion pair.

The efficacy of bases or salts as topical anesthetics for relieving cutaneous itch, burning, and pain in unbroken skin was investigated [355]. Aqueous solutions of the salts did not alleviate itching or burning in any of the subjects; however, saturated solutions of their bases in a mixture of water, 40% alcohol, and 10% glycerol were claimed to be effective. Transport phenomena across the stratum corneum are often dependent on the polarity of the drug and vehicle and on binding of the drug to keratin. Additional references on pharmacological effects can be found in Table 8.

Other Studies

Numerous investigators [179,180,183,201,370–372] reported on the formation of polymer–drug salts or resinate–drug salts as an approach to the physicochemical design of dosage forms. These include organic carboxylic acids with anionic exchange resins

TABLE 7 References on Bioavailability

Topic	Reference
Comparison of the GI absorption of aluminum acetylsalicylate and acetylsalicylic acid	158
Unusual dissolution behavior due to film formation	159
Effect of salts on release of proflavine	303
Drug absorption of aspirin and derivatives from the rectum	304
Effects of various substances on the absorption of tetracycline in rats	305
Effects of dosage form upon the GI absorption rate of salicylates	134
Determination of in vivo and in vitro release of theophyllineaminoisobutanol in a prolonged-action system	306
Ion-exchange resin salts for oral therapy (carbinoxamine)	307
Latentiation of dihydrosteptomycin by pamoate formation	11
Solid-state ophthalmic dosage systems in effecting prolonged release of pilocarpine in the cul-de-sac	18
Absorption of erythromycin in various pharmaceutical forms	308
Comparative study of the absorption of drugs from old and new rectal preparations	309
Absorption of salts of streptomycin, neomycin, viomycin, and streptothrycin	19
Influence of salt on onset and duration of tolbutamide action	154
Blood levels produced by three theophylline-containing elixirs	310
Oral absorption characteristics of naproxen	311
Effect of food on absorption of a new form of erythromycin propionate	312
Anion effect on the absorption of tetracycline from the rat stomach	251
Blood levels following oral administration of different novobiocin preparations	313
Absorption of iopanoic acid and its sodium salt	314
Oral absorption of secobarbital (quinalbarbitone) and its sodium salt	315
Absorption rate of barbiturates in humans	316
Morphine and atropine mucate	317
Excretion of bephenium salts in urine of human volunteers	318
Antituberculosis activity of polymethylenebis(isothiuronium) salts	319
Prolonged antitussive action of a resin-bound noscapine preparation	320
Pharmacology of sulfapyridine and sulfathiazole	321
Evaluation of plasma concentrations of propoxyphene utilizing a hybrid-principal-component analysis of variance technique	322
Antrycide, a new trypanocidal drug	323
Pralidoximemethanesulfonate, plasma levels and pharmacokinetics after oral administration to humans	324
Intestinal absorption of pralidoxime and other aldoximes	325
Blood plasma levels and elimination of salts of pralidoxime (2-PAM) in humans after oral administration	326
Enhancement of GI absorption of a quaternary ammonium compound by trichloroacetate	327
Relative bioavailability of phenoxymethylpenicillin preparations	328
Behavior of diclofenac salts in polar and poorly polar solvents	52
Sulfadiazine salts to reduce gingivitis	329
In vitro/in vivo evaluation of a liquid sustained-release dosage form of chlorpheniramine	330
Biliary excretion of erythomycin base and erythromycin estolate	331
Pharmacodynamics of fosfomycin after intravenous administration to humans	332
Pharmacodynamics of phosphonomycin after oral administration to humans	333
Comparative studies of distribution, excretion, and metabolism of ^{3}H-hydroxyzine and its ^{14}C-methiodide in rats	334

TABLE 7 *(continued)*

Reference	Topic	Reference
158	Pharmacokinetics of ampicillin trihydrate, ampicillin sodium, and dicloxacillin sodium following intramuscular injection	335
159	Physiological disposition of fenoprofen in humans, pharmacokinetic comparison of orally administered calcium and sodium salts	336
303	Pharmacokinetic comparison of two oral capsule formulations of ketoprofen–lysine salt	337
304	Bioavailability of fluoride in postmenopausal women	338
305	Pharmacokinetics of different formulations of ibuprofen and aspirin	339
134	Blood levels of isoetharine	340
306	Bioavailability of calcium from different salts	341
307	Relative bioavailability of the hydrochloride, sulfate, and ethyl carbonate salts of quinine	342
11	Absolute and relative bioavailability of lithium dosage forms in the beagle dog	343
18	Comparative bioavailability evaluation of erythromycin estolate capsules vs. enteric-coated erythromycin base tablets	344
308	Pharmacokinetics of quinidine in humans after intravenous, intramuscular, and oral administration	345
309	Intravenous pharmacokinetics and in vitro protein-binding studies of two new erythromycin salts	346
19	Comparative pharmacokinetics of zinc-65 sulfate and zinc-65 pantothenate injected intravenously in rabbits	347
154	Influence of first-pass effect on the systemic availability of propoxyphene	348
310	Rapidly dissolving tablets of theophylline	349
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[180,371] and basic drugs with sulfonic acid or carboxylic acid resinates [201]. The effects of various polymers and ion-exchange resins on drug release from hydroxypropylmethylcellulose (HPMC) [373], and polymer–drug salts [179,370,372] were studied. Most reports describe a retarded drug release because of the lower solubility of the drug–polymer or drug–resinate salt. Other papers reported on the coating of resinate–drug salts with different materials to determine the effect on the drug release rate [374–377]. Additional references on general pharmacy are given in Table 9.

Toxicological Considerations

The toxicity aspects of salts of a drug must include the pharmacological properties of the cation or anion used to form the salt as well as those of the free drug [388].

Toxicity of Salt Ion

Toxic reaction from ingestion of calcium salts of drugs is rare. If hypercalcemia occurs, calcium deposits in the kidney can cause a reduction of renal function. The principal toxic effects of lithium also involve the kidneys. Small amounts of lithium do not result in apparent damage; large amounts, however, can lead to irreversible damage.

TABLE 8 References on General Pharmacy and Pharmacological Effect

Topic	Reference
Morphine and atropine mucate	317
Naloxone mucate and morphine blockade in the mouse	356
Differential excretion of bromide and chloride ions and its role in bromide retention	357
Pharmacological study of calcium methionate	358
Synthesis and in vitro fungistatic evaluation of some N-substituted amide and amine salts of sorbic acid	359
Antiamebic studies on clamoxyquin in vitro and in experimentally infected animals	360
Adjunctive value of oral prophylaxis with the oximes pralidoxime lactate and prolidoxime methanesulfonate to therapeutic administration of atropine in dogs poisoned by inhaled sarin vapor	361
Pralidoxime methanesulfonate and atropine in the treatment of severe organophosphate poisoning	362
Efficacy and limitations of oxime-atropine treatment of organophosphorus anticholinesterase poisoning	363
Antitussive activity of enoxolone and its derivatives	364
Pharmacological properties of glycyrrhetinic acid hydrogen succinate (disodium salt)	365
Ganglionic blocking activity of diastereomeric dimethylaminobornyl acetates and their methiodides	366
A new potent nonnarcotic antitussive, 1-methyl-3-[bis(2-thienyl)methylene]piperidine; pharmacology and clinical efficacy	367
Comparison of the anticoagulant effect of the sodium and calcium salts of a new potent heparin after SC injection in beagle dogs	368
Local anesthetics: pharmacology and clinical applications	369

An apparent correlation was observed between lithium dosage and sodium intake [389]. With a low lithium dosage or high sodium intake rats were able to excrete all lithium given and sustained a reversible polyuria. Conversely, large amounts of lithium or reduced sodium intake resulted in irreversible kidney damage. Ammonium ion can be toxic in high concentrations and initiate CNS derangements. Oral toxicity of magnesium salts is rare, but may be present in the face of renal impairment. The symptoms include hypotension, muscle weakness, ECG changes, sedation, and confusion.

Sulfate ions given orally tend to be minimally absorbed and may act as a laxative. The nitrate ion is irritating to the GI tract, causing nausea and gastric distress. In addition, intestinal bacteria may convert the nitrate ion to nitrite which oxidizes hemoglobin to methemoglobin. The citrate ion can form a soluble complex with calcium which is poorly dissociable and rarely causes any toxic reactions. Tartrate ions are usually absorbed only minimally from the GI tract, but high concentrations reaching the circulation can cause renal damage. Acetate and lactate ions are normal metabolites and appear to be well tolerated in relatively large amounts. Iodide and bromide ions can produce iodism [390] and bromidism, respectively. Bromides are used as ingredients of some nonprescription preparations [391–394]. Bromide has a half-life of 12 days and tends to accumulate if taken for prolonged periods or if used by patients with low renal function.

Toxicity of Salt Form

Provided the salt-forming agents are nontoxic, the relative toxicities of a series of salts of a compound often reflect their aqueous solubility. For example, the ulcerogenic effect of five different salts of alprenolol was tested against placebo in a porcine esophageal model [395]. The salts with high water solubility, such as the hydrochloride and fumarate, produced the most serious esophageal lesions, whereas salts with lower solubility (benzoate, maleate, and sebacate) had no irritative effect. Similar reasoning has been used to explain the relative toxicities of various salts of quinapyramine [323], propoxyphene hydrochloride in rodents vs. the napsylate salt [396], salts of benzphetamine and etryptamine [397], and the sodium salt of iopanoic acid [398].

Salts of greater water solubility are not, however, always more toxic, and less soluble salts are not always less toxic. This was illustrated with methylpyridinium-2-aldoxime iodide (2-PAM iodide). In order to increase the water solubility of 2-PAM and eliminate undesirable side effects due to the iodide ion, various inorganic and organic salts were prepared [390]. Even though the aqueous solubility of most of these salts was many times higher than that of the iodide, their toxicity on a molar basis was not significantly different, with the exception of the dihydrogen phosphate salt which was 15% more toxic. Toxicity information about a representative group of oximes and their salts has been published [399]. Additional references on toxicological considerations of salt formation are given in Table 10.

Decision Tree for Salt Selection

As amply evidenced by the examples in this article, the range of salt forms available to the pharmaceutical scientist is broad and far reaching. The selection process, there-

TABLE 9 References on General Pharmacy

Topic	Reference
Relationship between salt form and biological activity of an antihypertensive	166
Effect of nonionic surfactants on the release rate of drugs from suppositories	131
Effect of metallic salts of EDTA on blood coagulation	378
Correlation between biological activity and some chromone-2-carboxylate salts	379
Hydrophobic anionic gel beads for swelling-controlled drug delivery	380
Complex formation between macromolecules and drugs; binding of drugs to the membrane in dialysis studies	381
Diffusion of salts through a lipoprotein interface	382
Influence of various counterions on the interaction of chlorhexidine with the hydrophilic contact lens polymer, poly(2-hydroxyethyl methacrylate)	383
Preparation and evaluation of directly compressed indomethacin, indomethacin sodium, and indomethacin meglumine tablets	384
Drug release from compression-molded films; preliminary studies with pilocarpine	385
Sparingly soluble salts for the preparation of oral sustained-release suspensions	386
L-649,923, the selection of an appropriate salt form and preparation of a stable oral formulation	387

TABLE 10 References on Toxicological Considerations

Topic	Reference
Toxicity of aspirin salts	400
Toxicity of polyene antibiotics	401
Toxicity and absorption of 2-sulfanilimidopyridine and its soluble sodium salt	402
Sorbic acid as fungistatic agent for foods	403
Toxicity and distribution of erythromycin	404
Further toxicological studies with erythromycin	405
Pharmacology and toxicology of erythromycin estolate	406
Erythromycin propionate, a review of case reports for side-effect data	407
New class of antibiotic salts of reduced toxicity	24
GI intolerance to oral iron preparations	408
Comparative toxicology of iron compounds	409
Influence of the dissolution rate of lithium tablets on side effects	175
Toxicity and tissue distribution studies on the hydrochloride, bismuth iodide complex, and a resinate of emetine	410
Bacitracin zinc in pharmaceutical preparations	195
New approach to quaternary ammonium compounds	203
Pharmacology of choline theophyllinate	411
Methemoglobinemia resulting from absorption of nitrates	412

fore, needs to be rational and streamlined to avoid unnecessary work. The inexperienced formulator can unwittingly request the medicinal chemist to prepare a "laundry" list of salt forms of the drug candidate for the presumed purpose of preformulation testing. Unfortunately, by the time all these salts have been isolated and characterized and the physicochemical tests performed, several valuable grams of test substance may have been consumed and valuable time may have been lost to the critical commercialization path. Similar views have been expressed by others [108,228,413,414]. Hence, there is a need for a decision tree to create a prototype thought process whereby a suitable salt form can be chosen in an efficient and timely manner with few false starts and the minimum expenditure of resources. The following decision tree (Fig. 1) is proposed to aid in this selection.

Salts of Acidic Compounds

If a hypothetical situation is chosen wherein a free acid form of a compound is selected for clinical development, it should be possible to hone in on the salt form of choice without unnecessarily burdening the development process per se.

Is a Salt Form Needed?

The first decision to be made concerns the viability of the neutral compound per se. If it is an oil, a solid form is preferred in most cases because an oil is difficult to purify and characterize, and it is difficult to maintain its potency. An oil is difficult to ship because of container compatibility and spillage; it is usually oxygen sensitive and needs to be packaged under nitrogen. Furthermore, batch-to-batch variability can create a real

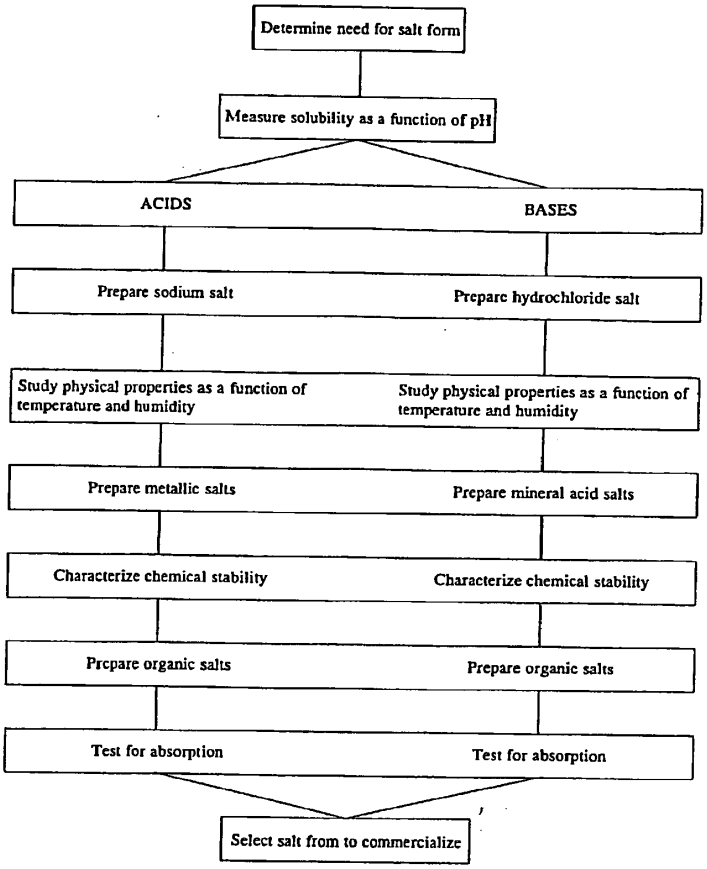

FIG. 1. Decision tree for salt selection.

problem for quality control. Exceptions include cases where a soft gelatin capsule preparation (or hard-shell starch capsule) is preferred for bioavailability purposes, for example, for an emulsion to target lymphatic absorption.

An oil may be acceptable for parenterals, if organic solvents are to be employed to facilitate administration. A cosolvent system is often used when there is no other way of enhancing the solubility of the free acid or base form [124]. Cosolvents are used for water-insoluble drugs such as taxol and cyclosporin.

Should the free acid be a high-melting water-soluble solid, there is generally no need to prepare a salt form. The importance of these criteria is discussed later.

Solubility as a Function of pH

If the free acid is a solid of reasonably high melting point (for example, >90°C), the solubility as a function of pH should be determined. To avoid the influence of buffer counterions on the solubility results, a pH-Stat to control pH is recommended. Likewise, control of ionic strength needs careful consideration if a metallic salt is employed. From a plot of log solubility vs. pH, the pKa of the substance can be calculated by the method outlined by Kramer and Flynn [124]. Should the solubility of the free acid be low (<100 μg/mL) at physiological pH (~5–8), and the therapeutic dose in the 100 mg range, bioavailability is most likely highly dissolution-rate dependent. In such cases, accepted pharmaceutical manipulation processes may need to be employed, including micronization, utilization of activated disintegrants, or a buffer to create a soluble salt form in situ during dissolution, or the addition of a solubilizing agent to the solid dosage form to improve wetting and enhance absorption (cyclodextrin or a surfactant such as a polysorbate).

Preparation of the Sodium Salt

The first salt form that should be prepared is the sodium salt if the patient does not have a restriction on sodium intake.

Unfortunately, the sodium salt of indomethacin was implicated in causing intestinal perforations when formulated in an osmotically driven device [415]. (Note that potassium bicarbonate was included as the osmotic driving agent.) Cases recording the adverse consequences of sodium salts per se are rare and the sodium salt therefore continues to be the salt form of choice.

Determination of the Physical Properties as a Function of Temperature and Humidity

If the sodium salt is sensitive to heat and moisture, its critical humidity at room temperature needs to be determined. Should the compound be hygroscopic at approximately 30% rh at room temperature, another salt form should be assessed since handling problems (stickiness, adherence to machine parts, flow, etc.) during manufacturing could be difficult and expensive to overcome. Moisture adsorption can also adversely affect stability (discussed later). Needless to say, if the salt shows no signs of crystallinity (no birefringence under polarized light), such amorphous materials are generally developed no further.

Frequently, a deliquescent or hygroscopic substance adsorbs moisture only to a stoichiometric amount. A possible strategy then is to investigate the formation of a stable hydrate by crystallizing the sodium salt from a water or aqueous alcoholic solvent system. If the water of hydration is retained at or above about 70°C in a well characterized mono- or dihydrate, this form might be a suitable candidate for commercialization. The requisite studies to characterize the resistance to moisture loss on milling or exposure to low humidity would need to be carried out before such a decision was made.

Frequently, hydrates exhibit a lower rate of dissolution than their anhydrous counterparts, and hence the possibility of reduced bioavailability would need to be assessed. In the case of piroxicam, the monohydrate exhibited a proclivity to induce ulceration in humans because of its increased GI contact time due to slower dissolution than the corresponding anhydrate.

At this point it is useful to examine the samples for a change in crystal structure, using techniques such as hot-stage microscopy, x-ray diffraction, or differential scanning calorimetry/thermogravimetric analysis (DSC/TGA). In this way, the proclivity for polymorphic transformation can be assessed early before surprises are found later in the development program. A decision can then be made to pursue the stable polymorphic form of the salt or to choose a completely new salt form.

Preparation of other Metal Salts

If the sodium salt proves to be unsuitable, a series of other metal salts may be tried, such as potassium, calcium, magnesium, or zinc. As the ionic cation potential increases, the bond distances become shorter and can result in higher melting points, and perhaps lower solubility and higher chemical stability [108,219,228]. Cations such as lithium, copper, or aluminum should be avoided because they may produce pharmacological effects.

Calcium salts are usually less hygroscopic than sodium salts and exhibit a characteristic negative heat of solution. This means that the solubility at 37°C is usually lower than at room temperature, creating a problem if the absorption is dissolution-rate dependent.

The alkalinity of metal salts can cause taste problems as well as handling problems by attacking metal machinery or leaching metals out of glass. In these cases, organic salts or other less alkaline salts should be explored.

Chemical Stability

Before a final selection is made, chemical stability under stressed heat and humidity conditions should be assessed. As a general rule, a tight, dense crystal with a high melting point tends less to react with the atmosphere or with excipients. Furthermore, in the formulation of a hydrolytically unstable compound, salts of low solubility result in less of the compound in solution and available for degradation. A suitable example is that of penicillin suspensions where procaine and benzathine salts have greater stability in aqueous vehicles than the corresponding potassium salt [218], although the thermal stability is better for the sodium or potassium salts in the dry state.

Amine salts (e.g., meglumine) have been employed with contrast agents such as diatrizoic acid to increase solubility. This cation has the particular advantage that autoclaving lowers the pH compared with the sodium salt [416,417]. This is due to the greater relative temperature sensitivity of the pKa for these amines compared to that of sodium hydroxide. As a result, there is less glass attack and less precipitation upon heat treatment.

Arginine has been used as an additive for cephalosporins where the pH of the highly concentrated solution is lower than that obtained when sodium carbonate is used for neutralization. For solutions of the same concentration, greater retention of potency is obtained after reconstitution for the arginine salt compared to the sodium salt [418].

Absorption Test

If the salts discussed so far meet the physicochemical criteria, and an absorption problem is suspected, measuring the octanol-water partition coefficient can sometimes serve as a predictor of absorption. Ultimately, there is no substitute but to measure bioavailability in an animal model.

To increase absorption, organic cations should be prepared, such as amino acids (lysine, arginine), glucoamines (meglumine), or hydroxyamines (diethanolamine or triethanolamine). For low potency compounds, an amino acid salt could result in a substantial molecular weight increase, requiring a much higher total dose, thereby negating the beneficial solubility enhancement. Their usefulness should be explored, however, because these salts usually increase solubility and therefore absorption. A good example is ibuprofen lysinate which exhibits greater aqueous solubility and better absorption than the free acid [339]. Unlike ibuprofen alone, this salt form does not need to be film-coated to prevent loss of potency on storage.

Salts are also employed to increase the absorption rate and hence speed of action, particularly for anti-inflammatory drugs (e.g., naproxen sodium vs. naproxen free acid, and diclofenac potassium vs. diclofenac sodium).

Salts of Basic Compounds

The reasons whether a salt form is preferred over the free base are the same as those for the free acid. Similarly, the reader is referred to the earlier discussion of solubility as a function of pH.

Preparation of the Hydrochloride Salt

The hydrochloride is by far the most popular salt form of basic compounds. By the simple addition of this mineral acid, most bases ionize and give a crystal adduct. The solvents for synthesis are usually selected by the medicinal chemist to accommodate the solubility of the neutral substance. The liquids employed for isolation of the salt are usually an alkane that is miscible with the reaction mixture. The range of anions available for salt formation depends on the pKa of the conjugate acid relative to the basicity of the drug itself. There should be at least one unit of separation between the pKa of the basic drug and that of the anion. Since hydrochloric acid is a very strong acid (pKa $\sim$ -6), it can form a salt with most basic drugs, in contrast with acetic acid, for example, which has a pKa of $\sim$ 4.8.

Determination of the Physical Properties as a Function of Temperature and Humidity

The hydrochlorides of weakly basic amines tend to disproportionate [166,215]. A similar phenomenon occurs during freeze-drying where the loss of hydrochloric acid is facilitated by the high vacuum applied. Thermal methods of analysis such as TGA and DSC (preferably simultaneous) are particularly useful in detecting such incompatibilities early in the development program.

Another frequent problem encountered with amine hydrochlorides is the common-ion effect. In the presence of chloride ion, such as in gastric fluid, the solubility of the

salt form is repressed because solubility is an equilibrium phenomenon, and the absolute value is controlled by the solubility product constant. Therefore, absorption rate may be low because release from the dosage form is dissolution-rate limited. This may vary from patient to patient, depending on the acidity level of the GI tract, and could lead to overdosing in conditions such as achlorhydria. In these cases, the formulator is tempted to micronize the free base and design a rapidly dissolving dosage form. Dissolution rate would, however, still be limited by the presence of chloride ion. A more favored option is to prepare a salt that has a higher innate solubility than the hydrochloride, but this does not solve the problem completely unless the drug is absorbed before the less soluble hydrochloride has a chance to form and precipitate.

The common-ion effect can also influence the the formulation of a parenteral, particularly in adjusting tonicity and osmotic pressure. Clearly, the use of sodium chloride is contraindicated when solubility is reduced because of the common ion effect. Substances such as dextrose are frequently employed as isoosmotic agents in these instances. The use of sodium chloride is not contraindicated when a "salting in" phenomenon is observed, as with some hormonal steroids. For example, normal saline increases the solubility of 17-deacetylnorgestimate 20-fold.

The strategies outlined in the section on acid salts equally apply if the hydrochloride is found to be hygroscopic or deliquescent. Because of the highly polar nature of the crystal surface, hydrochlorides frequently attract and retain moisture which can lead to decomposition and/or powder-handling problems. Metal surfaces can be attacked because the wetted powder frequently exhibits a very low pH.

Preparation of Other Mineral Acid Salts

Mineral acids other than hydrochloric, such as sulfuric, phosphoric, and hydrobromic, have been employed principally to reduce hygroscopicity and perhaps the acidity of a resulting solution. Sulfonic acids are being used more and more for various drug candidates because they can be manipulated to influence dissolution rate and reactivity. For instance, the mesylate salt is frequently highly soluble and therefore dissolves quickly. On the other hand, the hydrophobicity of the sulfonate can be increased by the incorporation of longer carbon chains (esylate, edisylate, isethionate, besylate, tosylate, pamoate (embonate), napsylate, xinafoate, and estolate). An example is propoxyphene, which with the help of the napsylate could be formulated in combination with aspirin, with which it is otherwise incompatible [419]. Apparently, the napsylate reduces wettability and hygroscopicity and therefore decreases the opportunity for the two compounds to react in a layer of moisture between them.

The use of the pamoate salt of the anthelmintic pyrantel allows the formulation of a long-acting, stable oral suspension with a local action in the intestine.

Chemical Stability

The reader is referred to the discussion on chemical stability in the section on acid salts. Again, a higher-melting crystal is chemically more stable [219]. Planar anions such as the napsylate or xinafoate are useful in raising the melting point because they impart symmetry to the crystal lattice. It therefore stands to reason that if a lower melting point is desired in order to generate an oil or a waxy material, a flexible nonsymmetrical anion such as oleate, undecylenate, or decanoate may be of some use. Salts of this nature are used in dosage forms such as oily injection depots or freon-based inhalation acrosols.

Chemical stability also correlates with wettability or interfacial tension between the crystal surface and moisture. Polyhydroxy acids are much more hydrophilic than the sulfonic acids described above and would be expected to be chemically less stable both in the neat or in the formulated state.

Preparation of Organic Salts

A reason that alternatives to mineral acid salts are sought relates to the high resulting acidity of solutions (and in liquid layers surrounding solid crystals) which can lead to container incompatibility and metal attack during processing. This acidity can cause pain on injection and precipitation in the parenteral admixture or in the vein, sometimes resulting in thrombosis. High acidity can also cause interactions with excipients and other drugs. Many of the problems can be avoided by choosing a hydroxylated conjugate acid with a pKa of about 3–4. Options include formate, acetate, glycolate, lactate, malate, gluconate, tartrate, citrate, succinate, malonate, fumarate, and maleate. Depending on the molecular weight of the parent compound, these anions rarely exhibit toxicity. However, if the total body load (insult) on the biological system is too great, toxic events eventually occur (caused by the drug or its conjugate anion); for example, maleate was identified to be responsible for causing renal failure during a toxicology study of a cannabinoid derivative.

Although formic acid is nontoxic per se, its salts are often contaminated with methyl and ethyl formate esters (reaction-solvent side products) which are toxic; this may account for its being used less than others.

Conjugate acids impart a degree of hydrophilicity to the crystal lattice with the result that the crystals are water soluble and frequently hygroscopic and have a lower melting point than the corresponding mineral acid salts. The melting point can be influenced either by size of the anion (acetate and maleic salts usually have a comparatively high melting point) or by symmetry (fumarates melt at lower temperatures than the corresponding isomer (cis-trans) maleates).

High water solubility is an advantage to the formulator since there is usually a higher dissolution rate as well as a higher rate and extent of absorption. For parenterals, organic cosolvents are to be avoided if possible, and increased aqueous solubility is a distinct advantage. By far the best salt to increase water solubility is the lactate. For parenterals it can be formed in situ during processing, and many lactates are used for injectables. Such salts, however, are invariably very hygroscopic and exhibit a low melting point. Thus, for solid dosage forms, they are cohesive and difficult to mill and process, and a compromise must be made in which another hydroxy acid, such as the acetate, is chosen.

Organic salts do not necessarily eliminate drug–excipient interactions. For example, microcrystalline cellulose has been shown to increase degradation of enalapril maleate [420] by reducing heats of fusion. Such a finding, however, is fairly unusual and the decision to examine drug–excipient compatibility can usually be postponed until the final selections are made [421].

Absorption Test

Absorption may be improved by selecting a salt form with greater aqueous solubility. Since absorption is a kinetic rather than an equilibrium phenomenon, the controlling

factor is the rate at which dissolved molecules are presented to the absorbing membranes. Soluble salt forms influence the dissolution rate and the kinetic phenomenon usually to a greater extent than reduction of particle size or the addition of a surfactant to an insoluble free base compound.

Absorption can be impaired when a hydrochloride precipitates in gastric juice due to the common-ion effect. In such cases, a hydroxy acid anion is clearly advantageous since dissolved molecules are more likely to be absorbed before the solubility product is exceeded for the chloride. Similarly, if a salt is insoluble at, say, pH 5(c.g., maleate pKa_2 is 6.3), absorption is likely to be compromised. Often, however, the situation is helped considerably when the dissociated anion acts as a buffer species with the salt and maintains the pH at a sufficiently low value that dissolution occurs in the localized cybotactic region. The anion is apparently diluted by GI fluids before precipitation can occur or ion exchange causes the formation of insoluble salts.

Absorption via the lymphatic system can also be enhanced by the formation of lipid soluble salts such as the oleate. The salt can be dissolved in oils or monoglycerides to assist in forming a microemulsion which is optimal for lymphatic transport. Long-acting depot injections can be enhanced by the formation of insoluble salts.

Utility of the Decision Tree

The decision tree shown in Fig. 1 was designed with the efficiency of the pharmaceutical scientist in mind. Although choice of a salt form is frequently beyond the formulator's control due to cost, toxicity, level of impurities, number of polymorphs, and yield, it is the pharmacist who is burdened with the selection responsibility. There is a choice. Formulators can either approach the matter arbitrarily in an empirical fashion or use a rigorous scientific method. Furthermore, they need to be efficient since this decision lies fairly and squarely on the critical path of the drug's development schedule, and any unnecessary delays due to indecision or a lack of predefined rational selection criteria can be seen as incompetence by peers in both discovery and in project management. Additionally, the criteria for selection must be linked directly to the clinical use situation, that is, the criteria differ quite substantially for a parenteral vs. a powder for inhalation.

Clearly, the selection process is an iterative one and the formula for success is to be able to keep the number of iterations to a minimum. With a cadre of counterions at their disposal, the formulator or medicinal chemist can easily screen for enhanced solubility at physiological pH, employing only a modicum of drug substance. (In the region of pH-independent solubility on the pH-solubility profile, the differences observed are due to the effect of the couterion only.) Then it is a matter of preparing only several salt form for experimentation, and these should be selected scientifically, based on knowledge of physicochemical constants derived from the free acid or base form. It thus becomes a compromise situation, balancing the desirable attributes vs. the undesirable ones and making the decision process transparent to all. An excellent case history where a similar philosophy was employed in selecting the arginine salt of an HMG-CoA reductase inhibitor was recently reported [413]. The decision tree as outlined in this article gives formulators some guidance in the requisite thought processes so that they can be successful in minimizing false starts and can rationally choose a suitable salt for clinical trials and eventual commercialization.

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Continuous Subcutaneous Infusion of Treprostinil, a Prostacyclin Analogue, in Patients with Pulmonary Arterial Hypertension

A Double-blind, Randomized, Placebo-controlled Trial

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Pulmonary arterial hypertension is a life-threatening disease for which continuous intravenous prostacyclin has proven to be effective. However, this treatment requires a permanent central venous catheter with the associated risk of serious complications such as sepsis, thromboembolism, or syncope. Treprostinil, a stable prostacyclin analogue, can be administered by a continuous subcutaneous infusion, avoiding these risks. We conducted a 12-week, double-blind, placebo-controlled multicenter trial in 470 patients with pulmonary arterial hypertension, either primary or associated with connective tissue disease or congenital systemic-to-pulmonary shunts. Exercise capacity improved with treprostinil and was unchanged with placebo; the between treatment group difference in median six-minute walking distance was 16 m ($p = 0.006$). Improvement in exercise capacity was greater in the sicker patients and was dose-related, but independent of disease etiology. Concomitantly, treprostinil significantly improved indices of dyspnea, signs and symptoms of pulmonary hypertension, and hemodynamics. The most common side effect attributed to treprostinil was infusion site pain (85%) leading to premature discontinuation from the study in 8% of patients. Three patients in the treprostinil treatment group presented with an episode of gastrointestinal hemorrhage. We conclude that chronic subcutaneous infusion of treprostinil is an effective treatment with an acceptable safety profile in patients with pulmonary arterial hypertension.

Keywords: treprostinil; prostacyclin analogue; primary pulmonary hypertension; pulmonary arterial hypertension associated with connective tissue disease; pulmonary arterial hypertension associated with congenital systemic-to-pulmonary shunts

Despite recent major therapeutic advances, pulmonary arterial hypertension remains a life-threatening disorder (1, 2). Continuous intravenous infusion of epoprostenol (prostacyclin) has been shown to improve exercise capacity, hemodynamics, and quality of life in primary pulmonary hypertension (3, 4) as well as in other forms of pulmonary arterial hypertension complicating scleroderma (5, 6) and congenital systemic-to-pulmonary shunts (7, 8). In addition, improved survival with epoprostenol has been demonstrated in one unblinded, randomized study of patients with severe primary pulmonary hypertension (3). However, despite these favorable outcomes, continuous intravenous infusion of epoprostenol is far from ideal as a treatment for severe pulmonary arterial hypertension due to its very short half-life (one to two minutes) requiring a continuous intravenous infusion. This delivery method is associated with frequent severe and potentially serious side effects (3, 5, 9). In addition, it is very costly (10). Thus, other modes of prostacyclin delivery are being considered using stable prostacyclin analogues administered orally (11, 12), subcutaneously (13), or by inhalation (14, 15).

Treprostinil, a stable prostacyclin analogue, shares pharmacological actions similar to epoprostenol (16, 17), with similar acute hemodynamic effects (18). However, in contrast to epoprostenol, treprostinil is chemically stable at room temperature and neutral pH and has a longer half-life (three to four hours) permitting continuous subcutaneous infusion rather than continuous intravenous infusion, avoiding the risks of severe infection and thrombosis (19). The objective of this study was to assess the effects of subcutaneous treprostinil on exercise capacity, disease symptoms, hemodynamics, and quality of life in patients with severe pulmonary arterial hypertension, including primary pulmonary hypertension as well as pulmonary arterial hypertension associated with connective tissue disease and congenital systemic-to-pulmonary shunts.

METHODS

Patients

Between November 1998 and October 1999, 470 patients were randomized from 24 centers in North America (Canada, Mexico, and the United States), and from 16 centers in the rest of the world (Australia, Austria, Belgium, France, Germany, Israel, Italy, Poland, Spain, UK). Eligible patients had pulmonary arterial hypertension in accordance with the inclusion and exclusion criteria summarized in Table 1. Patients with connective tissue disease had no pulmonary parenchymal disease as evidenced by lung function tests and a high-resolution computed tomography (CT) scan. Patients with congenital heart disease (left-to-right shunts) had either pulmonary arterial hypertension that developed a variable number of years after surgical correction, or presented with an inversion of the shunt due to the development of

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The members of the Treprostinil Study Group are listed in the online data supplement.

This article has an online data supplement, which is accessible from this issue's table of contents online at www.atsjournals.org

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TABLE 1. MAIN INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria
Primary pulmonary hypertension or pulmonary hypertension associated with connective tissue diseases or associated with congenital systemic to pulmonary shunts
Age between 8 and 75 yr
New York Heart Association (NYHA) functional class II, III, or IV
Significant pulmonary hypertension defined by
Mean pulmonary arterial pressure ≥ 25 mm Hg at rest
Mean pulmonary capillary wedge pressure ≤ 15 mm Hg
Pulmonary vascular resistance > 3 mm Hg/L/min
Ventilation perfusion lung scan or pulmonary angiography not indicative of thromboembolic disease
Exclusion criteria
Significant parenchymal pulmonary disease as evidenced by pulmonary function tests or high resolution CT scan
Porto pulmonary hypertension or HIV-associated pulmonary hypertension
Uncontrolled sleep apnea
History of left side heart disease
Other diseases associated with pulmonary hypertension (e.g., sickle cell anemia, shistosomiasis)
Baseline exercise capacity of less than 50 m or greater than 450 m walked in 6 min
Any new type of chronic therapy for pulmonary hypertension added within the last month
Any pulmonary hypertension medication discontinued within the last week except anticoagulants
Any use of prostaglandin derivatives within the past 30 d

Definition of abbreviations: CT = computed tomography; HIV = human immunodeficiency virus.

pulmonary hypertension and associated increase in pressures of the right heart (Eisenmenger complex). All patients gave written informed consent. The protocol was approved by the local ethics committee at each participating center.

Randomization and Treatment

Patients were randomly assigned to receive either continuous subcutaneous infusion of treprostinil (Remodulin; United Therapeutics Corporation, Research Triangle Park, NC) plus conventional therapy or continuous infusion of placebo (vehicle solution without treprostinil) plus conventional therapy. All patients had conventional therapy optimized for at least one month before enrollment. Conventional therapy could include oral vasodilators, oral anticoagulants, diuretics, and/or digitalis (20). Randomization was based on a permuted block design stratified on the basis of baseline exercise capacity and etiology of pulmonary arterial hypertension.

Treprostinil or placebo was administered using a positive pressure, microinfusion pump (MiniMed, Sylmar, CA). The infusion catheter was placed by the patient in the subcutaneous tissue of the abdominal wall. Chronic study drug infusion was initiated at the dose of 1.25 ng/kg/min. During the 12-week study, doses were increased to a maximum dose at which pulmonary hypertension signs and symptoms were improved while achieving an acceptable side effect profile. At Week 12, the maximum allowable dose was 22.5 ng/kg/min. These doses were selected on the basis of approximately equipotent pulmonary hemodynamic effects compared with those of prostacyclin (18).

Outcome Measures

The primary measure of efficacy was exercise capacity as defined by the maximum distance a patient could walk in six minutes (21). The unencouraged six-minute walk test was administered by a "blinded" tester not involved in the patient's daily care and unaware of the patient's treatment assignment. Each patient performed at least one practice walk test before the baseline assessment conducted before randomization. The walk test was then repeated at Weeks 1, 6, and 12.

Principal reinforcing endpoints of efficacy were signs and symptoms of pulmonary hypertension using a composite score including 16 signs or symptoms recorded at baseline and Weeks 1, 6, and 12; the Dyspnea Fatigue Rating (22) assessed at baseline and Weeks 1, 6, and 12; and the number of deaths, lung transplantations, or discontinuations for clinical deterioration. Secondary endpoints were assessment of shortness of breath immediately after the six-minute walk test using the Borg Dyspnea Scale (23) at baseline and Weeks 1, 6, and 12; cardiopulmonary hemodynamics measured by right heart catheterization at baseline and Week 12; global, physical, and emotional quality of life using the "Minnesota Living with Heart Failure Questionnaire" (24) assessed at baseline and Weeks 6 and 12.

Safety was assessed by comparison of adverse experiences in the two treatment groups and by laboratory assessments (including hemoglobin level, platelet count, leukocyte count, serum creatinine concentration, blood urea nitrogen, alkaline phosphatase, and alanine aminotransferase) at baseline and Week 12. An independent data safety monitoring board reviewed serious adverse events and deaths after 20%, 40%, and 60% of patients had completed the study.

Statistical Analysis

Changes in the distance walked in six minutes from baseline to Week 12 were compared between treatment groups using an intention-to-treat, nonparametric analysis of covariance, prespecified as the primary analysis. A least squares regression analysis was applied to calculate the six-minute walk distances as linear functions of baseline walk, vasodilator use, etiology, and study center. The standardized mid-ranks of the residuals from these linear regression analyses were then determined. Patients who discontinued the study due to death, clinical deterioration, or transplantation before Week 12 were assigned a standardized rank of 0. For patients who discontinued before Week 12 for any other reason, the standardized mid-rank from the last available assessment was carried forward. The ranks were then compared between treatment groups using the extended Cochran–Mantel–Haenszel test. Changes from baseline to Week 12 in the composite score of signs and symptoms of pulmonary hypertension, Dyspnea-Fatigue Rating, Borg Dyspnea Score, and Quality of Life scores were compared between treatment groups using the Wilcoxon rank sum test without imputation. Between treatment group changes in hemodynamic variables were compared using parametric analysis of covariance adjusting for baseline value without imputation. In analyses of possible treatment interactions, a significance level of $\alpha = 0.1$ was considered suggestive of a treatment effect.

RESULTS

Baseline Characteristics and Patient Disposition

Baseline demographic and hemodynamic characteristics of the two groups are shown in Tables 2 and 3, respectively. The two groups were well matched with respect of severity of pulmonary hypertension, duration of illness, and etiology of

TABLE 2. DEMOGRAPHIC CHARACTERISTICS AT BASELINE

Characteristic	Treprostinil (*n = 233*)	Placebo (*n = 236*)
Age, yr	44.6 ± 1.0	44.4 ± 0.9
Sex, n (%)		
Male	36 (16)	51 (22)
Female	197 (85)	185 (78)
Ethnic group, n (%)		
Black	13 (6)	8 (3)
White	198 (85)	198 (84)
Other	22 (9)	30 (13)
NYHA functional class, n (%)		
II	25 (11)	28 (12)
III	190 (82)	192 (81)
IV	18 (8)	16 (7)
6-min walk distance, m	326 ± 5	327 ± 6
Etiology of pulmonary hypertension, n (%)		
Primary pulmonary hypertension	134 (58)	136 (58)
Connective tissue disease	41 (17)	49 (20)
Congenital systemic to pulmonary shunts	58 (25)	51 (22)
Years since pulmonary hypertension diagnosis	4.3 ± 0.5	3.3 ± 0.5

Definition of abbreviation: NYHA = New York Heart Association.

TABLE 3. HEMODYNAMIC VARIABLES AT BASELINE

Variables	Treprostinil (N = 233)	Placebo (N = 236)
Heart rate, beats/min	82 ± 1	82 ± 1
Mean right atrial pressure, mm Hg	10 ± 0.4	10 ± 0.4
Mean pulmonary artery pressure, mm Hg	62 ± 1	60 ± 1
Mean pulmonary capillary wedge pressure, mm Hg	10 ± 0.3	9 ± 0.2
Cardiac index, L/min/m^2	2.4 ± 0.1	2.3 ± 0.1
Pulmonary vascular resistance index, units/m^2	26 ± 1	25 ± 1
Mean systemic artery pressure, mm Hg	90 ± 1	91 ± 1
Systemic vascular resistance index, units/m^2	38 ± 1	39 ± 1
Mixed venous oxygen saturation, %	62 ± 1	60 ± 1
Arterial oxygen saturation	92 ± 0.5	91 ± 0.5

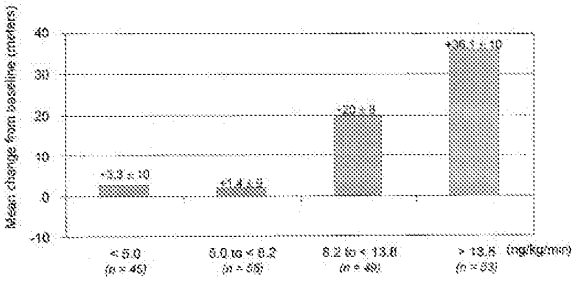

Figure 1. Mean change in the six-minute walk distance from baseline to Week 12 versus Week 12 trepostinil dose quartile.

pulmonary hypertension; 233 patients were randomized to treprostinil and 237 patients to placebo.

Primary Endpoint

Exercise capacity. All but one of the 470 randomized patients were included in the analysis of the primary endpoint; this patient, assigned to receive placebo, did not receive any study drug. The distance walked in six minutes improved at Week 12 in the treprostinil group by a median change of 10 m (−24 to +47 m; 25th–75th percentile) and remained essentially unchanged in the placebo group with a median change of 0 m (−44 to +32 m; 25th–75th percentile). The difference in median distance walked between the two groups at Week 12 was 16 m (95% CI, 4.4 m to 27.6 m, Hodges–Lehmann estimate of the median difference, $p = 0.006$).

Neither baseline demographic covariates nor disease etiology showed significant interaction with the change in exercise capacity. In contrast, a treatment interaction was observed with the baseline walking distance ($p = 0.03$), baseline New York Heart Association (NYHA) functional class ($p = 0.11$), and baseline mixed venous oxygen saturation ($p = 0.07$). Patients who were more compromised at baseline had a greater improvement in exercise capacity from baseline to Week 12. Severely ill patients who walked less than 150 m at baseline had an estimated treatment effect of +51 ± 16 m ($p = 0.002$) and less sick patients who walked more than 351 m at baseline had no substantial estimated treatment effect (−2 ± 12 m, $p = 0.869$). In addition, there was a relationship between the treprostinil dose achieved at Week 12 and the change in the 6-min walk distance. When patients were grouped by quartile of the dose achieved at Week 12, the highest quartile dose had the greatest improvement in six-minute walk distance, and the first and second quartile dose had small improvements ($p = 0.03$) (Figure 1).

Principal Reinforcing Endpoints

Signs and symptoms of pulmonary arterial hypertension. The signs and symptoms composite score improved in the treprostinil group from 7.6 ± 0.5 at baseline to 8.5 ± 0.5 at Week 12 compared with the placebo group, in which it worsened from 7.5 ± 0.4 at baseline to 7.4 ± 0.2, $p < 0.0001$ for the comparison between the treatment groups.

Dyspnea-Fatigue Rating. The Dyspnea-Fatigue Rating improved from 4.2 ± 0.1 at baseline to 5.4 ± 0.2 at Week 12 in the treprostinil group, whereas it worsened in the placebo group from 4.4 ± 0.1 to 4.3 ± 0.1, $p = 0.0001$ for the comparison between the treatment groups.

Death, transplantation, or clinical deterioration. Fourteen patients died while receiving the study drug (seven in each group). Five additional patients (two in the treprostinil group and three in the placebo group) died during the 12-week study period but after withdrawal of the study drug. Six patients in each group discontinued the study due to clinical deterioration; five patients receiving treprostinil and four receiving placebo were transitioned to continuous intravenous epoprostenol therapy. One placebo patient underwent lung transplantation and was alive at the end of the 12-week study period. The total number of deaths, transplantations, or discontinuations due to clinical deterioration was 13 patients in the treprostinil group versus 16 patients in the placebo group.

Secondary Endpoints

Borg Dyspnea Score. In the treprostinil group, patients had an improvement in the Borg Dyspnea Score from 4.3 ± 0.2 at baseline to 3.2 ± 0.2 at Week 12, versus an improvement in the placebo group from only 4.4 ± 0.2 to 4.2 ± 0.2, $p < 0.0001$ for the comparison of the treatment groups.

Cardiopulmonary hemodynamics. Changes in hemodynamic variables are shown in Table 4. Comparison of treatment groups showed that treprostinil-treated patients had significant improvement in mean right atrial pressure, mean pulmonary artery pressure, cardiac index, pulmonary vascular resistance, and mixed venous oxygen saturation.

Quality of life. Patients treated with treprostinil experienced a significant improvement in their physical dimension score at Week 12 ($p = 0.0064$) with a trend toward improvement in the global dimension score ($p = 0.17$) as compared with the placebo group.

Tolerability, Dose, Safety

No clinically significant changes in hematologic or biochemical variables were observed in either group. The most common adverse events are shown in Table 5. Infusion site pain was common in both treatment groups but was more common in the treprostinil group, 85% versus 27%, respectively. Eighteen patients (8%) in the treprostinil group discontinued their study treatment due to intolerable abdominal infusion site pain versus one in the placebo group. Adverse events classically related to the use of prostacyclin, such as diarrhea, jaw pain, flushing, and lower limb edema occurred more often in the treprostinil group. There were no reports of infusion site infections in either group.

By the end of the 12-week study period, the mean dose of the study drug received was 9.3 ng/kg/min versus 19.1 ng/kg/min in the placebo group ($p < 0.001$). Infusion system malfunctions were common, reported in 55 patients of the treprostinil group (24%) and in 77 patients of the placebo group (33%). Adverse events resulting from these dysfunctions were rare (four patients in each group) and had no clinically serious adverse consequences.

In addition, three patients in the treprostinil group presented with a gastrointestinal hemorrhage; each patient experienced

TABLE 4. CARDIOPULMONARY HEMODYNAMICS: CHANGE FROM BASELINE TO WEEK 12

	Treprostinil	Placebo	p Value
Heart rate, beats/min	−0.5 ± 0.8	−0.8 ± 0.7	ns
Mean right atrial pressure, mm Hg	−0.5 ± 0.4	+1.4 ± 0.3	0.0002
Mean pulmonary artery pressure, mm Hg	−2.3 ± 0.5	+0.7 ± 0.6	0.0003
Cardiac index, L/min/m^2	+0.12 ± 0.04	−0.06 ± 0.04	0.0001
Pulmonary vascular resistance index, units/m^2	−3.5 ± 0.6	+1.2 ± 0.6	0.0001
Mean systemic artery pressure, mm Hg	−1.7 ± 0.9	−1.0 ± 0.9	ns
Systemic vascular resistance index, units/m^2	−3.5 ± 0.9	−0.8 ± 0.8	0.0012
Mixed venous oxygen saturation, %	+2.0 ± 0.8	−1.4 ± 0.7	0.0001

melena and one patient experienced a small hematemesis and rectal bleeding. Two of these patients presented with excessively increased INR (4.0 and 3.14), one of whom had taken naproxen, a nonsteroidal antiinflammatory drug. Two of these patients required transfusion of one and three units of packed red blood cells, respectively. All three gastrointestinal hemorrhage episodes subsided spontaneously without adverse clinical consequences.

DISCUSSION

This study is the first double-blind, placebo-controlled trial conducted in pulmonary arterial hypertension; it is also the largest clinical trial with worldwide participation. The results show that continuous subcutaneous infusion of treprostinil, a stable prostacyclin analogue, is effective therapy in patients with primary pulmonary hypertension as well as in patients with pulmonary arterial hypertension associated with either connective tissue disease or congenital systemic-to-pulmonary shunts. Compared with continuous subcutaneous infusion of placebo, treprostinil consistently improved exercise capacity, indices of dyspnea, signs and symptoms of pulmonary arterial hypertension, cardiopulmonary hemodynamics, and the physical dimension of quality of life.

The distance walked in six minutes has been previously shown to be an independent predictor of mortality in primary pulmonary hypertension (3, 25). After 12 weeks, the difference in median distance walked between the two treatment groups was 16 m. Although significant, this difference appears moderate compared with previous results obtained with intravenous epoprostenol (3, 5). The relatively limited increase in the six-minute walk distance after three months of subcutaneous treprostinil may be explained by the inclusion of less compromised patients, and by the fact that the most important improvement in exercise capacity was observed in the sickest patients. Actually, in the sicker patients, the magnitude of the exercise capacity improvement was similar to that obtained with epoprostenol therapy (3, 5). In addition, in a proportion of patients, only a relatively low dose of treprostinil was achieved by Week 12 due to local infusion site pain. This likely limited the improvement in the six-minute walking distance, as the present results also show a relationship between the dose of treprostinil achieved and increase in six-minute walk distance. However, although limited in magnitude, the increase in the six-minute walk distance in treprostinil-treated patients really reflected clinical improvement as supported by the improvements in the Dyspnea-Fatigue Rating, signs and symptoms scores, and the Borg Dyspnea Score measured at the end of the exercise test indicating increased exercise with less dyspnea. The effectiveness of treprostinil is further supported by a significant improvement in the hemodynamic variables previously shown to be associated with mortality in primary pulmonary hypertension (26). These hemodynamic changes observed after 12 weeks of treprostinil therapy, although small, with average differences between study groups of only 3 mm Hg in mean pulmonary artery pressures and 0.3 L/min/m^2 in cardiac index, were of the same order of magnitude as those previously reported in randomized controlled trials of 12 weeks of intravenous epoprostenol in patients with primary pulmonary hypertension (3) or with pulmonary hypertension secondary to connective tissue disease (5). Chronic epoprostenol or treprostinil may induce more important improvements in exercise hemodynamics, accounting for the observed clinical improvement in patients with pulmonary arterial hypertension.

The large placebo-control group in the present trial offered a unique opportunity to observe the spontaneous evolution, over a period of three months, of stable NYHA class III patients with pulmonary arterial hypertension under optimal medical treatment but without prostacyclin therapy. It appears that such patients are remarkably stable, at least over a three-month period of time, with modest changes in exercise capacity, and a mortality of only 3%. This mortality rate after a relatively short observation period of only three months was actually expected on the basis of both the six-minute walk distances (25) and the hemodynamic profile (26) of the included patients. Much larger numbers of patients with the same disease severity and longer periods of observation would be necessary to show a treatment effect on mortality. The mortality rates in the present study are similar to those reported in a recent randomized, controlled trial of intravenous epoprostenol in patients with pulmonary arterial hypertension secondary to connective tissue disease (5). Intravenous epoprostenol was previously reported to decrease mortality in a randomized, controlled trial that differed from the present study by the inclusion of a smaller number of more severely ill patients, with lower exercise capacity and worse NYHA functional class (3).

In terms of safety, continuous subcutaneous infusion of treprostinil presents several advantages over continuous intravenous infusion of epoprostenol. Due to its short half-life (one to two minutes) and chemical instability, epoprostenol can be given only intravenously, and requires a permanently implanted cen-

TABLE 5. MOST FREQUENT ADVERSE EVENTS

Event	Treprostinil (*n* = 233) n (%)	Placebo (*n* = 236) n (%)	p Value
Infusion site pain	200 (85)	62 (27)	< 0.0001
Infusion site reaction	196 (83)	62 (27)	< 0.0001
Infusion site bleeding/bruising	79 (34)	102 (44)	ns
Headache	64 (27)	54 (23)	ns
Diarrhea	58 (25)	36 (16)	0.009
Nausea	52 (22)	41 (18)	ns
Rash	32 (14)	26 (11)	ns
Jaw pain	31 (13)	11 (5)	0.001
Vasodilatation	25 (11)	11 (5)	0.01
Dizziness	21 (9)	19 (8)	ns
Edema	21 (9)	6 (3)	0.002
Vomiting	12 (5)	14 (6)	ns

tral venous catheter and a portable infusion pump, as well as refrigeration during administration. Sepsis, thrombosis, paradoxical embolism, and interruptions of treatment due to accidental occlusions, perforations, and dislodgments of the catheter, and pump malfunction all have been reported under intravenous epoprostenol. Additionally, any interruption of intravenous delivery of epoprostenol may be associated with syncope, and even death, from an acute pulmonary hypertensive crisis (3–8). None of these life-threatening complications of intravenous epoprostenol therapy was observed in the present study.

Infusion site pain was the most common side effect attributed to treprostinil. Its mechanism remains unclear. It did not appear to be dose-related but seems correlated to the rate of dose increase. It often improved after several months of treatment and could be minimized by moving the infusion site every three days as opposed to every day. Topical cold and hot packs, topical and oral analgesics, and antiinflammatory drugs were variably effective.

There were three episodes of gastrointestinal hemorrhage reported in the treprostinil group. These serious adverse events were attributed to concomitant administration of anticoagulant therapy as indicated in severe pulmonary hypertension (2) in two patients, and the use of a nonsteroidal antiinflammatory drug in one patient with the known platelet antiaggregatory effects of prostacyclin. All of these gastrointestinal hemorrhage episodes rapidly resolved without adverse clinical consequences, after adjustment of anticoagulant therapy, and withdrawal of the antiinflammatory drug, but required a transfusion in two patients.

During the 12-week study period, five patients receiving subcutaneous treprostinil and discontinuing the study due to clinical deterioration were transitioned to intravenous epoprostenol.

In conclusion, chronic subcutaneous treprostinil is an effective therapy with an acceptable safety profile in patients with pulmonary arterial hypertension. Further clinical experience with chronic subcutaneous treprostinil will define its place as an alternative to intravenous epoprostenol in patients with pulmonary arterial hypertension.

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(54) Title: SOLUBLE FORM OSMOTIC DOSE DELIVERY SYSTEM

(57) Abstract

Disclosed is an osmotic pharmaceutical delivery system comprising (a) a semipermeable wall that maintains its integrity during pharmaceutical delivery and which has at least one passage therethrough; (b) a single, homogeneous composition within said wall, which composition consists essentially of (i) a pharmaceutically active agent; (ii) at least one non–swelling solubilizing agent which enhances the solubility of the pharmaceutically active agent; (iii) at least one non–swelling osmotic agent; and (iv) a non–swelling wicking agent dispersed throughout the composition which enhances the surface area contact of the pharmaceutical agent with the incoming aqueous fluid.

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SOLUBLE FORM OSMOTIC DOSE DELIVERY SYSTEM

The present invention relates to the field of osmotic pharmaceutical dose delivery systems and preparations, particularly preparations which can be administered orally.

Theeuwes *et al.*, U.S. Patent No. 3,916,899, discloses a drug delivery preparation that is said to release the pharmaceutical agent through openings in the wall of the tablet or capsule by the osmotic pressure differential that is set up between the concentration of pharmaceutical agent in the tablet or capsule interior and the exterior fluid environment of the patient when the medicament is taken orally. See, also, Theeuwes *et al.*, U.S. Patent No. 3,845,770 which discloses another preparation for osmotic pressure differential delivery of a pharmaceutical agent. In this original type of approach the interior of the tablet had a hydrophobic core surrounded by a hydrophilic layer within the tablet wall. As such, water entering the tablet remained in the hydrophilic layer and so very little drug was actually released.

It has been believed that this approach did not deliver the pharmaceutical agent as completely or efficiently as had previously been thought. Therefore, a different approach to releasing the pharmaceutical agent was developed. In this approach the interior of the tablet or capsule is characteristically of two layers, one

containing the pharmaceutical agent (again to be released through openings in the wall of the tablet or capsule) and the other being a layer of material that swells when coming into contact with water. These materials that swell or expand to an equilibrium state when exposed to water or other biological fluids are referred to as "osmopolymers". This volume expansion is used to physically force the pharmaceutical agent out through openings which have been formed in the wall, shell or coating during manufacture. The pharmaceutical agent is primarily released as insoluble particles, which therefore have limited bioavailability. This has commonly been referred to as the "push/pull" approach. See, for example, U.S. Patent Nos. 5,422,123; 4,783,337; 4,765,989; 4,612,008; and 4,327,725. The patent literature has taught that this approach was necessary to deliver adequate doses, at controlled rates and for extended times, of a broad variety of drugs. Other "osmotic delivery systems have also been described. See, for example, U.S. Patent Nos. 4,609,374; 4,036,228; 4,992,278; 4,160,020; and 4,615,698. The osmopolymers used in these types of systems are components whose functions are to swell when they interact with water and aqueous fluids. This swelling effect is defined in these patents as a property of embibing fluid so is to expand to a very high degree, usually exhibiting a 2 to 50 fold volume increase.

Summary of the Invention

In arriving at the present invention it has been discovered that it is possible to efficiently deliver therapeutically effective doses, at controlled rates and for extended times, of a broad variety of drugs without the need for polymers that swell or expand within the tablet wall so as to physically force the medicament particles out into their intended environment of use. As used herein the term "swell", i.e. that property which the present invention has been able to avoid, is used so as to have the same definition as in the patents described above. Further, the invention makes it possible to deliver agents which have limited aqueous solubility.

In accordance with the preferred invention, there is provided an osmotic delivery system, preferably in the form of a tablet, which dispenses a therapeutic agent having a limited solubility in water or physiological environments without the

use of osmopolymers or swelling agents to deliver the therapeutic agents. Further in accordance with the present invention, the therapeutic agent is incorporated into a composition which is capable of solubilizing the therapeutic agent whereby the therapeutic agent is delivered in a predominantly solubilized form.

In a preferred embodiment, the invention has combined appropriate solubilizing agents and, throughout the composition containing the solubilizing and pharmaceutical agent(s), a "wicking" agent which provides enhanced flow channels for the pharmaceutical agent which has been made predominantly into its solubilized form by the solubilizing agent(s) while still within the tablet or capsule. Thus, the drug is delivered out through passages in the coating wall by true osmosis predominantly in its solubilized form, rather than by physical force on a particulate form.

Accordingly, in one aspect, the invention provides an osmotic pharmaceutical delivery system comprising (a) a semipermeable wall that maintains its integrity during pharmaceutical delivery and which has at least one passage therethrough; (b) a single, homogeneous composition within said wall, which composition contains (i) a pharmaceutically active agent, (ii) at least one non-swelling solubilizing agent which enhances the solubility of the pharmaceutically active agent; (iii) at least one non-swelling osmotic agent and (iv) a non-swelling wicking agent dispersed throughout the composition which enhances the surface area contact of the pharmaceutical agent with the incoming aqueous fluid. The pharmaceutical agent is thus released in a predominantly soluble form.

Preferred non-swelling solubilizing agents include (i) agents that inhibit crystal formation of the pharmaceutical or otherwise acts by complexation therewith; (ii) a high HLB (hydrophilic-lipophilic balance) micelle-forming surfactant, particularly non-ionic and/or anionic surfactants; (iii) citrate esters; and combinations thereof, particularly combinations of complexation agents with anionic surfactants. Preferred non-swelling osmotic agents include sugars with ten or fewer rings, preferably five or fewer rings and most preferably two rings. Examples include fructose, lactose, xylitol and sorbitol. Preferred wicking agents include colloidal

silicon dioxide and polyvinyl pyrrolidone and sodium lauryl sulfate can also function as wicking agents.

Brief Description of the Drawings

The invention will now be further described by reference to a brief description of each of the accompanying drawings. The brief description and the drawings are in no way a limitation of the invention.

Figure 1A schematically illustrates the elementary osmotic dose delivery system of the prior art.

Figure 1B schematically illustrates the osmotic dose delivery system of the prior art.

Figure 2 schematically illustrates the osmotic dose delivery system of the present invention.

Figure 3 diagramatically shows the percent of nifedipine released by dosage forms of the invention containing formulations 1G (30 mg); 1C (30 mg); as shown on Table 1 as compared to Procardia XL®(Pfizer, Inc.; 30 mg).

Figure 4 diagramatically shows the percent of nifedipine released by dosage forms of the invention containing formulations 2B (47 mg); 2C (47 mg); and 2D (47 mg) as shown on Table 2 as compared to Procardia XL®(Pfizer, Inc.; 30 mg).

Figure 5 diagramatically shows the percent of nifedipine released by dosage forms of the invention containing formulations 3C (30 mg); 3H (30 mg); as shown on Table 3 as compared to Procardia XL®(Pfizer, Inc.; 30 mg).

Figure 6 diagramatically shows the percent of nifedipine released by forms of the invention containing formulations 4H (30 mg); 4C (90 mg); as shown on Table 4 as compared to Procardia XL®(Pfizer, Inc.; 30 mg).

Figure 7 diagramatically shows the percent of nifedipine released by forms of the invention containing formulations 5G (60 mg); 5H (60 mg); as shown on Table 5 as compared to Procardia XL®(Pfizer, Inc.; 60 mg).

Figure 8 diagramatically shows the percent of nifedipine released by forms of the invention containing formulations 6E (60 mg); 6F (60 mg); as shown on Table 6 as compared to Procardia XL®(Pfizer, Inc., New York; 60 mg).

Figure 9 diagramatically shows the percent of nifedipine released by forms of the invention containing formulation 6F (60 mg) with a 1% ethylcellulose seal coat as shown on Table 6 as compared to Procardia XL®(Pfizer, Inc., New York; 60 mg).

Detailed Description of Preferred Embodiments

The invention will now be described in more detail with respect to numerous embodiments and examples in support thereof.

The semipermeable wall of the elementry osmotic delivery system is composed of a polymeric material cast or sprayed onto the tablet to give a 2 - 15% coating weight. One example of a polymeric material includes, but is not limited to, cellulose acetate. The use of such polymeric material requires plasticizers for increased flexibility, durability, and stability. In the case of cellulose acetate, examples of suitable plasticizers are triethyl citrate (TEC), propylene glycol (PG), a mixture of TEC and PG in ratios ranging from 25% TEC plus 75% PG to 75% TEC plus 25% PG, Tween 80 or other polyoxyethylene sorbitan esters, triacetin, diethyl phthalate, polyethylene glycol, mineral oil, tributyl sebacate, and glycerol. The plasticizers are included as a weight ratio of cellulose acetate suitable for creating a semipermeable wall to achieve retainment of the bioactive substance while permitting water permeation to the core of the tablet.

The semi-permeable wall of the tablet can contain at least one passageway communicating the contents of the core with the exterior of the device, delivering the beneficial drug through the passageways from the elementary osmotic device. The size of an individual passageway can range from 100 microns to 1000 microns, more preferred 300 to 900 microns, most preferred 500 to 850 microns. One or

multiple passageways can be present to communicate the contents with the exterior of the tablet.

A wicking agent, defined as any material with the ability to draw water into the porous network of a delivery device is included in the core of this type of tablet formulation. A wicking agent can do this with or without swelling, but those used in the present invention are non-swelling wicking agents. Some materials can both wick water and swell, others can function as wicking agents only. The wicking agents are characterized by having the ability to undergo physisorption with water. Physisorption is defined as a form of adsorption in which the solvent molecules can loosely adhere to surfaces of the wicking agent via van der Waals interaction between the surface of the wicking agent and the adsorbed molecule. In the case of a drug delivery device, the adsorbed molecule is primarily water or other biological fluid which is mainly composed of water. A wicking agent that attracts water will ultimately have a volume that is essentially composed of the volume of wicking agent and the volume of water attracted to it. A material that swells will have a volume that is esentially composed of the volume of wicking/swelling agent, the volume of water attracted to it, and an additional volume created by steric and molecular forces.

The wicking agent included in the formulations described in this invention creates channels or pores in the core of the tablet. This facilitates the channeling of water molecules through the core of the tablet by physisorption. The function of the wicking agent is to carry water to surfaces inside the core of the tablet, thereby creating channels or a network of increased surface area. For the purposes of this invention, these wicking agents do not swell to any appreciable degree. For bioactive agents with low solubility in water, the wicking agent aids in the delivery of partially solubilized bioactive agent through the passageway in the semipermeable coating. Materials suitable for acting as wicking agents include, but are not limited to, colloidal silicon dioxide, kaolin, titanium dioxide, fumed silicon dioxide, alumina, niacinamide, sodium lauryl sulfate, low molecular weight polyvinyl pyrrolidone, m-pyrol, bentonite, magnesium aluminum silicate, polyester, polyethylene. Materials particularly suitable for the purpose of this invention include

the non-swellable wicking agent, examples of which are sodium lauryl sulfate, colloidal silicon dioxide, and low molecular weight polyvinylpyrrolidone.

Preferred non-swelling solubilizing agents include (i) agents that inhibit crystal formation of the pharmaceutical or otherwise acts by complexation therewith; (ii) a high HLB (hydrophilic-lipophilic balance) micelle-forming surfactant, particularly anionic surfactants; (iii) citrate esters; and combinations thereof, particularly combinations of complexation agents with anionic surfactants. Examples of the agents that inhibit crystal formation of the pharmaceutical or otherwise acts by complexation therewith include polyvinylpyrrolidone, polyethyleneglycol (particularly PEG 8000),α, β and δ cyclodextrins and other modified cyclodextrins. Examples of the high HLB, micelle-forming surfactants include non-ionic and/or anionic surfactants, such as Tween 20, Tween 60 or Tween 80; polyoxyethylene or polyethylene-containing surfactants, or other long chain anionic surfactants, particularly sodium lauryl sulfate. Examples of citrate ester derivatives that are preferred are the alkyl esters, particularly triethyl citrate. Combinations of these types of non-swelling solubilizing agents are especially effective. Preferred among such types of combinations are combinations of complexation agents and anionic surfactants. Particularly preferred examples of such combinations are polyvinylpyrrolidone with sodium lauryl sulfate and polyethyleneglycol with sodium lauryl sulfate.

Lubricants are also added to assure proper tableting, and these can include, but are not limited to: magnesium stearate, calcium, stearate, stearic acid, polyethylene glycol, leucine, glyceryl behenate, and hydrogenated vegetable oil. These lubricants should be present in amounts from 0.1-10% (w/w), with a preferred range of 0.3-3.0% (w/w).

Preferred lubricants for tableting include but are not limited to sodium stearyl fumarate, magnesium stearate, calcium stearate, zinc stearate, stearic acid, glycerol behenate, sodium lauryl sulfate, polyethylene glycol and hydrogenated vegetable oil. Particularly preferred lubricants are those which are soluble in water or gastric fluids or are readily emulsified. Combinations of lubricants are especially effective.

Lubricant combinations which are preferred are a small amount of hydrophobic lubricant with a larger amount of soluble or emulsifiable lubricant. The rate of use for lubricants extends from 0.25 to 10.0% with a preferred range of 1 to 4%.

The delivery system of the invention can be used to provide controlled release of any of a broad variety of therapeutically active agents. Examples include the following: cough suppressants, such as dextromethorphan hydrobromide and codeine; antihistamines such as chlorpheniramine maleate, brompheniramine maleate, loratidine, astemizole, diclofenac sodium and terfenadine; decongestants such as pseudoephedrine and phenylephrine; antihypertensives such as nifedipine, verapamil, enalapril and salts thereof, metoprolol, metoprolol succinate, metoprolol fumarate, metoprolol tartarate; calcium channel blockers such as verapamil, diltiazam, nifedipine, nimodipine, felodipine, nicardipine, isradipine and amlodipine; antidiabetic agents such as glipizide and ibromectin; proton pump inhibitors such as omeprazole; H2 receptor antagonists such as cimetidine, ranitidine, famotidine, nizatidine; carbamazepine; anti-Parkinson agents such as selegiline, carbidopa/levodopa, pergolide, bromocriptine, amantadine, trihexyphenidyl HC1; antiviral agents including antiherpesvirus agents such as acyclovir, famciclovir, foscarnet, ganciclovir; antiretroviral agents such as didanosine, stavudine, zalcitabine, zidovudine; and others such as amantadine, interferon alpha, ribavirin, rimantadine; and other therapeutic agents such as cimetidine, propiomazine, phenytoin, tacrine, propiazam, proplazam. The system of the present invention is particularly applicable to therapeutic agents which are insoluble or poorly soluble in water or aqueous environments at physiological pH.

In a preferred embodiment the system of the present invention is employed for dispensing nifedipine. In such a preferred embodiment, the composition is free of agents which prevents solubilization of the nifedipine such as the Group I and Group II metals and salts thereof. In such compositions preferred osmotic agents are sugars.

Example 1

Nifedipine Granulation/Tableting/Coating

(TEC) or another suitable wetting agent is added to enough water to produce a good dispersion which will atomize and pump well. Add between 50 to 100% of the PEG 8000. Next add between 50 to 100% of the nifedipine to the dispersion. Finally add between 25 to 75% of the Cab-o-Sil® to the binder dispersion. Mix for ~20 minutes before spraying. Also, other ingredients can be added to or removed from the dispersion as necessary. A dispersion is also not necessary, the binder may be a solution of PVP, PEG, surgar or other binder. The solution may be aqueous or organic. In some cases, a hot melt method of granulating may be preferred. In this case, the binder may be a molten wax, wax mixture or other material.

Charge a fluid bed bowl with osmagents (xylitol, sorbitol lactose, fructose, inositol, etc.). Add between 50 to 100% of the SLS, add the remaining PEG 8000, and add between 50-100% of the PVP K-25, add all or the remaining amount of Nitedipine and other ingredients as required.

Spray the dispersion onto the powder bed with a spray rate of 20-50 g/min which will produce granules of an adequate size for tableting. (Spray rate will vary with batch size.) Inlet air flow rate and temperature are adjusted to keep powder bed from over-granulating or becoming overly wet. (Typical range 100-250 CMH and 40-60°C, depending on batch size.)

Discharge granulation and add remaining sodium lauryl sulfate (SLS), polyvinyl pyrrolidone (PVP K-25), osmagents, polyethylene glycol (PEG), nifedipine and Cab-o-Sil® (colloidal silicon dioxide; Cabot Corporation) and mix in a V-blender or appropriate mixer for 2-5 minutes or as necessary. Add suitable lubricant such as Magnesium Stearate (approximately 0.5-1.5%) and blend 2-5 minutes or as necessary.

Discharge final blend from mixer and tablet on suitable tablet press. Coat tablets in pan coater or fluid bed dryer with spray rate of 30-100 g/min or higher (depending on batch size). The coating solution is prepared by dissolving ~5%

cellulose Acetate, NF (National Formulary) in Acetone or other suitable solvent then adding 25-45% plasticizers such as TEC or PG or mixture thereof.

Process may also be done by direct compression, high shear granulation, dry compression or slugging.

In some cases it may be desirable to modify the solubility characteristics of the osmagents, solubilizers, granulation or other ingredient to achieve a desired release profile.

One method for modifying the release profile is to use a hydrophobic coating method. Initially, all ingredients could be granulated together with a 0-20% PVP K 25 or PEG 8000 or other binder aqueous or organic solution to ensure that drug, sugars, and solubilizers are evenly distributed throughout the granules. Following this procedure, a coating agent such as hydrogenated castor oil, hydrogenated vegetable oil, type I, ethyl cellulose, glyceryl monostearate, Gelucire® or carnauba wax at 1-20% of the total formulation weight could be applied to 5-50% of the total granulation. The coating agent may be applied in a fluid bed by top spray, wurtser column coating, or rotor application; a pan coater equipped with a screen for coating granules may also be utilized. The hydrophobic agent could be applied in a melted state or dissolved in a suitable solvent in which it would be sprayed onto the granules. Both parts of the granulation, immediate and sustained release, could then be blended thoroughly by using a V-Blender before tableting.

Alternatively, the method presented above may be applied to a component or combination of components of the formulation. One or more of the osmagents may be granulated alone or in combination with other osmagents, solubilizers or other components of the core. These granules may then be coated alone or in combination with any other component of the core with the materials and methods described above. The coated granules can then be added to the rest of formulation by dry blending, or they may actually be granulated with the remainder of the formulation.

Alternatiavely, a hydrophobic granulation method may be utilized. In this method powdered wax is mixed together with the portion of the granulation to be coated (in the same percentage ranges already stated). Non-powdered wax may be utilized by milling the wax to a fine particle size. Wax mixtures may be formed by melting the wax, adding the desired component, allowing the mixture to congeal and then screening or milling the wax mixture to a fine particle size. The powdered wax or wax mixture is then added to the fluid bed with the portion of the granulation to be coated. The materials are granulated by increasing and controlling the inlet temperatures of the fluid bed (inlet temperature ~60-80°C, outlet temperature ~40-60°C), to cause the melting/congealing steps involved in the granulation process. In other instances a jacketed device could be used to granulate. Here, however, the temperature ranges would apply to the substance used in heating and cooling the device, such as steam, hot oil or water.

For sustained release agents which are not waxes, the granulation process can be carried out utilizing standard granulation techniques such as aqueous moist granulation or solvent granulation (in the same percentage ranges already stated). The sustained release agent may be dissolved or suspended in the granulating fluid or it may be dispersed with the powders to be granulated. The granules are formed and dried and finally added to the remainder of the formulation.

Again, the above granulation techniques may be applied to a portion of the entire formulation or any component or mixture of components in the formulation. The sustained release granules may then be combined with the remainder of the formulation by techniques previously discussed.

Finally, a matrix technique may be utilized. This technique involves adding a powdered wax at 5-30% of the total formulation weight, such as hydrogenated castor oil, glyceryl palmitostearate, glyceryl behenate, Gelucire®, PEG 8000 or any other non-swellable matrix forming agent known to one skilled in the art to the formulation. The wax may be granulated with any component or combination of components of the formulation with a 0-20% PVP K25 or PEG 8000 or other binder solution, or a roller compaction or slugging method may be used in the formation

of the granules. The granules are then added to the remainder of the formulation using the methods stated earlier.

The modified release osmagents, solubilizers or granulation may then be tableted after addition of a suitable lubricant. A single layer tablet would have all components of the formulation blended together and compressed. One or more holes may be provided to give the proper release. One or more holes may be provided on the tablet. It may be beneficial for a tablet to have a hole on both sides of the tablet so that the optimum release rate is achieved. One or more holes may be provided to achieve the desired release characteristics.

It is possible that any of the previously discussed excipients in combination with the tablet core may lower the melting point. The temperatures that the tablet should be exposed to in an aqueous color coating process may be extreme enough (~60°C) to partially melt the core and change the physico-chemical behavior of the tablet in dissolution or stability. To avoid this change, a solvent-based color coat was formulated at Shire Laboratories Inc., consisting of a 1:1 mixture of hydroxypropyl cellulose and HPMC, and 1% of a colored aluminum lake dispersed in a 70:30 IPA:Water solution. Because the color coat is solvent-based, the temperature that the tablets will be exposed to in the coating process is significantly lower (~35-40°C).

A one to two hour delay before the onset of dissolution may be beneficial. In order to provide this lag time a seal coat may be added to the tablet. The seal coat should provide a water impermeable barrier for no longer than two hours. Some polymers which would provide this type of coating include ethylcellulose, shellac, Eudragit RS. Other ingredients may be added to the polymers in order to modify the coating to achieve the desired lag time. A 1-10% weight gain should be applied to the tablets. The coating is applied as an aqueous or organic solvent solution or dispersion. The coating is typically applied in a coating pan or fluid bed equipped with a wurster column.

Example 2

Nifedipine Forulations

The following are examples of formulations of the single, homogeneous composition within the tablet wall of the dosage form of the invention.

Table 1

Ingredients	1A	1B	1C	1D	1E	1F	1G	1H
Fructose		43.5	21.5	49.6	44.5	37.2	20.5	18.5
Lactose 315	17	18	17	17	17	32	17	17
Sorbitol	43.5		21				21	19
PVPK25	15	15	15	12.7	15	12.5	15	10
PEG8000	10 (5*)	10 (5*)	10 (5*)	8.5 (4.2*)	10 (5*)	8.4 (4.2*)	10 (5*)	20 (10*)
TEC	1*	1*	1*	1.7*	1*	0.84*	1*	1*
SLS	3	3	3	3	3 (1.5*)	1.95 (1.25*)	3	3
Cab-o-Sil®	2.0 (0.5*)	1.0 (0.5*)	1 (0.5*)	0.92 (0.42)	1 (0.5*)	1.1 (0.4*)	1 (0.5*)	0.5
Nifedipine	8*	8*	8*	6.8*	8*	6.7	8*	8*
Mg Stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	3
K Sorbate							3	
Total	100	100	100	100	100	100	100	100

* Indicates in dispersion

Table 2

Ingredients	2A	2B	2C	2D	2E
Fructose					
Lactose 315					
Sorbitol	15.5	15.5	5.5	23.25	12.5
Xylitol	23.25	23.25	23.25	15.5	6.5
Mannitol					
PVPK-12PF					
PVP-K25	35	35	35	35	50
PEG8000	10(5*)	10*	20(10*)	10(5*)	10(5*)
SLS	5	5	5	5	10
Cab-o-Sil®	1(0.5*)	1(0.5*)	1(0.5)	1(0.5*)	
Nifedipine	8.25*	8.25*	8.25	8.25*	10
TEC	1*	1*	1*	1*	
Mg Stearate	1	1	1	1	1
Total	100	100	100	100	100

* Indicates in dispersion

Table 3

Ingredients	3A	3B	3C	3D	3E	3F	3G	3H
Fructose	21.5	20.5	19.5	16.5	18.5	17.5	17.5	16.5
Lactose 315	17	17	17	17	17	17	17	14.5
Sorbitol	23	21	23	21	21	20	20	18.5
PVPK25	15	15	15	15	15	15	15	15
PEG8000	10 (5*)	10 (5*)	10 (5*)	10 (5*)	10 (5*)	10 (5*)	10 (5*)	10 (5*)
TEC	1*	1*	1*	1*	1*		1*	1*
SLS	3	3	5	5	3	5	5	5
Cab-o-Sil®	1(0.5*)	1(0.5*)	1(0.5*)	1(0.5*)	1(0.5*)	1(0.5*)	1(0.5*)	1(0.5*)
Nifedipine	8*	8*	8*	8*	8*	8*	8*	8*
Mg Stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
K Sorbate		3		5	5			
Glycerol						5		
Cremophor EL**							5	
Inositol								10*
Total	100	100	100	100	100	100	100	100

* Indicates in dispersion

** Polyethylene glycol castor oil derivative (other suitable derivatives of castor oil are disclosed by the International Cosmetic Ingredient Dictionary (5th Ed.), Cosmetic Fragrance and Toiletry Association, Washington, D.C. (1993), *e.g.* at pages 479-481)

Table 4

Ingredients	4A	4B	4C	4D	4E	4F	4G	4H
Fructose	13	13	4.5	17.5	18.5	15.25	15.675	15.675
Lactose 315	10.5	10.5	4	17	17.5	30	16.15	16.15
Sorbitol	16	16	6	20	22		19.95	19.95
PVPK25	35	15	35	15	15	15	14.25	14.25
PEG8000	10 (5*)	35 (5*)	35 (5*)	10 (5*)	10 (5*)	10	9.5(4.75*)	9.5(4.75*)
TEC	1*	1*	1*	6*			0.95*	0.95*
SLS	5	5	5	5	5	5	5	5
Cab-o-Sil®	1.(0.5*)	1.0 (0.5*)	1.0 (0.5*)	1.0 (0.5*)	1.0 (0.5*)	1	.975 (0.475*)	.975 (0.475*)
Nifedipine	8*	8*	8*	8*	8*	8.25	7.6*	7.6*
Mg Stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
K Sorbate							4.75	4.75
Glycerol					2.5			
Cremophor EL						10		
Inositol							5	
Calcium Sulfate								5
Total	100	100	100	100	100	100	100	100

* Indicates in dispersion

Table 5

Ingredients	5A	5B	5C	5D	5E	5F	5G	5H
Xylitol	15.5	5	32.5		31.5	24.0	16.9	20
Sorbitol	15.0	5			15.5	15.5	15	18.75
Fructose		7.5		17.5				
Lactose		5						
PEG 8000	10	10	20	10		10(5*)		10
PVP K-25	35	35	15	15	35	35	50	35(5*)
TEC	1	1	1	1.0	1*	1*	1*	1*
Cab-o-Sil®	1.0	1	1		1 (0.5)	2 (1*)	1(0.5*)	1(0.5*)
Nifedipine	17	25	25	50.0	10	10	10.1	8.25
Mg Stearate	0.5	0.5	0.5	0.5	1	1	1	1
SLS	5.0	5	5	3		5	5	5
K Sorbate				3				
Total	100	100	100	100	100	100	100	100

* Indicates in dispersion

Table 6

Nifedipine Formulations

	6A	6B	6C	6D	6E	6F	6G	6H
Xylitol	27.5	27.5	25.5	30.8	28.5	32.5	34.5	25.5
Sorbitol	25	25	26	28.5	29	30	30	26
SLS	5	5	4.5	4.8	5	5	5	4.5
PVP K25	15(3*)	15(3*)	13.5 (2.7*)	14.2 (2.8*)	15(3*)	15(3*)	5	13.5
Nifedipine	15	15	18	14.2	20	15	17.5	18
Stearic Acid	1	11	1	1	1	1	2	1
Mag. Stearate	1	1	1	1	1	1	0.5	1
Cab-o-sil®	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Glycerol Behenate	10							
Stearic Acid (Binder)							5.0	
Stearic Acid Coated Xylitol			10	5				
Stearic Acid Coated 6E								10

Example 3

Comparative Percentage of Nifedipine Release

This example reports experiments which compared the percentage of nifedipine released by certain of the above formulations in dose delivery forms of the invention as compared to Procardia XL®(Pfizer, Inc.; 30 mg).

Materials and Methods

Dose delivery forms of the invention are placed in a Vankel Dissolution Apparatus containing simulated gastric fluid without enzymes and dissoluted for 20 to 24 hours. Samples of the dissolution media are taken periodically and analyzed by high performance liquid chromatography for nifedipine concentration. The calculated percent release is plotted versus time. Dose delivery forms of the invention and procardia XL tablets are tested in the same manner to produce effective comparisons.

Results

Figure 3 diagramatically shows the percent of nifedipine released by dosage forms of the invention containing formulations 1G (30 mg); 1C (30 mg); as shown on Table 1 as compared to Procardia XL®(Pfizer, Inc.; 30 mg).

Figure 4 diagramatically shows the percent of nifedipine released by dosage forms of the invention containing formulations 2B (47 mg); 2C (47 mg); and 2D (47 mg) as shown on Table 2 as compared to Procardia XL®(Pfizer, Inc.; 30 mg).

Figure 5 diagramatically shows the percent of nifedipine released by dosage forms of the invention containing formulations 3C (30 mg); 3H (30 mg); as shown on Table 3 as compared to Procardia XL®(Pfizer, Inc.; 30 mg).

Figure 6 diagramatically shows the percent of nifedipine released by forms of the invention containing formulations 4H (30 mg); 4C (90 mg); as shown on Table 4 as compared to Procardia XL®(Pfizer, Inc.; 30 mg).

Figure 7 diagramatically shows the percent of nifedipine released by forms of the invention containing formulations 5G (60 mg); 5H (60 mg); as shown on Table 5 as compared to Procardia XL®(Pfizer, Inc.; 60 mg).

Figure 8 diagramatically shows the percent of nifedipine released by forms of the invention containing formulations 6E (60 mg); 6F (60 mg); as shown on Table 6 as compared to Procardia XL®(Pfizer, Inc., New York; 60 mg).

Figure 9 diagramatically shows the percent of nifedipine released by forms of the invention containing formulation 6F (60 mg) with a 1% ethylcellulose seal coat as shown on Table 6 as compared to Procardia XL®(Pfizer, Inc., New York; 60 mg).

What Is Claimed Is:

1. An osmotic pharmaceutical delivery system comprising (a) a semipermeable wall that maintains its integrity during pharmaceutical delivery and which has at least one passage therethrough; (b) a single, homogeneous composition within said wall, which composition consists essentially of (i) a pharmaceutical agent, (ii) at least one non-swelling solubilizing agent which enhances the solubility of the pharmaceutical agent; (iii) at least one non-swelling osmotic agent and (iv) a non-swelling wicking agent dispersed throughout the composition

2. The pharmaceutical delivery system of claim 1 wherein the pharmaceutical agent is released through said at least one passage.

3. The pharmaceutical delivery system of claim 1 wherein the wall has a plurality of passages therethrough.

4. The pharmaceutical delivery system of claim 1 wherein the non-swelling solubilizing agent is selected from the group consisting of (i) agents that inhibit crystal formation of the pharmaceutical or otherwise act by complexation therewith; (ii) a high HLB (hydrophilic-lipophilic balance) micelle-forming surfactant, particularly anionic surfactants; (iii) citrate esters; and combinations thereof.

5. The pharmaceutical delivery system of claim 4 which comprises the combinations of at least one complexation agent with at least one anionic surfactant.

6. The pharmaceutical delivery system of claim 5 wherein the combination is selected from the group consisting of (i) a polyvinylpyrollidone and sodium lauryl sulfate and (ii) a non-swellable polyethyleneglycol and sodium lauryl sulfate.

7. The pharmaceutical delivery system of claim 1 wherein the at least one non-swelling osmotic agent is a sugar.

8. The pharmaceutical delivery system of claim 7 wherein the sugar has no more than ten rings.

9. The pharmaceutical delivery system of claim 8 wherein the sugar has no more than five rings.

10. The pharmaceutical delivery system of claim 9 wherein the sugar is selected from the group consisting of monosaccharides, disaccharides and trisaccharides.

11. The pharmaceutical delivery system of claim 9 wherein the sugar is selected from the group consisting of fructose, lactose, xylitol, inositol and sorbitol.

12. The pharmaceutical delivery system of claim 11 wherein the sugar is coated with a hydrophobic material.

13. The pharmaceutical delivery system of claim 1 wherein the non-swelling wicking agent is selected from the group consisting of colloidal silicon dioxide, polyvinyl pyrrolidone and sodium lauryl sulfate.

FIG. 1A
Prior Art

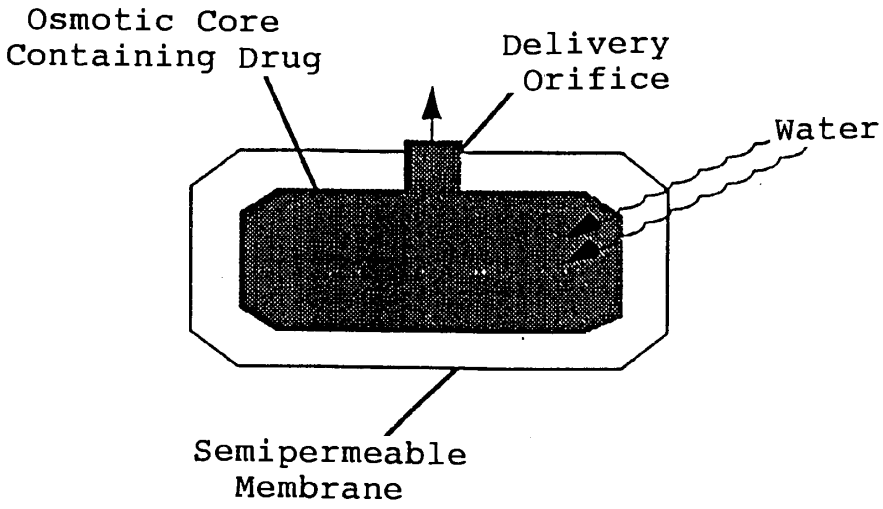


FIG. 1B
Prior Art

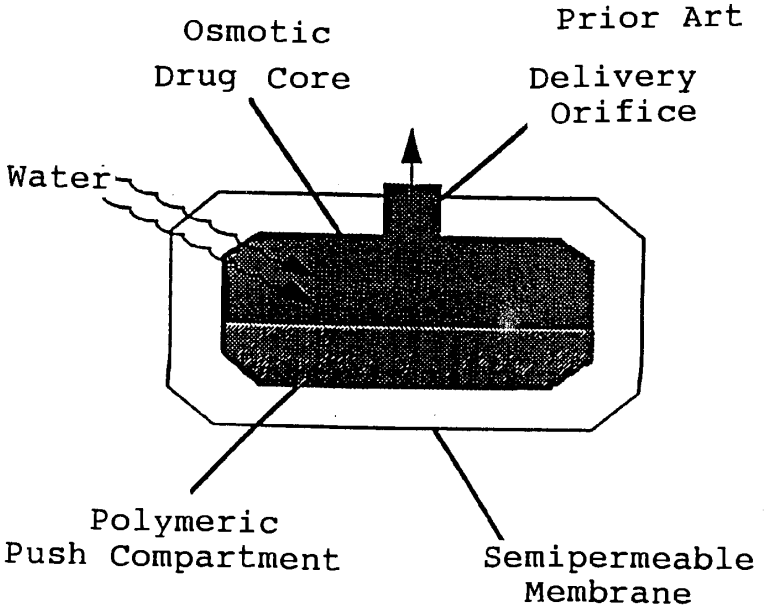


FIG. 2

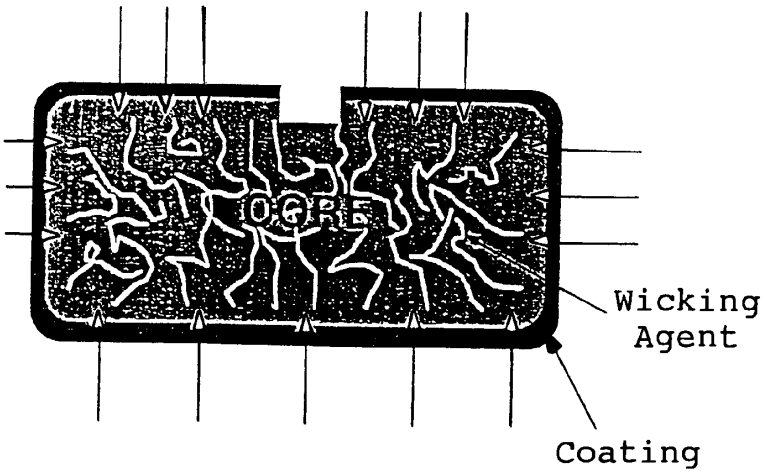


FIG. 3

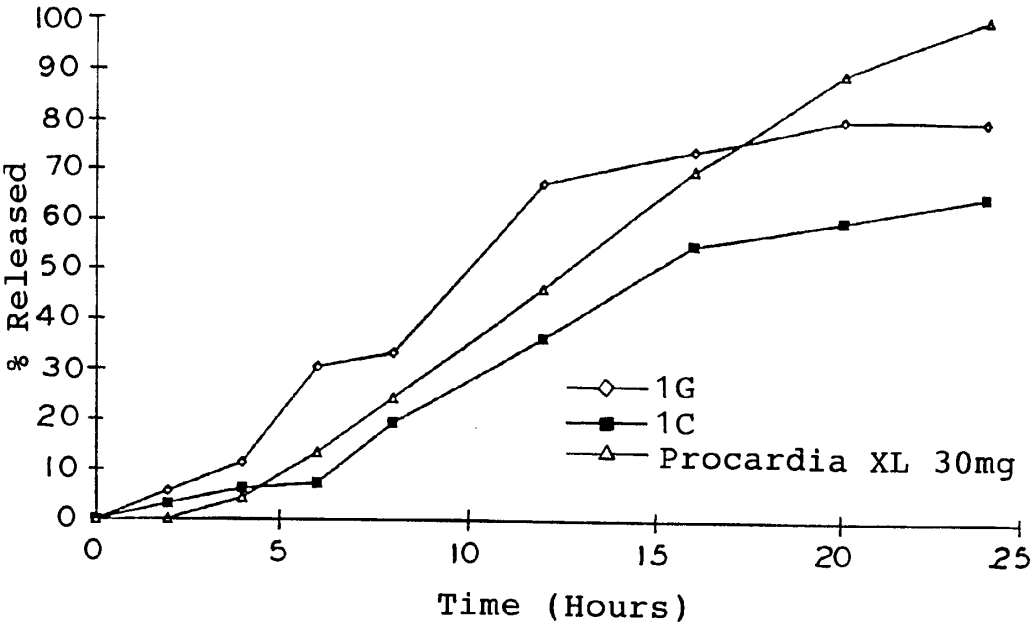


FIG. 4

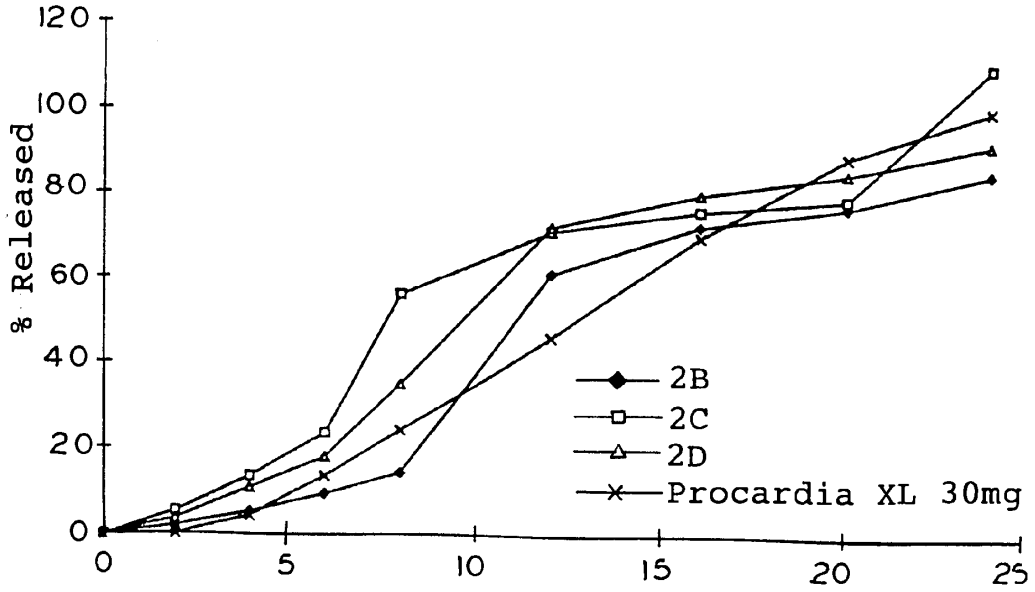


FIG. 5

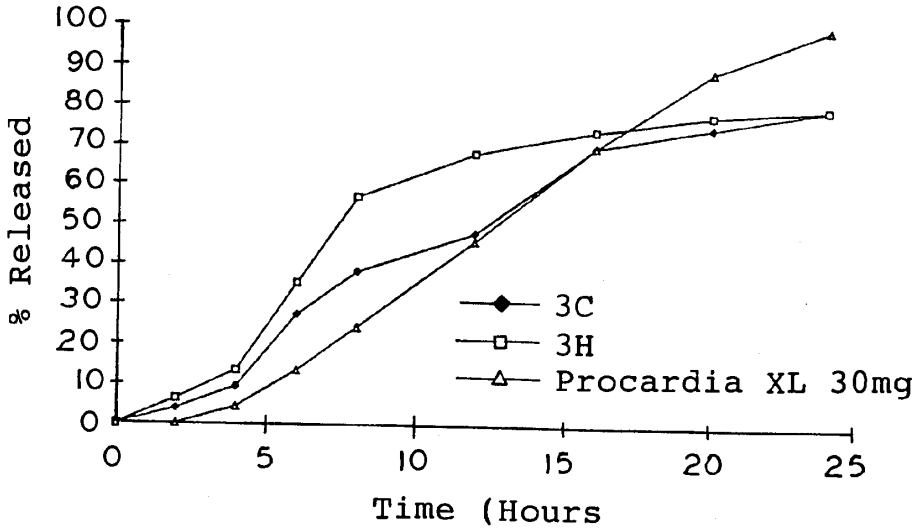


FIG. 6

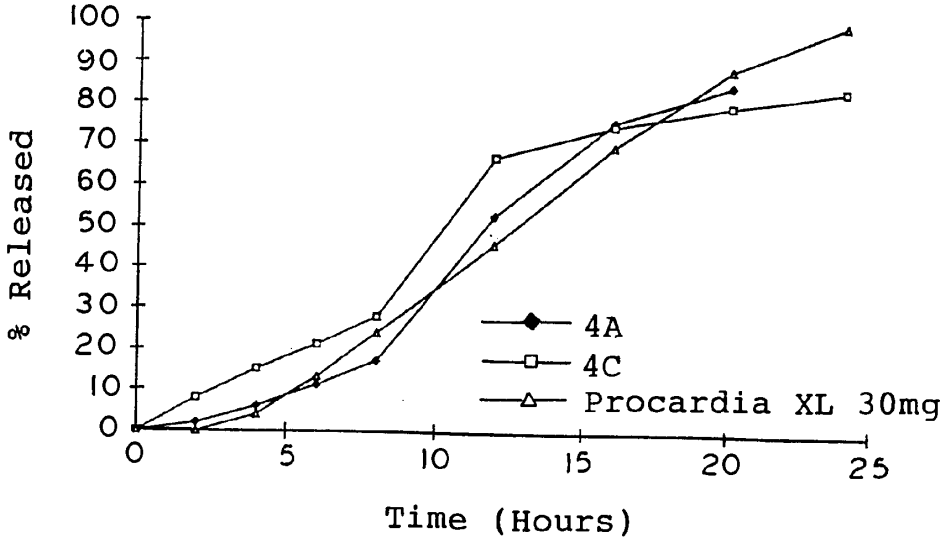


FIG. 7

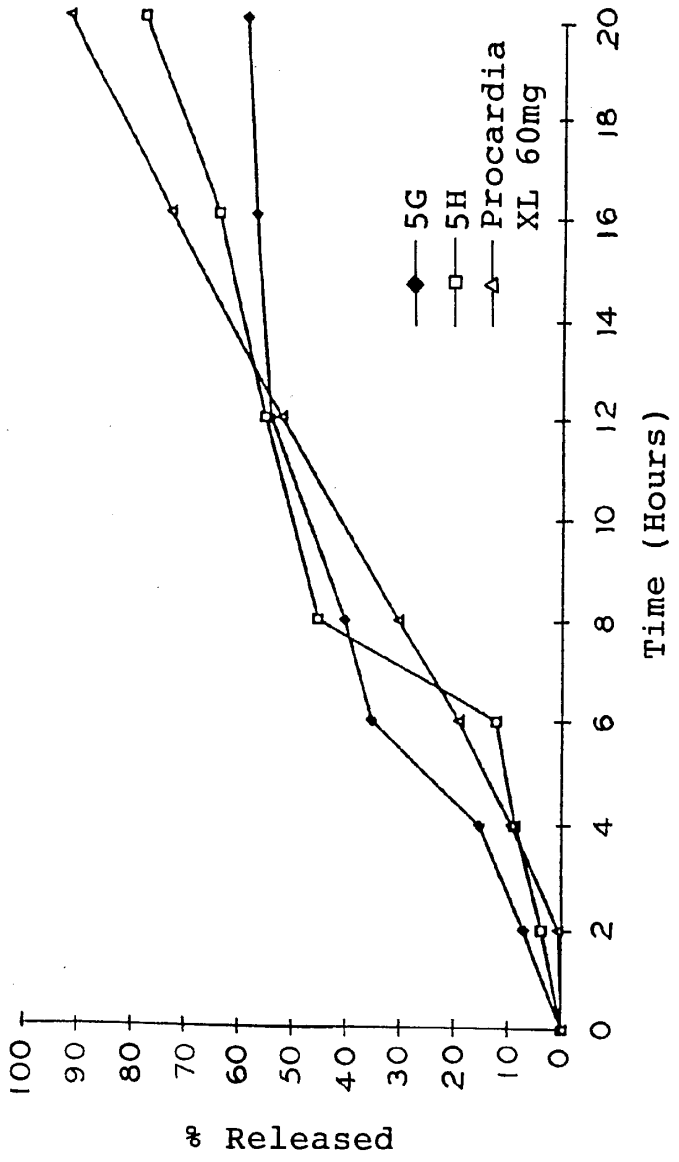


FIG. 8

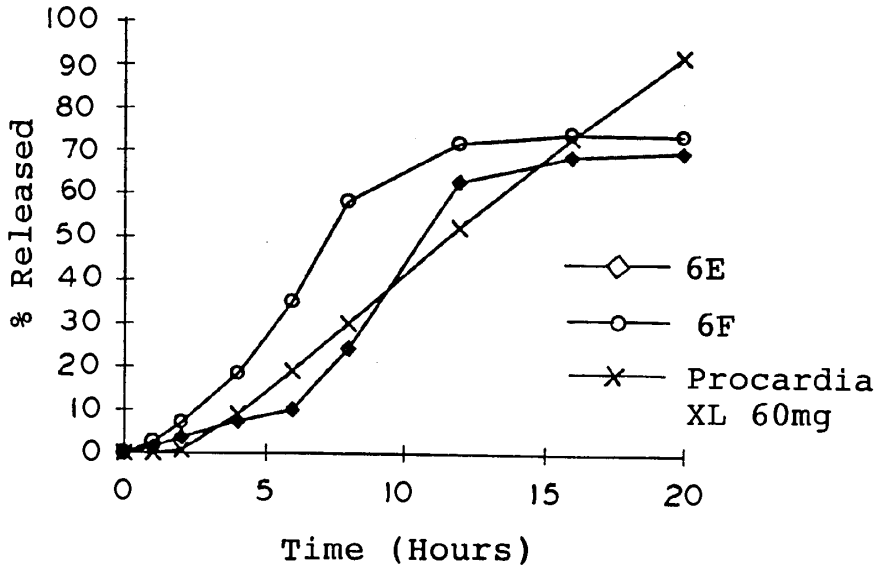
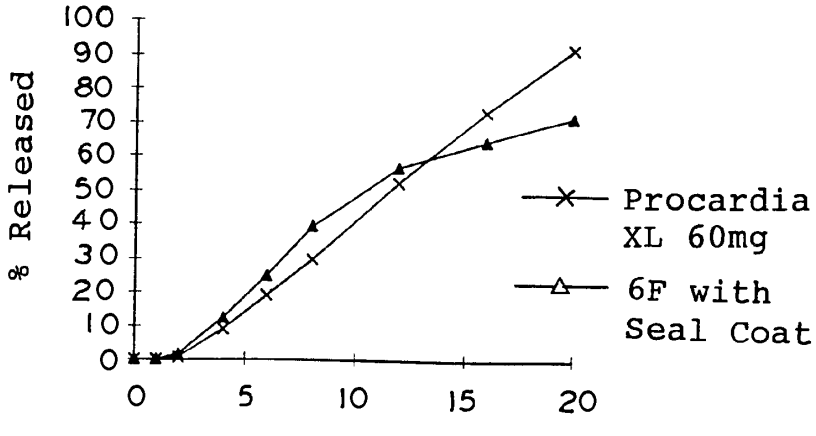


FIG. 9



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/18912

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 9/22, 9/44
US CL :424/468, 473, 474

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/468, 473, 474

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,654,005 A (CHEN et al.) 05 August 1997 (05/08/97), see column 3, line 30 through column 5, line 48.	1-13

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 02 JANUARY 1998	Date of mailing of the international search report 28 JAN 1998
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer JAMES M. SPEAR Telephone No. (703) 308-2351

Form PCT/ISA/210 (second sheet)(July 1992)★

Electronic Patent Application Fee Transmittal	
Application Number:	14849981
Filing Date:	10-Sep-2015
Title of Invention:	PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
First Named Inventor/Applicant Name:	Hitesh BATRA
Filer:	Stephen Bradford Maebius/Karen Strawderman
Attorney Docket Number:	080618-1581
Filed as Large Entity	
Filing Fees for Utility under 35 USC 111(a)	

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**180**

Electronic Acknowledgement Receipt	
EFS ID:	25050552
Application Number:	14849981
International Application Number:	
Confirmation Number:	6653
Title of Invention:	PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
First Named Inventor/Applicant Name:	Hitesh BATRA
Customer Number:	22428
Filer:	Stephen Bradford Maebius/Karen Strawderman
Filer Authorized By:	Stephen Bradford Maebius
Attorney Docket Number:	080618-1581
Receipt Date:	29-FEB-2016
Filing Date:	10-SEP-2015
Time Stamp:	15:15:15
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$180
RAM confirmation Number	1953
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		IDS.pdf	173823 b9a0d1b9eb3762f8b0b3e1d3538b79887f662995	yes	3
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Transmittal Letter		1	2	
	Information Disclosure Statement (IDS) Form (SB08)		3	3	
Warnings:					
Information:					
2	Non Patent Literature	Bighley.pdf	2623108 a302f7171ebdcd21bc35ebb4204bdac7ce97ceb9	no	49
Warnings:					
Information:					
3	Non Patent Literature	Simonneau.pdf	87871 2515adbd0748403b78c5ff7b1b13c94c58954171	no	5
Warnings:					
Information:					
4	Foreign Reference	WO9818452.pdf	1072536 6fbfe44c04082973ab341afba4af852cf6d4e707	no	32
Warnings:					
Information:					
5	Fee Worksheet (SB06)	fee-info.pdf	31018 4b0ee48da29604663c466f44643700521ee49b10	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	3988356		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor Name:	Hitesh BATRA
Title:	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
Application No.:	14/849,981
Filing Date:	9/10/2015
Examiner:	Yevgeny Valenrod
Art Unit:	1672
Confirmation No.:	6653

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR §1.56

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

Applicant submits herewith documents for the Examiner's consideration in accordance with 37 CFR §§1.56, 1.97 and 1.98.

Applicant respectfully requests that each listed document be considered by the Examiner and be made of record in the present application and that an initialed copy of Form PTO/SB/08 be returned in accordance with MPEP §609.

The submission of any document herewith is not an admission that such document constitutes prior art against the claims of the present application or that such document is considered material to patentability as defined in 37 CFR §1.56(b). Applicants do not waive any rights to take any action which would be appropriate to antedate or otherwise remove as a

competent reference any document submitted herewith. However, in accordance with MPEP § 609.04(a)(I), Applicant hereby states that for items for which the date of publication supplied does not include the month of publication, the year of publication is sufficiently earlier than the effective U.S. filing date and any foreign priority date so that the particular month of publication is not in issue.

TIMING OF THE DISCLOSURE

The listed documents are being submitted in compliance with 37 CFR §1.97(c), before the mailing date of any of a final action under 37 CFR §1.113, a notice of allowance under 37 CFR §1.311, or an action that otherwise closes prosecution in the application.

FEE

Fees in the amount of $180.00 to cover the fee associated with an information disclosure statement are being paid by credit card via EFS-Web.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this submission under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account Number 19-0741.

Respectfully submitted,

Date Feb. 29, 2016

By /Stephen B. Maebius/

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 672-5569
Facsimile: (202) 672-5399

Stephen B. Maebius
Attorney for Applicant
Registration No. 35,264

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/849,981	09/10/2015	Hitesh BATRA	080618-1581	6653

22428 7590 02/25/2016
Foley & Lardner LLP
3000 K STREET N.W.
SUITE 600
WASHINGTON, DC 20007-5109

EXAMINER	
VALENROD, YEVGENY	

ART UNIT	PAPER NUMBER
1672	

NOTIFICATION DATE	DELIVERY MODE
02/25/2016	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ipdocketing@foley.com

Office Action Summary	Application No. 14/849,981	Applicant(s) BATRA ET AL.	
	Examiner YEVGENY VALENROD	Art Unit 1672	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 9/1015.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) 1-10 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) 1-10 is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date 9/10/15; 10/13/15.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

The present application is being examined under the pre-AIA first to invent provisions.

DETAILED ACTION

Claim Rejections - 35 USC § 103

In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

The following is a quotation of pre-AIA 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under pre-AIA 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of pre-AIA 35 U.S.C. 103(c) and potential pre-AIA 35 U.S.C. 102(e), (f) or (g) prior art under pre-AIA 35 U.S.C. 103(a).

Claims 1-10 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Moriarty et al (Journal of Organic Chemistry, 2004, 69, 1890-1902) in view of Phares et al (WO 2005/007081 A2).

Scope of prior art

Moriarty et al disclose a method for preparing treprostinil. Said method comprises the steps of: (a) alkylation of benzindene triol and (b) hydrolysis of the product of step (a) (page 1895, Scheme 4, compounds **34** to **35** to **7;** page 1902 preparation of compounds **35** and **7**). 441g of treprostinil (compound 7) was prepared at 99.7% purity.

Ascertaining the difference

Moriarty fails to teach preparation of a diethanolamine salt of treprostinil.

Moriarty also fails to teach preparation of a pharmaceutical product comprising diethanolamine salt.

Secondary reference

Phares et al teach preparation of treprostinil diethanolamine by dissolving treprostinil acid and treating it with diethanolamine (page 22). Phares further discloses two polymorphs of treprostinil diethanolamine (page 85) and discloses stability via their moisture sorption/desorption data (figure 22).

Obviousness

One skilled in the art practicing the invention of Phares would have found it obvious to prepare a diethanolamine salt of treprostinil prepared by the method of Moriarty. Moriarty discloses a method for preparing a treprostinil acid which is a needed starting material for the process of Phares. The resulting salt would meet the limitations directed to pharmaceutical product because treprostinil diethanolamine is the sole claimed component of the claimed pharmaceutical product.

One skilled in the art would have found it obvious to prepare a pharmaceutical product from the treprostinil diethanolamine salt of Phares prepared from the treprostinil free acid that has been obtained by the process of Moriarty. One would also find it obvious to store the treprostinil diethanolamine salt prior to preparation of a pharmaceutical composition. On page 88 Phares describes minimal weight loss at 5%RH. One would simply store the product in an anhydrous environment to avoid loss of product.

Regarding the limitation directed to the level of impurities before and after formation of the diethanol amine salt from the starting batch of treprostinil: Phares meets the limitations directed to the method of preparing the diethanolamine salt of treprostinil. Phares teaches combining treprostinil with diethanol amine to form a salt and further obtains two different polymorphs of treprostinil via crystallization (page 85). Since the instantly claimed method is directed to the same sequence of steps the amount of impurities in the treprostinil diethanolamine is inherently lower than it was in the starting batch of treprostinil.

Regarding claim 8, directed to the claimed pharmaceutical composition being in solution. On page 58, Phares teaches a dosing solution comprising Treprostinil diethanolamine.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the claims at issue are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the reference application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP §

717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(l)(1) - 706.02(l)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/forms/. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to http://www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

Claims 1-10 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 24 and 26 of U.S. Patent No. 8,242,305 (‘305). Although the claims at issue are not identical, they are not patentably distinct from each other because:

Claim 24 of ‘305 is directed to a process for the preparation of compound IV (treprostinil). Said method comprises alkylation od benzindene triol to prepare compound (VI) followed by hydrolyzing compound (VI) and contacting the hydrolysis product with a base. In claim 26 the contacting base is diethanolamine.

Claims 1-10 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-3, 8-14, of copending Application No. 14/754,932 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because both the instant claims and claims of '932 are directed to a pharmaceutical product comprising treprostinil diethanolamine and a method of preparing said product via alkylation of benzindene triol, hydrolysis, contacting with a base to form a salt and isolation of the salt.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Conclusion

Claims 1-10 are pending

Claims 1-10 are rejected

Any inquiry concerning this communication or earlier communications from the examiner should be directed to YEVGENY VALENROD whose telephone number is (571)272-9049. The examiner can normally be reached on mon-fri 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Fereydoun G. Sajjadi can be reached on 571-572-3311. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/YEVGENY VALENROD/
Primary Examiner, Art Unit 1672

Notice of References Cited	Application/Control No. 14/849,981	Applicant(s)/Patent Under Reexamination BATRA ET AL.	
	Examiner YEVGENY VALENROD	Art Unit 1672	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
*	A	US-8,242,305 B2	08-2012	Batra; Hitesh	C07C51/08	562/466
	B	US-				
	C	US-				
	D	US-				
	E	US-				
	F	US-				
	G	US-				
	H	US-				
	I	US-				
	J	US-				
	K	US-				
	L	US-				
	M	US-				

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

PTO/SB/08 (modified)

Substitute for form 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	Unassigned
				Filing Date	Herewith
				First Named Inventor	Hitesh BATRA
				Art Unit	Unassigned
(use as many sheets as necessary)				Examiner Name	Unassigned
Sheet	1	of	4	Attorney Docket Number	080618-1581

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	A1	2002/0173672 A1	11/21/2002	Moriarty et al.	
	A2	2004/0176645 A1	09/09/2004	Moriarty et al.	
	A3	2005/0085540 A1	04/21/2005	Phares et al.	
	A4	2005/0101608 A1	05/12/2005	Santel, Donald J.	
	A5	2005/0165111 A1	07/28/2005	Wade et al.	
	A6	2005/0282903 A1	12/22/2005	Wade et al.	
	A7	2005/0282901 A1	12/22/2005	Phares et al.	
	A8	2007/0078182 A1	04/05/2007	Phares et al.	
	A9	2007/0078095 A1	04/05/2007	Phares et al.	
	A10	2008/0200449 A1	08/21/2008	Olschewski et al.	
	A11	2008/0249167 A1	10/09/2008	Phares et al.	
	A12	2008/0280986 A1	11/13/2008	Wade et al.	
	A13	2009/0036465 A1	02/05/2009	Roscigno et al.	
	A14	2009/0163738 A1	06/25/2009	Batra et al.	
	A15	4,306,075 A	12/15/1981	Aristoff, Paul A.	
	A16	4,306,076	12/15/1981	Nelson	
	A17	4,424,376 A	01/03/1984	Moniot et al.	
	A18	4,463,183 A	07/31/1984	Haslanger, Martin F.	
	A19	4,486,598 A	12/04/1984	Aristoff, Paul A.	
	A20	4,544,764 A	10/01/1985	Aristoff, Paul A.	
	A21	4,668,814	05/26/1987	Aristoff	
	A22	4,668,814 A	05/26/1987	Aristoff, Paul A.	
	A23	4,683,330 A	07/28/1987	Aristoff, Paul A.	
	A24	5,153,222 A	10/06/1992	Tadepalli et al.	
	A25	6,054,486 A	04/25/2000	Crow et al.	
	A26	6,441,245 B1	08/27/2002	Moriarty et al.	
	A27	6,521,212 B1	02/18/2003	Cloutier et al.	
	A28	6,528,688 B2	03/04/2003	Moriarty et al.	
	A29	6,700,025 B2	03/02/2004	Moriarty et al.	
	A30	6,756,033 B2	06/29/2004	Cloutier et al.	
	A31	6,765,117 B2	07/20/2004	Moriarty et al.	
	A32	6,803,386 B2	10/12/2004	Shorr et al.	
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Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Documents	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]
	A37	CA 2 710 726 A1	01/22/2012	Alphora Research Inc., CA		
	A38	CN 101891596 A	11/24/2010	Shanghai Techwell Biopharmaceutical Co. Ltd.		A ✓
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Examiner Signature		Date Considered	

4815-8251-5496.1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /YV/

PTO/SB/08 (modified)

Substitute for form 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	Unassigned
				Filing Date	Herewith
				First Named Inventor	Hitesh BATRA
				Art Unit	Unassigned
(use as many sheets as necessary)				Examiner Name	Unassigned
Sheet	2	of	4	Attorney Docket Number	080618-1581

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Documents	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]
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NON PATENT LITERATURE DOCUMENTS

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Examiner Signature		Date Considered	

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PTO/SB/08 (modified)

Substitute for form 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	Unassigned
				Filing Date	Herewith
				First Named Inventor	Hitesh BATRA
(use as many sheets as necessary)				Art Unit	Unassigned
				Examiner Name	Unassigned
Sheet	3	of	4	Attorney Docket Number	080618-1581

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Examiner Signature		Date Considered	

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PTO/SB/08 (modified)

Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(use as many sheets as necessary)* Sheet 4 of 4	***Complete if Known***	
	Application Number	Unassigned
	Filing Date	Herewith
	First Named Inventor	Hitesh BATRA
	Art Unit	Unassigned
	Examiner Name	Unassigned
	Attorney Docket Number	080618-1581

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Examiner Signature	/Yevgeny Valenrod/	Date Considered	02/22/2016

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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /YV/

PTO/SB/08 (modified)

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Date Submitted: OCT 13 2015

(use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	14/849,981
Filing Date	9/10/2015
First Named Inventor	Hitesh BATRA
Art Unit	1672
Examiner Name	Yevgeny Valenrod
Attorney Docket Number	080618-1581

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	B1	3,703,544	11/21/1972	Morozowich	
	B2	3,888,916	06/10/1975	Sinkula	

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Examiner Signature	/Yevgeny Valenrod/	Date Considered	02/22/2016

4816-8431-4921.1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /YV/

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14849981	BATRA ET AL.
	Examiner	**Art Unit**
	YEVEGENY VALENROD	1672

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	02/22/2016								
	1	✓								
	2	✓								
	3	✓								
	4	✓								
	5	✓								
	6	✓								
	7	✓								
	8	✓								
	9	✓								
	10	✓								

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	1	("8497393").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2016/02/22 13:03
L2	1	("8242305").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2016/02/22 13:03
L3	1	("4683330").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2016/02/22 13:03
L4	1	("4306075").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2016/02/22 13:03
L5	28	((Hitesh) near2 (Batra)).INV.	US-PGPUB; USPAT; USOCR	OR	ON	2016/02/22 13:03
L6	21	((Sudersan) near2 (Tuladhar)).INV.	US-PGPUB; USPAT; USOCR	OR	ON	2016/02/22 13:03
L7	29	((Raju) near2 (Penmasta)).INV.	US-PGPUB; USPAT; USOCR	OR	ON	2016/02/22 13:03
L8	235	((David) near2 (Walsh)).INV.	US-PGPUB; USPAT; USOCR	OR	ON	2016/02/22 13:03
L9	260	L5 or L6 or L7 or L8	US-PGPUB; USPAT; USOCR	OR	ON	2016/02/22 13:03
L10	23	L9 and treprostinil	US-PGPUB; USPAT; USOCR	OR	ON	2016/02/22 13:03
L11	516	c07c59/72.cpc.	US-PGPUB; USPAT; USOCR	OR	ON	2016/02/22 13:03
L12	867	(562/466).CCLS.	US-PGPUB; USPAT; USOCR	OR	OFF	2016/02/22 13:03
L13	1257	L11 or L12	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2016/02/22 13:03
L14	39	L13 and treprostinil	US-PGPUB; USPAT; USOCR	OR	ON	2016/02/22 13:03

EAST Search History (Prior Art)

L15	35	L14 and purity	US-PGPUB; USPAT; USOCR	OR	ON	2016/02/22 13:03
L16	33	L15 and HPLC	US-PGPUB; USPAT; USOCR	OR	ON	2016/02/22 13:03
L17	1	("6765117").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2016/02/22 13:03
L18	2	wo "2005007081"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2016/02/22 13:03
L19	2	"9242350"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2016/02/22 13:03
L20	1	("8242305").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2016/02/22 13:03
L21	1	("9156786").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2016/02/22 13:03

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BIB DATA SHEET

CONFIRMATION NO. 6653

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
14/849,981	09/10/2015 RULE	562	1672	080618-1581

APPLICANTS
United Therapeutics Corporation, Silver Spring, MD;

INVENTORS
Hitesh BATRA, Herndon, VA;
Sudersan M. TULADHAR, Silver Spring, MD;
Raju PENMASTA, Herndon, VA;
David A. WALSH, Palmyra, VA;

**** CONTINUING DATA ***************************
This application is a DIV of 13/933,623 07/02/2013 PAT 9156786
which is a CON of 13/548,446 07/13/2012 PAT 8497393
which is a CON of 12/334,731 12/15/2008 PAT 8242305
which claims benefit of 61/014,232 12/17/2007

**** FOREIGN APPLICATIONS ***************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****
09/23/2015

Foreign Priority claimed ☐ Yes ☑ No 35 USC 119(a-d) conditions met ☑ Yes ☐ No Verified and Acknowledged /YEVEGENY VALENROD/ Examiner's Signature	☐ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		VA	0	10	2

ADDRESS
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UNITED STATES

TITLE
PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®

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Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14849981	BATRA ET AL.
	Examiner	Art Unit
	YEVEGENY VALENROD	1672

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
EAST	2/22/2016	YV
Inventor	2/22/2016	YV

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/849,981	09/10/2015	Hitesh BATRA	080618-1581

CONFIRMATION NO. 6653

22428
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PUBLICATION NOTICE

Title:PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN?

Publication No.US-2015-0376106-A1
Publication Date:12/31/2015

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Substitute for form 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	14/849,981
Date Submitted: OCT 13 2015				**Filing Date**	9/10/2015
(use as many sheets as necessary)				**First Named Inventor**	Hitesh BATRA
Sheet	1	of	1	Art Unit	1672
				Examiner Name	Yevgeny Valenrod
				Attorney Docket Number	080618-1581

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Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Documents	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]
	B3	Steadymed Ltd., v. United Therapeutics Corporation, Petition for *Inter Partes* Review of U.S. Patent No. 8,497,393, under 37 CFR 42.100, dated October 1, 2015, with Exhibits 1009, 1010, 1017 and 1018.	
	B4	Ege, S., *Organic Chemistry Second Edition*, 1989, 541-547.	
	B5	Schoffstall et al., *Microscale and Miniscale Organic Chemistry Laboratory Experiments*, 2nd. Ed., 2004, 200-202.	
	B6	Wiberg, Kenneth, *Laboratory Technique in Organic Chemistry*, 1960, 112.	

Examiner Signature		Date Considered	

4816-8431-4921.1

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

STEADYMED LTD.,

Petitioner,

v.

UNITED THERAPEUTICS CORPORATION

Patent Owner.

Case IPR Unassigned

Patent No. 8,497,393

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 8,497,393 UNDER 37 C.F.R. § 42.100

Mail Stop "Patent Board"
Patent Trial and Appeal Board
U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

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TABLE OF EXHIBITS

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1001	U.S. Patent No. 8,497,393 to Batra, et al.	'393 Patent
1002 - 1	Prosecution History of U.S. Patent No. 8,242,305 (excerpts)	--
1002 - 2	Prosecution History of U.S. Patent No. 8,497,393	--
1003	U.S. Patent No. 6,765,117 to Moriarty, et al.	'117 Patent
1004	J. Org. Chem. 2004, 1890-1902 by Moriarty, et al.	Moriarty
1005	International Publication No. WO 2005/007081 to Phares, et al.	Phares
1006	Japanese Patent App. No. 56-122328A to Kawakami, et al. (Japanese)	Kawakami
1007	Certified English translation of Japanese Patent App. No. 56-122328A to Kawakami, et al.	Kawakami
1008	Ege, S. (1989). *Organic Chemistry Second Edition* (pp. 543-547)	Ege
1009	Declaration of Jeffrey D. Winkler, Ph.D.	Winkler Decl.
1010	*Curriculum Vitae* of Jeffrey D. Winkler, Ph.D.	--
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EXHIBIT	DESCRIPTION	ABBREVIATION
1012	Wiberg, Kenneth (1960), Laboratory Technique in Organic Chemistry (p. 112)	Wiberg
1013	U.S. Patent No. 6,441,245 to Moriarty, et al.	'245 Patent
1014	Schoffstall, "Microscale and Miniscale Organic Chemistry Laboratory Experiments," 200-202 (2d ed.) (2004)	Schoffstall
1015	U.S. Patent No. 3,703,544 to Morozowich, et al.	'544 Patent
1016	U.S. Patent No. 3,888,916 to Sinkula, et al.	'916 Patent
1017	"Getting Started in HPLC," Section 4D: Precision and Accuracy, available at http://www.lcresources.com/resources/getstart/4d01.htm (accessed Sept. 29, 2015)	--
1018	Gilbert, "Experimental Organic Chemistry: A Miniscule and Microscale Approach," 113-117 (5th. ed.) (2011)	Gilbert[1]

[1] For ease of reference, all citations to the above references are to the bates-labeled page number. Petitioner utilizes the "column, line number" format, however, for any referenced U.S. Patents (*i.e.,* Exhibit Nos. 1001, 1003, 1013, 1015, and 1016).

SteadyMed Ltd. ("Petitioner") in accordance with 35 U.S.C. §§ 311-319 and 37 C.F.R. § 42.100 *et seq.,* requests that the United States Patent and Trademark Office ("USPTO") proceed with an *inter partes* review of Claims 1-22 of U.S. Patent No. 8,497,393 (the '393 Patent") (Ex. 1001).

I. COMPLIANCE WITH FORMAL REQUIREMENTS

A. Mandatory Notices Under 37 C.F.R. § § 42.8(b)(1)-(4)

1. Real Party-in-Interest

SteadyMed Ltd., SteadyMed Therapeutics, Inc., and SteadyMed U.S. Holdings, Inc. are the real parties-in-interest.

2. Related Matters

Petitioner advises that to its knowledge there are no related matters to which it is a party. Petitioner further advises that the '393 Patent is subject to the following U.S. District Court litigations, currently pending in the District of New Jersey: (1) *United Therapeutics Corp. v. Sandoz, Inc.*, Civ. No. 14-cv-05499; (2) *United Therapeutics Corp. v. Teva Pharmaceuticals U.S.A., Inc.*, Civ. No. 14-cv-05498; and (3) *United Therapeutics Corp. v. Watson Laboratories, Inc.*, Civ. No. 15-cv-05723.

3. Lead And Back-Up Counsel

Pursuant to 37 C.F.R. § 42.8(b)(3) and 42.10(a), Petitioner provides the following designation of counsel: Lead counsel is Stuart E. Pollack (Reg. No. 43,862) and backup counsel is Lisa A. Haile (Reg. No. 38,347), both at email

address: Steadymed-IPR@dlapiper.com. Postal and hand delivery for both is DLA Piper LLP (US), 1251 Avenue of the Americas, 27th Floor, New York, New York 10020. Telephone for Dr. Pollack is (212) 335-4964; telephone for Dr. Haile is (858) 677-1456. The fax for both is (212) 335-8464.

4. Powers of Attorney and Service Information

Pursuant to 37 C.F.R. § 42.10(b), a Power of Attorney accompanies this Petition. Petitioner consents to service by email at Steadymed-IPR@dlapiper.com.

B. Proof of Service on the Patent Owner

As identified in the attached Certificate of Service, a copy of this Petition in its entirety is being served to Patent Owner ("Patentee") at the address listed in the USPTO's records by overnight courier pursuant to 37 C.F.R. § 42.6.

C. Fees

A fee of $26,200 has been paid for this Petition. Twenty-two (22) claims are being reviewed. The undersigned further authorizes the United States Patent and Trademark Office, including the Patent Trial and Appeal Board to charge any additional fee that might be due or required to Deposit Account No. 07-1896.

II. GROUNDS FOR STANDING

In accordance with 37 C.F.R. § 42.104(a), Petitioner certifies that the '393 Patent is available for *inter partes* review and that Petitioner is not barred or estopped from requesting an *inter partes* review challenging the patent claims on the grounds identified in this Petition.

III. STATEMENT OF PRECISE RELIEF REQUESTED

In accordance with 37 C.F.R. § 42.22, Petitioner respectfully requests that Claims 1-22 of the '393 Patent be found invalid for the reasons set forth below.

IV. IDENTIFICATION OF CHALLENGE

Inter partes review is requested in view of the following references:

- **Exhibit 1004**: J. Org. Chem. 2004, 1890-1902 by Moriarty, et al. ("Moriarty");
- **Exhibit 1005**: International Publication No. WO 2005/007081 to Phares, et al. ("Phares");
- **Exhibit 1006** (Japanese) and **Exhibit 1007** (English): Japanese Patent App. No. 56-122328A to Kawakami, et al. ("Kawakami");
- **Exhibit 1008**: *Organic Chemistry Second Edition* (pp. 543-547) by Ege ("Ege").

Pursuant to 37 C.F.R. § 42.63(b), Exhibit 1011 contains an affidavit attesting that a professional translator and interpreter fluent in the English and Japanese languages translated Kawakami (Ex. 1006).

Each of the patents and printed publications set forth below is prior art to the '393 Patent:

Ground	Proposed Statutory Rejections for the '393 Patent
1	Claims 1-5, 7-9, 11-14 and 16-20 are anticipated by Phares (Ex.

Ground	Proposed Statutory Rejections for the '393 Patent
	1005) pursuant to 35 U.S.C. §102(b).
2	Claims 1-5, 7-9, 11-14 and 16-20 are rendered obvious by a combination of Moriarty (Ex. 1004) in view of either Phares (Ex. 1005) or Kawakami (Exs. 1006 & 1007) pursuant to 35 U.S.C. §103.
3	Claims 6, 10, 15, 21 and 22 are rendered obvious by a combination of Moriarty (Ex. 1004) in view of either Phares (Ex. 1005) or Kawakami (Exs. 1006 & 1007) and further in view of Ege (Ex. 1008) pursuant to 35 U.S.C. §103.

Petitioner also relies on the Declaration of Jeffrey D. Winkler, Ph.D. (Ex. 1009) in further support of its arguments.

V. LEVEL OF ORDINARY SKILL IN THE ART

A person of ordinary skill in the area of chemistry at the time of the alleged invention would have a master's degree or a Ph.D. in medicinal or organic chemistry, or a closely related field. (Ex. 1009, Winkler Decl., ¶ 14). Alternatively, a person of ordinary skill would include an individual with a bachelor's degree and at least five years of practical experience in medicinal or organic chemistry. (*Id.*, at ¶ 14).

VI. SUMMARY OF THE '393 PATENT

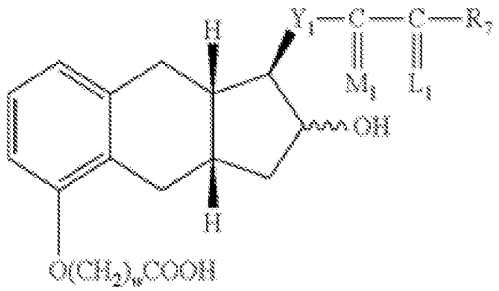
A. Brief Description of the '393 Patent

The '393 Patent is entitled "Process to Prepare Treprostinil, The Active Ingredient in Remodulin™." The claims of the '393 Patent are product-by-process claims. These claims include two independent (Claims 1 and 9) and twenty dependent claims.

The '393 Patent discloses an "improved process" to prepare prostacyclin derivatives such as treprostinil. (Ex. 1001, Abstract). Claim 1 is drawn to a product comprising a compound of a genus that includes the treprostinil compound, or a pharmaceutically acceptable salt thereof. Claim 9 is identical to Claim 1 except that it is drawn to a product comprising the specific treprostinil compound, a species of the genus of Claim 1, made by the same process.

Each of the independent claims includes limitations that the claimed compound is made by a process comprising three specified steps and one optional step: (a) alkylating a prostacyclin derivative (*e.g.*, a benzindene triol precursor to treprostinil acid) to form an alkylated prostacyclin derivative (*e.g.*, a benzindene nitrile precursor to treprostinil acid); (b) hydrolyzing the alkylated prostacyclin derivative with a base to form a prostacyclin acid (*e.g.*, treprostinil acid); (c) contacting the prostacyclin acid (*e.g.*, treprostinil acid) with a base to form a prostacyclin carboxylate salt (*e.g.*, a treprostinil salt); and (d) optionally reacting

the prostacyclin carboxylate salt (*e.g.*, a treprostinil salt) formed in step (c) with an acid to form a compound or a pharmaceutically acceptable salt of:



(Ex. 1001).

The alkylating and hydrolyzing steps in the synthesis of treprostinil and the other claimed compounds, as set forth in steps (a) – (b) of Claims 1 and 9, were fully disclosed in prior art to the '393 Patent, including U.S. Patent No. 6,765,117 (the '117 Patent) (Ex. 1003), and in Moriarty et al., J. Org. Chem., 1890-1902 (2004) (Ex. 1004, referred to as "Moriarty"), as well as other publications. Patent Owner admits that steps (a) ("alkylating") and (b) ("hydrolyzing") were in the prior art. (*See* Prosecution History (Ex. 1002-1), p. 109; '393 Patent, (Ex. 1001), col. 1, lines 22-28 (incorporating Moriarty (Ex. 1004), the '117 Patent (Ex. 1003), and U.S. Patent No. 6,441,245 (Ex. 1013) by reference, and col.7, lines 17-20 (describing '245 Patent's process as the same as in '393 Patent)).

The '393 Patent addresses an alleged "improvement" to Moriarty through the addition of steps (c) and optionally (d), which claim a standard, basic organic chemistry purification by a precipitation technique: converting a free carboxylic acid into a salt using a weak base and then precipitating it to remove potential impurities, and then, optionally converting the salt back to the free acid. (*See, e.g.,* Ex. 1001, col. 17, lines 27-40) (describing the benefits of the disclosed processes as providing a "better quality" final product that removes impurities). These precipitation procedures were well-known in the art – indeed, they are no more than basic organic chemistry techniques and standard chemical purification – and they were fully disclosed in numerous prior art references, including basic organic chemistry textbooks. Additionally, as discussed in greater detail below and in the accompanying Declaration of Jeffrey D. Winkler (Ex. 1009), the claimed '393 Patent process does not produce a product that is materially distinct from the product produced by the prior art.

B. Summary of the Prosecution History of the '393 Patent

The '393 Patent issued July 30, 2013 from application No. 13/548,446, filed July 13, 2012. Application No. 13/548,446 is a continuation of application No. 12/334,731, filed on December 15, 2008, now U.S. Patent No. 8,242,305. Both patents claim priority to provisional application No. 61/014,232, filed December 17, 2007.

During prosecution, the Examiner rejected the pending claims (substantially identical to issued Claims 1-22 of the '393 Patent) under 35 U.S.C. §102(b) as being anticipated by Moriarty (Ex. 1004; *see also* Ex. 1002-2, p. 295, 1/3/2013 Office Action; pp. 327-329, 5/15/2013 Office Action). As noted above, Moriarty discloses the synthesis for treprostinil, which involves, *inter alia*, the isolation of treprostinil prior to the formation of treprostinil salt. The Examiner stated that Moriarty discloses a compound having the same structure of the claimed product disclosed in the '393 Patent. (Ex. 1002-2, p. 295, 1/3/2013 Office Action; pp. 327-329, 5/15/2013 Office Action). The Examiner further stated that the claims are product-by-process claims, and since the product disclosed in the prior art is the same as the claimed product, the "patentability of the product does not depend on the method of its production." (*Id.*).

In response, Patent Owner submitted arguments and a Declaration under 37 C.F.R. §1.132 by Dr. David Walsh, one of the inventors, and Executive Vice President of Chemical Research and Development at United Therapeutics Corporation (the "Walsh Declaration") (Ex. 1002, pp. 346-350, Walsh Declaration). The Walsh Declaration provides data from "representative Certificates of Analysis" with impurity profiles for treprostinil free acid prepared according to the process of Moriarty (Ex. 1004), and treprostinil diethanolamine and treprostinil free acid prepared according to the process of the '393 Patent. (*Id.*).

Relying on the Walsh Declaration, Patent Owner differentiated its synthesis of treprostinil by emphasizing that its product (treprostinil) was different than the product of Moriarty (Ex. 1002-2, pp. 343-344, 6/5/2013 Remarks; pp. 346-350, Walsh Declaration) because: (1) the product of Moriarty is "physically different" than the instant claims, as a "base addition salt is formed *in situ* with treprostinil that has not been previously isolated"; and (2) the product of Moriarty contained more impurities:

> "In the response filed February 8, 2013, Applicants submitted that the product of Moriarty 2004 is physically different from the product of claims 1 and 10, in which a base addition salt is formed in situ with treprostinil that has not been previously isolated. Specifically, Applicants noted that when a batch of treprostinil acid made by the type of process disclosed in Moriarty 2004 was analyzed by the applicants, it was found to contain small amounts of 4 different impurities (benzindene triol, treprostinil methyl ester, and 2 different stereoisomers of treprostinil) […] Applicants explained that this physical difference in the product resulted directly from the steps recited in claims 1 and 10, in which a salt is formed in situ without previously isolating treprostinil."

(Ex. 1002-2, pp. 343-344). The Walsh Declaration demonstrated a treprostinil purity of 99.8%, above both Claim 2 and Claim 10's 99.5% purity level and Moriarty's 99.7% purity level, and according to Dr. Walsh, Moriarty's purity is really 99.4%, and not 99.7% as Moriarty reported. (Ex. 1002-2, pp. 347). These

alleged purity differences were intended to rebut the Examiner's statement that "[o]n page 1902 [of Moriarty] … [i]n the second column 99.7 pure compound 7 [treprostinil] is disclosed thereby meeting the purity limitations of claims 2 and 11." (Ex. 1002-2, pp. 327-328). In fact, these purity differences are illusory, and reflect differences in unclaimed process conditions and the precision of the HPLC instrument measuring impurities, and cannot confer patentability.

VII. CLAIM CONSTRUCTION

A claim subject to *inter partes* review receives the "broadest reasonable construction in light of the specification of the patent in which it appears." 42 C.F.R. § 42.100(b). This means that the words of the claim are given their plain meaning from the perspective of one of ordinary skill in the art unless that meaning is inconsistent with the specification. *In re Zletz*, 893 F.2d 319, 321 (Fed. Cir. 1989). Indeed, there is a "heavy presumption" that a claim term carries its ordinary and customary meaning. *CCS Fitness, Inc. v. Brunswick Corp.*, 288 F.3d 1359, 1366 (Fed. Cir. 2002). Here, each claim term carries its ordinary and customary meaning, with the exception of the following terms that should be construed:

"***Product***": "Product" appears in each independent Claim 1 and 9, and in dependent Claim 22. The broadest reasonable interpretation of "product" is "chemical composition." Both claims use the transition "comprising" ("a product comprising…" and "a process comprising…"), which is expressly defined in the

'393 Patent specification: "The expression 'comprising' means 'including but not limited to.' Thus, other non-mentioned substances, additives, carriers, or steps may be present." (Ex. 1001, col. 4, lines 23-24). "Product," is therefore properly defined as a "chemical composition," which includes the treprostinil compound along with other substances (including impurities). A composition connotes more than one element or ingredient; it is a chemical composition because treprostinil is a chemical and a composition containing treprostinil is a chemical composition. For these reasons, "product" should be construed as "a chemical composition."

"***A product comprising a compound of formula I/IV or a pharmaceutically acceptable salt thereof***" (Claims 1 & 9): This term appears in each independent claim, Claims 1 and 9. The broadest reasonable interpretation is "a chemical composition that includes, but is not limited to, a compound of Formula I, or a pharmaceutically acceptable salt thereof, and that may also include other non-mentioned substances (including impurities), additives, or carriers, without limitation as to the types or relative amounts thereof." Petitioner's proposed construction incorporates Patent Owner's definition of "comprising" in the '393 Patent specification (Ex. 1001, col. 4, lines 23-25). For example, isolating treprostinil during the process is included in the claims, since it is an additional process step allowed by the transitional phrase "comprising."

"***A process comprising***" and "***the process comprising***" (Claims 1 & 9): These terms appear in each independent claim, Claims 1 & 9. The broadest reasonable interpretation is "a process that includes, but is not limited to, the recited process steps, and may include, without limitation, any other non-recited steps." This construction is supported by Patent Owner's definition of "comprising" as meaning "including but not limited to" and that "other non-mentioned…steps may be present." (Ex. 1001, col. 4, lines 23-25). The term "comprising" dictates that while the claimed process must include the recited steps it is not otherwise limited and can include any other non-recited steps.

Because the claim construction standard in this proceeding differs from that used in U.S. district court litigations, Petitioner expressly reserves the right to assert different claim construction positions under the standard applicable in district court for any term of the '393 Patent in any district court litigations, should Petitioner become a party to any future litigation involving the '393 Patent.

VIII. THERE IS A REASONABLE LIKELIHOOD THAT AT LEAST ONE CLAIM OF THE '393 PATENT IS UNPATENTABLE

A. Identification of the References As Prior Art

Moriarty was published in 2004 in the Journal of Organic Chemistry, Volume 69, No. 6. (Ex. 1004). Moriarty is prior art to the '393 Patent under 35 U.S.C. §103, as a publication under § 102(b).

Phares was published January 27, 2005. (Ex. 1005). Phares is prior art to the '393 Patent under 35 U.S.C. §§102(b) and 103.

Kawakami was published September 25, 1981 to Kawakami, et al. (Exs. 1006 & 1007). Kawakami is prior art to the '393 Patent under 35 U.S.C. §103, as a publication under § 102(b).

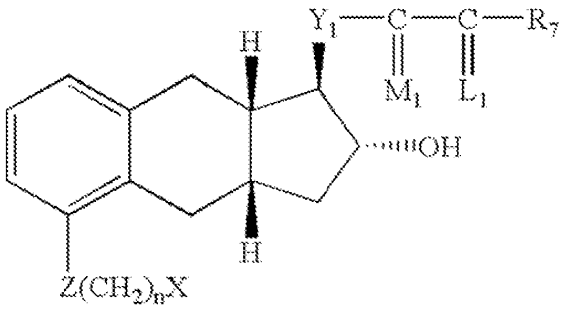
Ege was published in 1989 in *Organic Chemistry, Second Edition*, at pages 543-547. (Ex. 1008). Ege is prior art to the '393 Patent under 35 U.S.C. §103, as a publication under § 102(b).

B. State of the Prior Art & Summary of Invalidity Arguments

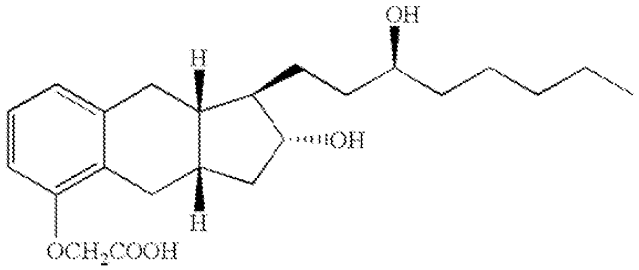
There are three separate – and strong – bases for invalidation of the '393 Patent: (1) the synthesis of the claimed compounds including treprostinil and treprostinil diethanolamine salt was well-known in the art; (2) the '393 Patent's only alleged "improvement" over the prior art involves nothing more than basic organic chemistry 101 – standard chemical purification through salt formation and precipitation, and this salt formation and purification step was carried out on treprostinil in the prior art; and (3) since the claims of the '393 Patent are product-by-process claims and the claimed process does not produce a product that is materially distinct from the product produced by the prior art, the claims of the '393 Patent are invalid as anticipated and obvious. Accordingly, all claims of the '393 Patent should be held invalid, as discussed in further detail below.

1. *Steps (a) – (b): The Synthesis of Treprostinil Was Well-Known*

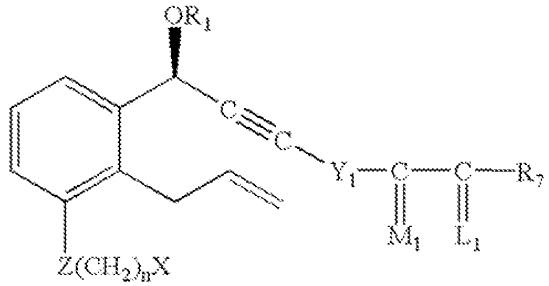
Before December 17, 2007, syntheses for numerous prostacyclin derivatives, such as treprostinil, and intermediate compounds useful in their syntheses were well-known. These prostacyclin derivatives and intermediates include the following general structures:



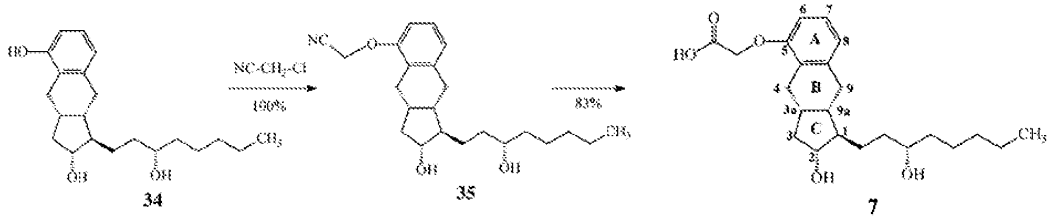
(*see e.g.*, the '117 Patent, Ex. 1003, Claim 1). For example, the '117 Patent (Ex. 1003) includes the synthesis of treprostinil (which is the case in which, Z is O, n is 1, X is COOH, Y_1 is CH_2CH_2-, M_1 is a H and a OH group in the S configuration (*i.e.*, the same stereoisomer configuration found in the structure of treprostinil (below)), L_1 is α-H; β-H, and R_7 is $–(CH_2)_3$-CH_3) amongst its many examples. In addition, both Moriarty (Ex. 1004) and Phares (Ex. 1005) further disclose syntheses of treprostinil. For example, Claim 3 of the '117 Patent (Ex. 1003) discloses the structure of treprostinil (below),



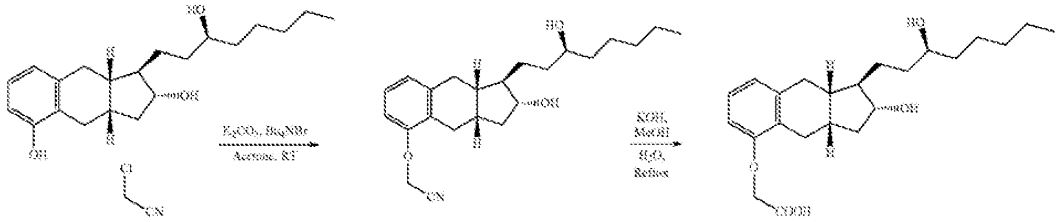
which is produced by a process for making 9-deoxy-PGF1-type compounds, the process comprising cyclizing the following starting compound:



As noted above, steps (a) – (b) of Claims 1 and 9 of the '393 Patent disclose the synthesis of prostacyclin derivative acids that include treprostinil acid, which is also disclosed in Moriarty (Ex. 1004) and the '117 Patent (Ex. 1003). For example, Moriarty (Ex. 1004) at p. 6 and p. 3 discloses the following synthetic scheme for making treprostinil acid:



And the '393 Patent (Ex. 1001) at cols. 9-10 discloses the same synthetic scheme for making treprostinil acid:



Accordingly, the only alleged "improvement" to Moriarty in the '393 Patent was the addition of step (c) and **optionally** step (d) of Claims 1 and 9.

2. *Steps (c) & (d): Formation of a Carboxylate Salt from a Carboxylic Acid and the Addition of an Acid to a Carboxylate Salt to Regenerate the Carboxylic Acid is Standard Chemical Purification Known in the Art*

Steps (c) and (d) of Claims 1 and 9 disclose nothing more than basic organic chemistry techniques for purification of a carboxylic acid, such as treprostinil acid, well described in the prior art years before December 17, 2007. The formation of a carboxylate salt, by the addition of a weak base to a neutral carboxylic acid, and the subsequent addition of a strong acid to regenerate carboxylic acid, as disclosed in steps (c) and (d), is standard chemistry purification – *i.e.*, organic chemistry 101. Indeed, similar general purification techniques were described in numerous textbooks and literature, such as basic introductory organic chemistry textbooks, well before the December 17, 2007 priority date for the '393 Patent. For example,

Wiberg (Ex. 1012), an organic chemistry lab textbook (Ex. 1012) provided to organic chemistry students, explicitly states:

> A typical example is the purification of a water-insoluble solid carboxylic acid by dissolving it in sodium hydroxide solution, filtering, precipitating the compound by the addition of acid. A similar procedure may be used with amines: dissolve the compound in acid and precipitate it with a base. These procedures usually work quite well in that they utilize a chemical reaction to aid in separation from nonacidic or nonbasic impurities.

(Ex. 1012, p. 6; *see also* Ex. 1009, Winkler Decl., ¶ 42). Similarly, Schoffstall (Ex. 1013), describes an experiment in which carboxylic acid is separated from neutral and basic organic compounds by conversion to a salt. Addition of an acid, such as HCl, then regenerates the carboxylic acid, which can then be filtered or extracted into an organic solvent. (Ex. 1013, pp. 3-40; *see also* Winkler Decl., ¶ 42). As the '393 Patent claims do not require isolation (or non-isolation) of the claimed treprostinil prior to formation of the treprostinil diethanolamine salt, general purification procedures, as disclosed in basic organic chemistry textbooks like Wiberg or Schoffstall, accordingly fall within the '393 Patent claims. *See also* (Ex. 1002-2, p. 343, 2/8/2013 Remarks ("…the steps recited in claims 1 and 10, in which a salt is formed *in situ* without previously isolating treprostinil").

More specifically, contacting a carboxylic acid of a prostacyclin derivative, such as treprostinil, with a base to form a salt, followed by the addition of a strong acid to regenerate the carboxylic acid, was a well-known chemical purification technique in the prior art. For example:

- ***Kawakami*** (Ex. 1007), entitled "Crystalline Amine Salt of Methanoprostacyclin Derivative, Manufacturing Method thereof, and **Purifying Method** thereof" (bolding added), is directed to the preparation and use of dicyclohexylamine (*i.e.*, a base) to form a crystalline dicyclohexylamine salt of a methanoprostacyclin derivative, in order to purify the methanoprostacyclin. Kawakami further discloses that the dicyclohexylamine salt of a methanoprostacyclin derivative can be easily reverted to the free methanoprostacyclin derivative by conventional methods (Ex. 1007, p. 6), such as treating the salt with a strong acid such as HCl or H_2SO_4. Per Kawakami, the salt that is obtained has "fairly high purity and the purity can be further improved by recrystallization as needed with the use of an appropriate solvent." (*Id.*).
- ***Phares*** (Ex. 1005), entitled "Compounds and Methods for Delivery of Prostacyclin Analogs," discloses that the preparation of treprostinil diethanolamine includes the step of adding and dissolving diethanolamine (*i.e.*, a base) to treprostinil that is dissolved in a 1:1 molar ratio mixture of ethanol:

water. (Ex. 1005, p. 24, bottom para.). This treprostinil diethanolamine can be further precipitated and purified to form the purer and more stable crystal form called "Form B." (Ex. 1005, pp. 85-93).

- ***Ege*** (Ex. 1008), an organic chemistry textbook, discloses that sodium benzoate (*i.e.*, a carboxylate salt) can be converted back to benzoic acid (*i.e.*, a carboxylic acid) by treatment with the acid HCl. (Ex. 1008, p. 8).

3. *The Claimed Treprostinil and Treprostinil Diethanolamine Salt is Not Distinct from the Prior Art*

As noted above and as recognized by the Patent Office during prosecution, the '393 Patent claims are product-by-process claims. The process limitations are not accorded any weight for determining the validity of the claims of the '393 Patent. *See, e.g., Amgen Inc. v. F. Hoffman-La Roche Ltd.*, 580 F.3d 1340, 1369 (Fed. Cir. 2009) ("In determining validity of a product-by-process claim, the focus is on the product and not the process of making it"); *see also* MPEP § 2113 (citing *In re Thorpe*, 777 F.2d 695, 698 (Fed. Cir. 1985)). The process in a product-by-process claim merits weight in reviewing the prior art only if it imparts some unique and novel property or structure in the resulting product. Such is not the case here. As noted during prosecution, Patent Owner differentiated its synthesis of treprostinil from Moriarty (Ex. 1004) by emphasizing that its product (treprostinil) contained less impurities than the product of Moriarty. Accordingly, there are three

reasons why the claimed treprostinil is not distinct from the same compound in the prior art:

(1) First, during prosecution, Patent Owner provided a declaration claiming to show that its purification method achieved 99.8% purity (Ex. 1002-2, p. 348) despite the admission in the '393 Patent itself that: "In one embodiment, the purity of compound of formula IV is at least 90.0%, 95.0%, 99.0%, 99.5%," ('393 Patent, Ex. 1001, col. 8, lines 66-67)[2] where the compound of Formula IV is treprostinil. This admission shows that the purity of treprostinil may be as low as 90.0%, and Patent Owner's suggestion that 99.8% is achieved or that greater than 99.5% is always achieved is based on a particular set of process steps that are not claimed and which must have been found after the filing date.

(2) Second, Patent Owner's claimed 99.5% purity, which Patent Owner's Walsh Declaration contends was unique (Ex. 1002-2, p. 347), and which is claimed in dependent Claims 2 and 10, is actually 0.2% ***less*** than the 99.7% purity measured by Moriarty in the prior art (*e.g.*, Ex. 1004, Moriarty, p. 13). As the synthesis of treprostinil was well-known in the art at the time of the alleged invention, a mere difference in degree of purity, such as 0.2%, is an insufficient bases for patentability and provides no material difference from the prior art. *See Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 739 (Fed. Cir. 2013) ("Results

[2] *See also* '393 Patent col.7, lines 14-15.

which differ by percentages are differences in degree rather than kind, where the modification of the percentage is within the capabilities of one skilled in the art at the time."). Additionally, inventor David Walsh, who provided a declaration contending that Moriarty produced an impurity level of 99.4% (Ex. 1002-2, p. 347), contrary to Moriarty's own 99.7% measurement, did not explain what process conditions contributed to the specific impurity levels he measured, and why his measurement differed from what Moriarty reported. (Ex. 1009, Winkler Decl., ¶¶ 65, 67). Indeed, the data in the Walsh Declaration was derived from a limited sample, which could result in significant batch-to-batch variations in the impurity profile of each batch of treprostinil. (Ex. 1009, Winkler Decl., ¶ 66).

(3) And, third, the difference between the 99.4% measured by Moriarty, and 99.5% claimed in the '393 Patent, *i.e.*, 0.1%, is a percentage that is well within experimental error for measuring impurities, as Dr. Winkler explains. (Ex. 1009, Winkler Decl., ¶¶ 68-70). Indeed, the '393 Patent itself discloses a purity of the claimed compound of 100.4% (Ex. 1001, col. 13, line 64), indicating, as Dr. Winkler notes, that the deviation for the instrument the inventors themselves were using was about ± 0.4%, far greater than the 0.1% difference, and comparable to the difference between 99.8% and 99.4% Dr. Walsh measured between alleged "'393 product" and Moriarty's product as measured by Dr. Walsh. (Ex. 1009, Winkler Decl., ¶ 70-71). Indeed, expected instrumental deviations and expected

precision of this equipment would explain the 0.3% difference between Moriarty's reported 99.7% value and Dr. Walsh's 99.4% value.

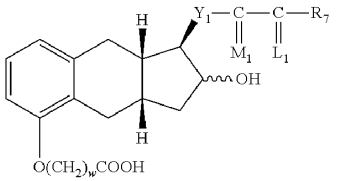
Accordingly, and as discussed in further detail below, since the synthesis of treprostinil, its subsequent purification steps involving reaction with a base such as diethanolamine to form a salt, and the optional reaction of an acid with the salt to regenerate the acid, were already well-known to those of skill in the art as noted in numerous prior art references, and the claimed treprostinil is not distinct from the same compound in the prior art, the '393 Patent (Ex. 1001) should be held invalid.

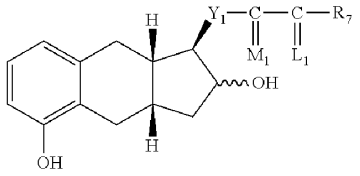
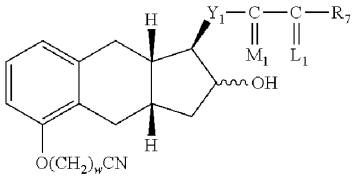
IX. CLAIM-BY-CLAIM EXPLANATION OF GROUNDS FOR UNPATENTABILITY

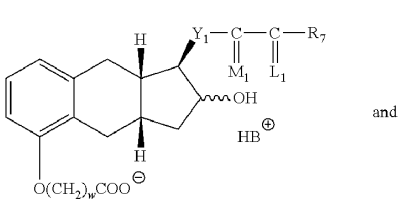
A. Ground 1: Detailed Explanation Under 37 C.F.R. § 42.104(b) of How Phares (Ex. 1005) Anticipates Claims 1-5, 7-9, 11-14 and 16-20 Under 35 U.S.C. § 102(b).

Phares (Ex. 1005) is §102(b) prior art to the '393 Patent. Phares anticipates Claims 1-5, 7-9, 11-14, and 16-20 as set forth in further detail below.

Claim 1

'393 Patent Claim Element	Disclosure in Phares (Ex. 1005)
1. (pre) A product comprising a compound of formula I (I)  or a pharmaceutically acceptable salt thereof, wherein said product is prepared by a process comprising	Ex. 1005, pp. 41-42 (w is 1, Y_1 is CH_2CH_2-, M_1 is a H and a OH group in the S configuration; α-H, L_1 is α-H; β-H, and R_7 is $-(CH_2)_3-CH_3$ in an enantiomer of Formula 2); pp. 85-93

'393 Patent Claim Element	Disclosure in Phares (Ex. 1005)
	(using treprostinil diethanolamine salt in clinical trials as a pharmaceutically acceptable salt); p. 99, Claim 49.
1. (a) alkylating a compound of structure II with an alkylating agent to produce a compound of formula III, (II)  (III)  wherein w=1, 2, or 3; Y_1 is trans-CH═CH—, cis-CH═CH—, —$CH_2(CH_2)_m$—, or —C≡C—; m is 1, 2, or 3; R_7 is (1) —C_pH_{2p}—CH_3, wherein p is an integer from 1 to 5, inclusive, (2) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3) alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl, with the proviso that R_7 is phenoxy or substituted phenoxy, only when R_3 and R_4 are hydrogen or methyl, being the same or different, (3) phenyl, benzyl, phenylethyl, or phenylpropyl optionally substituted on the aromatic ring by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3)alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl,(4) cis-CH═CH—CH_2—CH_3, (5) —$(CH_2)_2$—CH(OH)—CH_3, or (6) —$(CH_2)_3$—CH═$C(CH_3)_2$; —$C(L_1)$—R_7 taken together is (1) (C_4-C_7)cycloalkyl optionally substituted by 1 to 3 (C_1-C_5)alkyl; (2) 2-(2-furyl)ethyl, (3) 2-(3-thienyl)ethoxy, or (4) 3-	Ex. 1005, pp. 41-42.

'393 Patent Claim Element	Disclosure in Phares (Ex. 1005)
thienyloxymethyl; M_1 is α-OH:β-R_5 or α-R_5β-OH or α-OR_1:β-R_5 or α-R_5:β-OR_2, wherein R_5 is hydrogen or methyl, R_2 is an alcohol protecting group, and L_1 is α-R_3:β-R_4, α-R_4:β-R_3, or a mixture of α-R_3:β-R_4 and α-R_4:β-R_3, wherein R_3 and R_4 are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R_3 and R_4 is fluoro only when the other is hydrogen or fluoro,	
1. (b) hydrolyzing the product of formula III of step (a) with a base,	Ex. 1005, pp. 41-42.
1. (c) contacting the product of step (h) [*sic*] with a base B to form a salt of formula I_s. 	Ex. 1005, p. 24; pp. 85-93; p. 99, Claim 49.
1. (d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula I.	No disclosure needed as this step is optional.

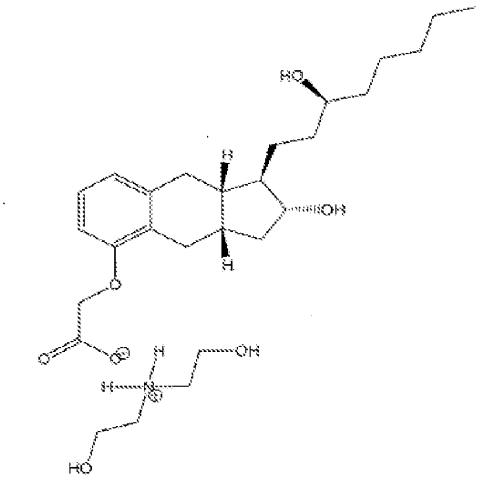
Phares inherently discloses the same synthesis of treprostinil as set forth in Claim 1 of the '393 Patent in the case where w is 1, Y_1 is CH_2CH_2-, M_1 is a H and a OH group in the S configuration; L_1 is α-H; β-H, and R_7 is $–(CH_2)_3$-CH_3. (Ex. 1005, at pp. 41-42; Ex. 1009, Winkler Decl., ¶ 48). Phares discloses the same treprostinil diethanolamine salt (Ex. 1005, p. 24; p. 99, Claim 49) as the '393 Patent (Ex. 1009, Winkler Decl., ¶¶ 50-53), and further discloses use of the treprostinil diethanolamine salt in the same "polymorph" (crystal form) – Form B –

as the '393 Patent. (Ex. 1001, col. 12, lines 34-51; Ex. 1005, pp. 90-91; Winkler Decl., ¶ 58). This salt is made by exactly the same process step as in Claim 1(c): by contacting the product of step (b) with diethanolamine base to form the salt whose structure is displayed in Phares Claim 49 (Ex. 1005, p. 99). This shows that Phares necessarily discloses the same process steps to make treprostinil diethanolamine salt claimed in the '393 Patent, and thus inherently anticipates Claim 1 of the '393 Patent. (Ex. 1009, Winkler Decl., ¶¶ 50-54).

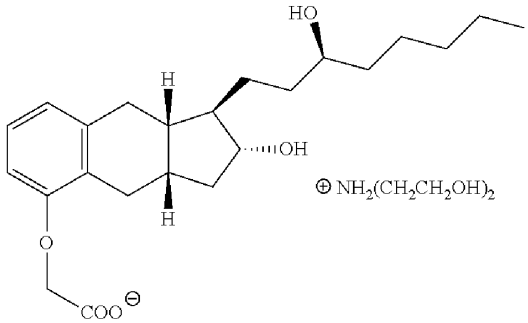
As even further confirmation that Phares discloses the same first two alkylating and hydrolyzing steps to make treprostinil as that disclosed in the '393 Patent, Phares details the same procedures as were used to make treprostinil in the '117 Patent and Moriarty reference but applies them to make (-)-treprostinil, the enantiomer of (+) -treprostinil enantiomer. (Phares, Ex. 1005, p. 42). Phares explains that "enantiomers of these compounds (including (-)-treprostinil) can be synthesized using the reagents and synthons of enantiomeric chirality of the above reagents," referring to the reaction scheme where "the enantiomer of the commercial drug (+)-Treprostinil was synthesized using the stereoselective intramolecular Pauson Khand reaction as a key step and Mitsunobu inversion of the side-chain hydroxyl group." (Ex. 1005, p. 42). Phares details the exact same alkylation and hydrolyzing steps (both included in Phares as "step (l)"). (Ex. 1005, p. 42). This is the identical procedure claimed in steps (a) and (b). (*Compare* Ex.

1005, p 42, "(1) i. $C1CH_2CN$, K_2CO_3. ii, KOH, CH_3OH, reflux. 83 % (2 steps)," with '393 Patent (Ex. 1001), Claim 1 steps (a) and (b) and '393 Patent col. 9 line 25 – col.11, line 37 ('393 Patent, Examples 1 and 2).)

Phares discloses in its Claim 49 the identical, pharmaceutically acceptable treprostinil diethanolamine salt that Claim 1 claims:



(Phares, Ex. 1005, p. 99, Claim 49), which may be compared to the same structure claimed in Claim 1 and 9 and displayed as corresponding to these claims in the '393 Patent:



('393 Patent, Ex. 1001, col. 8, lines 50-64). Other than a change in formatting, these two structures from Phares and the '393 Patent are identical. *See also* (Ex. 1009, Winkler Decl. ¶¶ 50-53).

In the '393 Patent, treprostinil diethanolamine Form B was made directly from precipitation in a mixed solvent of ethanol and ethanol acetate. In Phares (Ex. 1005), treprostinil diethanolamine Form B is made by first generating Form A from any of many possible mixed solvents, and then converting Form A to Form B in a second mixed solvent. No claim in the '393 Patent specifies what solvents should be used, and thus, all of these procedures fall within the '393 Patent claims. In both the '393 Patent and Phares (Ex. 1005), treprostinil diethanolamine salt Form B is made. Phares demonstrated that Form B is the more stable form as compared to Form A. (Ex. 1005, pp. 88-93; Winkler Decl., ¶ 59). Phares further discloses a melting point of 107º C (Ex. 1005, p. 91 & Fig. 21) for the Form B salt. The '393 Patent, however, discloses lower and broader melting point ranges for the Form B salt in the ranges of 104.3-106.3º C (Batch No. 1) and 104.7-106.6º C (Batch No. 3) (Ex. 1001, col. 12, line 65 – col. 13, line 11, Example 3), as well as 105.0-106.5º C (Batch No. 1) and 104.5-105.5 ºC (Batch No. 2) (Ex. 1001, col. 13, line 59, Example 4); *see also* (Ex. 1001, col. 12, lines 53-55 (noting Form B requires a melting point of the treprostinil diethanolamine salt of more than 104º C). The higher melting point disclosed in Phares is consistent with higher purity

for the product of Phares than the '393 Patent's product. (Ex. 1009, Winkler Decl., ¶ 60). As Phares necessarily discloses a higher purity of treprostinil diethanolamine as is disclosed and claimed in the '393 Patent, Phares inherently anticipates the '393 Patent's claims. *See also* (Ex. 1009, Winkler Decl., ¶ 62).

Additionally, Claim 1 claims both treprostinil diethanolamine salt and treprostinil free acid. The step of reacting the foregoing salt with an acid to form the compound of Formula I in Claim 1 of the '393 Patent (Ex. 1001) is optional. Therefore, no disclosure in Ex. 1005 is required to demonstrate anticipation of Claim 1. Moreover, the '393 Patent admits that step (d) is merely a "simple acidification with diluted hydrochloric acid" step, and not a novel step. (Ex. 1001 col.17, lines 34-36.)

Claim 2

'393 Patent Claim Element	**Prior Art Disclosure**
2. The product of claim 1, wherein the purity of compound of formula I in said product is at least 99.5%.	*See* disclosure for Claim 1.

As Phares discloses the same product and process of Claim 1, including making the most stable crystal form, Form B, of a higher melting point than that disclosed in the '393 Patent, as discussed *supra*, Phares necessarily discloses a salt of at least 99.5% purity. (Ex. 1009, Winkler Decl., ¶ 62).

Additionally, the degree of purity of 99.5% recited in Claim 2 is actually 0.2% ***less*** than the 99.7% reported by Moriarty (Ex. 1004, p. 13) – well within

experimental error. (Ex. 1009, Winkler Decl., ¶¶ 69-70). Patent Owner submitted a declaration from inventor Dr. David Walsh, which contended that the prior art Moriarty reference produced a purity level of only 99.4%, contrary to the 99.7% actually recited in Moriarty. (Ex. 1002-2, p. 347). Dr. Walsh does not explain what process conditions mattered in gaining the 99.4% result. (Ex. 1009, Winkler Decl., ¶ 67). Nevertheless, even if it were true that the prior art's purity level was only 99.4% instead of 99.7%, the difference between 99.4% and 99.5% is well within experimental error, as explained by Dr. Winkler. (Ex. 1009, Winkler Decl., ¶¶ 69-70). This 0.1% difference would not represent a significant deviation from the processes of the prior art in light of experimental error in the detection method that is used when high-liquid chromatography (HPLC) is used to determine levels of impurities. (*Id.,* at ¶ 68*)*. Indeed, even a difference of 0.2% between the claimed processes of the '393 Patent and the prior art, such as Moriarty (Ex. 1004), would be attributable to experimental error, and thus the claimed degree of purity under the claimed processes of the '393 Patent would present no distinction from the art. The '393 Patent itself discloses a purity of the claimed compound of 100.4% (Ex. 1001, col. 13, line 64), indicating, as Dr. Winkler notes, there the deviation in the reported data of ± 0.4% reflects a minimum deviation for the equipment the inventors used. (Ex. 1009, Winkler Decl., ¶ 70).

Claim 3

'393 Patent Claim Element	Prior Art Disclosure
3. The product of claim 1, wherein the alkylating agent is $Cl(CH_2)_wCN$, $Br(CH_2)_wCN$, or $I(CH_2)_wCN$.	Ex. 1005, p. 42 ($Cl(CH_2)_wCN$).

Phares discloses the alkylating agent is $ClCH_2CN$ which corresponds to $Cl(CH_2)_wCN$ where w is 1. (Ex. 1005, p. 42).

Claim 4

'393 Patent Claim Element	Prior Art Disclosure
4. The product of claim 1, wherein the base in step (b) is KOH or NaOH.	Ex. 1005, p. 42 (KOH).

Phares discloses that the base in step (b) is KOH. (Ex. 1005, p. 42).

Claim 5

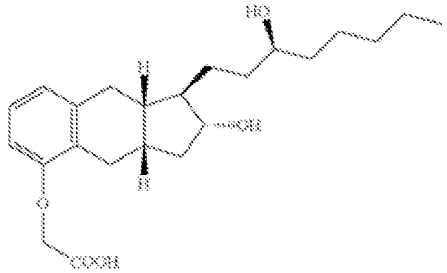
'393 Patent Claim Element	Prior Art Disclosure
5. The product of claim 1, wherein the base B in step (c) is selected from the group consisting of ammonia, N-methylglucamine, procaine, tromethamine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.	Ex. 1005, p. 24; pp. 57-58; p. 99, Claim 49.

Phares discloses the use of the base diethanolamine. (Ex. 1005, p. 24; p. 99, Claim 49). Phares (Ex. 1005, pp. 57-58) also discloses several other bases such as ammonia, magnesium, lysine, arginine and triethanolamine, all of which are recited in Claim 5 of the '393 Patent (Ex. 1001).

Claim 7

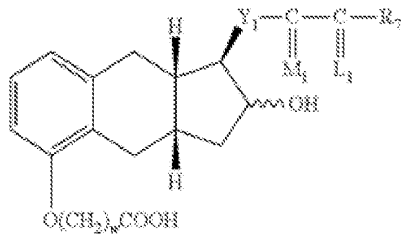
'393 Patent Claim Element	Prior Art Disclosure
7. The product of claim 1, wherein Y_1 is —CH_2CH_2—; M_1 is α-OH:β-H or α-H:β-OH; —$C(L_1)$-R_7 taken together is —$(CH_2)_4CH_3$; and w is 1.	*See* disclosure for Claim 1.

As discussed above, Phares (Ex. 1005) discloses a synthesis of treprostinil which has the following structure:



(*see e.g.,* Phares, Ex. 1005, pp. 41-42).

And the product (*i.e.*, Formula I) of Claim 1 of the '393 Patent (Ex. 1001) has the following generic structure:



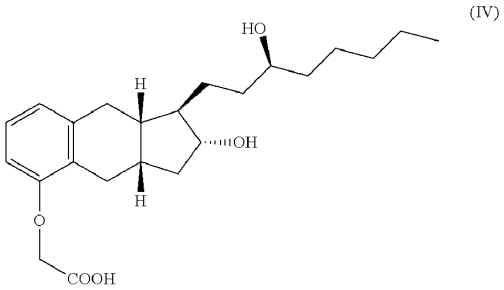
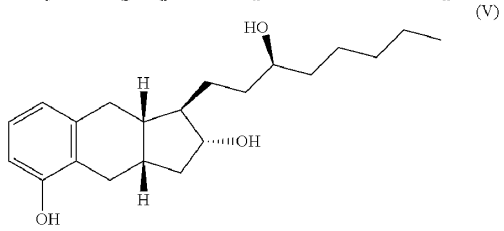
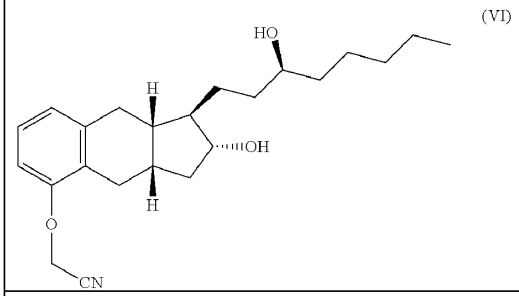
In treprostinil, Y_1 is —CH_2CH_2—; M_1 is a H and a OH group in the S configuration; —$C(=L_1)$-R_7 taken together is —$(CH_2)_4CH_3$; and w is 1. Therefore, the requirements of Claim 7 are satisfied.

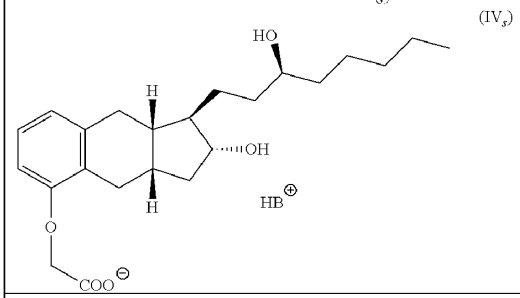
Claim 8

'393 Patent Claim Element	Prior Art Disclosure
8. The product of claim 1, wherein the process does not include purifying the compound of formula (III) produced in step (a).	Ex. 1005, pp. 41-42.

As discussed above, Phares (Ex. 1005, pp. 41-42) discloses that Formula 11b is converted to Formula 2 by treatment with the alkylating agent $ClCH_2CN$ followed by the base KOH. Phares' synthetic scheme, as disclosed on p. 42 (Ex. 1005), does not indicate that any intermediate compound is purified. Therefore, the requirements of Claim 8 are satisfied.

Claim 9

'393 Patent Claim Element	Prior Art Disclosure
9. (pre) A product comprising a compound having formula IV  (IV) or a pharmaceutically acceptable salt thereof, wherein the product is prepared by the process comprising	Ex. 1005, pp. 41-42 (enantiomer of Formula 2), pp. 85-93; p. 99, Claim 49.
9. (a) alkylating a compound of formula V with an alkylating agent to produce a compound of formula VI,  (V)  (VI)	Ex. 1005, pp. 41-42.
9. (b) hydrolyzing the product of formula VI of step (a) with a base,	Ex. 1005, pp. 41-42.

9. (c) contacting the product of step (h) [*sic*]with a base B to form a salt of formula IV_s, and 	Ex. 1005, p. 24; pp. 85-93; p. 99, Claim 49.
9. (d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula IV.	No disclosure needed as this step is optional.

See explanation under Claim 1.

Claim 11

'393 Patent Claim Element	**Prior Art Disclosure**
11. The product of claim 9, wherein the alkylating agent is $ClCH_2CN$.	Ex. 1005, p. 42

See explanation under Claim 3.

Claim 12

'393 Patent Claim Element	**Prior Art Disclosure**
12. The product of claim 9, wherein the base in step (b) is KOH.	Ex. 1005, p. 42

See explanation under Claim 4.

Claim 13

'393 Patent Claim Element	Prior Art Disclosure
13. The product of claim 9, wherein the base B in step (c) is selected from a group consisting of ammonia, N-methylglucamine, procaine, tromethamine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.	Ex. 1005, p. 24; pp. 57-58; pp. 85-93; p. 99, Claim 49.

See explanation under Claim 5.

Claim 14

'393 Patent Claim Element	Prior Art Disclosure
14. The product of claim 9, wherein the base B is diethanolamine.	Ex. 1005, p. 24; p. 57; pp. 85-93; p. 99, Claim 49.

See explanations under Claims 1 and 5.

Claim 16

'393 Patent Claim Element	Prior Art Disclosure
16. The product of claim 9, wherein the process does not include purifying the compound of formula (VI) produced in step (a).	Ex. 1005, pp. 41-42.

See explanation under Claim 8.

Claim 17

'393 Patent Claim Element	Prior Art Disclosure
17. The product of claim 16, wherein the base B in step (c) is selected from a group consisting of ammonia, N-methylglucamine, procaine, tromethamine, magnesium, L-lysinc [*sic*], L-arginine, triethanolamine, and diethanolamine.	Ex. 1005, p. 24; pp. 57-58; pp. 85-93; p. 99, Claim 49.

See explanation under Claim 5.

Claim 18

'393 Patent Claim Element	Prior Art Disclosure
18. The product of claim 17, wherein the base B is diethanolamine.	Ex. 1005, p. 24; p. 57; pp. 85-93; p. 99, Claim 49.

See explanations under Claims 1 and 5.

Claim 19

'393 Patent Claim Element	Prior Art Disclosure
19. The product of claim 1, wherein the base in step (b) is KOH or NaOH and wherein the base 13 [*sic*] in step (c) is selected from the group consisting of ammonia. N-methyl glucamine, procaine, tromethamine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.	Ex. 1005, p. 24; p. 42; pp. 57-58; pp. 85-93; p. 99, Claim 49.

See explanations under Claims 4 and 5.

Claim 20

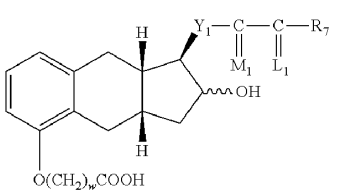
'393 Patent Claim Element	Prior Art Disclosure
20. The product of claim 9, wherein the base in step (b) is KOH or NaOH and wherein the base B in step (c) is selected from the group consisting of ammonia, N-methylglucamine, procaine, tromethamine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.	Ex. 1005, p. 24; p. 42; pp. 57-58; pp. 85-93; p. 99, Claim 49.

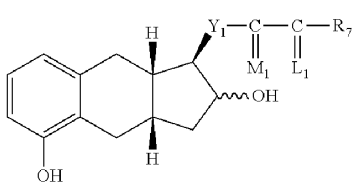
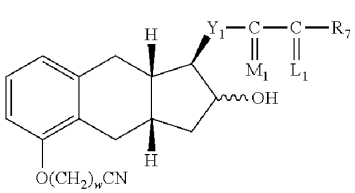
See explanations under Claims 4 and 5.

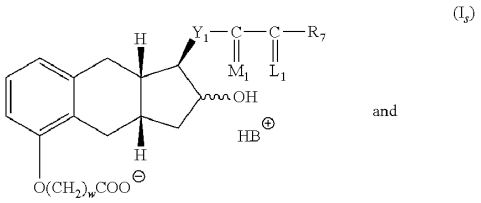
B. Ground 2: Detailed Explanation Under 37 C.F.R. § 42.104(b) of How Claims 1-5, 7-9, 11-14 and 16-20 are Obvious under 35 U.S.C. § 103(a) over Moriarty (Ex. 1004) with either Phares (Ex. 1005) or Kawakami (Exs. 1006 & 1007).

In addition to the anticipation challenges noted above, Claims 1-5, 7-9, 11-14, and 16-20 are rendered obvious under § 103 when considering Moriarty (Ex. 1004) in view of other prior art, including (but not limited to) either Phares (Ex. 1005) or Kawakami (Exs. 1006 & 1007).

Claim 1

'393 Patent Claim Element	Prior Art Disclosure
1. (pre) A product comprising a compound of formula I (I)  or a pharmaceutically acceptable salt thereof, wherein said product is prepared by a process comprising	Ex. 1004, p. 3; p. 6 (w is 1, Y_1 is CH_2CH_2-, M_1 is a H and a OH group in the S configuration, L_1 is α-H; β-H, and R_7 is $-(CH_2)_3$-CH_3 in Formula 7).

1. (a) alkylating a compound of structure II with an alkylating agent to produce a compound of formula III, (II)  (III)  wherein w=1, 2, or 3; Y_1 is trans-CH═CH—, cis-CH═CH—, —$CH_2(CH_2)_m$—, or —C≡C—; m is 1, 2, or 3; R_7 is (1) —C_pH_{2p}—CH_3, wherein p is an integer from 1 to 5, inclusive, (2) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3) alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl, with the proviso that R_7 is phenoxy or substituted phenoxy, only when R_3 and R_4 are hydrogen or methyl, being the same or different, (3) phenyl, benzyl, phenylethyl, or phenylpropyl optionally substituted on the aromatic ring by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3)alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl,(4) cis-CH═CH—CH_2—CH_3, (5) —$(CH_2)_2$—CH(OH)—CH_3, or (6) —$(CH_2)_3$—CH═$C(CH_3)_2$; —$C(L_1)$—R_7 taken together is (1) (C_4-C_7)cycloalkyl optionally substituted by 1 to 3 (C_1-C_5)alkyl; (2) 2-(2-furyl)ethyl, (3) 2-(3-thienyl)ethoxy, or (4) 3-thienyloxymethyl; M_1 is α-OH:β-R_5 or α-R_5β-OH or α-OR_1:β-R_5 or α-R_5:β-OR_2, wherein R_5 is hydrogen or methyl, R_2 is an alcohol protecting group, and L_1 is α-R_3:β-R_4, α-R_4:β-R_3, or a mixture of α-R_3:β-R_4 and α-R_4:β-R_3, wherein R_3 and R_4 are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R_3 and R_4 is fluoro only when the other is hydrogen or fluoro,	Ex. 1004, p. 6; p. 13.

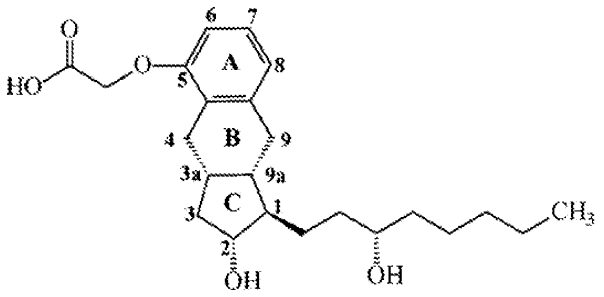
1. (b) hydrolyzing the product of formula III of step (a) with a base,	Ex. 1004, p. 6, p. 13.
1. (c) contacting the product of step (h) [*sic*] with a base B to form a salt of formula I_s.  (I_s) and	Ex. 1005, p. 24; pp. 85-93; p. 99, Claim 49; Ex. 1007, p. 6.
1. (d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula I.	No disclosure needed as this step is optional; *see also* Ex. 1007, p. 6.

Moriarty (Ex. 1004) discloses the synthesis (at p. 6) of treprostinil which is Formula 7 on p. 3. Formula 7 on p. 3 of Moriarty (Ex. 1004) is equivalent to Formula I of Claim 1 of the '393 Patent (Ex. 1001, col. 17) in the case where w is 1, Y_1 is CH_2CH_2-, M_1 is a H and a OH group in the S configuration, L_1 is α-H; β-H, and R_7 is $–(CH_2)_3$-CH_3.

Formula 34 on p. 6 of Moriarty (Ex. 1004, p. 6, 13) is alkylated by $ClCH_2CN$ to yield Formula 35 on p. 6. Formula 34 corresponds to Formula II in Claim 1 of the '393 Patent (Ex. 1001) in the case where Y_1 is CH_2CH_2-, M_1 is a H and a OH group in the S configuration, L_1 is α-H; β-H, and R_7 is $–(CH_2)_3$-CH_3. Formula 35 corresponds to Formula III in Claim 1 of the '393 Patent (Ex. 1001, col. 18) in the case where Y_1 is CH_2CH_2-, M_1 is a H and a OH group in the S configuration, L_1 is α-H; β-H, R_7 is $–(CH_2)_3$-CH_3 and w is 1. Ex. 1004 at p. 13

discloses that Formula 35 is hydrolyzed with a base (*i.e.*, aqueous KOH, followed by acidification) to yield Formula 7 (Moriarty, Ex. 1004, p. 3, p. 6).

Formula 7 of Moriarty is as follows:



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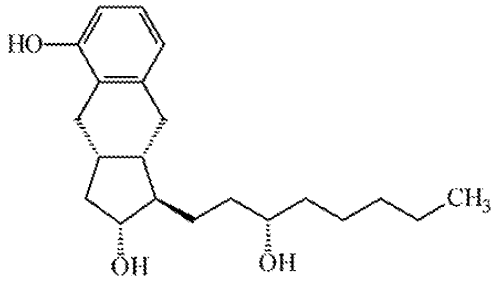
(Moriarty, Ex. 1004, p. 3, col. 1).

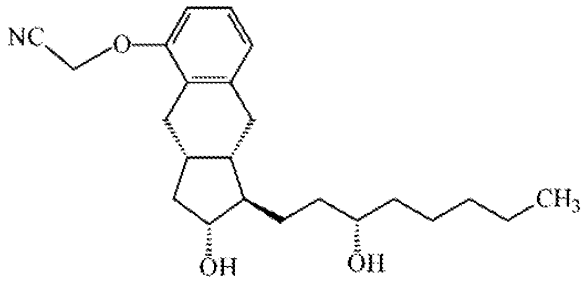
Formula 34 of Moriarty is as follows:



34

(Moriarty, Ex. 1004, p. 6).

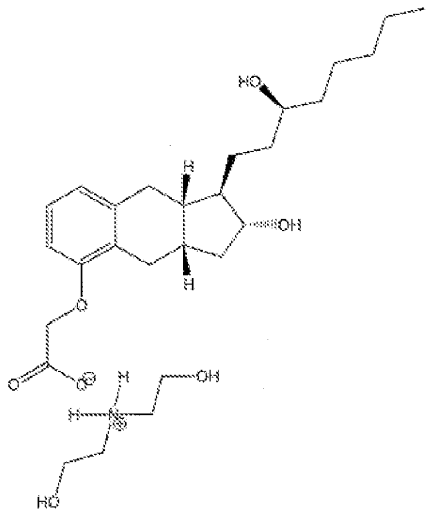
Formula 35 of Moriarty is as follows:



35

(Moriarty, Ex. 1004, p. 6).

While the step of reacting Formula 7 with a base to form a salt of Formula 7 is not disclosed in Moriarty (Ex. 1004), this step is disclosed in Phares (Ex. 1005). Phares (Ex. 1005, p. 24) discloses that treprostinil acid (which is equivalent to Formula 7 in Moriarty, Ex. 1004) is dissolved in a 1:1 molar ratio mixture of ethanol: water and diethanolamine (*i.e.*, the base) is added and dissolved. The solution is heated and acetone is added as an antisolvent during cooling. The resulting structure (below) corresponds to the salt of Formula I_s in Claim 1 of the '393 Patent (Ex. 1001):



(Phares, Ex. 1005, p. 99, Claim 49).

Petitioner notes that the formation of salts by the reaction of carboxylic acids with bases is a common reaction in organic chemistry and this process is well within the skill of one of ordinary skill in the art, as discussed above.

In addition, Kawakami discloses contacting a carboxylic acid of a prostacyclin derivative with a base to form a salt. (Exs. 1006 & 1007). Kawakami is directed to the preparation and use of dicyclohexylamine (i.e., a weak base similar in its reactivity to diethanolamine) to form a crystalline dicyclohexylamine salt of a methanoprostacyclin derivative. Ex. 1007, at p. 6, further discloses that the dicyclohexylamine salt of a methanoprostacyclin derivative can be easily reverted to the free methanoprostacyclin derivative by conventional methods. Furthermore, Kawakami (Ex. 1007) at p. 6 discloses that the salt that is obtained has fairly high

purity and the purity can be further improved by recrystallization as needed with the use of an appropriate solvent.

A person of ordinary skill in the art would be motivated to combine Moriarty (Ex. 1004) with either Phares (Ex. 1005) or Kawakami (Exs. 1006, 1007). (Ex. 1009, Winkler Decl., ¶ 74). Moriarty discloses steps (a) and (b) of Claim 1 of the '393 Patent. (Ex. 1004, p. 6, 13). Phares discloses step (c) of Claim 1 of the '393 Patent (Ex. 1005, p. 24), while Kawakami discloses that prostacyclin compounds (an example of which includes treprostinil), can be purified by using weak bases and forming salts (Ex. 1007, p. 6). Further, if desired, Kawakami discloses that the product can be turned back into the free acid as disclosed under the optional Claim 1(d). (*Id.*). Accordingly, a person of ordinary skill in the art would be motivated to combine Moriarty with either Phares or Kawakami to obtain a product of at least equal purity to that claimed in the '393 Patent. (Ex. 1009, Winkler Decl., ¶ 74).

Claim 2

'393 Patent Claim Element	**Prior Art Disclosure**
2. The product of claim 1, wherein the purity of compound of formula I in said product is at least 99.5%.	*See* disclosure for Claim 1.

As the combination of Moriarty (Ex. 1004) with either Phares (Ex. 1005) or Kawakami (Exs. 1006 & 1007) discloses the same process steps and product of the '393 Patent, the combination of these references would disclose a purity of at least

equal purity to that claimed in the '393 Patent. (Ex. 1009, Winkler Decl., ¶ 76); *see also supra* (Section B, Claim 2 discussing Phares).

Additionally, and as discussed *supra*, the degree of purity of 99.5% recited in Claim 2 is actually 0.2% ***less*** than the 99.7% reported by Moriarty (Ex. 1004, p. 13) – well within experimental error. (Ex. 1009, Winkler Decl., ¶¶ 69-70). Patent Owner submitted a declaration from inventor Dr. David Walsh, which contended that the prior art Moriarty reference produced a purity level of only 99.4%, contrary to the 99.7% actually recited in Moriarty. (Ex. 1002-2, p. 347). Dr. Walsh does not explain what process conditions mattered in gaining the 99.4% result. (Ex. 1009, Winkler Decl., ¶ 67). Nevertheless, even if it were true that the prior art's purity level was only 99.4% instead of 99.7%, the difference between 99.4% and 99.5% is well within experimental error, as explained by Dr. Winkler. (Ex. 1009, Winkler Decl., ¶¶ 69-70). This 0.1% difference would not represent a significant deviation from the processes of the prior art in light of experimental error in the detection method that is used when high-liquid chromatography (HPLC) is used to determine levels of impurities. (*Id*., at 68). Indeed, even a difference of 0.2% between the claimed processes of the '393 Patent and the prior art, such as Moriarty (Ex. 1004), would be attributable to experimental error, and thus the claimed degree of purity under the claimed processes of the '393 Patent would present no distinction from the art. The '393 Patent itself discloses a purity of the claimed

compound of 100.4% (Ex. 1001, col. 13, line 64), indicating, as Dr. Winkler notes, there the deviation in the reported data of ± 0.4% reflects a minimum deviation for the equipment the inventors used. (Ex. 1009, Winkler Decl., ¶ 70).

Claim 3

'393 Patent Claim Element	Prior Art Disclosure
3. The product of claim 1, wherein the alkylating agent is $Cl(CH_2)_wCN$, $Br(CH_2)_wCN$, or $I(CH_2)_wCN$.	Ex. 1004, p. 3; p. 6 ($Cl(CH_2)_wCN$).

As discussed above, Moriarty (Ex. 1004, p. 3 and p. 6) discloses that the alkylating agent is $ClCH_2CN$ which corresponds to $Cl(CH_2)_wCN$ where w is 1.

Claim 4

'393 Patent Claim Element	Prior Art Disclosure
4. The product of claim 1, wherein the base in step (b) is KOH or NaOH.	Ex. 1004, p. 3; p. 6 (KOH).

As discussed above, Moriarty (Ex. 1004, p. 6) discloses that the base in step (b) is KOH.

Claim 5

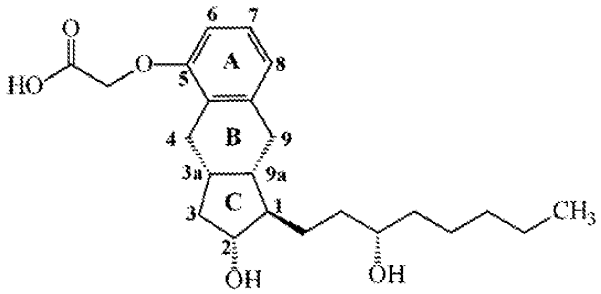
'393 Patent Claim Element	Prior Art Disclosure
5. The product of claim 1, wherein the base B in step (c) is selected from the group consisting of ammonia, N-methylglucamine, procaine, tromethamine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.	Ex. 1004, p. 6; p. 13; Ex. 1005, p. 24; pp. 57-58; pp. 85-93; p. 99, Claim 49; Ex. 1007, pp. 5-6.

As discussed above, Phares (Ex. 1005, p. 24; p. 99, Claim 49) discloses the use of the base diethanolamine. In addition, Phares (Ex. 1005, pp. 57-58) discloses several other bases that include ammonia, magnesium, lysine, arginine and triethanolamine, all of which are recited in Claim 5 of the '393 Patent (Ex. 1001).

Claim 7

'393 Patent Claim Element	**Prior Art Disclosure**
7. The product of claim 1, wherein Y_1 is —CH_2CH_2—; M_1 is α-OH:β-H or α-H:β-OH; —$C(L_1)$-R_7 taken together is —$(CH_2)_4CH_3$; and w is 1.	*See* disclosure for Claim 1.

As discussed above, the combination of references discloses a synthesis of treprostinil which has the following structure:



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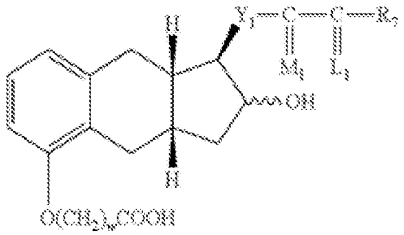
(*see e.g.,* Moriarty, Ex. 1004, col. 1, p. 3).

And the product (*i.e.*, Formula I) of Claim 1 of the '393 Patent (Ex. 1001) has the following generic structure:



In treprostinil, Y_1 is —CH_2CH_2—; M_1 is a H and a OH group in the S configuration; —$C(L_1)$-R_7 taken together is —$(CH_2)_4CH_3$; and w is 1. Therefore, the requirements of Claim 7 are satisfied.

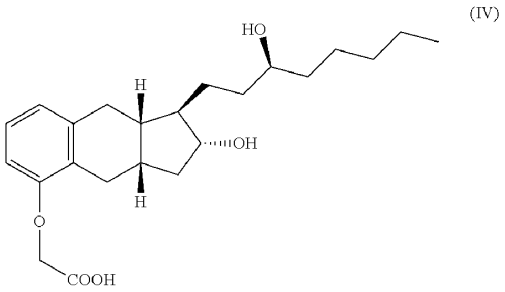
Claim 8

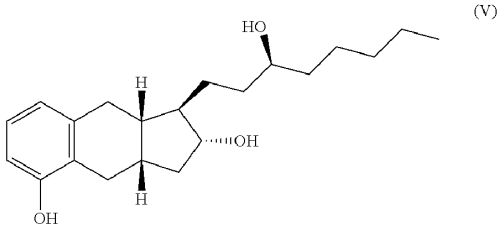
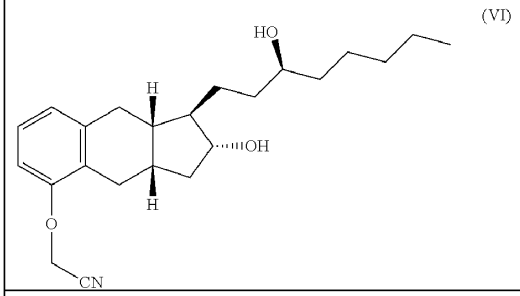
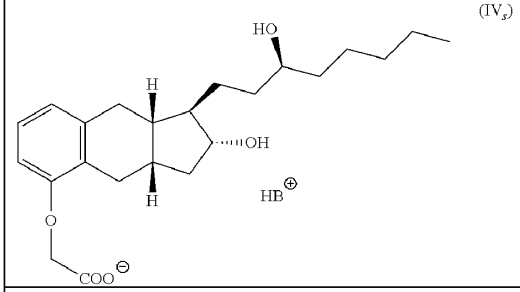
'393 Patent Claim Element	Prior Art Disclosure
8. The product of claim 1, wherein the process does not include purifying the compound of formula (III) produced in step (a).	Ex. 1004, p. 6; p. 13; Ex. 1005, pp. 41-42

Moriarty (Ex. 1004, p. 6 and p. 13) discloses that Formula 35 (which corresponds to Formula III in Claim 1 of the '393 Patent (Ex. 1001)) is purified. However, Phares (Ex. 1005) discloses that the purification of Formula 35 (as described in Moriarty) would not be necessary. Specifically, Phares (Ex. 1005, pp. 41-42) discloses that Formula 11b is converted to Formula 2 by treatment with the alkylating agent $ClCH_2CN$ followed by the base KOH. The synthetic scheme of Phares (p. 42) does not indicate that any intermediate compound is purified. In view of the foregoing, one of ordinary skill in the art would understand that the

treatment of Formula 11b with the alkylating agent could be followed by the hydrolysis with a base without purifying the product of the alkylation reaction. Furthermore, a person of ordinary skill in the art would be motivated to combine Phares (Ex. 1005, p. 42) with the teachings of Moriarty (Ex. 1004, p. 6; p. 13), since shortening the number of synthetic steps should increase efficiency and presumably lower costs. *See also* (Ex. 1009, Winkler Decl., ¶¶ 77-78).

Claim 9

'393 Patent Claim Element	**Prior Art Disclosure**
9. (pre) A product comprising a compound having formula IV  or a pharmaceutically acceptable salt thereof, wherein the product is prepared by the process comprising	Ex. 1004, p. 6

9. (a) alkylating a compound of formula V with an alkylating agent to produce a compound of formula VI,  (V)  (VI)	Ex. 1004, p. 6; p. 13
9. (b) hydrolyzing the product of formula VI of step (a) with a base,	Ex. 1004, p. 6; p. 13
9. (c) contacting the product of step (h) [*sic*] with a base B to form a salt of formula IV_s, and  (IV_s)	Ex. 1004, p. 6; p. 13; Ex. 1005, p. 24; pp. 85-93; p. 99, Claim 49; Ex. 1007, pp. 5-6
9. (d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula IV.	No disclosure needed as this step is optional

See explanation under Claim 1.

Claim 11

'393 Patent Claim Element	Prior Art Disclosure
11. The product of claim 9, wherein the alkylating agent is $ClCH_2CN$.	Ex. 1004, p. 6; p. 13

See explanation under Claim 3.

Claim 12

'393 Patent Claim Element	Prior Art Disclosure
12. The product of claim 9, wherein the base in step (b) is KOH.	Ex. 1004, p. 6; p. 13

See explanation under Claim 4.

Claim 13

'393 Patent Claim Element	Prior Art Disclosure
13. The product of claim 9, wherein the base B in step (c) is selected from a group consisting of ammonia, N-methylglucamine, procaine, tromethamine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.	Ex. 1004, p. 6; p. 13; Ex. 1005, p. 24; pp. 57-58; pp. 85-93; p. 99, Claim 49; Ex. 1007, pp. 5-6

See explanation under Claim 5.

Claim 14

'393 Patent Claim Element	Prior Art Disclosure
14. The product of claim 9, wherein the base B is diethanolamine.	Ex. 1004, p. 6; p. 13; Ex. 1005, p. 24; pp. 57-58; pp. 85-93; p. 99, Claim 49; Ex. 1007, pp. 5-6

See explanations under Claims 1 and 5.

Claim 16

'393 Patent Claim Element	Prior Art Disclosure
16. The product of claim 9, wherein the process does not include purifying the compound of formula (VI) produced in step (a).	Ex. 1004, p. 6; p. 13

See explanation under Claim 8.

Claim 17

'393 Patent Claim Element	Prior Art Disclosure
17. The product of claim 16, wherein the base B in step (c) is selected from a group consisting of ammonia, N-methylglucamine, procaine, tromethamine, magnesium, L-lysinc [*sic*], L-arginine, triethanolamine, and diethanolamine.	Ex. 1004, p. 6; p. 13; Ex. 1005, p. 24; pp. 57-58; pp. 85-93; p. 99, Claim 49

See explanation under Claim 5.

Claim 18

'393 Patent Claim Element	Prior Art Disclosure
18. The product of claim 17, wherein the base B is diethanolamine.	Ex. 1004, p. 6; p. 13; Ex. 1005, p. 22; p. 57; pp. 85-93; p. 99, Claim 49

See explanations under Claims 1 and 5.

Claim 19

'393 Patent Claim Element	Prior Art Disclosure
19. The product of claim 1, wherein the base in step (b) is KOH or NaOH and wherein the base 13 [*sic*] in step (c) is selected from the group consisting of ammonia. N-methyl glucamine, procaine, tromethamine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.	Ex. 1004, p. 6; p. 13; Ex. 1005, p. 24; pp. 57-58; pp. 85-93; p. 99, Claim 49; Ex. 1007, pp. 5-6

See explanations under Claims 4 and 5.

Claim 20

'393 Patent Claim Element	Prior Art Disclosure
20. The product of claim 9, wherein the base in step (b) is KOH or NaOH and wherein the base B in step (c) is selected from the group consisting of ammonia, N-methylglucamine, procaine, tromethamine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.	Ex. 1004, p. 6; p. 13; Ex. 1005, p. 24; pp. 57-58; pp. 85-93; p. 99, Claim 49; Ex. 1007, pp. 5-6

See explanations under Claims 4 and 5.

C. Ground 3: Detailed Explanation Under 37 C.F.R. § 42.104(b) of How Claims 6, 10, 15, 21 and 22 are Obvious under 35 U.S.C. § 103(a) over Moriarty (Ex. 1004) with Phares (Ex. 1005) or Kawakami (Exs. 1006 & 1007) and in further combination with Ege (Ex. 1008).

Claim 6

'393 Patent Claim Element	Prior Art Disclosure
6. The product of claim 1, wherein the acid in step (d) is HCl or H_2SO_4.	Ex. 1004, p. 6; p. 13; Ex. 1007, pp. 5-6; Ex. 1008, p. 8

As discussed above, Phares (Ex. 1005, p. 22) discloses forming the treprostinil diethanolamine salt. Also, as discussed above, Kawakami (Exs. 1006 & 1007) discloses forming a crystalline dicyclohexylamine salt of a methanoprostacyclin derivative. Kawakami (Ex. 1007, p. 6) further discloses that the dicyclohexylamine salt of a methanoprostacyclin derivative "can be easily reverted to the free methanoprostacyclin derivative by *conventional methods"* (emphasis added). In addition, Kawakami (Ex. 1007) at p. 6 discloses that the salt that is obtained has fairly high purity and the purity can be further improved by recrystallization as needed with the use of an appropriate solvent.

A person of ordinary skill in the art would understand that one such conventional method for converting the dicyclohexylamine salt of a methanoprostacyclin derivative to the free methanoprostacyclin derivative, or converting the treprostinil diethanolamine salt to treprostinil (*i.e.*, the free acid) is

by treating the salt with a strong acid such as HCl or H_2SO_4. *See* (Ex. 1009, Winkler Decl., ¶ 84). As further evidence as to the conventional nature of such a conversion, Petitioner also notes that Ege (Ex. 1008, p. 8) discloses that sodium benzoate (*i.e.*, a carboxylate salt) can be converted back to benzoic acid (*i.e.*, a carboxylic acid) by treatment with the acid HCl. *See* (Ex. 1009, Winkler Decl., ¶ 86).

A person of ordinary skill in the art would be motivated to include the carboxylate salt formation and regeneration of the neutral carboxylic acid with the syntheses of Moriarty (Ex. 1004, p. 6; p. 13) and Phares (Ex. 1005, p. 24), since Kawakami (Ex. 1007, p. 6) discloses that "the dicyclohexylamine salt obtained by the present invention can be easily reverted to a free methanoprostacyclin derivative [I] by conventional methods, and the resulting methanoprostacyclin derivative exhibits excellent crystallinity compared with substances not purified according to the present invention." Accordingly, a person of ordinary skill in the art would want to form the treprostinil diethanolamine salt, purify it, and then convert it back to its free form (*i.e.*, treprostinil) in order to obtain excellent crystallinity and increased purity. (Ex. 1009, Winkler Decl., ¶ 88). And Ege (Ex. 1008, p. 8) teaches that one such method for obtaining the free form of any carboxylic acid (including treprostinil) would be by treatment of the

corresponding carboxylate salt with a strong acid. *See also* (Ex. 1009, Winkler Decl., ¶ 88).

Claim 10

'393 Patent Claim Element	Prior Art Disclosure
10. The product of claim 9, wherein the purity of product of step (d) is at least 99.5%.	Ex. 1004, p. 6; p. 13; Ex. 1007, pp. 5-6; Ex. 1008, p. 8

The combination of Moriarty (Ex. 1004) and Phares (Ex. 1005) (or Kawakami, Exs. 1006 & 1007) and Ege (Ex. 1008) would disclose that the purity of treprostinil of at least equal purity to that of the '393 Patent, since the combination of these references discloses the same product and same process of Claim 9. (Ex. 1009, Winkler Decl., ¶ 89). As Dr. Winkler explains, as Phares (Ex. 1005) discloses the same polymorph Form B and a higher melting point than that disclosed in the '393 Patent, Phares discloses an even higher purity than that disclosed in the '393 Patent. (Ex. 1009, Winkler Decl., ¶¶ 58-60). Indeed, as discussed *supra*, Moriarty actually reports that the treprostinil made by Moriarty had 99.7% purity (Ex. 1004, p. 13) - although Patent Owner submitted a declaration from inventor Dr. David Walsh, which contended that the prior art Moriarty reference produced a purity level of only 99.4%, contrary to the 99.7% actually recited in Moriarty. (Ex. 1002-2, p. 347). Dr. Walsh does not explain what process conditions mattered in gaining the 99.4% result, and, moreover, there may

be significant batch-to-batch variation based on the limited sample set provided. (Ex. 1009, Winkler Decl., ¶¶ 66). Nevertheless, even if it were true that the prior art's purity level was only 99.4% instead of 99.7%, the difference between 99.4% and 99.5% is well within experimental error, as noted by Dr. Winkler. (Ex. 1009, Winkler Decl., ¶¶ 69-70).

Claim 15

'393 Patent Claim Element	Prior Art Disclosure
15. The product of claim 9, wherein the acid in step (d) is HCl.	Ex. 1004, p. 6; p. 13; Ex. 1007, pp. 5-6; Ex. 1008, p. 8

See explanation under Claim 6.

Claim 21

'393 Patent Claim Element	Prior Art Disclosure
21. The product of claim 1, wherein step (d) is performed.	Ex. 1004, p. 6; p. 13; Ex. 1007, pp. 5-6; Ex. 1008, p. 8

See explanation under Claim 6.

Claim 22

'393 Patent Claim Element	Prior Art Disclosure
22. The product of claim 21, wherein the product comprises a pharmaceutically acceptable salt formed from the product of step (d).	Ex. 1004, p. 6; p. 13; Ex. 1007, pp. 5-6; Ex. 1008, p. 8

Claim 22 recites that the "product of Claim 21, wherein the product comprises a pharmaceutically acceptable salt formed from the product of step (d)." The product of Claim 21 (which recites, the "product of Claim 1, wherein step (d) is performed) is a free carboxylic acid. Claim 22, therefore, effectively recites that a carboxylate salt (*i.e.,* a pharmaceutically acceptable salt) can be formed from a free carboxylic acid, which was well-known in the art prior to December 17, 2007. (*See* explanation under Claim 6).

X. CONCLUSION

In view of the foregoing, Petitioner respectfully requests that trial for *inter partes* review be instituted on Claims 1-22 of the '393 Patent, and those claims be canceled as invalid.

Date: October 1, 2015

/s Stuart E. Pollack /
Stuart E. Pollack, J.D. Ph.D.
Reg. No. 43,862
DLA Piper LLP (US)

Respectfully submitted,

/s Lisa A. Haile /
Lisa A. Haile, J.D., Ph.D.
Reg. No. 38,347
DLA Piper LLP (US)

CERTIFICATE OF SERVICE

The undersigned certify that a copy of the attached Petition for *Inter Partes* Review of U.S. Patent No. 8,497,393 and supporting materials were sent via overnight mail via private carrier on October 1, 2015, to the following:

Foley & Lardner LLP
3000 K Street N.W.
Suite 600
Washington, DC 20007-5109

United Therapeutics Corp.
1040 Spring Street
Silver Spring, MD 20910

Date: October 1, 2015

Respectfully submitted,

/s Stuart E. Pollack /
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Reg. No. 43,862
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/s Lisa A. Haile /
Lisa A. Haile, J.D., Ph.D.
Reg. No. 38,347
DLA Piper LLP (US)

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

STEADYMED LTD.

Petitioner,

v.

UNITED THERAPEUTICS CORPORATION

Patent Owner.

Case IPR Unassigned

Patent No. 8,497,393

DECLARATION OF JEFFREY D. WINKLER IN SUPPORT OF PETITION FOR *INTER PARTES* REVIEW OF CLAIMS 1 – 22 OF U.S. PATENT NO. 8,497,393

Mail Stop "Patent Board"
Patent Trial and Appeal Board
U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

TABLE OF CONTENTS

1. I have been retained by counsel for the Petitioner, SteadyMed Ltd., to offer technical opinions with respect to U.S. Patent No. 8,497,393 ("the '393 Patent") and prior art references cited in *inter partes review* proceedings for the '393 Patent.

2. I have reviewed the '393 Patent and, in assessing it, I have considered the teachings of the scientific literature before December 17, 2007, in light of general knowledge in the art before that date.

3. This declaration presents my opinion that Claims 1-22 of the '393 Patent would have been anticipated and/or obvious to a person of ordinary skill in the art before December 17, 2007. The technology of the '393 Patent involves nothing more than basic organic chemistry techniques – in my view, "organic chemistry 101" – all of which were well-known in the art prior to December 17, 2007.

I. QUALIFICATIONS

4. I am the Merriam Professor of Chemistry at the University of Pennsylvania, a position I have held since 2001. Prior to that time, I was a Professor of Chemistry from 1996 to 2001, and an Associate Professor of Chemistry from 1990 to 1996 at the University of Pennsylvania. I was an Assistant Professor of Chemistry at the University of Chicago from 1983 to 1990.

5. I have over 30 years of experience in the fields of organic and medicinal chemistry. My area of expertise includes design and synthesis of various biologically active natural and unnatural products, as well as mechanisms and stereochemistry in organic synthesis.

6. I earned my A.B. in Chemistry from Harvard College in 1977 and my Ph.D. in Chemistry from Columbia University in 1981.

7. I have an excellent reputation in the field of organic chemistry as evidenced by several awards, including the American Chemical Society Cope Scholar Award and an Alfred P. Sloan Fellowship.

8. I have co-authored numerous publications reporting results of my research in the field of organic chemistry in peer-reviewed journals. I have also presented numerous lectures on organic chemistry at national and international scientific meetings around the world.

9. Accordingly, I am an expert in the field of organic chemistry, and I have been an expert in this field since prior to December 17, 2007. Further information regarding my qualifications and credentials are fully set forth in my *curriculum vitae*, attached as Ex. 1010.

II. MATERIALS CONSIDERED

10. In forming my opinions, I have had available the materials cited in the Petition, the materials cited in this report, as well as those listed in the publications

listed on my *curriculum vitae* (Ex. 1010). In addition to these materials, I may consider additional documents and information in forming any supplemental opinions. To the extent I am provided additional documents or information, including any expert declarations in this proceeding, I may offer further opinions.

III. PERSONS OF ORDINARY SKILL IN THE ART ("POSA")

11. I understand that "one of ordinary skill in the art" is not a specific, real individual, but rather a hypothetical individual who is presumed to have known the relevant art at the time of the invention. In defining "one of ordinary skill in the art," I have been advised to consider factors such as the educational level and years of experience not only of the person or persons who have developed the invention that is the subject of the case, but also others working in the pertinent art at the time of the invention; the types of problems encountered in the art; the teachings of the prior art; patents and publications or other persons or companies; and the sophistication of the technology.

12. I have assessed the level of ordinary skill in the art based upon my review of the prior art, the patent, and my thirty years of working in the field of organic chemistry.

13. In this case, the inventors—Dr. Hitesh Batra, Sudersan Tuladhar, Raju Penmasta, and Dr. David Walsh—are all senior scientists or managers at United Therapeutics, according to their LinkedIn profiles. Similarly, the prior art is written

by very educated authors, including Dr. Ken Phares, a scientist in charge of United Therapeutics' pharmaceutical development program, who has many years of experience and a Ph.D. in Pharmaceutical Chemistry, as per his LinkedIn profile.

14. Given the high education level of the scientists actually working in this field, a person of ordinary skill in the art ("POSA") of chemistry at the time of the alleged invention would have a master's degree or a Ph.D. in medicinal or organic chemistry, or a closely related field. Alternatively, a person of ordinary skill would include an individual with a bachelor's degree and at least five years of practical experience in medicinal or organic chemistry.

15. As reflected in my qualifications set forth above and in my *curriculum vitae* (Ex. 1010), I qualified as a person of ordinary skill in the art at the time before December 17, 2007.

IV. LEGAL CONCEPTS THAT WERE EXPLAINED TO ME

A. Anticipation

16. I understand from counsel that the law recognizes a concept called "anticipation." As I understand it, a single prior art reference must disclose each and every element of a claim, either expressly or inherently, to anticipate the claim and render it invalid.

17. I understand that, to establish inherent anticipation, properties that are inherently anticipated must be necessarily present in a single prior art reference. I

understand that a prior art reference inherently discloses an element or limitation if science or technical information necessarily requires that the element or limitation is included in what was disclosed in the prior art reference. I also understand that these inherent properties cannot merely be probably or possibly present. It is my understanding that one of ordinary skill in the art may not have recognized the inherent characteristics or functioning of the prior art at the time.

B. Obviousness

18. I understand from counsel that the law recognizes a concept called "obviousness." I understand that a patent claim is invalid for obviousness if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious to a person of ordinary skill in the art at the time of the invention. I understand that for a single reference or a combination of references to render the claimed invention obvious, a person of ordinary skill in the art must have been able to arrive at the claims by modifying or combining the applied references.

19. It is my further understanding that there must be a motivation to combine or modify the applied references.

20. It is my further understanding that a person of ordinary skill in the art must have a reasonable expectation of success that making the combination will make the invention work.

C. Product-By-Process Claims

21. I understand that the challenged claims are "product by process" claims. I understand that this means that the claims cover a recited product made by a process that includes the recited process steps.

22. I further understand that as a result of the claims being classified as "product by process" claims, the claims should be analyzed both through the claimed product, and also through the processes that are recited in the claims. If the processes in the claims are in the prior art, then the claims are invalid. As noted below, I further understand the process in a product-by-process claim merits weight in comparing it to the prior art only if it imparts some unique and novel property or structure in the resulting product.

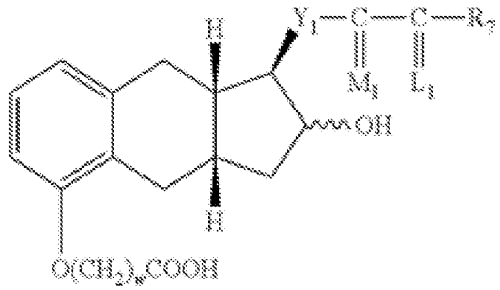
V. OVERVIEW OF THE '393 PATENT

23. I understand that the '393 Patent, entitled "Process to Prepare Treprostinil, Ingredient in Remodulin™, issued on July 30, 2013, and claims priority to a provisional application filed on December 17, 2007. I understand, therefore, that the priority date of the '393 Patent is December 17, 2007.

24. The '393 Patent discloses an "improved process" to prepare prostacyclin derivatives such as treprostinil. (Ex. 1001, Abstract).

25. Each of the independent claims includes limitations that the claimed compound is made by a process comprising three specified steps and one optional

step: (a) alkylating a prostacyclin derivative (*e.g.*, a benzindene triol precursor to treprostinil acid) to form an alkylated prostacyclin derivative (*e.g.*, a benzindene nitrile precursor to treprostinil acid); (b) hydrolyzing the alkylated prostacyclin derivative with a base to form a prostacyclin acid (*e.g.*, treprostinil acid); (c) contacting the prostacyclin acid (*e.g.*, treprostinil acid) with a base to form a prostacyclin carboxylate salt (*e.g.*, a treprostinil salt); and (d) optionally reacting the prostacyclin carboxylate salt (*e.g.*, a treprostinil salt) formed in step (c) with an acid to form a compound or a pharmaceutically acceptable salt of:



(Ex. 1001).

26. The alkylating and hydrolyzing steps in the synthesis of treprostinil and the other claimed compounds, as set forth in steps (a) – (b) of Claims 1 and 9, were fully disclosed in prior art to the '393 Patent, including U.S. Patent No. 6,765,117 (the '117 Patent) (Ex. 1003), and in Moriarty et al., J. Org. Chem. 1890-1902 (2004) (Ex. 1004, referred to as "Moriarty"), as well as other publications.

27. I understand that the '393 Patent inventors admit that steps (a) ("alkylating") and (b) ("hydrolyzing") were in the prior art. (*See* Ex. 1002-1, p. 109); '393 Patent, Ex. 1001, col. 1, lines 22-28 (incorporating Moriarty (Ex. 1004), the '117 Patent (Ex. 1003), and U.S. Patent No. 6,441,245 (Ex. 1013) by reference, and col.7, lines 17-20 (describing '245 Patent's process as the same as in '393 Patent)).

28. The '393 Patent addresses an alleged "improvement" to Moriarty through the addition of steps (c) and optionally 1(d), which claim a standard organic chemistry purification by a precipitation technique: converting a free carboxylic acid into a salt using a weak base and then precipitating it to remove potential impurities, and then, optionally converting the salt back to the free acid. (Ex. 1001, col. 19, lines 28-29).

29. These precipitation procedures were well-known in the art – indeed, they are no more than basic organic chemistry techniques and standard chemical purification – and they were fully disclosed in numerous prior art references, including basic organic chemistry textbooks.

VI. THE '393 PATENT IS INVALID

A. Summary

30. The prior art discloses all claims of the '393 Patent, as (1) the synthesis of the claimed compound, treprostinil, was well-known in the art well

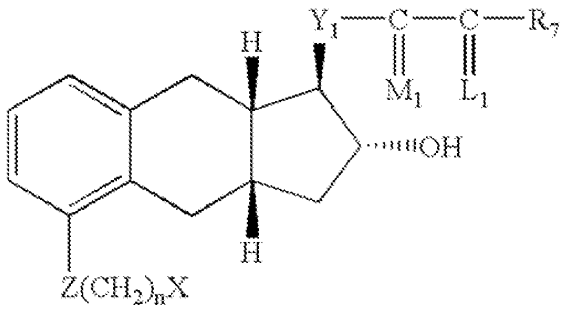
before December 17, 2007, the priority date for the '393 Patent, and (2) the '393 Patent's only alleged "improvement" over the prior art involves nothing more than basic organic chemistry 101 – standard chemical purification through salt formation and precipitation that I have taught and utilized throughout my over thirty years in the field of organic chemistry. Further, as discussed below, the claimed process of the '393 Patent does not produce a product that is materially distinct from the product produced by the prior art.

31. I outline my specific opinions related to anticipation and obviousness, below.

B. The Synthesis Of Treprostinil Was Well-Known

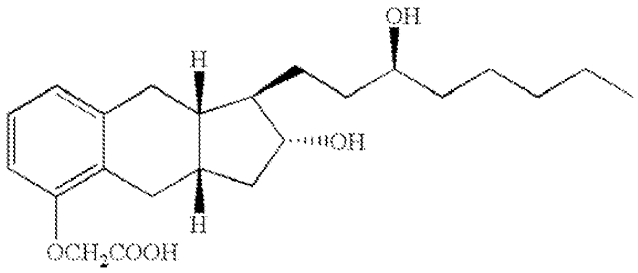
32. Before December 17, 2007, syntheses for numerous prostacyclin derivatives, such as treprostinil, and intermediate compounds useful in their syntheses were well-known.

33. These prostacyclin derivatives and intermediates include the following general structures:

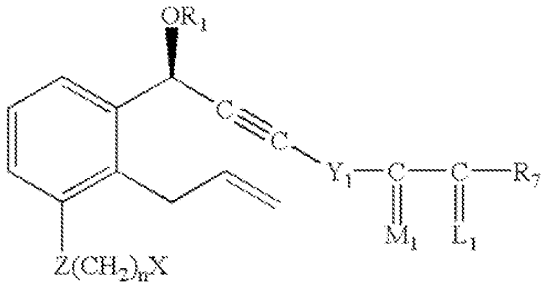


(*see e.g.*, the '117 Patent, Ex. 1003, Claim 1).

34. For example, the '117 Patent (Ex. 1003) includes the synthesis of treprostinil (which is the case in which, Z is O, n is 1, X is COOH, Y_1 is CH_2CH_2-, M_1 is a H and a OH group in the S configuration (*i.e.*, the same stereoisomeric configuration found in the structure of treprostinil (below)), L_1 is α-H; β-H, and R_7 is $–(CH_2)_3$-CH_3) amongst its many examples. In addition, both Moriarty (Ex. 1004) and prior art reference Phares (Ex. 1005) further disclose syntheses of treprostinil. For example, Claim 3 of the '117 Patent (Ex. 1003) discloses the structure of treprostinil (below),

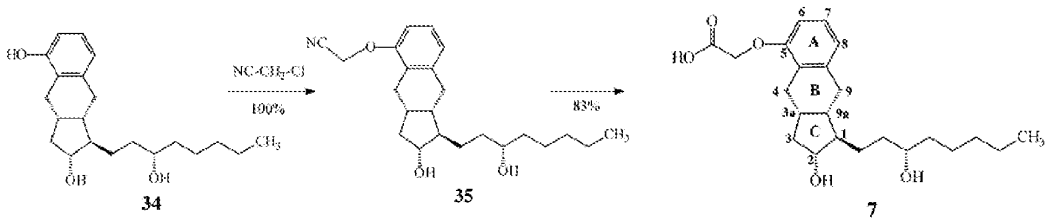


which is produced by a process for making 9-deoxy- PGF1-type compounds, the process comprising cyclizing the following starting compound:

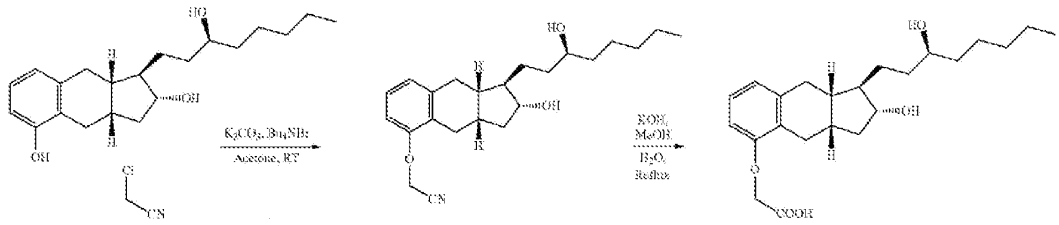


35. As noted above, steps (a) – (b) of Claims 1 and 9 of the '393 Patent disclose the synthesis of prostacyclin derivative acids that include treprostinil acid,

which is also disclosed in Moriarty (Ex. 1004) and the '117 Patent (Ex. 1003). For example, Moriarty (Ex. 1004) at p. 6 and p. 3 discloses the following synthetic scheme for making treprostinil acid:



36. And the '393 Patent (Ex. 1001) at columns 9-10 discloses the same synthetic scheme for making treprostinil acid:



37. Accordingly, the only alleged "improvement" to Moriarty in the '393 Patent was the addition of step (c) and **optionally** step (d) of Claims 1 and 9.

38. Despite the alleged claimed "improvement," the treprostinil compound made by the '393 Patent processes has comparable purity to the compound disclosed by Phares (Ex. 1005) based on an analysis of the melting point of the Form B salt, as explained in further detail below.

C. Formation of A Carboxylate Salt From a Carboxylic Acid and the Addition of an Acid to a Carboxylate Salt to Regenerate the Carboxylic Acid is Standard Chemical Purification

39. Steps (c) and (d) of Claims 1 and 9 disclose nothing more than basic organic chemistry techniques for purification of a prostacyclin compound, such as treprostinil, which was well-described in the prior art years before December 17, 2007.

40. A person of ordinary skill in the art would recognize that the formation of a carboxylate salt, by the addition of a weak base to a neutral carboxylic acid, and the subsequent addition of a strong acid to regenerate carboxylic acid, as disclosed in steps (c) and (d), is standard chemistry purification – *i.e.*, organic chemistry 101.

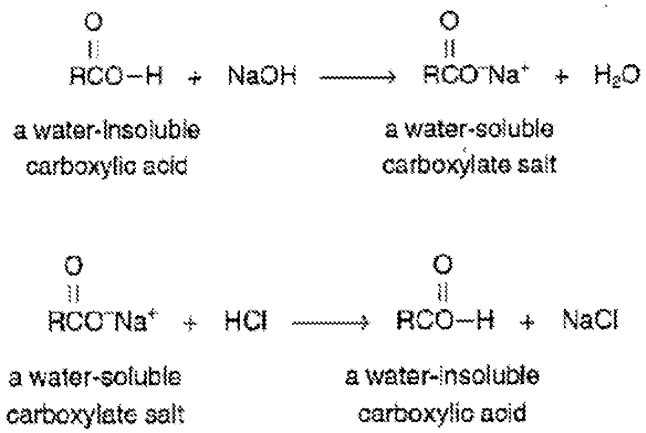
41. Similar general purification techniques were described in numerous textbooks and literature, such as basic introductory organic chemistry textbooks, well before the December 17, 2007 priority date for the '393 Patent. Indeed, I have taught these general purification techniques to my organic chemistry students for over thirty years.

42. For example, the following organic chemistry textbooks disclose similar purification techniques as those disclosed in the '393 Patent:

- ***Wiberg*** (Ex. 1012), entitled "Laboratory Technique in Organic Chemistry", an organic chemistry lab textbook provided to organic

chemistry students, explicitly states: "A typical example is the purification of a water-insoluble solid carboxylic acid by dissolving it in sodium hydroxide solution, filtering, precipitating the compound by the addition of acid. A similar procedure may be used with amines: dissolve the compound in acid and precipitate it with a base. These procedures usually work quite well in that they utilize a chemical reaction to aid in separation from nonacidic or nonbasic impurities." (Ex. 1012, p. 6).

- ***Schoffstall*** (Ex. 1014), entitled "Microscale & Miniscale Organic Chemistry Laboratory Experiments (Second Edition)" (pp. 3-4), similarly describes an experiment in which carboxylic acid is separated from neutral and basic organic compounds by conversion to a salt. Addition of an acid, such as HCl, then regenerates the carboxylic acid, which can then be filtered or extracted into an organic solvent:



43. More specifically, contacting a carboxylic acid of a prostacyclin derivative, such as treprostinil, with a base to form a salt, followed by the addition of a strong acid to regenerate the carboxylic acid, was a well-known chemical purification technique in the prior art. For example:

- ***Kawakami*** (Ex. 1007), entitled "Crystalline Amine Salt of Methanoprostacyclin Derivative, Manufacturing Method thereof, and **Purifying Method** thereof" (bolding added), is directed to the preparation and use of dicyclohexylamine (*i.e.*, a base) to form a crystalline dicyclohexylamine salt of a methanoprostacyclin derivative, in order to facilitate the purification of the methanoprostacyclin. Kawakami further discloses that the dicyclohexylamine salt of a methanoprostacyclin derivative can be easily reverted to the free methanoprostacyclin derivative by conventional methods (Ex. 1007, p. 6), such as treating the salt with a strong acid such as HCl or H_2SO_4. Per Kawakami, the salt that is obtained has "fairly high purity and the purity can be further improved by recrystallization as needed with the use of an appropriate solvent." (*Id.*).
- ***Phares*** (Ex. 1005), entitled "Compounds and Methods for Delivery of Prostacyclin Analogs," discloses that the preparation of treprostinil diethanolamine includes the step of adding diethanolamine (*i.e.*, a base)

to a solution of treprostinil acid in a 1:1 molar ratio mixture of ethanol: water. (Ex. 1005, p. 24, bottom para.).

- ***Ege*** (Ex. 1008), an organic chemistry textbook, discloses that sodium benzoate (*i.e.*, a carboxylate salt) can be converted back to benzoic acid (*i.e.*, a carboxylic acid) by treatment with the acid HCl.[1] (Ex. 1008, p. 8).

VII. ANTICIPATION ARGUMENTS

A. Phares Inherently Anticipates The Claims Of The '393 Patent

1. The Phares Reference

44. The Phares reference (Ex. 1005), is International Publication No. WO 2005/007081 to Phares, *et al*, entitled "Compounds and Methods for Delivery of Prostacyclin Analogs," and published January 27, 2005. It is prior art to the '393 Patent.

45. As previously discussed, I understand that the '393 Patent claims are product-by-process claims. I further understand the process in a product-by-process claim merits weight in comparing it to the prior art only if it imparts some unique and novel property or structure in the resulting product. No novel property or structure exists in the claimed treprostinil product as compared to the prior art.

---

[1] The following prior art includes other examples discussing purifying prostacyclin derivatives using a base to form a salt. *See, e.g.*, U.S. Patent No, 3,703,544, entitled "Process for Preparing the Tris(Hydroxy-Methyl – Aminomethane Salt of PGE2" (Ex. 1015, col. 4, lines 58-73); U.S. Patent No., 3,888,916 entitled "Amantadine salt of 16,16-dimethyl-PGE.sub.2". (Ex. 1016, col. 2, lines 47-57).

46. Further, I have reviewed the arguments presented in Ground 1 of the Petition and agree that at least for the reasons stated in the Petition, Claims 1-5, 11-14, and 16-20 are anticipated by Phares.

47. In particular, I was asked to opine whether: (1) Phares inherently discloses the same synthesis of treprostinil as disclosed in the '393 Patent; (2) Phares inherently discloses the same degree of purity of treprostinil as disclosed in the '393 Patent; and (3) whether the '393 patent processes result in a "physically different" or unique product over the prior art.

2. Phares Inherently Discloses the Same Synthesis of Treprostinil Under Independent Claims 1 & 9

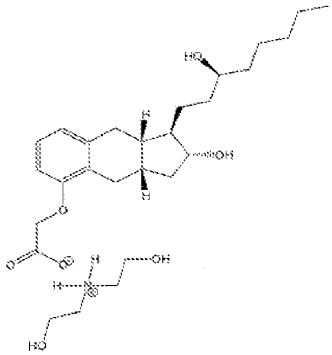
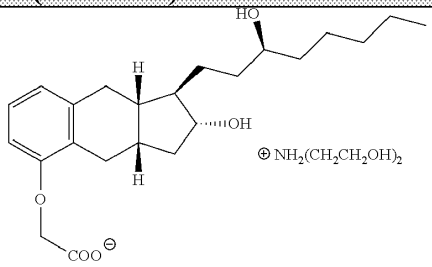
48. Phares inherently discloses the same synthesis of treprostinil as set forth in the independent claims, Claims 1 and 9, of the '393 Patent in the case where w is 1, Y_1 is CH_2CH_2-, M_1 is a H and a OH group in the S configuration; L_1 is α-H; β-H, and R_7 is $–(CH_2)_3$-CH_3. (Ex. 1005, pp. 41-42). Accordingly, Phares inherently anticipates both independent Claims 1 & 9.

49. I understand that Claim 1 is drawn to a product comprising a compound of a genus that includes the treprostinil compound, or a pharmaceutically acceptable salt thereof. Claim 9 is identical to Claim 1 except that it is drawn to a product comprising the specific treprostinil compound, a species of the genus of Claim 1, made by the same process. Accordingly, my analysis evaluates Claims 1 and 9 together.

50. I base my opinion on the following: (1) Phares discloses the *same* treprostinil diethanolamine salt (Ex. 1005, p. 24; pp.85-93; p. 99, Claim 49) as the '393 Patent, (2) Phares details the *same* procedures as were used to make treprostinil in the '117 Patent and Moriarty, but also details how to use them to make (-)-treprostinil, the enantiomer of (+)- treprostinil (Ex. 1005, p. 42), and (3) Phares discloses the treprostinil diethanolamine salt in the *same* "polymorph" (crystal form) – Form B – as the '393 Patent (Ex. 1001, col. 12, lines 34-51; Ex. 1005, pp. 90-91) as well as a higher melting point of the Form B salt than that reported in the '393 Patent. (Ex. 1005, p. 91).

51. First, the treprostinil diethanolamine salt is made by *exactly the same process step* as claimed in the '393 Patent's Claim 1(c) and 9(c): by contacting the product of step (b) with diethanolamine base to form the salt whose structure is displayed in Phares Claim 49. (Ex. 1005, p. 99, Claim 49).

52. For example, Phares discloses in its Claim 49 the identical, pharmaceutically acceptable treprostinil diethanolamine salt that Claim 1 claims:

Phares (Ex. 1005), Claim 49	'393 Patent (Ex. 1001), Claims 1 & 9 (column 8)
	

53. Other than a change in formatting, the two structures from Phares and the '393 Patent are identical.

54. As Phares necessarily discloses the same process steps to make treprostinil diethanolamine salt claimed in the '393 Patent and even discloses the same structure, Phares inherently anticipates Claims 1 and 9 of the '393 Patent.

55. Second, Phares also details the same Claim 1 and 9 steps (a) or (b) as were used to make treprostinil in the '117 Patent and Moriarty reference, but applies them to make (-)-treprostinil, the enantiomer of (+)- treprostinil (Ex. 1005, p. 42). The '393 Patent and prosecution history admits using these steps (a) and (b) in the prior art. ('393 Patent, (Ex. 1001), col. 1, lines 22-28 (incorporating Moriarty (Ex. 1004), the '117 Patent (Ex. 1003), and U.S. Patent No. 6,441,245 (Ex. 1013) by reference, and col.7, lines 17-20 (describing '245 Patent's process as the same as in the '393 Patent); *see also* Ex. 1002-1, p. 109).

56. Phares explains that the reaction scheme where "the enantiomer of the commercial drug (+)-Treprostinil was synthesized using the stereoselective intramolecular Pauson Khand reaction as a key step and Mitsunobu inversion of the side-chain hydroxyl group," (Ex. 1005, p. 42) was also used to make the (-)-treprostinil enantiomer, and then details the exact same alkylation and hydrolyzing steps (both included in Phares as "step (l)." (Ex. 1005, p. 42).

57. This is the *identical procedure* claimed in steps (a) and (b). (*Compare* Ex. 1005, p. 42, "1) i. C1CH2CN, K2CO3. ii, KOH, CH3OH, reflux. 83 % (2 steps)," with '393 Patent Claim 1 and 9 steps (a) and (b) and '393 Patent col. 9, line 25 – col. 11, line 37 ('393 Patent, Examples 1 and 2).) This provides further confirmation that under the doctrine of inherent anticipation, Phares anticipates Claims 1 & 9.

58. Third, Phares discloses the treprostinil diethanolamine salt in the same "polymorph" (crystal form) – Form B – as the '393 Patent. (Ex. 1001, col. 12, lines 34-51; Ex. 1005, pp. 90-91). Polymorphs are different crystalline forms of the same substance in which molecules may have different arrangements and/or different molecular conformations.

59. In both the '393 Patent and Phares (Ex. 1005), treprostinil diethanolamine salt Form B is made. Phares demonstrated that Form B is the more stable form as compared to Form A. (Ex. 1005, pp. 88-93). Phares further

discloses a melting point of 107º C (Ex. 1005, p. 91 & Fig. 21) for the Form B salt. The '393 Patent, however, discloses lower melting point ranges for the Form B salt in the ranges of 104.3-106.3º C (Batch No. 1) and 104.7-106.6º C (Batch No. 3) (Ex. 1001, col. 12, line 65 – col. 13, line 11, Example 3), as well as 105.0-106.5º C (Batch No. 1) and 104.5-105.5 ºC (Batch No. 2) (Ex. 1001, col. 13, line 59, Example 4); *see also* (Ex. 1001, col. 12, lines 53-55 (noting Form B requires a melting point of the treprostinil diethanolamine salt of more than 104º C).

60. The higher melting point disclosed in Phares is consistent with the product of Phares having higher purity than the '393 Patent's product. *See* (Gilbert, Ex. 1018, p. 6) (a higher melting point typically indicates that a product has higher purity).

61. Of note, in the '393 Patent, treprostinil diethanolamine Form B was made directly from precipitation in a mixed solvent of ethanol and ethanol acetate. In Phares (Ex. 1005), treprostinil diethanolamine Form B was made by first generating Form A from any of many possible mixed solvents, and then converting Form A to Form B in a second mixed solvent. No claim in the '393 Patent specifies what solvents should be used, and thus, all of these procedures described in Phares fall within the scope of the '393 Patent claims.

62. In summary, as Phares discloses the same product and same process of preparing the product disclosed in Claims 1 and 9, including making the most

stable crystal form (Form B) and preparing a product that melts at a higher temperature higher than that described in the '393 Patent, Phares necessarily discloses a salt of at least equal purity to the salt in the '393 Patent.

B. The '393 Patent Process Does Not Result In A "Physically Different" Or Unique Product Than The Prior Art

63. Having reviewed the prior art and the prosecution history, no unique or novel property is found in the resulting treprostinil product disclosed under the claims of the '393 Patent compared to the prior art. Accordingly, the '393 Patent processes do not result in a physically different or unique product than that disclosed in the prior art, and the '393 Patent processes are inherently anticipated by the prior art.

64. I base my opinion on an analysis of the prosecution history for the '393 Patent, and my experience as a professor of organic chemistry for over thirty years.

65. I understand that during prosecution of the '393 Patent, Patent Owner submitted a declaration by Dr. David Walsh, one of the inventors, and Executive Vice President of Chemical Research and Development at United Therapeutics Corporation. (Ex. 1002-2, pp. 346-350, Walsh Declaration). Patent Owner contended, based upon Dr. Walsh's measurement, that its purification method achieved 99.8% purity (Ex. 1002-2, pp. 348, Walsh Declaration), while the prior art Moriarty reference achieved "only" 99.4% (Ex. 1002-2, p. 347) (despite the fact

that Moriarty reported 99.7%, Ex. 1004, p. 13). Patent Owner claims 99.5% purity or above in Claims 2 and 10, but its use of the Walsh Declaration to support this claim is unsupportable, for the three reasons discussed below.

66. First, the data in the Walsh Declaration was derived from a limited sample set – indeed, *only two specific batches* of treprostinil – which were self-selected for presentation to the Patent Office. There could be significant batch-to-batch variations in the impurity profile of each batch of treprostinil, which does not provide sufficient evidence to support the conclusion that the purification method achieves 99.5% purity or above for the claimed treprostinil.

67. Second, variations in the processes of making the claimed product could also impact and vary the degree of purity of the product. For example, the claims do not require the use of any particular reaction conditions when carrying out steps (a)-(c) and optional step (d) of Claims 1 and 9. Thus, in performing the claimed process under the '393 Patent, varying levels of purity of the claimed product could be obtained as a result of variations in the different reagents, solvents, and reaction conditions utilized.

68. Third, a 0.1 percentage difference in purity between Walsh's measurement of Moriarty's purity (99.4%) and Claim 2 and Claim 10's 99.5% purity is well within experimental error for measuring impurities, and would not represent a significant deviation from the processes of the prior art.

69. Even a difference of 0.4%, as discussed below, between the claimed processes of the '393 Patent and the prior art, such as Moriarty (Ex. 1004), would be attributable to experimental error, and thus the claimed degree of purity under the claimed processes of the '393 Patent presents no distinction from the prior art.

70. Indeed, the literature on HPLC's precision indicates that the "RSD" or "relative standard deviation" for a typical instrument is about 1%. (Ex. 1017.) In the present case, we can estimate the precision of the equipment the inventors actually used, since the inventors found that Example 4's Batch 1 had an HPLC Assay of 100.4%, which is obviously greater than the 100% value theoretically achievable. (Ex. 1001, col. 13, lines 50-65). This deviation between experimental and theoretical shows that the instrument can have variations of at least 0.4%, which is greater than the differences in purity that the inventors offered to support their contention regarding greater purity over the prior art.

71. Accordingly, the '393 Patent processes do not result in a physically different or unique product than that disclosed in the prior art, and the '393 Patent processes would still be inherently anticipated by the prior art.

VIII. OBVIOUSNESS ARGUMENTS

72. I have reviewed the arguments presented in Grounds 2 & 3 of the Petition and agree for at least the reasons stated in the Petition that: (1) Claims 1-5, 7-9, 11-14 and 16-20 are obvious over Moriarty (Ex. 1004) in view of either

Phares (Ex. 1005) or Kawakami (Exs. 1006 & 1007), and (2) Claims 6, 10, 15, 21 and 22 are obvious over Moriarty (Ex. 1004) in view of Phares (Ex. 1005) or Kawakami (Exs. 1006 & 1007) and further in view of Ege (Ex. 1008).

73. In particular, I was asked to opine, whether, in view of these references, a person of ordinary skill in the art would be motivated to combine the cited references with a reasonable expectation of success to obtain the claimed product of the '393 Patent.

A. The Motivation To Combine Moriarty With Phares Or Kawakami

1. The Purification Step and the Purity of Treprostinil Salt

74. A person of ordinary skill in the art would be motivated to combine Moriarty (Ex. 1004) with either Phares (Ex. 1005) or Kawakami (Ex. 1006 & 1007). Moriarty discloses steps (a) and (b) of Claim 1 of the '393 Patent. (Ex. 1004, p. 6, 13). Phares discloses step (c) of Claim 1 of the '393 Patent (Ex. 1005, p. 24), while Kawakami discloses that prostacyclin compounds (of which treprostinil is an example) can be purified by using weak bases and forming salts (Ex. 1007, p. 6). Further, if desired, the product can be turned back into the free acid as disclosed under the optional Claim 1(d). (*Id.*). Accordingly, a person of ordinary skill in the art would be motivated to combine Moriarty with either Phares or Kawakami to obtain a product of at least equal purity to that claimed in the '393 Patent.

75. Furthermore, Kawakami (Ex. 1007) at p. 6 discloses that the salt that is obtained has fairly high purity and the purity can be further improved by recrystallization as needed with the use of an appropriate solvent. Therefore, a person of ordinary skill in the art would be motivated to combine Moriarty (Ex. 1004) with the teachings of Phares (Ex. 1005) or Kawakami (Exs. 1006 & 1007) in order to obtain a purer compound, as proven by Kawakami and noted *supra*.

76. The combination of Moriarty (Ex. 1004) and Phares (Ex. 1005) (or Kawakami, Exs. 1006 & 1007) discloses the same process steps and same product of the '393 Patent. For the same reasons discussed above regarding Phares, the purity of the combinations would be of at least equal purity to that claimed in the '393 Patent.

2. Purification of the Product of the Alkylation Reaction

77. Moriarty (Ex. 1004, p. 3 and p. 6) discloses that Formula 35 (which corresponds to Formula III in Claim 1 of the '393 Patent (Ex. 1001)) is purified. Phares (Ex. 1005) discloses that the purification of Formula 35 (as described in Moriarty) would not be necessary. Specifically, Phares (Ex. 1005, pp. 40-42) discloses that Formula 11b is converted to Formula 2 by treatment with the alkylating agent $ClCH_2CN$ followed by the base KOH. The synthetic scheme of Phares (p. 42) does not indicate that any intermediate compound is purified.

78. In view of the foregoing, a person of ordinary skill in the art would understand that the treatment of Formula 34 (Moriarty) with the alkylating agent could be followed by the hydrolysis with a base without purifying the product of the alkylation reaction. Furthermore, a person of ordinary skill in the art would be motivated to combine Moriarty (Ex. 1004, p. 3, p. 6) with Phares (Ex. 1005, p. 42), since shortening the number of synthetic steps should increase efficiency and presumably lower costs.

3. Regeneration of Carboxylic Acid

79. A person of ordinary skill in the art would be motivated to include the carboxylate salt formation and regeneration of the neutral carboxylic acid with the syntheses of Moriarty (Ex. 1004, p. 3; p. 6) and Phares (Ex. 1005, p. 24), since Kawakami (Ex. 1007, p. 6) discloses that "the dicyclohexylamine salt obtained by the present invention can be easily reverted to a free methanoprostacyclin derivative [I] by conventional methods, and the resulting methanoprostacyclin derivative exhibits excellent crystallinity compared with substances not purified according to the present invention." Accordingly, a person of ordinary skill in the art would want to form the treprostinil diethanolamine salt, purify it, and then convert it back to its free form (*i.e.*, treprostinil) in order to obtain excellent crystallinity and increased purity. And Ege (Ex. 1008, p. 8) teaches that one such

method for obtaining the free form of any carboxylic acid (including treprostinil) would be by treatment of the carboxylate salt with a strong acid.

B. The Reasonable Expectation Of Success That The Combination Of Moriarty With Phares Or Kawakami Will Work As Intended

80. There is a more than a reasonable expectation of success that the reaction of treprostinil with diethanolamine would be successful. Phares (Ex. 1005, p. 24, p. 99, Claim 49) performed the same reaction and it was successful. Kawakami (Ex. 1006 & 1007) shows that using the technique of making a salt was successful in purifying a prostacyclin compound. (Ex. 1007, p. 6).

81. In addition, with respect to Claims 8 and 16, there is a reasonable expectation of success that the product of the alkylation reaction in step (a) of Claims 8 and 16 does not need to be purified before performing the hydrolysis reaction in step (b). Phares (Ex. 1005, pp. 40-42) discloses a synthesis of treprostinil in which the product of the alkylation reaction is not purified before performing the hydrolysis reaction.

C. The Motivation To Combine Moriarty With Phares Or Kawakami In View Of Ege

82. Moriarty (Ex. 1004) combined with Phares (Ex. 1005) or Kawakami (Exs. 1006 & 1007), as I explained above, discloses a synthesis of treprostinil that includes the steps (a), (b) and (c) of Claims 1 and 9.

83. However, Kawakami (Ex. 1007, p. 6) further discloses that the dicyclohexylamine salt of a methanoprostacyclin derivative "can be easily reverted to the free methanoprostacyclin derivative by *conventional methods*" (emphasis added). In addition, Kawakami (Ex. 1007) at p. 6 discloses that the salt that is obtained has fairly high purity and the purity can be further improved by recrystallization as needed with the use of an appropriate solvent.

84. A person of ordinary skill in the art would understand that one such conventional method for converting the dicyclohexylamine salt of a methanoprostacyclin derivative to the free methanoprostacyclin derivative, or converting the treprostinil diethanolamine salt to treprostinil (*i.e.*, the free acid) is by treating the salt with a strong acid such as HCl or H_2SO_4.

85. The addition of a strong acid to a carboxylate salt to regenerate the neutral carboxylic acid is a common reaction in organic chemistry and this process is well within the skill of one of ordinary skill in the art (indeed, a process that I teach to my organic chemistry students), as discussed above.

86. As further evidence as to the conventional nature of such a conversion, Ege (Ex. 1008, p. 8) discloses that sodium benzoate (i.e., a carboxylate salt) can be converted back to benzoic acid (i.e., a carboxylic acid) by treatment with the acid HCl. Ege is an introductory organic chemistry textbook.

87. A person of ordinary skill in the art would be motivated to include the carboxylate salt formation and regeneration of the neutral carboxylic acid with the syntheses of Moriarty (Ex. 1004, p. 3; p. 6) and Phares (Ex. 1005, p. 24), since Kawakami (Ex. 1007, p. 6) discloses that "the dicyclohexylamine salt obtained by the present invention can be easily reverted to a free methanoprostacyclin derivative [I] by conventional methods, and the resulting methanoprostacyclin derivative exhibits excellent crystallinity compared with substances not purified according to the present invention."

88. Accordingly, a person of ordinary skill in the art would want to form the treprostinil diethanolamine salt, purify it, and then convert it back to its free form (*i.e.*, treprostinil) in order to obtain excellent crystallinity and increased purity. And Ege (Ex. 1008, p. 8) teaches that one such method for obtaining the free form of treprostinil or any carboxylic acid would be by treatment of the carboxylate salt with a strong acid.

89. Additionally, the combination of Moriarty (Ex. 1004) and Phares (Ex. 1005) (or Kawakami, Exs. 1006 & 1007) and Ege (Ex. 1008) would disclose that the purity of treprostinil of at least equal purity to that claimed in the '393 Patent, since the combination of these references discloses the same product and same process of Claims 1 and 9.

D. The Reasonable Expectation Of Success That The Combination Of Moriarty With Phares Or Kawakami In View Of Ege Will Work As Intended

90. There is a reasonable expectation of success that the conversion of treprostinil diethanolamine salt back to its free form (*i.e.*, treprostinil) by the use of a strong acid (*i.e.*, HCl) would be successful. As discussed immediately above, the addition of a strong acid to a carboxylate salt to regenerate the neutral carboxylic acid is a common reaction in organic chemistry and this process is well within the skill of one of ordinary skill in the art.

I declare under penalty of perjury that the foregoing is true and correct.

Executed on October __1____, 2015.

Jeffrey D. Winkler, Ph.D.

I declare under penalty of perjury that the foregoing is true and correct.

Executed on October __1____, 2015.

Jeffrey D. Winkler, Ph.D.

CURRICULUM VITAE

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Undergraduate:	Harvard College. September 1973-June 1977. A. B. cum laude in Chemistry, 1977.
PROFESSIONAL EXPERIENCE:	Merriam Professor of Chemistry, University of Pennsylvania, January 2001-
	Professor, University of Pennsylvania Department of Chemistry, July 1996-
	Founding Member, University of Pennsylvania Center for Cancer Pharmacology, May 1998-present
	Associate Professor, University of Pennsylvania, Department of Chemistry, July 1990-June 1996
	Member, University of Pennsylvania Cancer Center, July 1993-present
	Assistant Professor, University of Chicago, Department of Chemistry, September 1983-June 1990
AWARDS & HONORS:	Elected Member, John Morgan Society, 2014 Visiting Scholar, Harbin University of Science and Technology, 2013 Fellow, Japan Society for the Promotion of Science, 2010 Lindback Award for Distinguished Teaching, 2007 Philadelphia Organic Chemists' Club Award, 2006

American Chemical Society Cope Scholar Award, 2000
Chairman, Philadelphia Organic Chemists' Club, 1995
American Cyanamid Young Faculty Award, 1989-1992
NIH-NCI Research Career Development Award, 1988-1993
Alfred P. Sloan Research Fellow, 1987-1989
Merck Foundation Award for Faculty Development, 1985
American Cancer Society Postdoctoral Fellow, 1982-1983

PROFESSIONAL ACTIVITIES

Member, National Institutes of Health Study Section, SBCB, 2010-2016
Associate Editor, *Organic Letter*s, 1999-
Petroleum Research Fund Advisory Board, 2009-
Faculty Senate Committee on Faculty and the Academic Mission, University of Pennsylvania, 2009-12013; Chair, 2011-2012
Faculty Liason, Trustees' Student Life Committee, University of Pennsylvania, 2014-

INVITED LECTURES SINCE 2002:

2002-2003
Plenary Lecturer, French-American Chemical Society, 2002
Pfizer Lecturer, University of
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Novartis Lecturer, University of Texas at Austin
University of Rochester
Emory University
Alan Johnson Lecturer, University of Sussex, UK
Invited Speaker, Gordon Research Conference on Natural Products, July 2003

2003-2004
Stanford University
University of California at Berkeley
Glaxo Smith Kline
Amgen
Biogen
Yale University
Boston College
State University of New York at Stony Brook

2004-05
Plenary Speaker, Belgian Organic Chemistry Symposium
Abbott Laboratories Distinguished Lecturer in Organic Synthesis, Notre Dame University
California Institute of Technology

2005-2006
GlaxoSmithKline Symposium Lecture

Wyeth Synthesis Course (Princeton, Collegeville, Pearl River, Cambridge)

2006-2007
Roche Lectureship, University of Colorado
Invited Lecturer, 12th Brazilian Meeting on Organic Synthesis

2007-2008
Bristol-Myers Squibb
University of Wisconsin-Madison

2008-2009
National Taiwan University
National Tsing Hua University, Taiwan
Keynote Speaker, 9th International Symposium on Organic Reactions, 2008 (Chiayi, Taiwan)

2009-2010
Hamilton College
Kyoto University, Katsura Campus
Kyoto University, Yoshida North Campus
Tokyo Institute of Technology
University of Tokyo
Chiba University
Hokkaido University
Tohoku University
Eli Lilly and Company
Pfizer Cambridge

2010-2011

University of Cambridge
University College London
Imperial College London
University of Cardiff
Paristech
University of Lyon
ETH
Invited Lecturer, Breslow Symposium, Anaheim, CA

2011-2012

Plenary Lecturer, 1st Korea International Forum on Organic Chemistry, Seoul
Frontiers in Chemistry Lecture, Case Western Reserve University
University of Iowa
University of Maryland Eastern Shores
Towson University

2012-2013

Morgan State University
University of Maryland Eastern Shores
Plenary Lecture, Paquette Symposium, Ohio State University
Amgen (Thousand Oaks, CA)
Harbin Institute of Technology
Shanghai Institute of Organic Chemistry
Peking University
Tsinghua University
University of Science and Technology of China (USTC)
Soochow University
Glaxo (Shanghai)
Fudan University

2013-2014

Muhlenberg College
Cutaneous Oncology Retreat, Villanova Conference Center
Invited Speaker, "PAINS, Promiscuity and Probes-Are Drug and Probe Development Mutually Exclusive?" 248th ACS National Meeting - San Francisco, CA - August 2014

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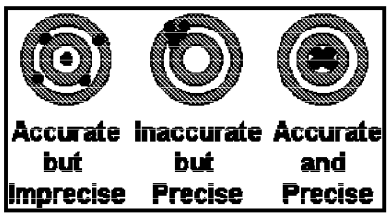
Getting Started in HPLC

Section 4D. Precision and Accuracy

People often confuse "precision" with "accuracy". Both words suggest that we are doing careful work and getting the right answers in quantitative analysis. But precision is not the same as accuracy, and it is important to know what we are talking about. Accuracy means getting an answer that is correct. Precision means being able to get the same answer for a particular sample every time, when we repeat an analysis on that sample.



Let's use an example from the LC lab. Suppose we weigh out 500 mg of aspirin and dissolve it in a 100 mL flask. The concentration of aspirin in our sample will then be :

(quantity) / (volume) = (500 mg)/(l00 mL)

= 5.00 mg/mL

of aspirin.

Now let's send 25 mL of this solution to three different laboratories: lab A, lab B and lab C. Each lab then analyzes the sample for aspirin (by means of HPLC) 6 times and reports the results to us as shown below right (Correct Concentration = 5.00 mg/mL)

The results for lab A all fall quite close to each other: 5.40-5.45 mg/mL aspirin. When replicate analyses on a sample agree closely, as in this example, we say that the assay is precise. That is, a precise analysis is a reproducible analysis. However we also see that these values (5.40-5.45) are not very close to the true value of 5.00 mg/mL. The average value (5.42 mg/mL) is about 8% too high.

LAB A	LAB B	LAB C
5.45	5.18	5.03
5.40	4.80	4.98
5.42	5.20	5.00
5.43	5.06	5.03
5.40	5.15	4.98
5.41	4.98	5.03
PRECISE	**IMPRECISE**	**PRECISE**
INACCURATE	**ACCURATE**	**ACCURATE**

Now consider the results for lab B. These range from 4.80 to 5.18 mg/mL. When we see values that scatter this much, we say that the analysis is not very precise or is imprecise. However if we average these values for lab B, we see that the average value (5.06 mg/mL) is pretty close to the true value of 5.00 mg/mL. So even though lab B does not report precise values, the

values reported are closer to the true value than for lab A. We say that lab B is accurate - even if it is imprecise.

Finally for lab C in the above example, we see that the values reported (4.98-5.03 mg/mL) agree with each other quite well, and the average value (5.01 mg/mL) is also close to the correct value of 5.00. So lab C can be said to be both precise and accurate.

Both accuracy and precision are important in HPLC analysis. However it is much easier to measure precision than it is to measure accuracy. We can easily rerun a sample several times and show that the results are reproducible or precise. It is often more difficult to know the exact concentration of some compound in a given sample - particularly a "real" sample that comes to us in some strange mixture. This often results in laboratories reporting answers that appear precise but are actually wrong (inaccurate). It is actually much more important that our answers be accurate than precise, although good accuracy also requires good precision. The bottom line is: if you have shown that your analysis is precise, don't assume that it is also accurate. Accuracy has to be demonstrated in a different way.

While we are talking about precision - which is essential to good HPLC results - it is important to mention a common error in quantitative analysis. This is the practice of using too few decimals in recording results or carrying out calculations. Be sure to retain enough SIGNIFICANT FIGURES in all weights, volumes and calculations. Generally in LC analysis we want to have at least 4 significant figures in every number, and sometimes more. For example, if weighing out a sample, make sure that the sample weight after subtracting off the tare weight has at least 4 significant figures as shown at the right.

	CORRECT	INCORRECT
flask	124.3433 g	124.34 g
flask+sample	123.8877 g	123.89 g
sample	0.4556 g	0.45 g

The most common measures of precision in chromatographic measurements are the standard deviation, the relative standard deviation, and the coefficient of variation. Detailed definition of these measures is outside the scope of this course; it can be found in any textbook on quantitative analysis or statistics. In practice, the values are computed automatically by the data system or a computer spreadsheet.

Very briefly, the standard deviation is a measure of the amout of possible random error in a series of replicate measurements. For truly random errors, two-thirds of the values will lie within ±1 standard deviation of the mean, 95% of the values will lie within ±2 standard deviations of the mean, and 99% of the the values will lie within ±3 standard deviations of the mean. The estimated standard deviation for a quantity is symbolized by a lower-case sigma (σ).

The relative standard deviation is the standard deviation as a fraction of the mean value. Thus, if we measure a concentration of 9.52 mg/mL with a standard deviation of 0.110 mg/mL, the relative standard deviation is:

RSD = 0.1 10/ 9.52 = 0.0115

In practice, this often expressed at the coefficient of variation (CV), sometimes also called "percent relative standard deviation" (%RSD). This is simply the relative standard deviation expressed as a percentage instead of as a decimal fraction. The CV for the example above is 1.15% (the percentage equivalent to the fraction 0.0115). To convert from RSD to CV, multiply the RSD by 100.

We can now re-examine the results of the aspirin analysis at three different laboratories that we discussed near the top of the page. The mean, standard deviation, and CV give us a more meaninful picture of the laboratories' performance than the terms "precise" or "imprecise".

For most purposes, HPLC methods are expected to have CV values on the order of 1%. Less precision may me acceptable in the case of extremely low-level samples or where a simple yes/no decision is required. The expected precision will usually be stated as part of the method specification.

	LAB A	LAB B	LAB C
	5.45	5.18	5.03
	5.40	4.80	4.98
	5.42	5.20	5.00
	5.43	5.06	5.03
	5.40	5.15	4.98
	5.41	4.98	5.03
MEAN	**5.42**	**5.06**	**5.01**
STD. DEV.	**0.019**	**0.15**	**0.025**
CV	**0.35%**	**4.6%**	**0.36%**

Mini-Quiz

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Experimental Organic Chemistry

A Miniscale and Microscale Approach

FIFTH EDITION

John C. Gilbert

Santa Clara University

Stephen F. Martin

University of Texas at Austin

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27. In the process of a recrystallization, if crystals do not form upon cooling the solution, it is often recommended that the inside of the flask be scratched at the air–liquid interface with a glass stirring rod. What purpose does this serve, and how does it work? What else might be done to induce crystallization?
28. Should some loss of sample mass be expected even after the most carefully executed recrystallization? Explain.
29. In general, what solvent should be used to rinse the filter cake during the vacuum filtration step of a recrystallization? Should this solvent be cooled prior to use?
30. Why do you seldom see high-boiling solvents used as recrystallization solvents?
31. At the end of a recrystallization, where should the *impurities* be located?
32. A student has been asked to recrystallize 1.0 g of impure stilbene from ethanol. Provide a set of standard step-by-step instructions for recrystallization of this sample so as to maximize the purity and yield obtained.
33. An important product from a multistep synthesis must be recrystallized to remove a small amount of an impurity. However, all the available solvents each individually fail to be suitable recrystallization solvents. Offer a solution to this problem using only the available solvents. (*Hint:* Consider binary solvents.)
34. A suspension of decolorizing carbon (charcoal) is often administered to poison victims.
    a. Speculate on the purpose decolorizing carbon serves in this particular application. (*Hint:* It is similar to the way in which decolorizing carbon is used in a recrystallization.)
    b. How is the charcoal ultimately removed from the victim?

3.3 PHYSICAL CONSTANTS: MELTING POINTS

Physical Constants

See more on *Melting Point*

Physical constants of compounds are numerical values associated with measurable properties of these substances. These properties are *invariant* and are useful in the identification and characterization of substances encountered in the laboratory so long as accurate measurements are made under specified conditions such as temperature and pressure. Physical constants are useful only in the identification of *previously known* compounds, however, because it is not possible to predict the values of such properties accurately. Among the more frequently measured physical properties of organic compounds are **melting point (mp), boiling point (bp), index of refraction (n), density (d), specific rotation ([α]),** and **solubility.** Melting points, discussed below, boiling points, described in Section 4.2, and solubilities, outlined in Section 3.2, are the properties most commonly encountered. Index of refraction and density are mentioned in Chapter 25. Specific rotation is discussed in Chapters 7 and 23 but applies only to molecules that are **optically active.** Whether the substance is known or unknown, such values, along with other properties like color, odor, and crystal form, should be recorded in the laboratory notebook.

The values of one or two of the common physical properties *may* be identical for more than one compound, but it is most unlikely that values of several such

properties will be the same for two different compounds. Consequently, a list of physical constants is a highly useful way to characterize a substance. Extensive compilations of the physical constants are available (Chap. 26). One of the most convenient is the *CRC Handbook of Chemistry and Physics,* which contains a tabulation of the physical constants and properties of a large number of inorganic and organic compounds. *The Handbook of Tables for Organic Compounds* is especially useful for organic compounds. Neither of these books is comprehensive; rather, they contain entries for only the more common organic and inorganic substances. So many compounds are known that multi-volume sets of books are required to list their physical properties (Chap. 26).

Melting Point of a Pure Substance

The melting point of a substance is defined as the temperature at which the liquid and solid phases exist in equilibrium with one another without change of temperature. Ideally, addition of heat to a mixture of the solid and liquid phases of a pure substance at the melting point will cause no rise in temperature until all the solid has melted. Conversely, removal of heat from the equilibrium mixture will produce no decrease in temperature until all the liquid solidifies. This means that the melting and freezing points of a pure substance are identical.

The melting point is expressed as the temperature *range* over which the solid starts to melt and then is completely converted to liquid. Consequently, rather than a melting *point,* what is actually measured is a **melting range,** although the two terms are used interchangeably. If a crystalline substance is pure, it should melt over a narrow or sharp range, which will normally be no more than 1 °C if the melting point is determined carefully. The melting ranges reported for many "pure" compounds may be greater than 1 °C because the particular compound was not quite pure or the melting point was not measured properly. The process of melting may actually begin by "softening," as evidenced by an apparent shrinking of the solid, but such softening is difficult to observe. Thus, for our purposes, the start of melting is defined as the temperature at which the first tiny droplet of liquid can be detected. Note that it is improper and inexact to report a single temperature, such as 118 °C, for a melting point; rather, a range of 117–119 °C or 117.5–118.0 °C, for example, should be recorded.

Effect of Impurities on Melting Points

Many solid substances prepared in the organic laboratory are initially impure, so the effect of impurities on melting-point ranges deserves further discussion. Although this topic is discussed in freshman chemistry textbooks, a brief review of its basic principles is given here.

The presence of an impurity generally *decreases* the melting point of a pure solid. This is shown graphically by the melting-point–composition diagram of Figure 3.1, in which points *a* and *b* represent the melting points of pure *A* and *B*, respectively. Point *E* is called the **eutectic point** and is determined by the equilibrium composition at which *A* and *B* melt in constant ratio. In Figure 3.1, this ratio is 60 mol % *A* and 40 mol % *B;* an impure solid composed of *A* and *B* in this ratio would be called a **eutectic mixture.** The temperature at the eutectic point is designated by *e*.

Now consider the result of heating a solid mixture composed of 80 mol % *A* and 20 mol % *B*, a sample that might be considered as "impure *A*." As heat is applied to the solid, its temperature will rise. When the temperature reaches *e*, *A* and *B* will both begin to melt in the constant ratio defined by the composition at the eutectic point. Once all of the "impurity" *B* has melted, only solid *A* will be left in equilibrium with the melt. The remaining solid *A* will continue to melt as additional heat is supplied, and the percentage of *A* in the melt will increase, changing the composition of the

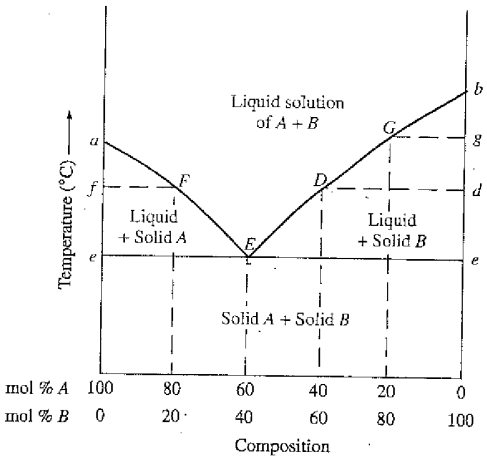

Figure 3.1
Melting-point–composition diagram for two hypothetical solids, A and B.

melt from that of the eutectic mixture. This increases the vapor pressure of *A* in the solution according to Raoult's law (Eq. 4.2) and raises the temperature at which solid *A* is in equilibrium with the molten solution. The relationship between the equilibrium temperature and the composition of the molten solution is then represented by curve *EF* in Figure 3.1. When the temperature reaches *f*, no solid *A* will remain and melting of the sample will be complete. The impure sample *A* exhibits a melting "point" that extends over the relatively broad temperature range *e–f*. Because melting both begins and ends below the melting point of pure *A*, the melting point of *A* is said to be *depressed*.

The foregoing analysis is easily extended to the case in which substance *B* contains *A* as an impurity. In Figure 3.1, this simply means that the composition of the solid mixture is to the right of point *E*. The temperature during the melting process would follow curve *ED* or *EG*, and the melting range would now be *e–d* or *e–g*.

A sample whose composition is exactly that of the eutectic mixture (point *E*, Fig. 3.1) will exhibit a sharp melting point at the eutectic temperature. This means a eutectic mixture can be mistaken for a pure compound, because both have a sharp melting point.

From a practical standpoint, it may be very difficult to observe the initial melting point of solid mixtures, particularly with the capillary-tube melting-point technique used in the Experimental Procedure that follows. This is because the presence of only a minor amount of impurity means that only a tiny amount of liquid is formed in the stage of melting that occurs at the eutectic temperature. In contrast, the temperature at which the last of the solid melts (points *d* and *g*, Fig. 3.1) can be determined accurately. Consequently, a mixture containing smaller amounts of impurities will generally have both a higher final melting point and a narrower observed melting-point range than one that is less pure.

The broadening of the melting-point range that results from introducing an impurity into a pure compound may be used to advantage for identifying a pure substance. The technique is commonly known as a **mixed melting-point** and is illustrated by the following example. Assume that an unknown compound *X* melts at 134–135 °C, and you suspect it is either urea, H_2NCONH_2, or *trans*-cinnamic acid, $C_6H_5CH{=}CHCO_2H$, both of which melt in this range. If *X* is mixed intimately with urea and the melting point of this mixture is found to be lower than that of the pure

compound and pure urea, then urea is acting as an impurity, and the compound cannot be urea. If the mixture melting point is identical to that of the pure compound and of urea, the compound is identified as urea. Obviously, this procedure is useful in identifying compounds only when authentic samples of the likely possibilities are available.

A convenient and rapid method for ascertaining the purity of a solid is measuring its melting point. A narrow melting-point range ordinarily signals that the sample is *pure*, although there is a *low* probability that the solid is a eutectic mixture. If recrystallizing a sample changes an originally broad melting range to a narrow one, the reasonable conclusion is that the recrystallization was successful in purifying the solid. Should the melting-point range remain broad after recrystallization, the sample may be contaminated with solvent and additional drying is required. It is also possible that the recrystallization was not completely successful in removing impurities, in which case the solid should be recrystallized using the same solvent. If this fails to narrow the melting range satisfactorily, recrystallization should be performed with a different solvent.

Micro Melting-Point Methods

The determination of accurate melting points of organic compounds can be time-consuming. Fortunately, micro methods are available that are convenient, require negligible amounts of sample, and give melting-point data that are satisfactory for most purposes. The technique using the capillary-tube melting-point procedure is the one used most commonly in the organic laboratory.

There are practical considerations in determining melting points, and some of them are briefly noted here. First, the observed melting-point range depends on several factors, including the quantity of sample, its state of subdivision, the rate of heating during the determination, and the purity and chemical characteristics of the sample. The first three factors can cause the observed melting-point range to differ from the true value because of the time lag for transfer of heat from the heating medium to the sample and for conduction of heat within the sample. For example, if the sample is too large, the distribution of heat may not be uniform, and inaccurate melting ranges will result. A similar problem of nonuniform heat distribution is associated with using large crystals. It will be difficult to pack the sample tightly in the capillary melting tube, and the airspace that results causes poor conduction of heat. If the rate of heating is too fast, the thermometer reading will lag behind the actual temperature of the heating medium and produce measurements that are low. The chemical characteristics of the sample may be important if the compound tends to decompose on melting. When this occurs, discoloration of the sample is usually evident, and it may be accompanied by gas evolution. The decomposition products constitute impurities in the sample, and the true melting point is lowered as a result. The reporting of melting points for compounds that melt with decomposition should reflect this, as in "mp 195 °C (dec)."

In determining the melting point of a compound, valuable time can be wasted waiting for melting to occur if the proper slow rate of heating is being used on a sample whose melting point is unknown. It is considerably more efficient to prepare two capillary tubes containing the compound being studied and to determine the approximate melting point by rapidly heating one of them, and then allowing the heating source to cool 10–15 °C below this approximate melting point before obtaining an accurate melting point with the second sample.

The accuracy of any type of temperature measurement ultimately depends on the quality and calibration of the thermometer. A particular thermometer may provide accurate readings in some temperature ranges but may be off by a degree or two in others. Melting points that have been determined using a calibrated

thermometer may be reported in the form "mp 101–102 °C (corr.)," where "corr." is the abbreviation for "corrected"; the corresponding abbreviation for values obtained with an uncalibrated thermometer is "uncorr." for "uncorrected."

Calibration involves the use of standard substances for the measurement of the temperature at a series of known points within the range of the thermometer and the comparison of the observed readings with the true temperatures. The difference between the observed and the true temperature measurement provides a correction that must be applied to the observed reading. Calibration over a range of temperatures is necessary because the error is likely to vary at different temperatures.

EXPERIMENTAL PROCEDURES

Melting Points

Purpose To determine melting points using the capillary-tube method.

SAFETY ALERT

1. **If a burner is used in this experiment, be sure that no flammable solvents are nearby. Keep the rubber tubing leading to the burner away from the flame. Turn off the burner when it is not being used.**
2. **Some kinds of melting-point apparatus, such as the Thiele tube, use mineral or silicone oils as the heat transfer medium. These oils may not be heated safely if they are contaminated with even a few drops of water. Heating these oils above 100 °C may produce splattering of hot oil as the water turns to steam. Fire can also result if spattered oil comes in contact with open flames. Examine your Thiele tube for evidence of water droplets in the oil. If there are any, either change the oil or exchange tubes. Give the contaminated tube to your instructor.**
3. **Mineral oil is a mixture of high-boiling hydrocarbons and should not be heated above 200 °C because of the possibility of spontaneous ignition, particularly when a burner is used for heating. Some silicone oils may be heated to about 300 °C without danger (Sec. 2.9).**
4. **Be careful to avoid contact of chemicals with your skin. Clean up any spilled chemicals immediately with a brush or paper towel.**
5. **If you use a Thiele tube, handle it carefully when you are finished, because the tube cools slowly. To avoid burns, take care when removing it from its support.**

A ■ Calibration of Thermometer

Procedure

Preparation Sign in at **www.cengage.com/login** to answer Pre-Lab Exercises, access videos, and read the MSDSs for the chemicals used or produced in this procedure. Read or review Sections 2.7 and 2.9.

Apparatus Capillary melting-point tubes, packing tube, and melting-point apparatus.

Protocol Carefully determine the capillary melting points of a series of standard substances. A list of suitable standards is provided in Table 3.2. The temperatures

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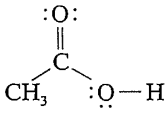
14

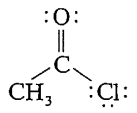
Carboxylic Acids and Their Derivatives I. Nucleophilic Substitution Reactions at the Carbonyl Group

A ∘ L O O K ∘ A H E A D

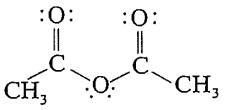
Carboxylic acids and their derivatives are compounds in which a carbonyl group is bonded to an atom that has at least one pair of nonbonding electrons on it. Acetic acid and its derivatives are examples.



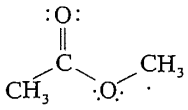
acetic acid
a carboxylic acid



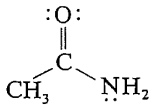
acetyl chloride
an acid chloride



acetic anhydride
an acid anhydride

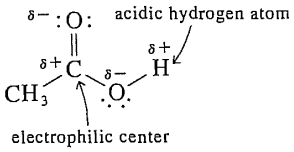


methyl acetate
an ester

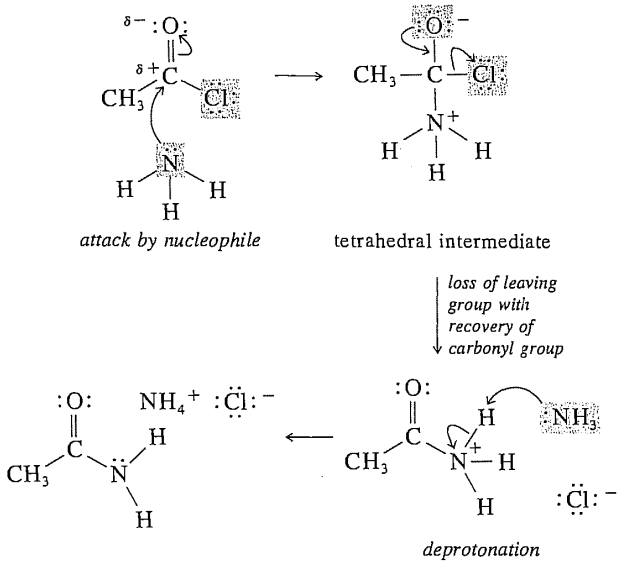


acetamide
an amide

Carboxylic acids are strong organic acids. Also, the carbon atom of the carbonyl group is electrophilic and reacts with nucleophiles.



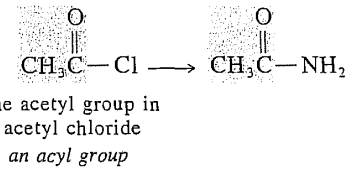
An acid derivative may be thought of as having been created from a carboxylic acid by replacement of the hydroxyl group of the carboxyl group by another atom or group. This group either is a good leaving group or may be converted to a good leaving group by protonation. Acids and acid derivatives, therefore, undergo nucleophilic substitution reactions, an example of which is the reaction of acetyl chloride with ammonia.



Most nucleophilic substitution reactions of acids and acid derivatives have two steps.

1. Nucleophilic attack on the carbon atom of the carbonyl group, with formation of a tetrahedral intermediate.
2. Loss of a leaving group, with the recovery of the carbonyl group.

In the reaction shown above, the acetyl group, an acyl group, is transferred from a chlorine atom to a nitrogen atom.



These important reactions of acid derivatives are called acylation, or acyl-transfer, reactions.

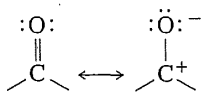
The reactions of acid derivatives differ from those of aldehydes and ketones, which do not have good leaving groups bonded to the carbonyl group. The first step of the reaction with nucleophiles is the same for acid derivatives as it is for aldehydes and ketones (p. 504, for example). Unlike aldehydes and ketones, however, acid derivatives undergo nucleophilic substitution rather than nucleophilic addition.

This chapter will emphasize the interconversions of the different acid derivatives through nucleophilic substitution reactions.

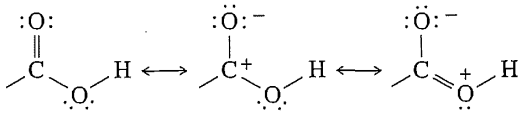
14.1 PROPERTIES OF THE FUNCTIONAL GROUPS IN CARBOXYLIC ACIDS AND THEIR DERIVATIVES

A. The Functional Groups in Carboxylic Acids and Their Derivatives

Carboxylic acids are organic compounds that contain the carboxyl group, a functional group in which a hydroxyl group is directly bonded to the carbon atom of a carbonyl group. Interaction between the carbonyl group and the hydroxyl group affects the properties of both. For example, the carbonyl group in acids is not as electrophilic as the carbonyl group in aldehydes and ketones. A comparison of the resonance contributors possible for a carbonyl group and for a carboxyl group shows why this is so.



resonance contributors for a carbonyl group



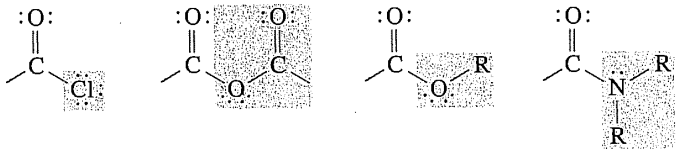
resonance contributors for a carboxyl group

The carbon atom of the carbonyl group in an aldehyde or ketone is an electrophilic center that reacts with a variety of nucleophiles, such as alcohols (p. 499), amine derivatives (p. 503), and organometallic reagents (p. 491). In carboxylic acids, the electrophilicity of the carbonyl group is modified by the presence of nonbonding electrons on the oxygen atom of the hydroxyl group. Donation of these electrons to the carbonyl group transfers some of the positive character of the carbonyl carbon atom to that oxygen atom. For that reason, many reagents that react easily with the carbonyl group of aldehydes or ketones react more slowly or only in the presence of powerful catalysts when attacking the carbonyl group of a carboxylic acid or an acid derivative.

The hydroxyl group of a carboxylic acid is unlike the hydroxyl group of an alcohol. The drain of electrons away from the hydroxyl group by the carbonyl group increases the positive character of the hydrogen atom and stabilizes the carboxylate

anion (p. 95). The hydrogen atom of the hydroxyl group of a carboxylic acid is much more easily lost as a proton than is the hydrogen atom of the hydroxyl group of an alcohol. The acidity of carboxylic acids is discussed further in Section 14.3.

In an **acid chloride,** the hydroxyl group of a carboxylic acid has been replaced by a chlorine atom. In an **acid anhydride,** the anion corresponding to a carboxylic acid has taken the place of the original hydroxyl group. In an **ester,** an alkoxyl group replaces the hydroxyl group. In an **amide,** an amino group is the replacement.



acid chloride acid anhydride ester amide

In each acid derivative, the atom bonded directly to the carbonyl group has at least one pair of nonbonding electrons on it and can therefore interact with the carbonyl group in the same way the hydroxyl group does in carboxylic acids. Also, each of the groups shaded above either is a good leaving group or may be converted into a good leaving group by protonation. These structural features are important in the chemistry of acids and acid derivatives.

PROBLEM 14.1

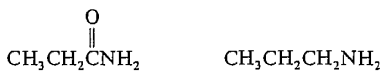
(a) Write structural formulas for propanoic acid, $CH_3CH_2CO_2H$, and its acid chloride, acid anhydride, ethyl ester, and amide.
(b) Write equations for the reactions that you would expect between propanoic acid and concentrated sulfuric acid. Repeat the process for ethyl propanoate and propanamide. (Reviewing Section 3.2 may be helpful.)
(c) Encircle any good leaving groups that you see in the structural formulas you have written in parts a and b.

PROBLEM 14.2

Write resonance contributors for propanoic acid and its acid chloride, acid anhydride, ethyl ester, and amide, showing in each case how the polarity of the carbonyl group is affected by the presence of an adjacent atom having a pair of nonbonding electrons.

PROBLEM 14.3

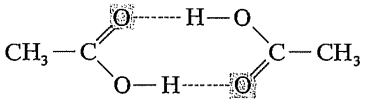
Propanamide is much less basic than propylamine.



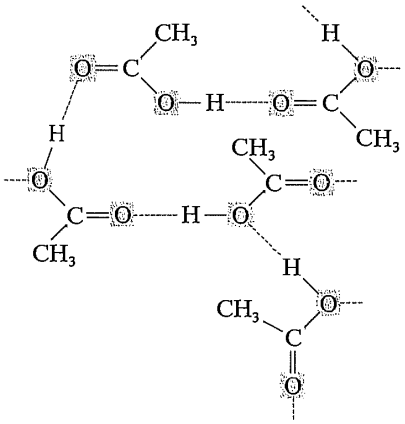
How would you explain this fact in light of the resonance contributors that you wrote for the amide in Problem 14.2? (You may want to review the factors affecting basicity on pp. 102–104).

B. Physical Properties of Low-Molecular-Weight Acids and Acid Derivatives

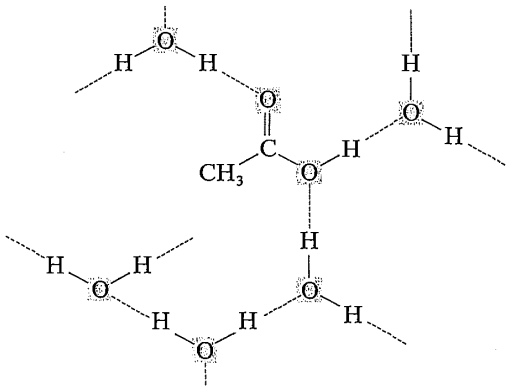
Carboxylic acids of low molecular weight have boiling points that are relatively high, and they are very soluble in water. Molecular weight determinations indicate that carboxylic acids exist as dimers even in the vapor state. All of these data suggest that the carboxyl group participates both as a donor and an acceptor in extensive hydrogen bonding, as illustrated below for acetic acid in the vapor state, in the liquid state, and in solution in water.



dimer of acetic acid held together by hydrogen bonding in the vapor state



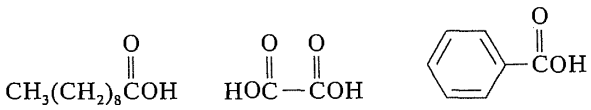
network of hydrogen bonding between molecules of acetic acid in the liquid state



acetic acid, hydrogen bonded to water molecules in aqueous solution

Carboxylic acids with no other functional group and fewer than ten carbon atoms in the chain are liquids at room temperature. Acetic acid has a particularly high melting point, 16.7 °C, for a compound with such a low molecular weight and is known as **glacial acetic acid** in its pure state. It is a liquid at room temperature but freezes easily in an ice bath, a phenomenon that has practical importance in the laboratory. Oxalic acid and the larger dicarboxylic acids, as well as the aromatic carboxylic acids, are all solids at room temperature.

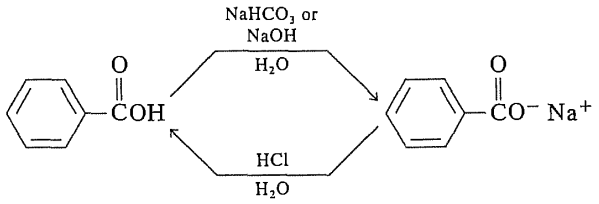
$HCOH$	CH_3COH	$CH_3CH_2CH_2CH_2COH$
formic acid	acetic acid	pentanoic acid
bp 100.5 °C	bp 118.2 °C	bp 186.4 °C
mp 8.4 °C	mp 16.7 °C	mp −34.5 °C
completely soluble in water	completely soluble in water	solubility 3.7 g in 100 g of water



$CH_3(CH_2)_8COH$	HOC—COH	benzoic acid
decanoic acid	oxalic acid	
bp 270.0 °C		
mp 31.3 °C	mp 187 °C	mp 122 °C
solubility 0.015 g in 100 g of water	solubility 9.0 g in 100 g of water	solubility 0.29 g in 100 g of water

Monocarboxylic acids and dicarboxylic acids of low molecular weight are soluble in water. When the hydrocarbon portion of the molecule has more than about five carbon atoms for each carboxyl group, solubility decreases. The high-molecular-weight carboxylic acids are almost insoluble in water.

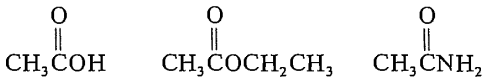
Carboxylic acids that have low solubility in water, such as benzoic acid, are converted to water-soluble salts by reaction with aqueous base (p. 95). Protonation of the carboxylate anion by a strong acid regenerates the water-insoluble acid. These properties of carboxylic acids are useful in separating them from reaction mixtures containing neutral and basic compounds.



benzoic acid
covalent,
insoluble in water

sodium benzoate
ionic,
soluble in water

The importance of hydrogen bonding to the physical properties and solubility in water of carboxylic acids is demonstrated by comparing acetic acid with two of its derivatives, an ester and an amide.



CH_3COH	$CH_3COCH_2CH_3$	CH_3CNH_2
acetic acid	ethyl acetate	acetamide
bp 118 °C	bp 77 °C	mp 82 °C
completely soluble in water	solubility 8.6 g in 100 g of water	solubility 97.5 g in 100 g of water

Acetic acid boils at 118 °C and is fully miscible with water, but its ethyl ester has a boiling point of 77 °C and a solubility of 8.6 g in 100 g of water. Ethyl acetate cannot hydrogen bond to itself in the liquid state. In water, it can serve only as a hydrogen-bond acceptor at its oxygen atoms. Therefore, it has a low boiling point and relatively low solubility in water. Acetamide, on the other hand, is a solid (mp 82 °C) with a very high solubility in water. The hydrogen atoms on the nitrogen atom of an amide participate strongly in hydrogen bonding, a fact of crucial importance to the structure of proteins, which are polyamides (p. 1150).

PROBLEM 14.4

Predict which compound in each of the following series will have the highest solubility in water and which will have the lowest.

(a) $CH_3CH_2CH_2CH_2\overset{O}{\overset{\|}{C}}OH$, $CH_3CH_2\overset{O}{\overset{\|}{C}}OCH_2CH_3$, $CH_3CH_2CH_2CH_2\overset{O}{\overset{\|}{C}}O^-Na^+$

(b) $CH_3CH_2CH_2\overset{O}{\overset{\|}{C}}OH$, $CH_3CH_2CH_2CH_2OH$, $CH_3CH_2\overset{O}{\overset{\|}{C}}OCH_2CH_3$

(c) $CH_3CH_2CH_2\overset{O}{\overset{\|}{C}}OCH_2CH_3$, $CH_3CH_2CH_2\overset{O}{\overset{\|}{C}}NH_2$, $CH_3CH_2CH_2\overset{O}{\overset{\|}{C}}O(CH_2)_4CH_3$

14.2 NOMENCLATURE OF CARBOXYLIC ACIDS AND THEIR DERIVATIVES

A. Naming Carboxylic Acids

The systematic name of an alkyl carboxylic acid is derived by replacing the **e** at the end of the name of the hydrocarbon having the same number of carbon atoms in the chain with **-oic acid.** The carboxyl function is always assumed to be the first carbon atom of the chain. The presence of other substituents is indicated by assigning a name and a position number to each one. The two smallest carboxylic acids, formic acid (from *formica,* Latin for ant) and acetic acid (from *acetum,* Latin for vinegar), are usually known by their common names.

$HCOH$ — methanoic acid, formic acid

CH_3COH — ethanoic acid, acetic acid

CH_3CH_2COH — propanoic acid, propionic acid

$CH_3CH_2CH_2COH$ — butanoic acid, butyric acid

$CH_3CH_2CH(CH_3)CH_2COH$ — 3-methylpentanoic acid

$CH_3CH(OH)COH$ — 2-hydroxypropanoic acid, lactic acid

$CH_3CH_2CH_2CH_2CH(Cl)COH$ — 2-chlorohexanoic acid

$CH_3CH(CH_3)CH_2CH(OH)CH_2CH_2COH$ — 4-hydroxy-6-methylheptanoic acid

$CH_2=CHCOH$ — propenoic acid, acrylic acid

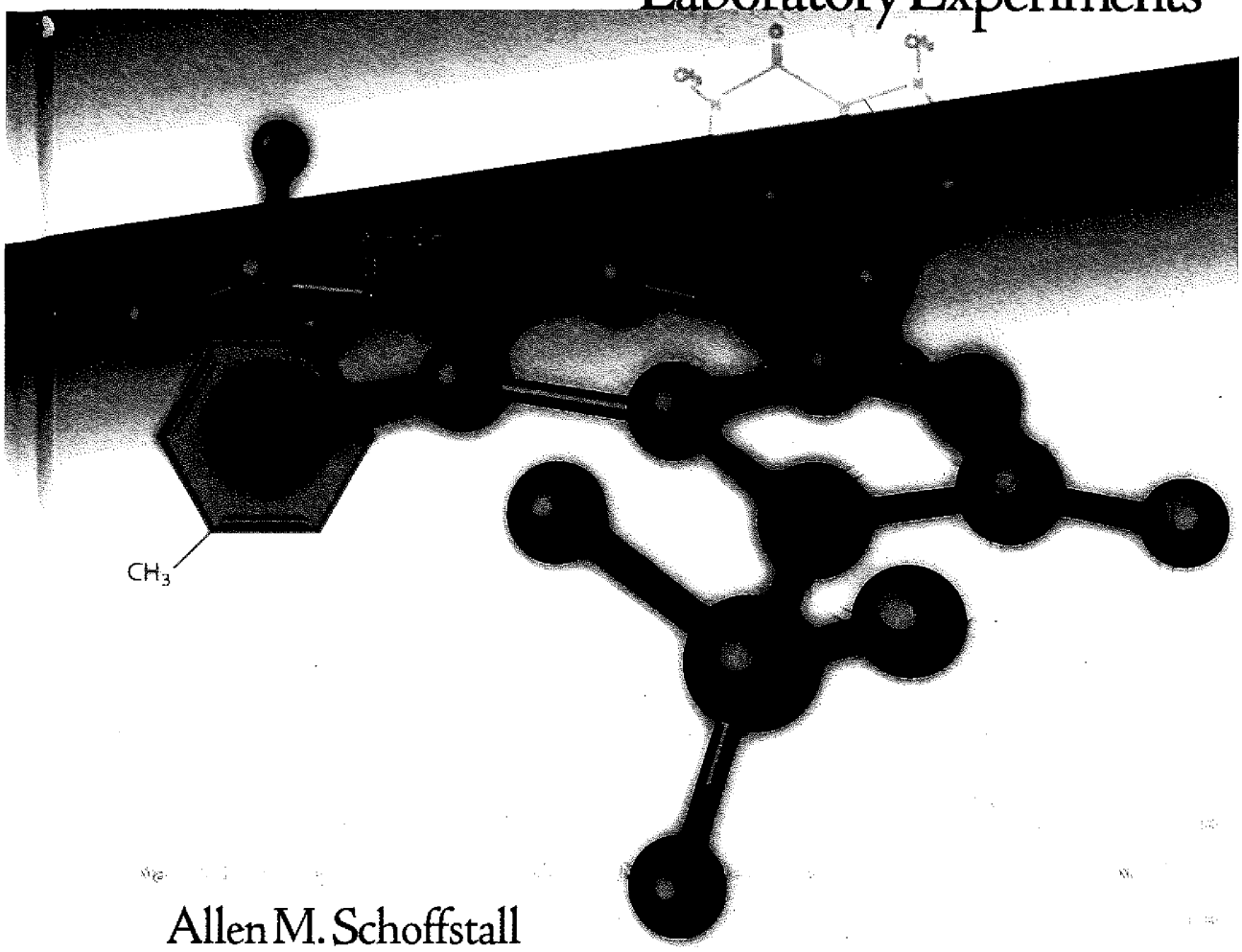
$CH_3C(=O)COH$ — 2-oxopropanoic acid, pyruvic acid

$CH_3CH(+NH_3)CO^-$ — 2-aminopropanoic acid, alanine

Microscale and Miniscale

ORGANIC CHEMISTRY

Laboratory Experiments



Allen M. Schoffstall
Barbara A. Gaddis
Melvin L. Druelinger

Second Edition

Results and Conclusions for Part B

1. Calculate the percent recovery for the recrystallization process. Explain why it is not 100%.
2. Explain and evaluate the effectiveness of the recrystallization solvent in terms of percent recovery and purity of the recrystallized solid.
3. Suggest other solvents or solvent pairs that might have been used for this recrystallization.

Cleanup & Disposal

Place the solvents used for recrystallization in a container labeled "nonhalogenated organic solvent waste." Aqueous solutions can be washed down the drain with water.

Critical Thinking Questions *(The harder one is marked with a ❖.)*

1. List the main criteria for selecting a recrystallization solvent.
2. When is it necessary to use a solvent-pair recrystallization?
3. Why should the recrystallization solvent have a fairly low boiling point?
4. ❖ Will the following pairs of solvents be suitable for doing a solvent-pair recrystallization? Explain.
   a. ethanol (bp 78.5°C) and water
   b. methylene chloride (bp 40°C) and water
   c. dimethylformamide (bp 153°C) and diethyl ether (bp 37°C)
5. If a solute is soluble in cold solvent, is it necessary to test the solubility of the solute in the same solvent when hot? Explain.
6. Arrange the following solvents in order of increasing polarity: ethanol, ethyl acetate, petroleum ether, toluene, and acetone.
7. Methylene chloride (CH_2Cl_2) is polar, whereas carbon tetrachloride (CCl_4) is nonpolar. Explain.
8. Carbon disulfide (CS_2) is sometimes used as a recrystallization solvent. Will this solvent dissolve polar or nonpolar compounds? Explain.

Experiment 3.5: Separations Based upon Acidity and Basicity

Extraction is a technique in which a solute is transferred from one solvent to another. In this experiment, you will investigate acid-base extraction. You will:

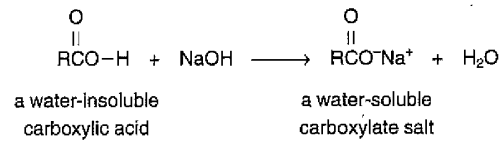
- determine the solubilities of an organic acid, an organic base, and a neutral organic compound.
- design a flow scheme to separate an organic acid, an organic base, and a neutral compound.
- use microscale extraction techniques to separate and isolate each component of a mixture of naphthalene, benzoic acid, and ethyl 4-aminobenzoate.
- use miniscale extraction techniques to separate and isolate a mixture of benzoic acid and ethyl 4-aminobenzoate.

Techniques

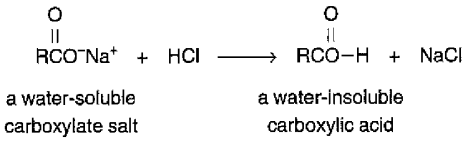
Technique C	Melting point
Technique F	Vacuum filtration
Technique I	Drying and extraction

Background

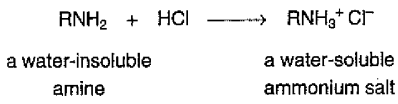
A water-insoluble, acidic organic compound such as a carboxylic acid or phenol can be easily separated from neutral and basic organic compounds by conversion to a water-soluble salt.



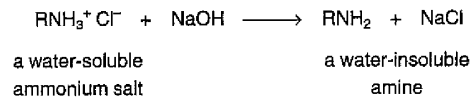
Neutral and basic organic compounds remain in the organic layer. The two layers can then be separated. Addition of HCl to the aqueous layer regenerates the water-insoluble carboxylic acid, which can then be filtered or extracted into an organic solvent:



A similar scheme can be used to separate a basic compound, such as a water-insoluble amine, from neutral or acidic organic compounds by conversion of the amine to a water-soluble salt:



Neutral compounds and acidic organic compounds remain in the organic solvent, where they can be removed. Addition of sodium hydroxide to the aqueous layer regenerates the amine, which is now insoluble in the aqueous solution. The amine can be filtered or extracted into an organic solvent.

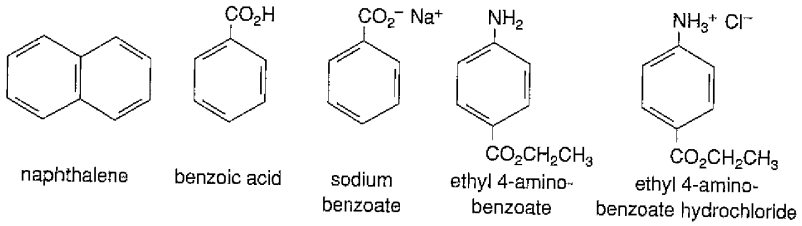


The neutral compound remains in the organic solvent, where it can be recovered by drying the solution to remove traces of water, filtering off the drying agent, and evaporating the solvent.

In this exercise, the solubilities of an organic acid (benzoic acid), an organic base (ethyl 4-aminobenzoate), a neutral compound (naphthalene), and the organic salts (ethyl 4-aminobenzoate hydrochloride and sodium benzoate) will be tested in methylene chloride and water.

From the solubilities, you will construct a flow scheme outlining the separation of naphthalene, benzoic acid, and ethyl 4-aminobenzoate. In Part B, you will use the flow

scheme to separate a mixture of naphthalene, benzoic acid, and ethyl 4-aminobenzoate in microscale. In Part C, you will use the flow scheme to separate a mixture of benzoic acid and ethyl 4-aminobenzoate in miniscale.



naphthalene | benzoic acid | sodium benzoate | ethyl 4-amino-benzoate | ethyl 4-amino-benzoate hydrochloride

The instructor may substitute other compounds for those shown here.

Prelab Assignment

1. Read Technique I on the theory and technique of extraction and do all assigned problems.
2. Construct a solubility table similar to Table 3.5-1 in the experimental section.
3. Identify the conjugate acid/conjugate base pairs for the structures above.
4. Write the reaction (if any) and give the products for the reaction of each pair of reagents below. If no reaction occurs, write NR. Indicate whether the product will be water-soluble or water-insoluble.
   a. benzoic acid with NaOH.
   b. sodium benzoate with HCl.
   c. ethyl 4-aminobenzoate with HCl.
   d. ethyl 4-aminobenzoate hydrochloride with NaOH.
   e. naphthalene and NaOH.
   f. ethyl 4-aminobenzoate with NaOH.
5. Determine whether each of the five compounds is predominantly ionically or covalently bonded. Based upon this answer, indicate whether the compound would be expected to be more soluble in water or more soluble in methylene chloride.

Experimental Procedure

Safety First!

Always wear eye protection in the laboratory.

1. Wear eye protection at all times in the laboratory.
2. Wear gloves when handling reagents in this experiment.
3. Methylene chloride is a toxic irritant and a suspected carcinogen. Do not breathe the vapors. Work under the hood or in a well-ventilated area.
4. NaOH and HCl are corrosive and toxic and can cause burns.

Part A: Determination of Solubilities

Obtain 20 small, dry test tubes or a spot plate. Place approximately 10–20 mg of benzoic acid into four of the test tubes or wells; place 10–20-mg of sodium benzoate into four other test tubes or wells. Repeat, using 10–20-mg samples of the other solutes. It is

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PREFACE

Although there are a number of monographs available which deal with an aspect of the techniques required in dealing with organic compounds, there has for some time been no book which gives a brief description of most of the important techniques. This book is written in an effort to fill this need and is directed mainly to the advanced undergraduate or beginning graduate student who is about to undertake a program of research work.

Each of the three types of matter, liquids, solids and gases, is considered with respect to both its properties and the methods of purification. It is felt that an understanding of the properties of the substances adds materially to the appreciation of the methods of purification. Methods which involve distribution between two phases are then considered. Finally, the reaction itself is examined in relation to the apparatus and techniques involved.

In organic chemical laboratory technique, the use of the proper apparatus is important. A drawing of a commonly used piece of equipment has generally been provided to accompany the description of each method. These drawings are for the most part derived from the working drawings used in the shops at the University of Washington, and in most cases all important dimensions are given in millimeters.

In writing a book of this type, it is very difficult to give credit to

a specific designer for a piece of equipment or to the originator of a technique. The art of laboratory work in organic chemistry has evolved from the experiments and modifications of many technicians, and only rarely can the contribution of an individual be specifically recognized.

Kenneth B. Wiberg

CONTENTS

ing homogeneity, particularly of natural products. If the material is fractionally crystallized, giving perhaps 8 to 10 fractions from the head fraction to the tail fraction (8 to 10 layers), and if these fractions are compared and found to be identical, it is reasonable to assume that the material is homogeneous.

The alembic shown in Fig. 2-21 is particularly useful in fractional crystallization, since it permits convenient adjustment of the amount of solvent and prevents loss of solvent during the prolonged refluxing sometimes required to bring the material into solution.

Precipitation

In some cases, the most convenient method for the purification of a solid consists in precipitating it from a solution in which it is contained as a derivative. A typical example is the purification of a water-insoluble solid carboxylic acid by dissolving it in sodium hydroxide solution, filtering, and precipitating the compound by the addition of acid. A similar procedure may be used with amines: dissolve the compound in acid and precipitate it with a base. These procedures usually work quite well in that they utilize a chemical reaction to aid in separation from nonacidic or nonbasic impurities.

Another method of precipitation involves precipitating the compound as a derivative and then converting the derivative back to the original compound. An example of this is to dissolve an amine in ether, precipitate it as the hydrochloride by passing in hydrogen chloride, and convert the hydrochloride back to the amine with sodium hydroxide solution. Again, this method is useful because it involves separation through the use of a reaction.

One method of precipitation which is usually relatively unsuccessful involves dissolving the compound in one solvent and precipitating by the addition of another solvent in which it is insoluble. This procedure usually leads to coprecipitation and relatively little purification. If two solvents are to be used, the compound should be recrystallized from a mixture of the two solvents as described in the preceding section.

Distillation

If the compound is relatively impure, crystallization usually entails considerable loss of material, and several recrystallizations are required to effect complete purification. The procedure often may be

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This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor Name:	Hitesh BATRA
Title:	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
Appl. No.:	14/849,981
Filing Date:	9/10/2015
Examiner:	Yevgeny Valenrod
Art Unit:	1672
Confirmation Number:	6653

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR §1.56

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

Applicant submits herewith documents for the Examiner's consideration in accordance with 37 CFR §§1.56, 1.97 and 1.98.

Applicant respectfully requests that each listed document be considered by the Examiner and be made of record in the present application and that an initialed copy of Form PTO/SB/08 be returned in accordance with MPEP §609.

The submission of any document herewith is not an admission that such document constitutes prior art against the claims of the present application or that such document is considered material to patentability as defined in 37 CFR §1.56(b). Applicants do not waive any

rights to take any action which would be appropriate to antedate or otherwise remove as a competent reference any document submitted herewith.

CONCISE EXPLANATION OF RELEVANCE

Document B3 is a Petition for *Inter Partes* Review filed against parent patent U.S. 8,497,393, dated October 1, 2015, including Exhibits 1009, 1010, 1017 and 1018. Documents B1-B2 and B4-B6 are exhibits from said IPR Petition which are prior art items not already of record in the present application.

TIMING OF THE DISCLOSURE

The listed documents are being submitted in compliance with 37 CFR §1.97(b), before the mailing date of the first Office Action on the merits.

Although Applicant believes that no fee is required, the Commissioner is hereby authorized to charge any additional fees which may be due to Deposit Account No. 19-0741.

Respectfully submitted,

Date OCT 13 2015

By _____

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 672-5569
Facsimile: (202) 672-5399

Stephen B. Maebius
Attorney for Applicant
Registration No. 35,264

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
14/849,981	09/10/2015	1629	1600	080618-1581	10	2

CONFIRMATION NO. 6653

FILING RECEIPT

22428
Foley & Lardner LLP
3000 K STREET N.W.
SUITE 600
WASHINGTON, DC 20007-5109

Date Mailed: 09/25/2015

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Hitesh BATRA, Herndon, VA;
Sudersan M. TULADHAR, Silver Spring, MD;
Raju PENMASTA, Herndon, VA;
David A. WALSH, Palmyra, VA;

Applicant(s)

United Therapeutics Corporation, Silver Spring, MD;

Assignment For Published Patent Application

United Therapeutics Corporation, Silver Spring, MD

Power of Attorney: The patent practitioners associated with Customer Number 22428

Domestic Priority data as claimed by applicant

This application is a DIV of 13/933,623 07/02/2013 PAT 9156786
which is a CON of 13/548,446 07/13/2012 PAT 8497393
which is a CON of 12/334,731 12/15/2008 PAT 8242305
which claims benefit of 61/014,232 12/17/2007

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access - A proper **Authorization to Permit Access to Application by Participating Offices** (PTO/SB/39 or its equivalent) has been received by the USPTO.

If Required, Foreign Filing License Granted: 09/23/2015

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 14/849,981**

Projected Publication Date: 12/31/2015

Non-Publication Request: No

Early Publication Request: No
Title

PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®

Preliminary Class

514

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

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No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 14/849,981

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	280
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	600
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	720
TOTAL CLAIMS (37 CFR 1.16(i))	10 minus 20 =	*			OR	x 80 =	0.00
INDEPENDENT CLAIMS (37 CFR 1.16(h))	2 minus 3 =	*				x 420 =	0.00
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						0.00
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	1600

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

To: ipdocketing@foley.com,,
From: PAIR_eOfficeAction@uspto.gov
Cc: PAIR_eOfficeAction@uspto.gov
Subject: Private PAIR Correspondence Notification for Customer Number 22428

Sep 25, 2015 05:23:34 AM

Dear PAIR Customer:

Foley & Lardner LLP
3000 K STREET N.W.
SUITE 600
WASHINGTON, DC 20007-5109
UNITED STATES

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Application	Document	Mailroom Date	Attorney Docket No.
14849981	APP.FILE.REC	09/25/2015	080618-1581

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UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT APPLICATION INFORMATION RETRIEVAL SYSTEM

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor Name: Hitesh BATRA

Title: AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®

Prior Appl. No.: 13/933623

Prior Appl. Filing Date: 7/2/2013

Examiner: Unassigned

Art Unit: Unassigned

CONTINUING PATENT APPLICATION TRANSMITTAL LETTER

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

Transmitted herewith for filing under 37 C.F.R. § 1.53(b) is a:

[ ] Continuation [**X**] Division [ ] Continuation-In-Part (CIP)

of the above-identified copending prior application in which no patenting, abandonment, or termination of proceedings has occurred. Priority to the above-identified prior application is hereby claimed under 35 U.S.C. § 120 for this continuing application. The entire disclosure of the above-identified prior application is considered as being part of the disclosure of the accompanying continuing application and is hereby incorporated by reference therein.

[ ] Applicant claims small entity status under 37 CFR 1.27.

Enclosed are:

[**X**] Description, Claim(s), and Abstract (24 pages).

[**X**] Executed Declarations (4 pages).

[**X**] Power of Attorney (1 pages).

[**X**] Information Disclosure Statement, Form PTO-SB08.

[**X**] Application Data Sheet (37 CFR 1.76).

The adjustment to the number of sheets for EFS-Web filing follows:

Number of Sheets		**EFS-Web Adjustment**	**Number of Sheets for EFS-Web**
24	x	75%	18

The filing fee is calculated below at the large entity rate:

	Number Filed		**Included in Basic Fee**	**Extra**		Rate		Fee Totals
Basic Filing Fee						$280.00	=	$280.00
Search Fee						$600.00		$600.00
Examination Fee						$720.00		$720.00
Size Fee	18	-	100	= 0	x	$400.00		$0.00
Total Claims:	10	-	20	= 0	x	$80.00	=	$0.00
Independent:	2	-	3	= 0	x	$420.00	=	$0.00
If any Multiple Dependent Claim(s) present:					+	$780.00	=	$0.00
Surcharge under 37 CFR 1.16(e) for late filing of Executed Declaration or late payment of filing fee					+	$140.00	=	$0.00
Prioritized Examination fee (Track I) under 37 C.F.R. § 1.17 (c)								$0.00
Processing Fee (Track I) under 37 C.F.R. § 1.17 (i)								$0.00
TOTAL FILING FEE:							=	$1600.00
Assignment Recordation Fee:					+	$40.00	=	$0.00
Processing Fee under 37 CFR 1.17(i) for Late Filing of English Translation of Application:					+	$140.00	=	$0.00
Publication Fee								$0.00
TOTAL FEE							=	$1600.00

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The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by the credit card payment instructions in EFS-Web being incorrect or absent, resulting in a rejected or incorrect credit card transaction, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741.

Please direct all correspondence to the undersigned attorney or agent at the address indicated below.

Respectfully submitted,

Date SEP 10 2015

By _____

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 672-5569
Facsimile: (202) 672-5399

Stephen B. Maebius
Attorney for Applicant
Registration No. 35,264

Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
First Named Inventor/Applicant Name:	Hitesh Batra
Filer:	Kristel Schorr/Karen Walker
Attorney Docket Number:	080618-1581

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Utility application filing	1011	1	280	280
Utility Search Fee	1111	1	600	600
Utility Examination Fee	1311	1	720	720
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**1600**

Electronic Acknowledgement Receipt	
EFS ID:	23450626
Application Number:	14849981
International Application Number:	
Confirmation Number:	6653
Title of Invention:	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
First Named Inventor/Applicant Name:	Hitesh Batra
Customer Number:	22428
Filer:	Kristel Schorr/Karen Walker
Filer Authorized By:	Kristel Schorr
Attorney Docket Number:	080618-1581
Receipt Date:	10-SEP-2015
Filing Date:	
Time Stamp:	14:04:28
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$1600
RAM confirmation Number	299
Deposit Account	
Authorized User	
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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		Specification.pdf	249682 948fa5633d23d7b4923d73b8ef3bab6a1b357c6c	yes	24

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Specification	1	21
	Claims	22	23
	Abstract	24	24

Warnings:					
Information:					
2	Application Data Sheet	ADS.pdf	632788 f9fa0eb6574621bcd0717afc35f3fd9a83920dac	no	7
Warnings:					
Information:					
This is not an USPTO supplied ADS fillable form					
3	Oath or Declaration filed	Declaration.pdf	256572 674b08c500ebf0a8829bea1e9875aab84ae857ac	no	4
Warnings:					
Information:					
4	Power of Attorney	POA.pdf	116513 77ebc675ac09a2143d9def4fd3e22d309202a0d0	no	1
Warnings:					
Information:					
5		IDS.pdf	489028 c81912e02804f487307e4d509b2cc7cfd687ade9	yes	6

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**

	Transmittal Letter		1	2	
	Information Disclosure Statement (IDS) Form (SB08)		3	6	
Warnings:					
Information:					
6	Transmittal of New Application	Transmittal.pdf	103067 5b41cff075efa2147a4bc1221030a284200a2ed4	no	4
Warnings:					
Information:					
7	Fee Worksheet (SB06)	fee-info.pdf	35437 b441eb8a3445bbf030ebdff2757160c8c0742627	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	1883087		

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New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a Divisional of U.S. Application No. 13/933,623, filed July 2, 2013, which is a Continuation of U.S. Application No. 13/548,446, filed July 13, 2012, which is a Continuation of U.S. Application No. 12/334,731, filed December 15, 2008, which claims priority from U.S. Provisional Patent Application 61/014,232, filed December 17, 2007, the entire contents of which are incorporated herein by reference.

BACKGROUND

[0002] The present invention relates to a process for producing prostacyclin derivatives and novel intermediate compounds useful in the process.

[0003] Prostacyclin derivatives are useful pharmaceutical compounds possessing activities such as platelet aggregation inhibition, gastric secretion reduction, lesion inhibition, and bronchodilation.

[0004] Treprostinil, the active ingredient in Remodulin®, was first described in US patent 4,306,075. Treprostinil, and other prostacyclin derivatives have been prepared as described in Moriarty, et al in *J. Org. Chem.* 2004, 69, 1890-1902, *Drug of the Future*, 2001, 26(4), 364-374, U.S. Pat. Nos. 6,441,245, 6,528,688, 6,765,117 and 6,809,223. Their teachings are incorporated by reference to show how to practice the embodiments of the present invention.

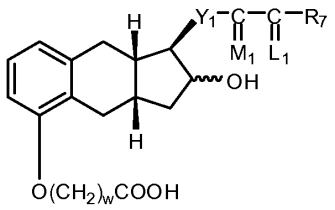
[0005] U.S. Patent No. 5,153,222 describes use of treprostinil for treatment of pulmonary hypertension. Treprostinil is approved for the intravenous as well as subcutaneous route, the latter avoiding septic events associated with continuous intravenous catheters. U.S. patents Nos. 6,521,212 and 6,756,033 describe administration of treprostinil by inhalation for treatment of pulmonary hypertension, peripheral vascular disease and other diseases and conditions. U.S. patent No. 6,803,386 discloses administration of treprostinil for treating cancer such as lung, liver, brain, pancreatic, kidney, prostate, breast, colon and head-neck cancer. U.S. patent application publication No. 2005/0165111 discloses treprostinil treatment of ischemic lesions. U.S. patent No. 7,199,157 discloses that treprostinil treatment improves kidney functions. U.S. patent application publication No. 2005/0282903 discloses treprostinil

treatment of neuropathic foot ulcers. U.S. application No. 12/028,471 filed February 8, 2008, discloses treprostinil treatment of pulmonary fibrosis. U.S. 6,054,486 discloses treatment of peripheral vascular disease with treprostinil. U.S. patent application 11/873,645 filed October 17, 2007 discloses combination therapies comprising treprostinil. U.S. publication No. 2008/0200449 discloses delivery of treprostinil using a metered dose inhaler. U.S. publication No. 2008/0280986 discloses treatment of interstitial lung disease with treprostinil. U.S. application No. 12/028,471 filed February 8, 2008 discloses treatment of asthma with treprostinil. U.S. 7,417,070, 7,384,978 and U.S. publication Nos. 2007/0078095, 2005/0282901, and 2008/0249167 describe oral formulations of treprostinil and other prostacyclin analogs.

[0006] Because Treprostinil, and other prostacyclin derivatives are of great importance from a medicinal point of view, a need exists for an efficient process to synthesize these compounds on a large scale suitable for commercial production.

SUMMARY

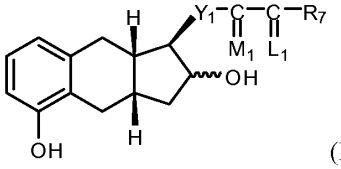
[0007] The present invention provides in one embodiment a process for the preparation of a compound of formula I, hydrate, solvate, prodrug, or pharmaceutically acceptable salt thereof.



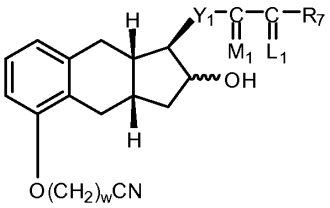
(I)

[0008] The process comprises the following steps:

(a) alkylating a compound of structure II with an alkylating agent to produce a compound of formula III,



(II)



(III)

wherein

w= 1, 2, or 3;

Y_1 is trans-CH=CH-, cis-CH=CH-, $-CH_2(CH_2)_m-$, or -C≡C-; m is 1, 2, or 3;

R_7 is

(1) $-C_pH_{2p}-CH_3$, wherein p is an integer from 1 to 5, inclusive,

(2) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3) alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl, with the proviso that R_7 is phenoxy or substituted phenoxy, only when R_3 and R_4 are hydrogen or methyl, being the same or different,

(3) phenyl, benzyl, phenylethyl, or phenylpropyl optionally substituted on the aromatic ring by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3)alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl,

(4) cis-CH=CH-CH_2-CH_3,

(5) $-(CH_2)_2-CH(OH)-CH_3$, or

(6) $-(CH_2)_3-CH=C(CH_3)_2$;

wherein $-C(L_1)-R_7$ taken together is

(1) (C_4-C_7)cycloalkyl optionally substituted by 1 to 3 (C_1-C_5)alkyl;

(2) 2-(2-furyl)ethyl,

(3) 2-(3-thienyl)ethoxy, or

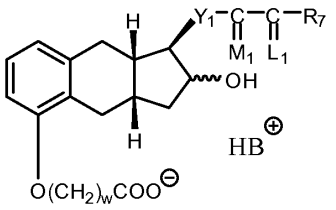
(4) 3-thienyloxymethyl;

M_1 is α-OH:β-R_5 or α-R_5:β-OH or α-OR_2:β-R_5 or α-R_5:β-OR_2, wherein R_5 is hydrogen or methyl, R_2 is an alcohol protecting group, and

L_1 is α-R_3:β-R_4, α-R_4:β-R_3, or a mixture of α-R_3:β-R_4 and α-R_4:β-R_3, wherein R_3 and R_4 are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R_3 and R_4 is fluoro only when the other is hydrogen or fluoro.

(b) hydrolyzing the product of step (a) with a base,

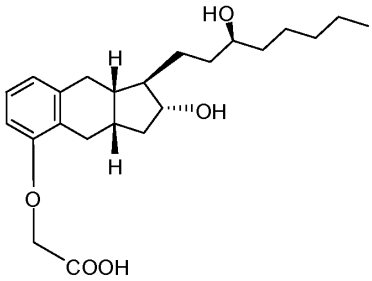
(c) contacting the product of step (b) with a base B to for a salt of formula I_s



(I_s)

(d) reacting the salt from step (c) with an acid to form the compound of formula I.

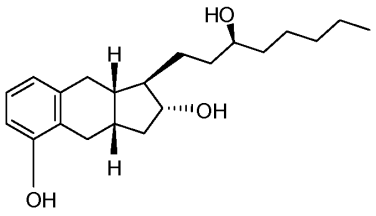
[0009] The present invention provides in another embodiment a process for the preparation of a compound of formula IV.



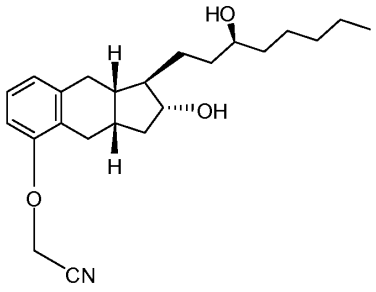
(IV)

[0010] The process comprises the following steps:

(a) alkylating a compound of structure V with an alkylating agent to produce a compound of formula VI,



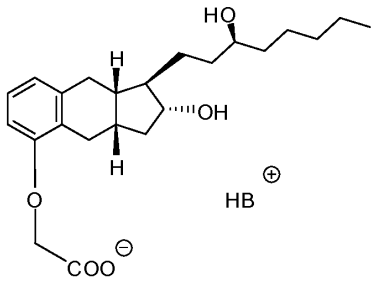
(V)



(VI)

(b) hydrolyzing the product of step (a) with a base,

(c) contacting the product of step (b) with a base B to for a salt of formula IV_s, and



(IV_s)

(d) reacting the salt from step (b) with an acid to form the compound of formula IV.

DETAILED DESCRIPTION

[0011] The various terms used, separately and in combinations, in the processes herein described are defined below.

[0012] The expression "comprising" means "including but not limited to." Thus, other non-mentioned substances, additives, carriers, or steps may be present. Unless otherwise specified, "a" or "an" means one or more.

[0013] C_{1-3}-alkyl is a straight or branched alkyl group containing 1-3 carbon atoms. Exemplary alkyl groups include methyl, ethyl, n-propyl, and isopropyl.

[0014] C_{1-3}-alkoxy is a straight or branched alkoxy group containing 1-3 carbon atoms. Exemplary alkoxy groups include methoxy, ethoxy, propoxy, and isopropoxy.

[0015] C_{4-7}-cycloalkyl is an optionally substituted monocyclic, bicyclic or tricyclic alkyl group containing between 4-7 carbon atoms. Exemplary cycloalkyl groups include but not limited to cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl.

[0016] Combinations of substituents and variables envisioned by this invention are only those that result in the formation of stable compounds. The term "stable", as used herein, refers to compounds which possess stability sufficient to allow manufacture and which maintains the integrity of the compound for a sufficient period of time to be useful for the purposes detailed herein.

[0017] As used herein, the term "prodrug" means a derivative of a compound that can hydrolyze, oxidize, or otherwise react under biological conditions (*in vitro* or *in vivo*) to provide an active compound. Examples of prodrugs include, but are not limited to,

derivatives of a compound that include biohydrolyzable groups such as biohydrolyzable amides, biohydrolyzable esters, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, and biohydrolyzable phosphate analogues (*e.g.*, monophosphate, diphosphate or triphosphate).

[0018] As used herein, "hydrate" is a form of a compound wherein water molecules are combined in a certain ratio as an integral part of the structure complex of the compound.

[0019] As used herein, "solvate" is a form of a compound where solvent molecules are combined in a certain ratio as an integral part of the structure complex of the compound.

[0020] "Pharmaceutically acceptable" means in the present description being useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes being useful for veterinary use as well as human pharmaceutical use.

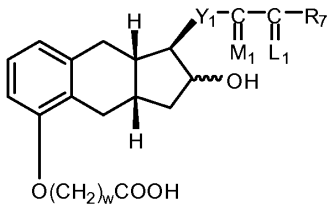
[0021] "Pharmaceutically acceptable salts" mean salts which are pharmaceutically acceptable, as defined above, and which possess the desired pharmacological activity. Such salts include acid addition salts formed with organic and inorganic acids, such as hydrogen chloride, hydrogen bromide, hydrogen iodide, sulfuric acid, phosphoric acid, acetic acid, glycolic acid, maleic acid, malonic acid, oxalic acid, methanesulfonic acid, trifluoroacetic acid, fumaric acid, succinic acid, tartaric acid, citric acid, benzoic acid, ascorbic acid and the like. Base addition salts may be formed with organic and inorganic bases, such as sodium, ammonia, potassium, calcium, ethanolamine, diethanolamine, N-methylglucamine, choline and the like. Included in the invention are pharmaceutically acceptable salts or compounds of any of the formulae herein.

[0022] Depending on its structure, the phrase "pharmaceutically acceptable salt," as used herein, refers to a pharmaceutically acceptable organic or inorganic acid or base salt of a compound. Representative pharmaceutically acceptable salts include, *e.g.*, alkali metal salts, alkali earth salts, ammonium salts, water-soluble and water-insoluble salts, such as the acetate, amsonate (4,4-diaminostilbene-2, 2 -disulfonate), benzenesulfonate, benzonate, bicarbonate, bisulfate, bitartrate, borate, bromide, butyrate, calcium, calcium edetate, camsylate, carbonate, chloride, citrate, clavulariate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexafluorophosphate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride,

hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, N-methylglucamine ammonium salt, 3-hydroxy-2-naphthoate, oleate, oxalate, palmitate, pamoate (1,1-methene-bis-2-hydroxy-3-naphthoate, einbonate), pantothenate, phosphate/diphosphate, picrate, polygalacturonate, propionate, p-toluenesulfonate, salicylate, stearate, subacetate, succinate, sulfate, sulfosalicylate, suramate, tannate, tartrate, teoclate, tosylate, triethiodide, and valerate salts.

[0023] The present invention provides for a process for producing treprostinil and other prostacyclin derivatives and novel intermediate compounds useful in the process. The process according to the present invention provides advantages on large-scale synthesis over the existing method. For example, the purification by column chromatography is eliminated, thus the required amount of flammable solvents and waste generated are greatly reduced. Furthermore, the salt formation is a much easier operation than column chromatography. Moreover, it was found that the product of the process according to the present invention has higher purity. Therefore the present invention provides for a process that is more economical, safer, faster, greener, easier to operate, and provides higher purity.

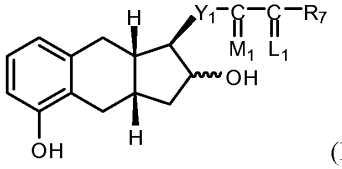
[0024] One embodiment of the present invention is a process for the preparation of a compound of formula I, or a hydrate, solvate, prodrug, or pharmaceutically acceptable salt thereof.



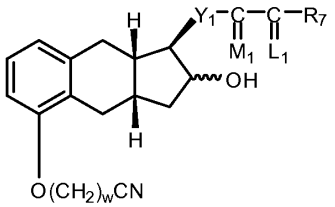
(I)

[0025] The process comprises the following steps:

(a) alkylating a compound of formula II with an alkylating agent to produce a compound of formula III,



(II)



(III)

wherein

w= 1, 2, or 3;

Y_1 is trans-CH=CH-, cis-CH=CH-, $-CH_2(CH_2)_m-$, or -C≡C-; m is 1, 2, or 3;

R_7 is

(1) $-C_pH_{2p}-CH_3$, wherein p is an integer from 1 to 5, inclusive,

(2) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3) alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl, with the proviso that R_7 is phenoxy or substituted phenoxy, only when R_3 and R_4 are hydrogen or methyl, being the same or different,

(3) phenyl, benzyl, phenylethyl, or phenylpropyl optionally substituted on the aromatic ring by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3)alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl,

(4) cis-CH=CH-CH_2-CH_3,

(5) $-(CH_2)_2$-CH(OH)-CH_3, or

(6) $-(CH_2)_3$-CH=$C(CH_3)_2$;

wherein -$C(L_1)$-R_7 taken together is

(1) (C_4-C_7)cycloalkyl optionally substituted by 1 to 3 (C_1-C_5)alkyl;

(2) 2-(2-furyl)ethyl,

(3) 2-(3-thienyl)ethoxy, or

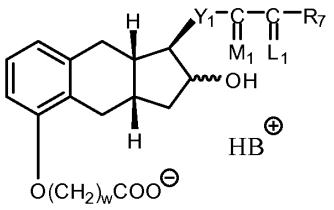
(4) 3-thienyloxymethyl;

M_1 is α-OH:β-R_5 or α-R_5:β-OH or α-OR_2:β-R_5 or α-R_5:β-OR_2, wherein R_5 is hydrogen or methyl, R_2 is an alcohol protecting group, and

L_1 is α-R_3:β-R_4, α-R_4:β-R_3, or a mixture of α-R_3:β-R_4 and α-R_4:β-R_3, wherein R_3 and R_4 are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R_3 and R_4 is fluoro only when the other is hydrogen or fluoro.

(b) hydrolyzing the product of step (a) with a base,

(c) contacting the product of step (b) with a base B to for a salt of formula I_s

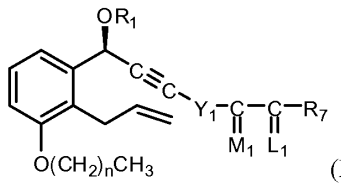


(I_s)

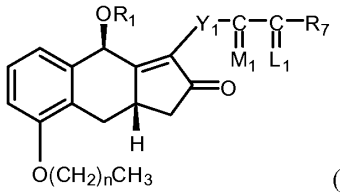
(d) reacting the salt from step (c) with an acid to form the compound of formula I.

[0026] In one embodiment, the compound of formula I is at least 90.0%, 95.0%, 99.0%.

[0027] The compound of formula II can be prepared from a compound of formula XI, which is a cyclization product of a compound of formula X as described in U.S. Pat. No. 6,441,245.



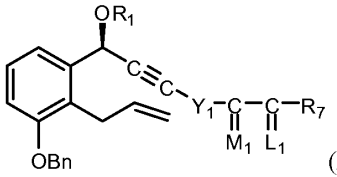
(X)



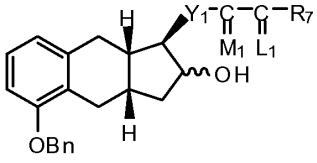
(XI)

Wherein n is 0, 1, 2, or 3.

[0028] The compound of formula II can be prepared alternatively from a compound of formula XIII, which is a cyclization product of a compound of formula XII as described in U.S. Pat. No. 6,700,025.

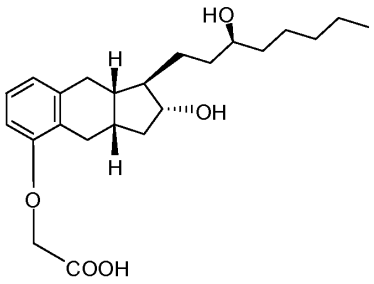


(XII)



(XIII)

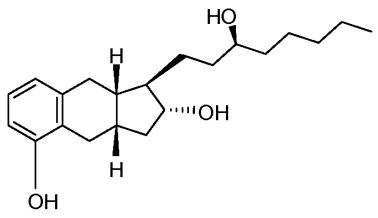
[0029] One embodiment of the present invention is a process for the preparation of a compound having formula IV, or a hydrate, solvate, or pharmaceutically acceptable salt thereof.



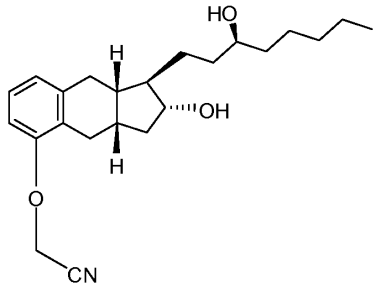
(IV)

[0030] The process comprises

(a) alkylating a compound of structure V with an alkylating agent such as $ClCH_2CN$ to produce a compound of formula VI,



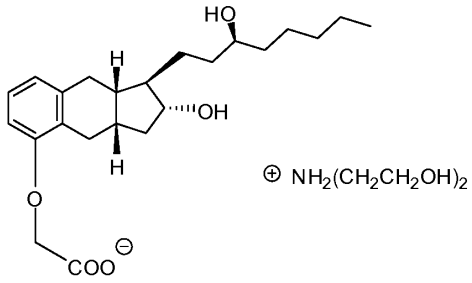
(V)



(VI)

(b) hydrolyzing the product of step (a) with a base such as KOH,

(c) contacting the product of step (b) with a base B such as diethanolamine to for a salt of the following structure, and



(d) reacting the salt from step (b) with an acid such as HCl to form the compound of formula IV.

[0031] In one embodiment, the purity of compound of formula IV is at least 90.0%, 95.0%, 99.0%, 99.5%.

[0032] In one embodiment, the process further comprises a step of isolating the salt of formula IV_S.

[0033] In one embodiment, the base B in step (c) may be ammonia, N-methylglucamine, procaine, tromethanine, magnesium, L-lysine, L-arginine, or triethanolamine.

[0034] The following abbreviations are used in the description and/or appended claims, and they have the following meanings:

"MW" means molecular weight.

"Eq." means equivalent.

"TLC" means thin layer chromatography.

"HPLC" means high performance liquid chromatography.

"PMA" means phosphomolybdic acid.

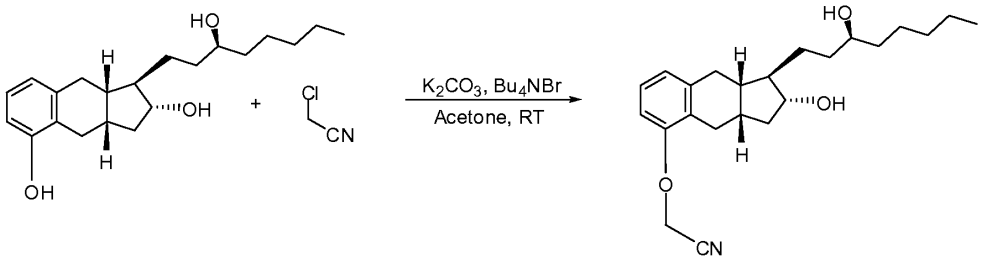
"AUC" means area under curve.

[0035] In view of the foregoing considerations, and specific examples below, those who are skilled in the art will appreciate that how to select necessary reagents and solvents in practicing the present invention.

[0036] The invention will now be described in reference to the following Examples. These examples are not to be regarded as limiting the scope of the present invention, but shall only serve in an illustrative manner.

EXAMPLES

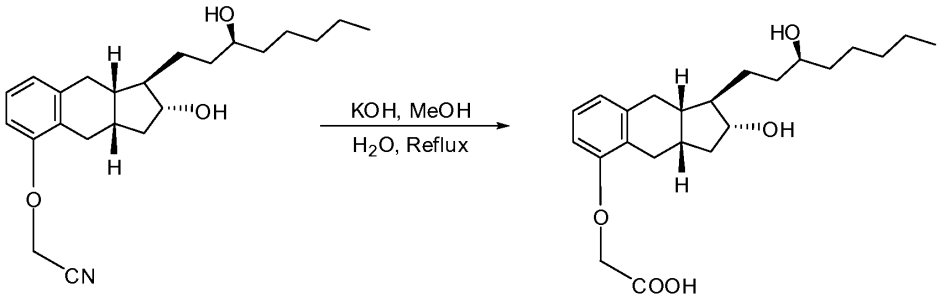
Example 1. Alkylation of Benzindene Triol



Name	MW	Amount	Mol.	Eq.
Benzindene Triol	332.48	1250 g	3.76	1.00
K_2CO_3 (powder)	138.20	1296 g	9.38	2.50
$ClCH_2CN$	75.50	567 g	7.51	2.0
Bu_4NBr	322.37	36 g	0.11	0.03
Acetone	--	29 L	--	--
Celite®545	--	115 g	--	--

[0037] A 50-L, three-neck, round-bottom flask equipped with a mechanical stirrer and a thermocouple was charged with benzindene triol (1250 g), acetone (19 L) and K_2CO_3 (powdered) (1296 g), chloroacetonitrile (567 g), tetrabutylammonium bromide (36 g). The reaction mixture was stirred vigorously at room temperature (23±2°C) for 16-72 h. The progress of the reaction was monitored by TLC. (methanol/CH_2Cl_2; 1:9 and developed by 10% ethanolic solution of PMA). After completion of reaction, the reaction mixture was filtered with/without Celite pad. The filter cake was washed with acetone (10L). The filtrate was concentrated *in vacuo* at 50-55°C to give a light-brown, viscous liquid benzindene nitrile. The crude benzindene nitrile was used as such in the next step without further purification.

Example 2. Hydrolysis of Benzindene Nitrile



Name	MW	Amount	Mol.	Eq.
Benzindene Nitrile	371.52	1397 g*	3.76	1.0
KOH	56.11	844 g	15.04	4.0
Methanol	--	12 L	--	--
Water	--	4.25 L	--	--

*Note: This weight is based on 100% yield from the previous step. This is not isolated yield.

[0038] A 50-L, cylindrical reactor equipped with a heating/cooling system, a mechanical stirrer, a condenser, and a thermocouple was charged with a solution of benzindene nitrile in methanol (12 L) and a solution of KOH (844 g of KOH dissolved in 4.25 L of water). The reaction mixture was stirred and heated to reflux (temperature 72.2°C). The progress of the reaction was monitored by TLC (for TLC purpose, 1-2 mL of reaction mixture was acidified with 3M HCl to pH 1-2 and extracted with ethyl acetate. The ethyl acetate extract was used for TLC; Eluent: methanol/CH_2Cl_2; 1:9, and developed by 10% ethanolic solution of PMA). After completion of the reaction (~5 h), the reaction mixture was cooled to -5 to 10°C and quenched with a solution of hydrochloric acid (3M, 3.1 L) while stirring. The reaction mixture was concentrated *in vacuo* at 50-55°C to obtain approximately 12-14 L of condensate. The condensate was discarded.

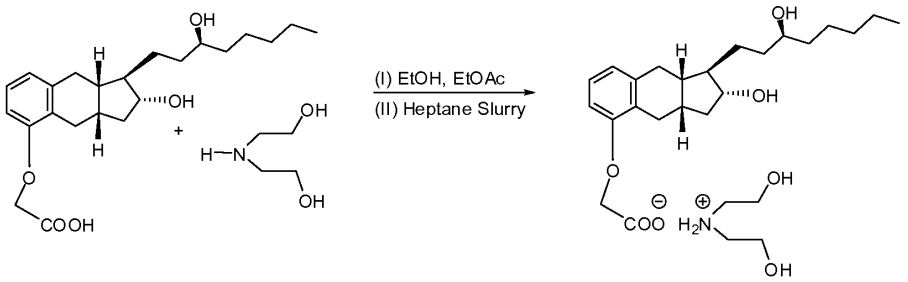
[0039] The aqueous layer was diluted with water (7-8 L) and extracted with ethyl acetate (2 × 6 L) to remove impurities soluble in ethyl acetate. To aqueous layer, ethyl acetate (22 L) was added and the pH of reaction mixture was adjusted to 1-2 by adding 3M HC1 (1.7 L) with stirring. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 × 11 L). The combined organic layers were washed with water (3 × 10 L) and followed by washing with a solution of $NaHCO_3$ (30 g of $NaHCO_3$ dissolved in 12 L of water). The organic layer was further washed with saturated solution of NaCl (3372 g of NaCl dissolved in water (12 L)) and dried over anhydrous Na_2SO_4 (950-1000 g), once filtered.

[0040] The filtrate was transferred into a 72-L reactor equipped with mechanical stirrer, a condenser, and a thermocouple. To the solution of treprostinil in reactor was added activated carbon (110-130 g). The suspension was heated to reflux (temperature 68-70°C) for at least one hour. For filtration, a pad of Celite®545 (300-600 g) was prepared in sintered glass

funnel using ethyl acetate. The hot suspension was filtered through the pad of Celite®545. The Celite®545 was washed with ethyl acetate until no compound was seen on TLC of the washings.

[0041] The filtrate (pale-yellow) was reduced to volume of 35-40 L by evaporation *in vacuo* at 50-55°C for direct use in next step.

Example 3. Conversion of Treprostinil to Treprostinil Diethanolamine Salt (1:1)



Name	MW	Amount	Mol	Eq
Treprostinil	390.52	1464 g*	3.75	1.0
Diethanolamine	105.14	435 g	4.14	1.1
Ethanol	--	5.1 L	--	--
Ethyl acetate	--	35L**	--	--
Treprostinil Diethanolamine Salt (seed)	--	12 g	--	--

*Note: This weight is based on 100% yield from benzindene triol. It is not isolated yield. The treprostinil was carried from previous step in ethyl acetate solution and used as such for this step.

**Note: The total volume of ethyl acetate should be in range of 35-36 L (it should be 7 times the volume of ethanol used). Approximately 35 L of ethyl acetate was carried over from previous step and additional 1.0 L of ethyl acetate was used for rinsing the flask.

[0042] A 50-L, cylindrical reactor equipped with a heating/cooling system, a mechanical stirrer, a condenser, and a thermocouple was charged with a solution of treprostinil in ethyl acetate (35-40 L from the previous step), anhydrous ethanol (5.1 L) and diethanolamine (435 g). While stirring, the reaction mixture was heated to 60-75°C, for 0.5-1.0 h to obtain a clear solution. The clear solution was cooled to 55±5°C. At this temperature, the seed of

polymorph B of treprostinil diethanolamine salt (~12 g) was added to the clear solution. The suspension of polymorph B was stirred at this temperature for 1 h. The suspension was cooled to 20±2°C overnight (over a period of 16-24 h). The treprostinil diethanolamine salt was collected by filtration using Aurora filter equipped with filter cloth, and the solid was washed with ethyl acetate (2 × 8 L). The treprostinil diethanolamine salt was transferred to a HDPE/glass container for air-drying in hood, followed by drying in a vacuum oven at 50±5°C under high vacuum.

[0043] At this stage, if melting point of the treprostinil diethanolamine salt is more than 104°C, it was considered polymorph B. There is no need of recrystallization. If it is less than 104°C, it is recrystallized in EtOH-EtOAc to increase the melting point.

Data on Treprostinil Diethanolamine Salt (1:1)

Batch No.	Wt. of Benzindene Triol (g)	Wt. of Treprostinil Diethanolamine Salt (1:1) (g)	Yield (%)	Melting point (°C)
1	1250	1640	88.00	104.3-106.3
2	1250	1528	82.00*	105.5-107.2
3	1250	1499	80.42**	104.7-106.6
4	1236	1572	85.34	105-108

**Note*: In this batch, approximately 1200 mL of ethyl acetate solution of treprostinil before carbon treatment was removed for R&D carbon treatment experiments.

***Note*: This batch was recrystallized, for this reason yield was lower.

Example 4. Heptane Slurry of Treprostinil Diethanolamine Salt (1:1)

Name	Batch No.	Amount	Ratio
Treprostinil Diethanolamine Salt	1	3168 g	1
Heptane	--	37.5 L	12

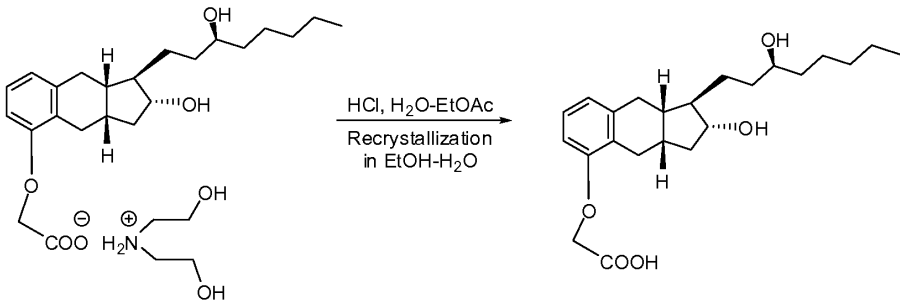
Name	Batch No.	Amount	Ratio
Treprostinil Diethanolamine Salt	2	3071 g	1
Heptane	--	36.0 L	12

[0044] A 50-L, cylindrical reactor equipped with a heating/cooling system, a mechanical stirrer, a condenser, and a thermocouple was charged with slurry of treprostinil diethanolamine salt in heptane (35-40 L). The suspension was heated to 70-80°C for 16-24 h. The suspension was cooled to 22±2°C over a period of 1-2 h. The salt was collected by filtration using Aurora filter. The cake was washed with heptane (15-30 L) and the material was dried in Aurora filter for 1 h. The salt was transferred to trays for air-drying overnight in hood until a constant weight of treprostinil diethanolamine salt was obtained. The material was dried in oven under high vacuum for 2-4 h at 50-55°C.

Analytical data on and Treprostinil Diethanolamine Salt (1:1)

Test	Batch 1	Batch 2
IR	Conforms	Conforms
Residue on Ignition (ROI)	<0.1% w/w	<0.1% w/w
Water content	0.1% w/w	0.0% w/w
Melting point	105.0-106.5°C	104.5-105.5°C
Specific rotation $[\alpha]^{25}_{589}$	+34.6°	+35°
Organic volatile impurities		
• Ethanol	• Not detected	• Not detected
• Ethyl acetate	• Not detected	• <0.05% w/w
• Heptane	• <0.05% w/w	• <0.05% w/w
HPLC (Assay)	100.4%	99.8%
Diethanolamine	Positive	Positive

Example 5. Conversion of Treprostinil Diethanolamine Salt (1:1) to Treprostinil



[0045] A 250-mL, round-bottom flask equipped with magnetic stirrer was charged with treprostinil diethanolamine salt (4 g) and water (40 mL). The mixture was stirred to obtain a clear solution. To the clear solution, ethyl acetate (100 mL) was added. While stirring, 3M HC1 (3.2 mL) was added slowly until pH ~1 was attained. The mixture was stirred for 10 minutes and organic layer was separated. The aqueous layer was extracted with ethyl acetate (2 × 100 mL). The combined organic layers was washed with water (2 × 100 mL), brine (1 × 50 mL) and dried over anhydrous Na_2SO_4. The ethyl acetate solution of treprostinil was filtered and the filtrate was concentrated under vacuum at 50°C to give off-white solid. The crude treprostinil was recrystallized from 50% ethanol in water (70 mL). The pure treprostinil was collected in a Buchner funnel by filtration and cake was washed with cold 20% ethanolic solution in water. The cake of treprostinil was air-dried overnight and further dried in a vacuum oven at 50°C under high vacuum to afford 2.9 g of treprostinil (Yield 91.4%, purity (HPLC, AUC, 99.8%).

Analytical data on Treprostinil from Treprostinil Diethanolamine Salt (1:1) to Treprostinil

Batch No.	Yield	Purity (HPLC)
1	91.0%	99.8% (AUC)
2	92.0%	99.9% (AUC)
3	93.1%	99.7% (AUC)
4	93.3%	99.7% (AUC)
5	99.0 %	99.8% (AUC)
6	94.6%	99.8% (AUC)

Example 6. Comparison of the former process and a working example of the process according to the present invention

Step No.	Steps	Former Process (Batch size: 500g)	Working example of the Process according to the present invention (Batch size: 5 kg)
Nitrile			
1	Triol weight	500 g	5,000 g
2	Acetone	20 L (1:40 wt/wt)	75 L (1:15 wt/wt)
3	Potassium carbonate	1,300 g (6.4 eq)	5,200 g (2.5 eq)
4	Chloroacetonitrile	470 g (4.2 eq)	2,270 g (2 eq)
5	Tetrabutylammonium bromide	42 g (0.08 eq)	145 g (0.03 eq)
6	Reactor size	72-Liter	50- gallon
7	Reflux time	8 hours	No heating, Room temperature (r.t.) 45 h
8	Hexanes addition before filtration	Yes (10 L)	No
9	Filter	Celite	Celite
10	Washing	Ethyl acetate (10 L)	Acetone (50 L)
11	Evaporation	Yes	Yes
12	Purification	Silica gel column Dichloromethane:0.5 L Ethyl acetate: 45 L Hexane: 60 L	No column
13	Evaporation after column	Yes	No
14	Yield of nitrite	109-112 %	Not checked
Treprostinil (intermediate)			
15	Methanol	7.6 L (50-L reactor)	50 L (50-gal reactor)
16	Potassium hydroxide	650 g (8 eq)	3,375g (4 eq)
17	Water	2.2 L	17 L

18	% of KOH	30%	20%
19	Reflux time	3-3.5 h	4-5 h
20	Acid used	2.6 L (3 M)	12 L (3 M)
21	Removal of impurities	3 × 3 L Ethyl acetate	2 × 20 L Ethyl acetate
22	Acidification	0.7 L	6.5 L
23	Ethyl acetate extraction	5 × 17 L = 35 L	90+45+45 = 180 L
24	Water washing	2 × 8 L	3 × 40 L
25	Sodium bicarbonate washing	Not done	120 g in 30L water + 15 L brine
26	Brine washing	Not done	1 × 40 L
27	Sodium sulfate	1 kg	Not done
28	Sodium sulfate filtration	Before charcoal, 6 L ethyl acetate	N/A
29	Charcoal	170 g, reflux for 1.5 h, filter over Celite, 11 L ethyl acetate	Pass hot solution (75°C) through charcoal cartridge and clean filter, 70 L ethyl acetate
30	Evaporation	Yes, to get solid intermediate treprostinil	Yes, adjust to 150 L solution
Treprostinil Diethanolamine Salt			
31	Salt formation	Not done	1,744 g diethanolamine, 20 L ethanol at 60-75°C.
32	Cooling	N/A	To 20°C over weekend; add 40 L ethyl acetate; cooled to 10°C
33	Filtration	N/A	Wash with 70 L ethyl acetate
34	Drying	N/A	Air-dried to constant wt., 2 days
Treprostinil (from 1.5 kg Treprostinil diethanolamine salt)			
35	Hydrolysis	N/A	15 L water + 25 L ethyl acetate + HCl
36	Extraction	N/A	2 × 10 L ethyl acetate
37	Water wash	N/A	3 × 10 L

38	Brine wash	N/A	1 × 10 L
39	Sodium sulfate	N/A	1 kg, stir
40	Filter	N/A	Wash with 6 L ethyl acetate
41	Evaporation	N/A	To get solid, intermediate Treprostinil
42	Crude drying on tray	1 or 3 days	Same
43	Ethanol & water for cryst.	5.1 L + 5.1 L	10.2 L + 10.2 L (same %)
44	Crystallization in	20-L rotavap flask	50-L jacketed reactor
45	Temperature of crystallization	2 h r.t., fridge -0°C 24 h	50°C to 0°C ramp, 0°C overnight
46	Filtration	Buchner funnel	Aurora filter
47	Washing	20% (10 L) cooled ethanol-water	20% (20 L) cooled ethanol-water
48	Drying before oven	Buchner funnel (20 h) Tray (no)	Aurora filter (2.5 h) Tray (4 days)
49	Oven drying	15 hours, 55°C	6-15 hours, 55°C
50	Vacuum	<-0.095 mPA	< 5 Torr
51	UT-15 yield weight	~ 535 g	~ 1,100 g
52	% yield from triol)	~ 91%	~ 89%
53	Purity	~ 99.0%	99.9%

[0046] The quality of treprostinil produced according to this invention is excellent. The purification of benzindene nitrile by column chromatography is eliminated. The impurities carried over from intermediate steps (i.e. alkylation of triol and hydrolysis of benzindene nitrile) are removed during the carbon treatment and the salt formation step. Additional advantages of this process are: (a) crude treprostinil salts can be stored as raw material at ambient temperature and can be converted to treprostinil by simple acidification with diluted hydrochloric acid, and (b) the treprostinil salts can be synthesized from the solution of treprostinil without isolation. This process provides better quality of final product as well as saves significant amount of solvents and manpower in purification of intermediates.

[0047] Although the foregoing refers to particular preferred embodiments, it will be understood that the present invention is not so limited. It will occur to those of ordinary skill

in the art that various modifications may be made to the disclosed embodiments and that such modifications are intended to be within the scope of the present invention.

[0048] All of the publications, patent applications and patents cited in this specification are incorporated herein by reference in their entirety.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising treprostinil or a pharmaceutically acceptable salt thereof, said composition prepared by a process comprising providing a starting batch of treprostinil having one or more impurities resulting from prior alkylation and hydrolysis steps, forming a salt of treprostinil by combining the starting batch and a base, isolating the treprostinil salt, and preparing a pharmaceutical composition comprising treprostinil or a pharmaceutically acceptable salt thereof from the isolated treprostinil salt, whereby a level of one or more impurities found in the starting batch of treprostinil is lower in the pharmaceutical composition, and wherein said alkylation is alkylation of benzindene triol.

2. The pharmaceutical composition of claim 1, wherein the salt is isolated in crystalline form.

3. The pharmaceutical composition of claim 2, wherein the isolated salt is at least 99.8% pure.

4. The pharmaceutical composition of claim 1, wherein the base is selected from the group consisting of sodium, ammonia, potassium, calcium, ethanolamine, diethanolamine, N-methylglucamine, and choline.

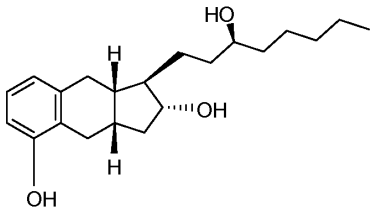
5. The pharmaceutical composition of claim 4, wherein the base is diethanolamine.

6. The pharmaceutical composition of claim 1, wherein the base is combined with treprostinil that has not been previously isolated.

7. The pharmaceutical composition of claim 1, wherein the isolated salt is stored at ambient temperature.

8. The pharmaceutical composition of claim 1, which is a pharmaceutical solution.

9. A process of preparing a pharmaceutical product comprising treprostinil or a pharmaceutically acceptable salt thereof, comprising alkylating a triol intermediate of the formula:



hydrolyzing the resulting compound to form treprostinil, forming a salt of treprostinil stable at ambient temperature, storing the treprostinil salt at ambient temperature, and preparing a pharmaceutical product from the treprostinil salt after storage, wherein the pharmaceutical product comprises treprostinil or a pharmaceutically acceptable salt thereof.

10. A pharmaceutical product prepared by the process of claim 9.

ABSTRACT

This present invention relates to an improved process to prepare prostacyclin derivatives. One embodiment provides for an improved process to convert benzindene triol to treprostinil via salts of treprostinil and to purify treprostinil.

PTO/AIA/14 (07-14)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	080618-1581
	Application Number	
Title of Invention	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1 Remove

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	080618-1581
	Application Number	
Title of Invention	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®	

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Postal Code	22963	Country	US

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

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For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

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Application Information:

Title of the Invention	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®		
Attorney Docket Number	080618-1581	Small Entity Status Claimed	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)		Suggested Figure for Publication (if any)	

Filing By Reference :

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Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	◉ Customer Number	○ US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	22428		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing this information in the application data sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.
When referring to the current application, please leave the application number blank.

Prior Application Status			Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	Division of	13/933623	2013-07-02
Prior Application Status			Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
13/933623	Continuation of	13/548446	2012-07-13
Prior Application Status			Remove

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Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
13/548446	Continuation of	12/334731	2008-12-15
Prior Application Status		Remove	
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
12/334731	Claims benefit of provisional	61/014232	2007-12-17

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Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)[i] the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Remove

Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button.

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

Authorization to Permit Access:

☒ Authorization to Permit Access to the Instant Application by the Participating Offices

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In accordance with 37 CFR 1.14(h)(3), access will be provided to a copy of the instant patent application with respect to: 1) the instant patent application-as-filed; 2) any foreign application to which the instant patent application claims priority under 35 U.S.C. 119(a)-(d) if a copy of the foreign application that satisfies the certified copy requirement of 37 CFR 1.55 has been filed in the instant patent application; and 3) any U.S. application-as-filed from which benefit is sought in the instant patent application.

In accordance with 37 CFR 1.14(c), access may be provided to information concerning the date o f filing this Authorization.

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

◉ Assignee	○ Legal Representative under 35 U.S.C. 117	○ Joint Inventor
○ Person to whom the inventor is obligated to assign.	○ Person who shows sufficient proprietary interest	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor :

If the Applicant is an Organization check here. ☒

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Address 2			
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Country	US	Postal Code	20910
Phone Number		Fax Number	

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Email Address	

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Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not subsitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Assignee 1

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication . An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

If the Assignee or Non-Applicant Assignee is an Organization check here. ☒

Organization Name	United Therapeutics Corporation

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1	1040 Spring Street		
Address 2			
City	Silver Spring	**State/Province**	MD
Country i	US	Postal Code	20910
Phone Number		Fax Number	
Email Address			

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button.

Signature:

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Signature				Date (YYYY-MM-DD)	SEP 10 2015
First Name	Stephen B.	Last Name	Maebius	Registration Number	35264

Additional Signature may be generated within this form by selecting the Add button.

PTO/AIA/14 (07-14)
Approved for use through 04/30/2017. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	080618-1581
	Application Number	
Title of Invention	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®	

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

PTO/AIA/01 (modified)

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)	080618-1256

Title of Invention	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®

As the below named inventor, I hereby declare that:

This declaration is directed to:

☒ The attached application, or

☐ United States application or PCT international application number _____ filed on _____.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than (5) years, or both.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: Hitesh BATRA Date (Optional): June 4, 2013

Signature: _____

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

PTO/AIA/01 (modified)

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)	080618-1256

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LEGAL NAME OF INVENTOR

Inventor: Sudersan M. TULADHAR Date (Optional): Jun 4, 2013

Signature: _____

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

PTO/AIA/01 (modified)

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LEGAL NAME OF INVENTOR

Inventor: Raju PENMASTA Date (Optional): Jun 04 2013

Signature: Raju Penmasta

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

PTO/AIA/01 (modified)

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)	080618-1256

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LEGAL NAME OF INVENTOR

Inventor: David A. WALSH Date (Optional): June 4, 2013

Signature: David A. Walsh

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

PTO/AIA/80 (07-12)
Approved for use through 11/30/2014. OMB 0651-0035
U.S. Patent and Trademark Office; U.S DEPARTMENT OF COMMERCE

POWER OF ATTORNEY TO PROSECUTE APPLICATIONS BEFORE THE USPTO

I hereby revoke all previous powers of attorney given in the application identified in the attached statement under 37 CFR 3.73(c).

I hereby appoint:

☑ Practitioners associated with Customer Number: 22428

OR

☐ Practitioner(s) named below (if more than ten patent practitioners are to be named, then a customer number must be used):

Name	Registration Number	Name	Registration Number

As attorney(s) or agent(s) to represent the undersigned before the United States Patent and Trademark Office (USPTO) in connection with any and all patent applications a ssigned only to the undersigned according to the USPTO assignment records or assignments docu ments attached to this form in accordance with 37 CFR 3.73(c).

Please change the correspondence address for the application identified in the attached statement under 37 CFR 3.73(c) to:

☑ The address associated with Customer Number: 22428

OR

☐	Firm or Individual Name		
	Address		
	City		
	Country		
	Telephone		Email

Assignee Name and Address: United Therapeutics Corporation
1040 Spring Street
Silver Spring, Maryland 20910

A copy of this form, together with a statement under 37 CFR 3.73(c) (Form PTO/SB/96 or equivalent) is required to be Filed in each application in which this form is used. The statement under 37 CFR 3.73(c) may be completed by one of The practitioners appointed in this form, and must identify the application in which this Power of Attorney is to be filed.

SIGNATURE of Assignee of Record
The individual whose signature and title is supplied below is authorized to act on behalf of the assignee

Signature		Date	12/11/12
Name	Andrew J. Fisher	Telephone	202-742-1208
Title	Chief Strategic Officer & Deputy General Counsel		

This collection of information is required by 37 CFR 1.31, 1.32 and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor Name:	Hitesh BATRA
Title:	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
Appl. No.:	Unassigned (DIV of 13/933,623)
Filing Date:	Herewith
Examiner:	Unassigned
Art Unit:	Unassigned

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR §1.56

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

Applicant submits herewith documents for the Examiner's consideration in accordance with 37 CFR §§1.56, 1.97 and 1.98.

Applicant respectfully requests that each listed document be considered by the Examiner and be made of record in the present application and that an initialed copy of Form PTO/SB/08 be returned in accordance with MPEP §609.

Applicant requests that, in accordance with 37 CFR §1.98(d), the Examiner review all applications relied on for an earlier effective filing date under 35 U.S.C. 120, including application no. 12/334,731, filed 12/15/2008; application no. 13/548,446, filed 7/13/2012; application no. 13/933623, filed 7/2/2013, for copies of references of record therein that are not being provided here; although Applicant would be pleased to provide copies of any such documents at the Examiner's request.

The submission of any document herewith is not an admission that such document constitutes prior art against the claims of the present application or that such document is considered material to patentability as defined in 37 CFR §1.56(b). Applicants do not waive any rights to take any action which would be appropriate to antedate or otherwise remove as a competent reference any document submitted herewith.

TIMING OF THE DISCLOSURE

The listed documents are being submitted in compliance with 37 CFR §1.97(b), within three (3) months of the filing date of the application.

Although Applicant believes that no fee is required, the Commissioner is hereby authorized to charge any additional fees which may be due to Deposit Account No. 19-0741.

Respectfully submitted,

Date SEP 10 2015

By _____

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 672-5569
Facsimile: (202) 672-5399

Stephen B. Maebius
Attorney for Applicant
Registration No. 35,264

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 1 of 4

Complete if Known	
Application Number	Unassigned
Filing Date	Herewith
First Named Inventor	Hitesh BATRA
Art Unit	Unassigned
Examiner Name	Unassigned
Attorney Docket Number	080618-1581

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	A1	2002/0173672 A1	11/21/2002	Moriarty et al.	
	A2	2004/0176645 A1	09/09/2004	Moriarty et al.	
	A3	2005/0085540 A1	04/21/2005	Phares et al.	
	A4	2005/0101608 A1	05/12/2005	Santel, Donald J.	
	A5	2005/0165111 A1	07/28/2005	Wade et al.	
	A6	2005/0282903 A1	12/22/2005	Wade et al.	
	A7	2005/0282901 A1	12/22/2005	Phares et al.	
	A8	2007/0078182 A1	04/05/2007	Phares et al.	
	A9	2007/0078095 A1	04/05/2007	Phares et al.	
	A10	2008/0200449 A1	08/21/2008	Olschewski et al.	
	A11	2008/0249167 A1	10/09/2008	Phares et al.	
	A12	2008/0280986 A1	11/13/2008	Wade et al.	
	A13	2009/0036465 A1	02/05/2009	Roscigno et al.	
	A14	2009/0163738 A1	06/25/2009	Batra et al.	
	A15	4,306,075 A	12/15/1981	Aristoff, Paul A.	
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	A17	4,424,376 A	01/03/1984	Moniot et al.	
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	A19	4,486,598 A	12/04/1984	Aristoff, Paul A.	
	A20	4,544,764 A	10/01/1985	Aristoff, Paul A.	
	A21	4,668,814	05/26/1987	Aristoff	
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	A23	4,683,330 A	07/28/1987	Aristoff, Paul A.	
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	A25	6,054,486 A	04/25/2000	Crow et al.	
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	A27	6,521,212 B1	02/18/2003	Cloutier et al.	
	A28	6,528,688 B2	03/04/2003	Moriarty et al.	
	A29	6,700,025 B2	03/02/2004	Moriarty et al.	
	A30	6,756,033 B2	06/29/2004	Cloutier et al.	
	A31	6,765,117 B2	07/20/2004	Moriarty et al.	
	A32	6,803,386 B2	10/12/2004	Shorr et al.	
	A33	6,809,223 B2	10/26/2004	Moriarty et al.	
	A34	7,199,157 B2	04/03/2007	Wade et al.	
	A35	7,384,978 B2	06/10/2008	Phares et al.	
	A36	7,417,070 B2	08/26/2008	Phares et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Documents	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]
	A37	CA 2 710 726 A1	01/22/2012	Alphora Research Inc., CA		
	A38	CN 101891596 A	11/24/2010	Shanghai Techwell Biopharmaceutical Co. Ltd.		A ✓
	A39	CN 101891715 A	11/24/2010	Shanghai Techwell Biopharmaceutical Co. Ltd.		A ✓
	A40	EP 0 004 335 A2	10/03/1979	Hoechst AG		A
	A41	EP 0 087 237 B1	05/14/1986	The Upjohn Company		

Examiner Signature		Date Considered	

4815-8251-5496.1

Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(use as many sheets as necessary)* Sheet 2 of 4	***Complete if Known***	
	Application Number	Unassigned
	Filing Date	Herewith
	First Named Inventor	Hitesh BATRA
	Art Unit	Unassigned
	Examiner Name	Unassigned
	Attorney Docket Number	080618-1581

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Documents	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]
	A42	EP 0 159 784 B1	06/07/1989	The Upjohn Company		
	A43	EP 0 175 450 B1	03/22/1989	The Upjohn Company		
	A44	EP 0 496 548 A1	07/29/1992	Purdue Research Foundation		
	A45	JP 56-122328 A	09/25/1981	Sumitomo Chem. Co.		✓
	A46	JP 59-044340 A	03/12/1984	Sankyo Co. Ltd.		✓
	A47	WO 98/39337 A1	09/11/1998	Hoechst AG		A
	A48	WO 99/21830 A1	05/06/1999	United Therapeutics Corporation		
	A49	WO 03/070163 A2	08/28/2003	United Therapeutics Corporation		
	A50	WO 2005/007081 A2	01/27/2005	United Therapeutics Corporation		
	A51	WO 2007/134292 A2	11/22/2007	United Therapeutics Corporation		
	A52	WO 2008/100977 A2	08/21/2008	N.V. Organon		
	A53	WO 2009/117095 A1	09/24/2009	Arena Pharmaceuticals, Inc.		
	A54	WO 2012/009816 A1	01/26/2012	Alphora Research Inc.		

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]
	A55	ALEXANDER et al., "The Synthesis of Benzindene Prostacyclin Analogs as Potential Antiulcer Agents," Prostaglandins, 1986, 32(5):647-653.	
	A56	ARISTOFF et al., "Synthesis and Structure-Activity Relationship of Novel Stable Prostacyclin Analogs," Advances in Prostaglandin, Thromboxane, and Leukotriene Research, Samuelsson et al., .Eds., 1983, 11:267-274	
	A57	ARISTOFF et al., "Synthesis of Benzopyran Prostaglandins, Potent Stable Prostacyclin Analogs, Via an Intramolecular Mistunobu Reaction," Tetrahedron Letters, 1984, 25(36):3955-3958.	
	A58	ARISTOFF et al., "Total Synthesis of a Novel Antiulcer Agent via a Modification of the Intramolecular Wadsworth-Emons-Wittig Reaction," J. Am. Chem. Soc., 1985, 107:7967-7974.	
	A59	BATRA et al., "Crystallization Process Development for a Stable Polymorph of Treprostinil Diethanolamine (UT-15C) by Seeding," Organic Process Research & Development, 2009, 13:242-249.	
	A60	BELCH et al., "Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of AS-013, a Prostaglandin E1 Prodrug, in Patients with Intermittent Claudication," Circulation, May 6, 1997, 95(9):2298-2302.	
	A61	CHEMBURKAR et al., "Dealing with the Impact of Ritonavir Polymorphs on the Late Stages of Bulk Drug Process Development," Organic Process Research & Development, 2000, 4:413-417.	
	A62	CHUNG et al., "Promoters for the (Alkyne)hexacarbonyldicobalt-Based Cyclopentenone Synthesis," Organometallics, 1993, 12:220-223.	
	A63	CLARK et al., "High-Performance Liquid Chromatographic Method for Determining the Enantiomeric Purity of a Benzindene Prostaglandin by a Diastereomeric Separation," Journal of Chromatography, 1987, 408:275-283.	

Examiner Signature		Date Considered	

Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(use as many sheets as necessary)* Sheet 3 of 4	***Complete if Known***	
	Application Number	Unassigned
	Filing Date	Herewith
	First Named Inventor	Hitesh BATRA
	Art Unit	Unassigned
	Examiner Name	Unassigned
	Attorney Docket Number	080618-1581

NON PATENT LITERATURE DOCUMENTS

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	A64	HARDINGER et al., "Triply-Convergent Syntheses of Two Homochiral Arene-Fused Prostacyclin Analogs Related to U68,215," Bioorganic & Medicinal Chemistry Letters, 1991, 1(1):79-82.	
	A65	HICKS et al., "A Practical Titanium-Catalyzed Synthesis of Bicyclic Cyclopentenones and Allylic Amines," J. Org. Chem., 1996, 61:2713-2718.	
	A66	JEONG et al., "Catalytic Version of the Intramolecular Pauson-Khand Reaction," J. Am. Chem. Soc., 1994, 116:3159-3160.	
	A67	KHAND et al., "Organocobalt Complexes. Part II. Reaction of Acetylenehexacarbonyl-dicobalt Complexes, $(R^1C_2R^2)Co_2(CO)_6$, with Norbornene and its Derivatives," J. Chem. Soc., J.C.S. Perkin I., 1973, 977-981.	
	A68	MATHRE et al., "A Practical Enantioselective Synthesis of α,α-Diaryl-2-pyrrolidinemethanol. Preparation and Chemistry of the Corresponding Oxazaborolidines," J. Org. Chem., 1991, 56:751-762.	
	A69	Moriarty et al., "The Intramolecular Asymmetric Pauson-Khand Cyclization as a Novel and General Stereoselective Route to Benzindene Prostacyclins: Synthesis of UT-15 (Treprostinil)," *J. Org. Chem.* 2004, 69, 1890-1902.	
	A70	MULZER et al., "Asymmetric Synthesis of Carbacyclin Precursors by Pauson-Khand Cyclization," Liebigs Ann. Chem., 1988, 891-897.	
	A71	NELSON, Norman A., "Prostaglandin Nomenclature," J. Med. Chem., September 1974, 17(9):911-918.	
	A72	PAGENKOPF et al., "Photochemical Promotion of the Intramolecular Pauson-Khand Reaction. A New Experimental Protocol for Cobalt-Catalyzed [2 + 2 + 1] Cycloadditions," J. Am. Chem. Soc., 1996, 118:2285-2286.	
	A73	PAGENKOPF, Brian L., "Substrate and Reagent Control of Diastereoselectivity in Transition Metal-Mediated Process: Development of a Catalytic Photo Promoted Pauson-Khand Reaction," Diss. Abstr. Int., 57(12):7535, 1977, Abstract.	
	A74	PATTERSON et al., "Acute Hemodynamic Effects of the Prostacyclin Analog 15AU81 in Severe Congestive Heart Failure," Am. J. Cardio., 1995, 75:26A-33A.	
	A75	PAULSON, Peter L., "The Khand Reaction," Tetrahedron, 1985, 41(24):5855-5860.	
	A76	SCHORE, Neil E., "Transition-Metal-Mediated Cycloaddition Reactions of Alkynes in Organic Synthesis," Chem. Rev., 1988, 88:1081-1119.	
	A77	SHAMBAYATI et al., "N-Oxide Promjoted Pauson-Khand Cyclizations at Room Temperature," Tetrahedron Letters, 1990, 31(37):5289-5292.	
	A78	SNELL et al., "Investigating the Effect of Impurities on Macromolecule Crystal Growth in Microgravity," Crystal Growth & Design, 2001, 1(2):151-158.	
	A79	Sorbera et al. "UT-15. Treatment of Pulmonary Hypertension Treatment of Peripheral Vascular Disease," *Drug of the Future*, 2001, 26(4), 364-374.	
	A80	TAKANO et al., "Enantiodivergent Synthesis of Both Enantiomers of Sulcatol and Matsutake Alcohol from (R)-Epichlorohydrin," Chemistry Letters, 1987, 2017-2020.	

Examiner Signature		Date Considered	

Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(use as many sheets as necessary)* Sheet 4 of 4	***Complete if Known***	
	Application Number	Unassigned
	Filing Date	Herewith
	First Named Inventor	Hitesh BATRA
	Art Unit	Unassigned
	Examiner Name	Unassigned
	Attorney Docket Number	080618-1581

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]
	A81	VIEDMA, Cristobal, "Selective Chiral Symmetry Breaking during Crystallization: Parity Violation of Cryptochiral Environment in Control?" Crystal Growth & Design, 2007, 7(3):553-556.	
	A82	WHITTLE et al., "Antithrombotic Assessment and Clinical Potential of Prostacyclin Analogues," Progress in Medicinal Chemistry, Ellis et al. Eds., 1984, Chapter 6, Vol. 21, 238-279.	
	A83	ZHANG et al., "A Nickel(0)-Catalyzed Process for the Transformation of Enynes to Bicyclic Cyclopentenones," J. Org. Chem., 1996, 61:4498-4499.	

Examiner Signature		Date Considered	