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)

VIDEO DEPOSITION OF

ROBERT R. RUFFOLO, JR., PHD

Wilson Sonsini Goodrich & Rosati

1700 K Street NW, Suite 500

Washington, DC 20006

Friday, August 19, 2016

9:29 a.m.

Reported by:

Denise D. Vickery, CRR/RMR JOB NO. 178626

A P P E A R A N C E S

For Petitioner:

DLA PIPER LLP (US)

1251 Avenue of the Americas

New York, NY 10020-1104

BY: STUART E. POLLACK, ESQ.

-and-

33 Arch Street, 26th Floor

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BY: MAYA PRAKASH CHOKSI, ESQ.

For Patent Owner and the Witness:

WILSON SONSINI GOODRICH & ROSATI

900 South Capital of Texas Highway

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Austin, TX 78746-5546

BY: ROBERT DELAFIELD, ESQ.

A P P E A R A N C E S (Continued)

For Patent Owner:

FOLEY & LARDNER LLP

Washington Harbour

3000 K Street, NW, Suite 600

Washington, DC 20007-5109

BY: STEPHEN B. MAEBIUS, ESQ.

Also Present:

Solomon Francis, Videographer

I N D E X

E X H I B I T S

E X H I B I T S

(Exhibits attached to transcript.)

P R O C E E D I N G S

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THE VIDEOGRAPHER: Good morning. This begins Media Unit No. 1 of the audiovisual deposition of Dr. Robert Ruffolo taken in the matter of SteadyMed Limited, Petitioner versus United Therapeutics Corporation, Patent Owner, before the Patent Trial and Appeal Board, IPR No. 2016-00006.

This deposition is being held at the law offices of Wilson Sonsini Goodrich & Rosati located at 1700 K Street, Northwest, Washington, DC on August 19, 2016 at approximately 9:29 a.m.

My name is Solomon Francis and our court reporter, Denise Vickery, for Elisa Dreier Reporting Corp. located at 950 Third Avenue, New York, New York.

For the record, would counsel introduce themselves and whom they represent.

MR. POLLACK: Stuart E. Pollack, DLA Piper LLP(US) on behalf of the petitioner, SteadyMed Limited.

MS. CHOKSI: Maya Choksi, DLA

Piper, on behalf of the petitioner.

MR. DELAFIELD: Bobby Delafield, Wilson Sonsini Goodrich & Rosati, on behalf of United Therapeutics and the witness.

MR. MAEBIUS: And Steven Maebius from Foley & Lardner LLP on behalf of patent owner.

THE VIDEOGRAPHER: At this time, will the court reporter please swear in or affirm the witness.

- - -

ROBERT R. RUFFOLO, JR., PHD

called for examination, and, after having been duly sworn, was examined and testified as follows:

EXAMINATION

THE VIDEOGRAPHER: Please proceed, counsel.

BY MR. POLLACK:

Q. Good morning, Dr. Ruffolo.

A. Good morning.

Q. To get started, if you could just state your name and your current position for the record.

A. Okay. My name is Robert Richard

Ruffolo, and I am the retired president of research and development at Wyeth and the retired senior corporate VP of Wyeth and I -- and self-employed as a pharmaceutical consultant.

Q. Do you have like a consulting company or agency?

A. Yes, I do. It's -- it's Ruffolo Consulting, LLC.

Q. And that's a company that you are the only member of?

A. Yes, I am.

Q. Have you been deposed before?

A. Yes, I have.

Q. How many times have you been deposed before?

A. Well, maybe 10.

Q. Just briefly, can you tell me what kinds of cases those 10 cases were?

A. Yes. In -- four of those were in two cases of product liability for companies that I worked for where I was a company witness as well as an expert witness in both of those cases, and then the remaining depositions were in cases like this.

Q. Those were patent litigation cases?
A. Yes, they were.
Q. Okay. And about six depositions?
A. About -- yeah, about six.
MR. POLLACK: Just to get some formalities out of the way, I'm going to mark as Ruffolo Deposition Exhibit 1 the Petitioner's Notice of Deposition of Robert R. Ruffolo, Ph.D.
(Document marked for identification purposes as Ruffolo Exhibit 1.)
THE WITNESS: Thank you.
BY MR. POLLACK:
Q. And are you in attendance here today for this deposition in response to petitioner's notice of deposition?
A. Yes, I am.
Q. Have you testified in any other -- you understand this is a proceeding called an inter partes review?
A. Yes, I do. Yes.
Q. Okay. Have you testified in any other inter partes review?
A. No, I don't believe so.

Q. In the six patent litigations that you testified in, what did those concern?

A. Do you want the specific company, law firms?

Q. Yeah. Yes.

A. Okay. I'll do the best I can.

Q. Okay.

A. One was Gardiner Roberts and the drug was an ACE inhibitor and Tandrolapril. Tandolapril, I think. Trandolapril, I think.

Q. Trandolapril?

A. I think so. I can't be certain. I just simply don't remember.

Q. Okay.

A. Then --

Q. Was that for the brand name company or for the generic company that you were testifying?

A. That one was for the generic and --

Q. Do you remember which company?

A. Yes. It was Novartis. Sandoz, their generic division.

Q. Okay.

A. Then there --

Q. Let me ask you. Was that

Sanofi-Aventis on the other side or --

A. It was Boehringer Ingelheim.

Q. Boehringer Ingelheim.

A. So that's why I'm not sure of the drug match. I don't remember. That was the first one I did quite a while ago.

Q. Okay. What did you testify about in that case?

A. It was mostly about the R&D process in that case. I was an expert on -- on R&D process, regulatory requirements, and the FDA.

Then there was another case. The law firm was Goodwin Procter. The drug was Azilect, and I represented the patent holder in that case, and that the patent holder was Teva, a generic company, but they do have --

Q. Right.

A. -- some, as you know I'm sure, they have a few branded drugs that they developed. And then there was --

Q. Let me ask you. What was your testimony about in that case?

A. Oh, it was everything basically. So I was originally hired -- there were 21 parts to that case. So I was originally hired

just to do the R&D part, but then I did -- ended up doing 17 of the 21 parts. So I did virtually everything on that.

Q. Infringement, invalidity?

A. Yes, and all of the science related to stereochemistry and the R&D process and so on. It was a very long case, and that one did go to trial.

Q. Who won?

A. We did.

Q. Okay. What about in the ACE inhibitor case? Who won?

A. That one was settled and I never asked the settlement terms, but I was told that the client was -- was pleased with the settlement.

Q. Okay.

A. So that's all I know.

Then I did one with -- and still in the process -- Perkins Coie on esomeprazole, and I did, I think, two depositions on that one and I think I did two on the one with Goodwin Procter. And --

Q. You were on the generic side then not the AstraZeneca side?

A. I was on the generic side on that one, yes.

Q. You said you did two depositions. Were there two different cases?

A. No, there was one case. I did two and sometimes I do two, and I never know exactly why.

Q. Okay. What was that? What was your testimony about?

A. That one was on crystal structure, physical properties of molecules. The, again, always the R&D process, FDA regulation as -- and pharmaceutics in that case as well.

Q. Let me ask you. Are you an expert on crystal structure? Is that one of your areas?

A. It depends how you describe expert. Being president of research and development, I supervised every single group.

Q. Sure.

A. And these are groups of thousands of people each. So in the pharmaceutics group, it would be thousand -- a thousand people and I -- and I've obviously had to review and evaluate and assess all that work. But I also

had extensive training in physical properties of molecules, physical chemistry, organic chemistry, extensive medicinal chemistry. So that's -- so I wouldn't -- I'm a pharmacologist by training, so...

Q. Right. What does that mean, to be a pharmacologist? Does that mean you're basically an animal guy?

A. Well, yeah, to put it crudely. I study and discover drugs based on animal models of disease, and pharmacology is basically the study of drugs in living systems. And it's -- it's not necessarily animals, but I've studied drugs personally from the gene all the way up to the animal. And then, of course, I am involved and have always been involved in clinical trial design. So in a sense, I do it from the gene to the human but --

Q. The work that you personally did in the lab, was it more animal focused or more gene focused or where would you say your work was?

A. It was all of them. I would say it's fairly balanced, and also a good part of my career was based on stereochemistry and

structure activity relationships, which involves a great deal of organic chemistry. So I have very broad training.

And so to get back to your question, I don't necessarily pass myself off as an expert in all those areas, but I have extensive experience because I've managed, well, tens of thousands of scientists and been responsible for large R&D groups. At Wyeth, it was 7,000 people in every single discipline from the gene through the human.

So -- so that's my -- my experience.

Q. You said -- which areas do you pass yourself off as an expert?

A. I --

MR. DELAFIELD: Objection. Vague.

THE WITNESS: The -- certainly I am a pharmacologist and I feel competent to deal with all areas of pharmacology in all therapeutic areas, and I am -- I am, indeed, recognized worldwide as an expert in stereochemistry and in structure activity relationships, which is a complex intermix

between chemistry and pharmacology. And I've directed my own personal chemistry laboratories.

BY MR. POLLACK:

Q. How many people working in those chemistry laboratories that you directed?

A. In the -- because those laboratories were involved in making compounds primarily for me in my laboratories because I kept my laboratory throughout my entire career in the industry, both in the structure activity field and in the stereochemistry field.

So those laboratories would have three or four people, usually a Ph.D. or a master's level of person and several technical staff, but I also was responsible for all of medicinal chemistry at Wyeth, which would have about 500 chemists, and all of the analytical chemistry laboratories, which would have, oh, maybe 3-, 400 chemists. And as you can imagine, I had to resolve issues related to those areas which often cause us problems in drug development.

Q. Okay. In other words, you didn't know the details of everything those 8- to 900

people were doing, I assume, day to day?

A. No, I didn't know all the details of everything that they were doing day to day, but ultimately I was responsible for making the decisions with respect to drug discovery and even development that came from all those groups. Those had to be my personal decisions. I was responsible for that.

Q. Right. You were the decider?

A. Yes. So I needed to be deeply enough involved in the science to make those kinds of decisions.

Q. Okay. I assume, though, you relied on the advice of the medicinal chemists and analytical chemists in making those decisions?

A. Yes. I, as an executive, would rely on the best people around me, but ultimately I had to make those decisions and sometimes, actually not uncommonly, experts disagree, and I would still have to make that decision.

Q. All right. We were talking about your patent cases.

A. Oh, I'm sorry. Could you remind me where?

Q. Yes. We were last on esomeprazole, which you were doing with Perkins Coie.

A. Perkins Coie. And --

Q. Let me ask you. You said you talked about crystal structure in that case.

What did you talk about in regard to crystal structure in that case?

A. Oh, polymorphs, amorphic, amorphous forms. Mixtures between polymorphs and amorphous, X-ray crystal, X-ray crystallography, XRPD, Raman spectra. All of the technologies involved in determining crystal structure and the pharmaceutics involved in formulating crystal structures, and there were other. Also, of course, as I said, the R&D process and regulatory process and FDA.

Q. Okay. All right. What's the next case on your list?

A. Oh. There is a case that just happened to be on a drug that I discovered and I held the patent on where I testified both as an expert witness for a former employer as well as an expert scientifically on the drug. The drug is called carvedilol and the law firm was Fish, et al. I don't remember the other names.

In fact, that's still ongoing and --

Q. Fish & Richardson?

A. Yes, that's right.

And -- and I testified on behalf of the patent holder, obviously. And that involved every single aspect of that drug from the first day that I touched it until even now and that included, well, basically everything.

Q. Were you the inventor on the patent in that case?

A. Yes.

Q. So are you an expert in that case or you're testifying as the fact witness --

A. Both.

Q. -- in that case?

A. Both. Because I was a company employee and obviously I'm the world's expert on that drug and so -- and that turned out to be a very, very important, highly visible drug. I mean, that drug changed how heart failure is treated. It's now the standard of care for this disease. So -- so I was hired to do both roles.

Q. What's the patent about? What is it that was invented?

A. The patent is about congestive heart failure.

Q. What about congestive heart failure?

A. Well, the contention in that case is that the drug, which is a beta blocker, among many other activities that it has, all of which are relevant to heart failure, were discovered in my laboratory -- my laboratories at the time -- was obvious and, of course, beta blockers at the time and still are contraindicated by the FDA and that's the FDA's most significant warning against the use of such drugs.

And so the company challenging that -- and I don't remember, I should, I gave my deposition a few months ago, but I don't remember -- is arguing that it's obvious. And, of course, how could it be obvious if it's contraindicated? And, of course, I also had internal notes of all of the opposition within at that time GlaxoSmithKline, who was my employer at that time, against developing that drug because they thought it would kill people.

And so as the person who had to

live all that and waking up every morning thinking everybody says I'm going to kill people with this drug in these clinical trials and now it's a standard of care, it clearly wasn't obvious.

Q. That's it?

A. So that's basically what my role was.

Q. Is the patent on the chemical?

A. The patent is on the use in heart failure --

Q. Use in heart failure. Okay.

A. -- which is mainly what the drug is sold for. It wasn't invented for that reason.

Q. Someone else invented the chemical; right?

A. Another person synthesized -- first synthesized that and -- and the use was in dispute for a number of years. And when my laboratories -- and I was the senior vice president in the company at that time, but my laboratories were pointing us into the direction of heart failure, and that wasn't a very popular decision given, again, the FDA's contraindication for drugs like that in heart

failure.

So it was quite literally a very difficult situation for 17 years, although I loved every minute of it, but that drug did not have a lot of friends until the FDA approved it as, and the Wall Street Journal indicated it was one of the top three developments of all time in medicine.

Q. Your role in that was in supervising the clinical trials or what was your role?

A. It was everything. My role was everything. I ran all of the preclinical discovery work. I was on the team. In fact, I wrote the entire development plan for that drug early on, and I was on the team that monitored every step of that process, including the clinical trials. I had input into everything.

Q. Okay. And are there any other cases?

A. There may be, but I'm not -- they're not coming to mind.

Q. Okay.

A. Sorry. That's -- that's all I'm coming up with right now.

Q. Okay. Anything else you're working on right now?

A. Yes. Obviously this and there are two others that are just beginning right now, and in one of them I don't even know yet all of the issues. I know that they fall in my area of expertise and -- and so there are two of those.

Q. Other than this particular proceeding that we're doing right now, have you done any other work for United Therapeutics?

A. No, I have not done anything with United Therapeutics before.

Q. Okay. So this is including any litigations or anything else on this same drug?

A. No, nothing on any. I don't think I've ever had any contact with United Therapeutics before.

Q. And what about with either of the law firms that are present here on behalf of United Therapeutics, either Foley & Lardner or Wilson Sonsini? Had you worked with them before?

A. No, I had not.

Q. When did you first get hired to

work on these IPRs?

A. I believe it was April of last year.

Q. April 2015?

A. Yes, I believe so. Around that -- that period.

Q. And how did you get hired?

A. I was contacted by Mr. Delafield, and that's how I got contacted.

Q. What's your -- what's your hourly rate?

A. $500 an hour.

Q. And that's what you're being paid in this case?

A. Yes, it is.

Q. And is that what you were paid in -- approximately in your other cases as well?

A. Of the recent ones, yes, and the first one or two was a little bit less than that.

Q. About how much less?

A. 400 I think.

Q. Do you have an idea how much time you've spent working on this IPR?

A. I would guess between 30 and 40 hours maybe.

Q. That's it, the 30 to 40?

A. I'm guessing. I -- that's something in that range, plus or minus.

Q. Okay. Have you sent either Wilson Sonsini or United or Foley & Lardner an invoice?

A. I sent Wilson et al. two or three invoices, I think. Could be four.

Q. Okay. Do you have an estimate of how much the invoices totaled?

MR. DELAFIELD: Objection. Relevance.

THE WITNESS: I guess they may have totaled between 30 and 40 thousand dollars maybe.

BY MR. POLLACK:

Q. Okay. So that sounds more like maybe 60 hours?

A. Well, there were expenses included in that and -- and so it could have been more than 30 or 40 hours. I just don't remember.

Q. Okay. Somewhere between 30 and 60; does that sound fair?

A. I'm not sure it would be as high as 60.

Q. Okay. 30 and 50?

A. Maybe.

Q. Okay.

A. I'm sorry. I meant to say something at the beginning and I forgot.

I have one change in my expert report that -- that I'd like to make.

Q. Okay.

A. It was --

Q. Tell you what. Let's --

A. Wait till then?

Q. Yeah.

A. Okay.

Q. I'll bring out the expert report and I'll ask you about that.

A. Okay.

MR. POLLACK: I'm going to mark as Ruffolo Deposition Exhibit 2 UT Exhibit 2023, the curriculum vitae of Robert Ruffolo.

(Document marked for identification purposes as Ruffolo Exhibit 2.)

THE WITNESS: Thank you.

BY MR. POLLACK:

Q. Can you confirm for me that that is your CV?

A. Yes, this is my CV.

Q. Okay. Are there any corrections you want to make to the CV?

A. Not -- not that I know of.

Q. And if you can turn to page 13 in the exhibit.

A. Okay.

Q. I just wanted to look at the section that says "Expert Witness in Lawsuits."

A. Uh-huh.

Q. So the first two cases, one is a SmithKline Beecham litigation?

A. Yes.

Q. Okay. And the second is a Wyeth Pharmaceuticals litigation?

A. Yes.

Q. Were those both product liability kinds of cases?

A. Yes, they were. They were the two that I --

Q. That you mentioned?

A. -- mentioned earlier, yes.

Q. What was the SmithKline Beecham one about?

A. Well, that was the diet drug litigation. The so-called Fen-Phen.

Q. Fen-Phen?

A. Yes.

Q. What was your testimony about in that case? Were you an expert or a fact witness?

A. I was both a fact witness and an expert witness because it fell within my field of autonomic pharmacology and so I served both roles.

Q. Okay. Were you involved at all in the development of Fen-Phen?

A. Oh, no, no. SmithKline Beecham made phentermine, and I think that drug maybe hit the market before I was born.

Q. Uh-huh. Yeah, right.

Okay. So why did they involve you in -- in that case?

A. I was the highest ranking scientist in the organization, and the phentermine is an indirectly acting sympathomimetic amine, and

that happens to be one of my fields of expertise and so I was both a fact witness and an expert witness.

Q. And what did you do in the Wyeth case?

A. It was basically the same type role. I was the president of research and development and, as I said, senior corporate VP and -- and so I was obviously the senior scientist in the company, but it's also an area that I knew a great deal about. It was pharmacological as well as clinical.

Q. And then we have two patent litigations. Those are the first two that you and I discussed today?

A. Yes, those first two.

Q. Okay. And the first one is the Gardiner Roberts one --

A. Right.

Q. -- correct?

And the second is the Goodwin Procter one?

A. That's correct.

Q. Okay. I see the other ones aren't -- aren't listed.

A. Yeah, I don't know what -- what -- when I made this one, and those others are very recent and so I probably haven't added -- I just didn't add it yet.

Q. Okay. Do you know when this CV was made? When it was last updated?

A. Oh, let's see what publication number there is.

Oh, maybe a year or two ago. Being retired, I'm not publishing so much anymore and so this CV doesn't get updated as frequently. So I don't -- I don't know when it was, but it's relatively current, but I haven't updated it in a little while.

Q. Okay. You didn't have a chance to update it with the additional litigations?

A. No, and also I didn't -- don't know -- on almost all of them, I had to sign some order issued by a judge saying you can't disclose anything about it and so it's -- I'm not sure I was allowed to list it. These were cases that were finished and the others are, I think, all still ongoing, and I didn't know if I'm allowed to do that.

Q. Okay. Do you still update your CV

-- do you -- do you update your CV yourself or do you have someone do it for you?

A. Now I do it myself.

Q. Back when you were in at Wyeth, you had someone do it for you?

A. Well, I had an army of -- of assistants and so I didn't have to do that myself.

Q. Okay. Let's mark a third exhibit, which will be your declaration.

A. Okay.

(Document marked for identification purposes as Ruffolo Exhibit 3.)

THE WITNESS: Thank you.

BY MR. POLLACK:

Q. All right. Ruffolo 3 is titled declaration of Robert -- Ruffolo 3 is entitled "Declaration of Robert R. Ruffolo, Jr., Ph.D. in Support of Patent Owner Response to Petition."

Can you just verify for me that this is the declaration that you submitted?

A. Yes, this is -- this is my declaration.

Q. Are there any corrections that you would like to make to your --

A. Yeah. Yes.

Q. -- declaration?

A. There's one on page 26, and I apologize. I caught this in the penultimate draft and I forgot to add it.

On page 26, five lines up from the bottom.

Q. Uh-huh. This is in paragraph 56?

A. Yes, and on that line it says "toxic to humans, and yet may not be identified." It should read "and yet still would be identified."

And I found that and I just failed to carry that through in the final draft.

So it should read "and yet still would be identified or qualified."

Q. Okay. Can you do me a favor? Can you read the whole sentence with the corrected language for the record?

A. Yes. Where does it start? Okay.

"Based on the present FDA and ICH guidelines, a potentially toxic impurity that is not demonstrated to be a risk in animals,

could still present -- could still be present in a drug substance at a level resulting in exposures of up to 1 milligram per day that could, in fact, be toxic to humans, and yet still identified and qualified -- still be identified and qualified."

Can I write that correction on this draft?

Q. Sure.

A. Just in case we --

Q. Yeah.

A. (Marking). Okay.

Q. So it's actually two corrections; right? "Still" after the word "could"? "Could present -- could still be present"?

A. "And yet may still be identified and qualified."

Q. Yes. You also added the word "still" after about two lines up from that?

A. Oh, no, I'm sorry. If I -- if I said that --

Q. You didn't?

A. -- I was -- I was correct. There was only that one correction on that one line. So not -- "not need to" should be "still."

Q. Okay. Could you do me a favor then? Can you read the sentence as you would like it --

A. Okay.

Q. -- to be --

A. Sure.

Q. -- into the record?

A. Okay.

"Based on the present FDA and ICH guidelines, a potentially toxic impurity that is not demonstrated to be a risk in animals, could be present in a drug substance at a level resulting in exposures of up to 1 milligram per day that could, in fact, be toxic to humans, and yet may still be qualified -- identified and qualified."

Q. And who discovered that error?

A. I did when I was reviewing my declaration.

Q. Okay. How was this declaration drafted?

A. About a year ago, I put together a draft of this declaration by myself and sent it to Mr. Delafield.

Q. Okay. So that's before you saw any

-- a year ago would mean that would be before you saw any dec -- at that time had you seen the declaration of Professor Winkler?

A. I may have. I may have.

Q. Okay.

A. It would have been around that time when I would have first reviewed that and I -- I may or may not have. I don't know.

Q. Okay. But at that time you hadn't seen the decision of the Patent Trial and Appeal Board regarding institution of this review?

A. Again, I don't recall if I did or didn't at the time I prepared the first draft. I just don't remember.

Q. Did you -- did you revise the draft after that?

A. Oh, probably 20 or 30 times.

Q. Did Mr. Delafield suggest revisions to your draft?

MR. DELAFIELD: Objection. Just -- just caution the witness not to disclose any privileged communications between us, so...

THE WITNESS: Not much. This is

my draft and his suggestions were few, if any. There might be a couple of legal sentences, but that's something that I certainly wouldn't understand on my own.

BY MR. POLLACK:

Q. Right. For example, if you turn to page 10 paragraph 18 and going through --

A. Uh-huh.

Q. -- page 12, did you draft those paragraphs?

A. Yeah, that's what I was referring to. That's where -- where he would have helped me or made suggestions because I am not an attorney and would not have been able to do that on my own.

Having said that, I in every draft after that was added, which was early on, I revised over and over. That's how I operate. I do draft after draft after draft until every word is exactly the way I want it, despite the fact that I missed the correction, and so -- but I -- so -- so, yes, that I was helped with that.

Q. Other than the correction you pointed us to in paragraph 56, are there any

other corrections that you'd like to point out?

A. Not that I'm aware of.

Q. Are there any other opinions regarding this case that you'd like to express as you sit here today that are not in your declaration?

A. I -- I've read so many things. I don't recall that there are other opinions. I was asked to deal with long-felt need and that was pretty much what my -- my task was and so that's what I focused on, but I am familiar with other aspects that I've -- you know, based on my reading.

Q. Okay. But as you sit here today, there are no other opinions that you intend to provide in this case other than what's in your declaration?

A. This is what I was asked to -- to testify about.

Q. Okay. And by "this" we're referring to --

A. This document. The contents of my --

Q. -- Ruffolo Exhibit 3?

A. Correct.

Q. As you said, this is a report on long-felt need?

A. Yes. Yes, it is.

Q. What's your understanding of long-felt need? What is that?

A. Well, again, not being an attorney, my understanding of long-felt need is something that results in an improvement in a product that has a significance and something that other people hadn't done. That's my simple layman's understanding.

Q. You said it had a significance. A significance to whom?

A. Well, I'm assuming to anybody. I don't know that it applies to any individual case in terms of your general question.

Q. Well, do you know, does -- does a long-felt need to be something that was recognized or understood in the art?

A. I don't understand.

Q. Maybe I used too many patent terms.

Does a long-felt need need to be something that other people felt a need for?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: Could -- could you define "other people" for me? I'm sorry. I just --

BY MR. POLLACK:

Q. Well, besides yourself, for example.

MR. DELAFIELD: Same objection.

THE WITNESS: I would assume somebody would have to think it was an improvement or -- or a significant change.

BY MR. POLLACK:

Q. I'm not asking about an improvement.

Long-felt need. That's like a yearning for something. Would that be a fair way to describe it?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: I suppose that would perhaps be -- be something that would -- would represent a long-felt need.

BY MR. POLLACK:

Q. Okay. Do you know when the '393 patent was filed, was there -- have you identified anyone who expressed a desire or a

need that was addressed by the '393 patent?

A. Well, based on almost 40 years of experience in the industry dealing with the FDA, the FDA is always looking for the highest level of purity that's possible and practical and -- and obviously so did physicians and patients, and so that to me would represent a long-felt need.

Q. Okay. But did you identify anyone, say anyone in the FDA or elsewhere, who stated or expressed a need or desire for a purer treprostinil?

MR. DELAFIELD: Objection. Compound and vague.

THE WITNESS: The FDA in general is always looking for the highest level of purity, but specifically they do so for drugs like this that are exquisitely potent and used on a chronic basis where exposure to -- to impurities, especially those that are structurally related to the drug, have the same pharmacophore, we call it, and that are going to be given for the life of the patient and, therefore, exposure would be over a long period.

For those types of drugs, they are especially interested in higher levels of purity and lower levels of impurity.

BY MR. POLLACK:

Q. Now, you understand when this patent was filed, treprostinil was an approved drug being used by patients; correct?

A. Yes.

MR. DELAFIELD: Objection. Vague.

BY MR. POLLACK:

Q. Okay. Now, my question, which you really didn't answer, was: Did you identify anyone at the FDA or elsewhere who expressed at the time this patent was filed a need or a desire for a purer treprostinil?

MR. DELAFIELD: Objection. Asked and answered.

THE WITNESS: The FDA has that desire for every drug to have an increase in purity, even if it's already in the market, and I've had to deal with that before as well.

And -- and they're especially receptive to that with drugs that are

exquisitely potent and drugs that are given on a chronic basis, and so that's -- and the fact that they allowed the specification to change indicates to me that they believed that this was a significant change.

BY MR. POLLACK:

Q. Okay. But you don't know of any document, either from the FDA or from in the literature or from any physicians, asking for a change in purity for treprostinil at the time this patent was filed or before?

MR. DELAFIELD: Objection. Asked and answered.

THE WITNESS: The -- I don't know if whether or not anyone from the FDA asked for that, but it doesn't need to be the FDA. A company can have a desire to increase purity and, again, because the FDA permitted it and they don't actually really like making changes unless they're significant, they did so and changed the specification.

BY MR. POLLACK:

Q. So the FDA changed the specification?

A. Ultimately you can't change a specification without FDA approval.

Q. Sure, but --

A. So they ultimately changed the specification at the request of UTC.

Q. They allowed UTC to change the specification?

A. They approved the change that UTC had suggested after a detailed analysis. That's one of the things they have to do. These are considered significant changes by the FDA.

Q. Can you turn to your paragraph 69 and in particular I'm looking on page 34 of your declaration, Exhibit 3.

A. Okay. 69 I think starts on 30 -- 33 it starts.

Q. Right.

A. Which page would you like me?

Q. I'd like you to focus on 34 but, you know, feel free to read whatever you need to read.

A. Okay.

Q. I'm going to ask you about the first full sentence on 34, which reads:

I have repeatably -- excuse me.

"I have repeatedly observed during the course of my career that the FDA balances their strong desire for the highest levels of purity against the practical need for a company to be able to manufacture the drug product reliability" -- I'm sorry.

A. Reliably.

Q. Reliably. Let me read the whole sentence again.

A. Okay.

Q. "I have repeatedly observed during the course of my career that the FDA balances their strong desire for the highest levels of purity against the practical need for a company to be able to manufacture the drug product reliably."

Did I read that correctly this time?

A. Yes, you did.

Q. Okay. Finally.

You still agree with that sentence?

A. Oh, yes.

Q. Okay.

A. Yes.

Q. Doesn't that sentence mean that the FDA is not going to insist on the highest purity possible because there are practical concerns with making a drug purer and purer and purer; isn't that the case?

MR. DELAFIELD: Objection. Mischaracterizes the document.

THE WITNESS: That's only partially correct.

BY MR. POLLACK:

Q. What's incorrect about it?

A. Your -- your description left out the fact that the FDA can, in fact, insist that you increase purity.

Q. Did the FDA do that in the case of treprostinil? Did they insist that UT increase purity?

A. I don't know.

MR. DELAFIELD: Objection. Compound.

THE WITNESS: Yeah, I don't know whether they did or did not.

BY MR. POLLACK:

Q. Do you know if anyone else insisted that United Therapeutics increase purity?

A. I don't know if United Therapeutics insisted on it themselves. They obviously wanted to do that because they took the issue to the FDA, and after a long review period and significant rebuttal by the FDA, as is normal as with any submission to the FDA, the FDA agreed and approved that change.

Q. Let me ask you.

I can always purify a drug further just by purifying it again and again and again; isn't that so?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: Not necessarily, no.

BY MR. POLLACK:

Q. But in many cases I can; right?

A. Yeah, in some cases you can.

Q. Right. Now, one reason for not doing that is when I do that, one, it's expensive and, two, it decreases yield; correct?

MR. DELAFIELD: Objection. Lack of foundation.

THE WITNESS: Not necessarily.

BY MR. POLLACK:

Q. But in many cases?

MR. DELAFIELD: Same objection.

THE WITNESS: It can happen, yes. That can happen.

BY MR. POLLACK:

Q. And that's one reason that scientists need to balance purity against other manufacturing considerations; correct?

MR. DELAFIELD: Same objection.

THE WITNESS: I was not talking about scientists. I was talking about FDA.

BY MR. POLLACK:

Q. Okay. Well, what about scientists then? What's your opinion about scientists?

A. A vast majority of scientists in the pharmaceutical industry wouldn't be involved in any of this at all.

Q. Okay. What kind of people would be involved in this at all?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: Could you be more specific in -- in what you're asking in "this"?

BY MR. POLLACK:

Q. Well, you just made the statement that a vast majority of scientists --

A. Would not.

Q. -- would not be involved in this at all. So I'm asking -- I'm just following up on the language you used.

What are you referring to? Who would be involved?

MR. DELAFIELD: Same objection.

THE WITNESS: There could be scientists in the -- in the laboratory at the laboratory level. Scientists in the kilo plant. Scientists in the scale-up facilities. And scientists inside the company in the manufacturing group who could want to produce a product that is, you know, has higher level of purity.

BY MR. POLLACK:

Q. Okay. Looking at only those scientists you've just identified, would it be the case that those scientists would balance manufacturing and other concerns against higher purity?

MR. DELAFIELD: Objection.

Vague and lacks foundation.

THE WITNESS: Most of those scientists that I mentioned wouldn't have any idea of the impact that additional purity would have on the practicality and expense because they don't work -- the majority of what I listed -- in the -- the large-scale manufacturing facilities.

BY MR. POLLACK:

Q. Okay. Well, which scientists would know about that impact?

A. Inside manufacturing facilities are process research chemists, and they make estimates of the cost of adding a purification step and, of course, some purification steps decrease cost. They don't all increase. Many do, but they don't all.

Q. Are you a process research chemist?

A. Process research chemists -- chemistry reported to me as did the kilo plant chemists and the process transfer chemists that transfer the process to the manufacturing facilities. They all reported to me.

Q. Well, you were president of the company so everyone reported to you; right?

A. I was president of research and development.

Q. Yeah. So everyone?

A. Not --

Q. All the scientists?

A. Not the company.

Q. Sure. But all the scientists reported to you?

A. There are some scientists in the manufacturing facility that did not report to me.

Q. Okay. But my question was: Are you a process research chemist?

A. I have extensive training in chemistry, but I am not a process research chemist per se, no.

Q. Okay. Let me ask you.

A. However, those decisions, as I said earlier when we were talking about another area, ultimately were mine, and -- and I was responsible for reaching those decisions and making them.

Q. So when you made those decisions, didn't -- didn't you balance purity against other manufacturing concerns?

A. Yes, I did.

Q. If you could turn to page 12 in your declaration, Exhibit 3, paragraph 24.

A. 24, yes.

Q. And you say there:

"I understand that SteadyMed's expert, Dr. Winkler, in his declaration has opined that a POSA" -- do you understand that to be a person of ordinary skill in the art?

A. Yes, I do.

Q. Let me start it again then.

"I understand that SteadyMed's expert, Dr. Winkler, in his declaration has opined that a person of ordinary skill in the art 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.'"

Do you disagree with that statement?

A. Yes, I do disagree with that statement.

Q. Why?

A. Based on my experience in the pharmaceutical industry, a person involved in the type of chemistry that we're talking about in the patent is a very high level. I consider it to be complex chemistry, and I would have changed that to be a Ph.D. in -- I would have taken out master's degree. I have not seen master's degree chemists make these kinds of decisions or -- or judge this type of chemistry. I would have had the level set higher.

Q. Okay. Because Dr. Winkler's level is too low?

A. I believe it's too low based on my experience working in the industry and that I would have set that higher.

Q. Okay. Let me ask you then.

If he had written that a person of ordinary skill in the art would have a Ph.D. in medicinal or organic chemistry, or a closely related field, would you agree with that?

A. I would agree with that based on my experience on the types of people that actually do this work because I've managed those people

for many, many years.

Q. Then let me ask you.

Under that -- oh, what about the next, his alternative? Do you disagree that an individual with a bachelor's and five years of experience would be skilled enough?

A. I have --

MR. DELAFIELD: Objection. Vague.

THE WITNESS: I have not observed in my experience someone with a bachelor's degree and five years of experience to be capable of judging and making decisions based on that kind of chemistry.

And if I could add, while I agree with the -- with what we just discussed that a Ph.D. in medicinal chemistry or organic chemistry, I don't believe that's sufficient either.

I would add several years of experience in the pharmaceutical industry on top of that. A graduating Ph.D. in chemistry or medicinal chemistry couldn't judge this type of chemistry in real life in

the pharmaceutical industry.

BY MR. POLLACK:

Q. Okay. Now, it says "a Ph.D. in medicinal or organic chemistry, or a closely related field."

In your view, what would be appropriate closely related fields?

A. Pharmaceutical chemistry, analytical chemistry, stereochemistry, physical chemistry. Another specialized field is physical pharmaceutics.

Q. Anything else?

A. That's all that's coming to mind. There may be others.

Q. Okay. Am I correct then that you, yourself, you don't have a Ph.D. in medicinal chemistry or organic chemistry or physical chemistry or analytical chemistry or physical pharmaceutics or -- or even pharmaceutics; is that correct?

A. No, I have extensive training in all those areas, but I do not have a Ph.D. in that area. I have a Ph.D. in pharmacology.

Q. Right. Okay. So you wouldn't meet this person of ordinary skill in the art that

we were just discussing, this standard?

MR. DELAFIELD: Objection.

Vague.

THE WITNESS: As you recall, I also indicated experience in the pharmaceutical industry as being required, and in that regard, I believe I would be a POSA.

BY MR. POLLACK:

Q. Okay. But you don't have the Ph.D. that you required?

A. Not -- not the P -- well, it says "or related field." My Ph.D. is in pharmacology dealing with stereochemistry and structure activity relationships, and I consider those to be highly chemistry-dominated disciplines and that would fit in a closely related field.

Q. Okay. But when I asked you which fields you would include, you didn't include pharmacology.

MR. DELAFIELD: Objection.

Asked and answered.

BY MR. POLLACK:

Q. Is that fair?

A. I -- well, if you're asking would I include pharmacology with those qualifications that I just listed, I would agree to that. That that would be -- that would fit a POSA.

Q. So --

A. Just -- just pharmacology without those qualifications that I just listed for you, I would not list a Ph.D. only in pharmacology without the qualifications, which I do have.

Q. Okay. Yeah, let me make sure I understand then the qualifications.

So it's a Ph.D. in pharmacology plus what? What else would you need?

A. Plus experience in structure activity relationships and stereochemistry, which in my case would -- would, in fact, fit that description, and I suppose there are others. There are pharmacologists that have experience in analytical chemistry and so on.

Q. Do you have experience in analytical chemistry?

A. Yes, I do.

Q. What's your experience in analytical chemistry?

A. In addition to having managed hundreds of medicinal -- of analytical chemists, I have taken as part of my training, both as an undergraduate in pharmacy school and as a graduate student, physical chemistry, analytical chemistry, pharmaceutical analytical chemistry, quantitative analytical chemistry, and obviously a great deal of medicinal chemistry and organic chemistry.

Q. Okay. I didn't ask you earlier.

Have you worked on any other -- maybe I did ask you.

Have you worked on any other inter partes reviews, or is this your first one?

A. I believe this is my first one.

Q. Okay. Let's go to paragraph 28 of your report.

And there you say that in forming your opinions, you've reviewed several documents.

Who provided you with those documents?

A. The compilation of the documents was sent to me by Mr. Delafield, but most of those documents were documents that I

identified early in the preparation of my first draft of this report.

Q. Do you recall which documents you identified and which ones Mr. Delafield provided?

MR. DELAFIELD: Objection. To the extent it discloses communications, I instruct you not to answer.

THE WITNESS: So I should not answer?

MR. DELAFIELD: Well, you're asking him who provided what, which I think --

MR. POLLACK: He is an expert. He's not a fact witness.

MR. DELAFIELD: I know but --

MR. POLLACK: So I'm asking the basis of his, you know, reliance. If he relied on your stuff, that stuff is not privileged.

MR. DELAFIELD: Okay. But he can answer in terms of what he provided.

THE WITNESS: I provided documents from the FDA, from the ICH, some references related to the FDA, documents

related to purity issues and -- and effects of trace impurities. The effect that trace impurities can have on a patient.

BY MR. POLLACK:

Q. Which documents had to do with the effects of trace impurities on patients?

A. There --

MR. DELAFIELD: Objection. Vague.

THE WITNESS: There is a document on penicillin contamination, cephalosporin contamination, bacterial contamination -- not bacterial -- bacterial component contamination.

BY MR. POLLACK:

Q. E. coli component?

A. E. coli.

Q. And that was in insulin?

A. That's correct.

Q. And the penicillin contamination, that was in other antibiotics?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: I'm sorry. Could you --

BY MR. POLLACK:

Q. The penicillin contamination, that was concern for other antibiotics?

A. No.

Q. Oh, that was concern for which drugs?

A. For any --

MR. DELAFIELD: Objection. Vague.

THE WITNESS: It was concern for any drug manufactured by a company that makes -- that also makes a penicillin analog.

BY MR. POLLACK:

Q. Okay. As far as you know, United Therapeutics doesn't make any antibiotics; correct?

A. I don't know.

Q. You don't know?

A. No.

Q. Are you aware at all of what drugs --

A. I'm sorry?

Q. Are you aware at all of what drugs United Therapeutics makes?

A. I'm only aware of this, of this product.

Q. Okay. So you're not aware that treprostinil is the only drug substance that is sold by United Therapeutics?

A. I --

MR. DELAFIELD: Objection. Lacks foundation.

THE WITNESS: I don't know very much about United Therapeutics beyond this product and -- and this litigation.

BY MR. POLLACK:

Q. And you didn't look into whether or not United Therapeutics made any -- any antibiotics?

MR. DELAFIELD: Objection. Asked and answered.

THE WITNESS: No, I did not.

BY MR. POLLACK:

Q. Okay. And you didn't look into whether or not United Therapeutics works with E. coli or any other kinds of bacteria?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: No, I did not.

MR. POLLACK: I'm going to mark as Ruffolo Exhibit 4 a document also called Exhibit 1001 in the case. It's US patent number 8,497,393.

(Document marked for identification purposes as Ruffolo Exhibit 4.)

THE WITNESS: Thank you.

MR. DELAFIELD: Thank you.

BY MR. POLLACK:

Q. I assume you reviewed this patent thoroughly in forming your opinion?

A. Yes, I did.

Q. Okay. And this is the patent at issue in this IPR proceeding; correct?

A. Yes, that's my understanding.

Q. Okay. If you could turn to the claims of the patent, they begin at column 17.

Now, do you see claim 1 there?

A. Yes, I do.

Q. Tell me, how many compounds would you say are claimed in claim 1? Do you have an estimate?

MR. DELAFIELD: Objection. Vague. Calls for speculation.

THE WITNESS: There are many compounds. I have no idea how many. I couldn't estimate, but there potentially are many.

BY MR. POLLACK:

Q. Millions?

A. I don't know.

Q. You didn't look into that?

A. I didn't look into the number of compounds. No, I did not count them.

Q. Okay. But it's at least thousands; right? Is that fair?

MR. DELAFIELD: Objection. Lacks foundation. Calls for speculation.

THE WITNESS: It's a good many compounds. I don't know the quantitation.

BY MR. POLLACK:

Q. Okay. Well, you're an expert in chemistry, I understand.

So based on that, can you give me some estimate looking at the --

A. That misstates --

Q. -- number of groups there?

A. That misstates --

MR. DELAFIELD: Objection.

Form.

THE WITNESS: -- my prior testimony.

BY MR. POLLACK:

Q. Okay. Would you correct it for me?

A. Yes. I did not claim I was an expert in chemistry. I claimed I had extensive training in chemistry.

Q. Okay. Thank you.

What can you tell me then about the purity of some of the other compounds that are in claim 1?

MR. DELAFIELD: Objection. Outside the scope of his declaration. Lacks foundation.

THE WITNESS: Again, I am -- was told to prepare for long-felt need. This is not something I've been asked to do, and I don't know what purity of other compounds would be.

BY MR. POLLACK:

Q. Well, you said you were asked to prepare a long-felt need.

Are you talking about the long-felt need for the compounds in claim 1 or is that

not part of your opinion?

MR. DELAFIELD: Objection.

Vague.

THE WITNESS: I prepared to talk about treprostinil and not other compounds.

BY MR. POLLACK:

Q. Okay. So as you sit here today, there's nothing you can tell me about the long-felt need for all those other compounds in claim 1?

A. No, there's nothing I can tell you about the long-felt need for those other compounds.

Q. What about claim 2? Is there anything you can tell me about the long-felt need for the compounds of claim 2 which -- which relates to claim 1?

MR. DELAFIELD: Objection.

Vague.

THE WITNESS: I'm sorry. Could you repeat the question?

BY MR. POLLACK:

Q. Sure. Is there anything or do you have any opinion regarding the long-felt need of the compounds in claim 2, which is a

dependent claim, from claim 1?

Let me step back a second.

Do you understand what a dependent claim is? I don't want to --

A. Yes, I think I do.

Q. What -- what's your understanding?

A. The dependent claims follow on from the independent claims. It's about all I understand.

Q. Okay. So you need everything in the independent claim plus something else in the dependent claim; is that how it works?

MR. DELAFIELD: Objection. Calls for legal conclusion.

THE WITNESS: Can you say that again, please?

BY MR. POLLACK:

Q. Yeah. In your understanding, you need everything that's in the independent claim plus what's in the dependent claim and that's how the claim is read?

MR. DELAFIELD: Same objection.

THE WITNESS: Again, I'm not an attorney and I -- my understanding is basic as what I just described.

BY MR. POLLACK:

Q. Can you describe it again?

A. That it follows a dependent claim, but I don't know everything that's included or not included.

Q. Oh, okay. What did you mean by "follows" then?

MR. DELAFIELD: Same objection.

THE WITNESS: To put it crudely, the -- not crudely, but probably in an unsophisticated manner, not being an attorney.

The dependent claim is related to the independent claim, but I don't understand the legal significance between those, and it's not something I think about or was asked to comment on and not something I've been trained to do.

BY MR. POLLACK:

Q. You said, though, it was related, but what's your understanding of the relationship?

MR. DELAFIELD: Objection. Asked and answered. Outside the scope of his declaration.

THE WITNESS: I can't be more specific than I -- than I have been. I'm sorry. I just don't have the legal training to do that.

BY MR. POLLACK:

Q. Okay. You're not sure how it's related?

MR. DELAFIELD: Objection. Mischaracterizes testimony.

THE WITNESS: Just as I said, it is related. In terms of specifically how, I don't know.

BY MR. POLLACK:

Q. So let me get back then. Let me ask again then.

Are you here to give an opinion about the long-felt need for the compounds in claim 2?

A. I'm here to give testimony on the long-felt need of treprostinil.

Q. And treprostinil only?

A. And the diethanolamine salt.

Q. And the diethanolamine salt as well?

A. Yeah.

Q. Okay.

A. I consider them the same. They're both -- one is a salt and one is a free acid. That's similar compounds.

Q. Well, let me ask you.

Claim 9. Do you know which one is claim 9?

A. Yes.

Q. Okay.

A. I'm just reading it.

Q. Am I correct that claim 9 includes both treprostinil and the diethanolamine salt and other salts?

A. I agree that claim 9 includes treprostinil and it would include the diethanolamine salt and other pharmaceutically acceptable salts.

Q. Fair enough. Let's start with other pharmaceutically acceptable salts.

What can you tell me about the long-felt need and the purity of those other pharmaceutically acceptable salts?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: Those other salts,

to my knowledge, aside from the diethanolamine salts, are not on the market; and as I described before, the long-felt need is by the FDA and those other salts not being marketed products or being developed for the market, as far as I know, would have -- would be of no interest to the FDA.

So I don't believe there would be -- I'm not here to talk about the long-felt need of something that is not a product.

BY MR. POLLACK:

Q. You're saying there is no long-felt need for something that is not a product?

MR. DELAFIELD: Objection. Mischaracterizes testimony.

THE WITNESS: There may be, but I'm not prepared to talk about that, and I don't believe the FDA would have an interest.

BY MR. POLLACK:

Q. Okay. What about -- you understand when claim 9 is completed, step (d) is only optional; right?

A. No, I don't agree with that.

Q. You see where it says "optionally reacting the salt"?

A. Yes.

Q. Okay. In your view, that's not optional?

A. Because in the chemical structure directly above -- above that, we see the free acid, the -- the reaction involving step (d) would have to take place to generate that salt -- to generate that free acid.

Q. You see, though, that it doesn't just show the free acid.

A. I'm -- yeah.

Q. It shows "or a pharmaceutically acceptable salt thereof"?

A. Yeah.

Q. You see that?

A. Correct. I'm sorry. Can I rephrase my answer?

Q. Please.

A. The structure -- chemical formula 4, Roman numeral 4 in claim 9, is the result of step (d) and -- and so because that compound is part of this patent, step (d) is not optional when it comes to making that compound.

Q. Okay. But you can also make, instead of making that compound, you can make a pharmaceutically acceptable salt; correct?

A. That's correct. You can make a pharmaceutically --

Q. Right.

A. -- acceptable salt.

Q. For example, treprostinil diethanolamine salt is a pharmaceutically acceptable salt?

A. Yes, it is a pharmaceutically acceptable salt.

Q. And if I don't carry out -- I can make treprostinil diethanolamine salt without carrying out step (d); is that correct?

A. That's correct, and so my reference to that being not optional was specifically when I referred to the free acid of treprostinil.

Q. Okay. But you'd agree with me the claim doesn't just include the free acid. It also includes the salts?

A. It includes the salts.

Q. Okay.

A. The pharmaceutically acceptable

salts.

Q. Okay. And so when step (d) is not carried out and the pharmaceutically acceptable salts are made, what can you tell me about the purity of the treprostinil diethanolamine salt?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: The purity of the diethanolamine salt, based upon the material I've reviewed, is -- is quite high and higher than previous methods for preparation.

BY MR. POLLACK:

Q. Okay. Was there -- because I didn't see this in your report -- in your declaration. So that's why I'm asking.

Are you giving an opinion regarding the long-felt need for a treprostinil diethanolamine salt made according to the patent?

A. Yes, I'm giving an opinion on the marketed products.

Q. Okay. What evidence do you have that there was a long-felt need for a purer treprostinil diethanolamine salt?

A. As I explained earlier, for marketed products, the FDA is always looking for higher levels -- the highest levels of purity that are possible and practical, and especially so for drugs that have exquisitely potent pharmacophores and drugs that are given chronically, and that applies to both the free acid and the diethanolamine salt.

Q. Okay. Other than that general concept, do you have any statements from the FDA or anyone else specifically addressing the purity or commenting on the purity of the treprostinil diethanolamine salt?

A. Yes.

MR. DELAFIELD: Objection. Vague.

THE WITNESS: Yes. The FDA, one, in -- in granting the change clearly supported the increase in purity, and in the January 2009 letter submitted to the FDA answering questions from the FDA, of the three questions that the FDA had, two of them were related to purity of treprostinil and the diethanolamine salt.

So, yes, the FDA did have

concerns about purity when evaluating the new manufacturing process.

BY MR. POLLACK:

Q. Okay. You know what? Let's take a look at that. Can we mark as Ruffolo Deposition Exhibit 6 -- is it 6 or 5? -- 5. Can we mark as Ruffolo Deposition Exhibit 5 what's also been marked as UT Exhibit 2006, a letter from United Therapeutics to Norman Stockbridge at the FDA.

A. I'm sorry. Did I say 2009 before?

Q. It's a 2009 letter. You're correct.

A. Oh, okay. Okay. I'm sorry.

Q. Its exhibit number is 2006.

A. Oh, okay. My misunderstanding.

Q. Former exhibit number.

(Document marked for identification purposes as Ruffolo Exhibit 5.)

THE WITNESS: Thank you.

BY MR. POLLACK:

Q. Okay. So is Ruffolo Exhibit 5 the letter to the FDA that you were just referring to?

A. Yes, it is.

Q. If you could turn to page 2 of the letter, do you see there's a heading with a bullet point regarding "Benzindene triol"?

A. Yes, I do.

Q. Okay. And do you see underneath that there's a paragraph that talks about their Chicago facility?

A. Yes, I do.

Q. Okay. In fact, this letter concerns a change in manufacturing which -- in which United Therapeutics wished to move their plant from Chicago to Maryland; correct?

A. That's my --

MR. DELAFIELD: Objection. Mischaracterizes the document.

THE WITNESS: That -- that's part of my understanding, but also to approve a new manufacturing process.

BY MR. POLLACK:

Q. And one of the changes in that new manufacturing process is they're going to [redacted] instead of [redacted]; isn't that correct?

A. That's correct.

Q. Okay. And, in fact, changing how the [redacted] is [redacted] and [redacted] that can affect purity as well; isn't that correct?

MR. DELAFIELD: Objection. Lacks foundation. Vague.

THE WITNESS: Can you repeat the question?

BY MR. POLLACK:

Q. Sure. Changing how -- what [redacted] is used can change the purity as well; isn't that correct?

MR. DELAFIELD: Same objections.

THE WITNESS: The -- a change in the [redacted] of the [redacted] can have effects, and the FDA was clearly worried about impurities because it mattered so much. That's why there's so much guidelines on purity. They're worried about impurities that carry over into the final product.

BY MR. POLLACK:

Q. Right. And that change in [redacted] has nothing to do with the change in process that concerns the '393 patent in this case?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: Can you ask that again, please?

BY MR. POLLACK:

Q. Sure. That change in [redacted] that's not the type of change that's described in the '393 patent?

MR. DELAFIELD: Same objection.

THE WITNESS: The change in the [redacted]?

BY MR. POLLACK:

Q. Right.

A. Okay. So could you ask it one more time, please?

Q. Sure.

A. Because now I've got --

Q. Okay.

A. I'm just trying to figure out what you were asking. It wasn't quite clear to me. I'm sorry.

Q. The change in [redacted] --

A. Yes.

Q. -- in this process --

A. The change of [redacted].

Q. -- that's not something that's described anywhere in the '393 patent?

MR. DELAFIELD: Same objections.

THE WITNESS: The '393 patent, the [redacted] is not [redacted]. It's something else many steps earlier.

BY MR. POLLACK:

Q. Now, let's take a look at that first paragraph after the bullet point, and the first sentence says:

"Historically at our Chicago facility, UT-15C."

Do you know what UT-15C is?

A. Yes, I do.

Q. Okay. What is it?

A. It's treprostinil free acid.

Q. Okay. You're sure that's not treprostinil diethanolamine salt?

You see how it's referred to as "UT-15C intermediate"?

A. Intermediate. Yes. I'm sorry. Intermediate. Yes, I -- can I -- can I start from the beginning --

Q. Absolutely.

A. -- of this letter and review?

(Reviewing document).

Yes, I -- I change my answer. It is not the free acid. I believe it is the -- the diethanolamine salt. I believe it's the diethanolamine salt.

Q. Okay. That's my understanding as well.

A. Okay.

Q. I just wanted to make sure we get the record correct.

"Historically at our Chicago facility, UT-15C" -- that's the diethanolamine salt; correct?

A. Yes, I believe so.

Q. Okay.

-- "is not a compound that was used during the conversion of [redacted] to treprostinil."

Did I read that correctly?

A. Yes.

Q. Then they say:

"This new process was necessary for the production of UT-15C API for our investigational oral formulation (IND 71,537),

but it also affords an additional purification step and an improvement in the process to synthesize treprostinil API."

Did I read that correctly?

A. Yes, you did.

Q. Okay. And in that sentence, they're referring to purification of treprostinil free acid; is that fair?

A. I believe so.

Q. Well, I mean, you've --

A. That's how I would read that.

Q. Okay. I mean, in your declaration, you focused on this --

A. Yes.

Q. -- exhibit; correct?

A. Yes.

Q. Okay. And then the next sentence it says:

"The data in Table 5 from the validation report (VAL-00131) show several impurities detected at low levels below the ICH identification limit of [redacted] percent."

Do you see that?

A. Yes, I do.

Q. Okay. And reading that together

with the next sentence, which reads:

"These impurities are not carried through to the final API, treprostinil as described below."

Based on those two sentences, there are impurities in the treprostinil diethanolamine salt; is that fair?

MR. DELAFIELD: Objection. Mischaracterizes the document.

THE WITNESS: Well, I'd like to see Table 5.

BY MR. POLLACK:

Q. Do you have -- you're commenting on this document.

Did you review Table 5 in your analysis?

A. I don't recall.

Q. Okay. Will you agree with me, though, that there's a set of impurities that are described?

MR. DELAFIELD: Objection. Vague. Mischaracterizes the document.

THE WITNESS: Can I read that paragraph again?

BY MR. POLLACK:

Q. Absolutely.

A. (Reviewing document). Okay.

So could you ask the question again, please?

Q. Sure. So according to this paragraph, there are certain impurities that were found in treprostinil diethanolamine salt, also known as UT-15C; correct?

MR. DELAFIELD: Objection. Mischaracterizes the document.

THE WITNESS: I don't know of any compound that doesn't have impurities. So, you know, that doesn't surprise me that there would be impurities.

BY MR. POLLACK:

Q. Okay. But, I mean, this paragraph is describing that there's some impurities?

MR. DELAFIELD: Same objections. Asked and answered.

THE WITNESS: And, again, it's identify- -- it's saying that their impurities. I haven't seen Table 5 that I recall, and if you have it, I'd like to look at it, but it's something that would be common to any chemical reaction that

produces a drug, even one that lowers impurities. There are still going to be impurities.

BY MR. POLLACK:

Q. Yeah. What I want to know is: What can you tell me about the impurities that they found in the UT-15C salt using this process?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: Again, I'm here to talk about long-felt need, but if you show me Table 5, I can answer that question.

BY MR. POLLACK:

Q. Right. You've never looked at Table 5, though?

A. I --

MR. DELAFIELD: Objection. Asked and answered.

THE WITNESS: I said I didn't recall if I did or not.

BY MR. POLLACK:

Q. As you sit here now, you don't recall anything about Table 5?

A. I have --

MR. DELAFIELD: Same objections.

THE WITNESS: I have reviewed thousands of tables, and I don't know if I reviewed Table 5 or not. So if I could look at it, I can answer your question, but I can't do it off the top of my head.

BY MR. POLLACK:

Q. Okay. So as you sit here now, you're not able to tell me what the impurities are that would be in that Table 5?

MR. DELAFIELD: Objection. Vague. Asked and answered. Lacks foundation.

THE WITNESS: Not -- not unless you show me Table 5 I can't. Couldn't possibly remember all that.

BY MR. POLLACK:

Q. Okay. Let me ask you this then.

Can you tell me how the impurities that were found in Table 5 in this process differ from the impurities in any other process used to make treprostinil diethanolamine salt?

MR. DELAFIELD: Same objections.

THE WITNESS: The -- if you're asking with respect to Table 5?

BY MR. POLLACK:

Q. Right.

A. I need to see Table 5.

Q. And just to be clear, Table 5 is a document owned by United Therapeutics?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: I didn't know that, but whoever owns it, if you can show it to me, I can try and answer your question.

BY MR. POLLACK:

Q. But you are relying on this document and in forming your opinion you didn't say, hey, I need to see Table 5, as far as you recall?

A. I may have seen it. I don't recall because as I said, I reviewed quite literally thousands of tables, and I don't recall if I've seen this one. I may have. I don't recall.

Q. Do you recall seeing any tables regarding the impurities in treprostinil diethanolamine salt?

A. Yes, I do.

Q. What document was that?

A. I saw the Walsh declaration.

Q. All right. Anything else?

A. There may have been others, but that's the one that's coming to mind.

Q. And based on the Walsh declaration, are you able to opine on any differences between the impurities in treprostinil diethanolamine salt according to the patent and any other methods of making the diethanolamine salt?

MR. DELAFIELD: Objection. Lacks foundation.

THE WITNESS: I can only comment on Dr. Walsh's conclusion where he indicates that to be the case but, you know, again, I'm here to talk about long-felt need. I'm happy to answer that question if you can show me the table so I can make the comparison.

BY MR. POLLACK:

Q. By the "table" you mean the VAL-00131?

A. Yes.

Q. Okay.

A. But I simply can't do it from

memory.

Q. Yeah. Okay. Do you see at the top of this document it says "Protective Order Material"?

A. Yes.

Q. Okay. And do you understand that this is a -- considered a confidential and secret document by United Therapeutics?

MR. DELAFIELD: Objection. Lacks foundation. Mischaracterizes the document.

THE WITNESS: I see "Protective Order Material." I don't know what that means, but I assumed everything I looked at is confidential material.

BY MR. POLLACK:

Q. Well, you think the patent is confidential material?

A. No. I mean, everything -- all of the documents that are not public in the public domain.

Q. So you understand this is not a public document?

MR. DELAFIELD: Objection. Lacks foundation. Asked and answered.

THE WITNESS: I believe this is not a public document.

BY MR. POLLACK:

Q. Right. In fact, you signed a protective order?

A. Yes, that's what I was referring to. That's why I -- I said I didn't, you know, couldn't disclose certain things and so I -- to me, this is a confidential document, yes.

Q. Right. And what that means is, other than the group of us in this room, a few people at United Therapeutics, and a very small group of people at the FDA who were specifically involved, no one in the public has seen the information in this document?

MR. DELAFIELD: Objection.

BY MR. POLLACK:

Q. Is that fair?

MR. DELAFIELD: Objection. Lacks foundation.

BY MR. POLLACK:

Q. Is that your understanding?

MR. DELAFIELD: Objection. Lacks foundation. Mischaracterizes testimony.

THE WITNESS: I don't know. I assume that's true. I don't know.

BY MR. POLLACK:

Q. Okay. But as far as you know, no physician in the public has seen this document?

MR. DELAFIELD: Same objections.

THE WITNESS: Say it again. I'm sorry, please.

BY MR. POLLACK:

Q. No physician in the public has seen this document?

A. Outside of the FDA?

Q. Yeah.

A. I assume they haven't.

Q. And even at the FDA, only the -- most likely only the people who are involved with this application would have seen this document?

MR. DELAFIELD: Objection. Lacks foundation.

THE WITNESS: The -- there would be a good number of people at the FDA who would have had access to this document. I don't know who would review it, but all the way up to the final signature, which would

include a division director would have had access to it. I don't know who would have seen it.

BY MR. POLLACK:

Q. Right. Well, you're familiar with the FDA process; right?

A. Of course.

MR. DELAFIELD: Objection. Vague.

THE WITNESS: Of course.

BY MR. POLLACK:

Q. So this kind of detailed chemistry review, about how many people do you think at the FDA would have looked at this?

A. Oh.

MR. DELAFIELD: Objection. Calls for speculation and vague.

THE WITNESS: I could only guess.

BY MR. POLLACK:

Q. Okay.

A. I don't know the exact number.

Q. Okay. But it would be a small number?

MR. DELAFIELD: Same objections.

THE WITNESS: What does "small" mean?

BY MR. POLLACK:

Q. Five people?

MR. DELAFIELD: Same objections.

THE WITNESS: My guess is it would be more than that.

BY MR. POLLACK:

Q. More than 10?

MR. DELAFIELD: Same objections.

THE WITNESS: I don't know, but it could be. We're talking about approval of a manufacturing process. That's considered a major change according to the ICH, and so major changes undergo extensive review.

BY MR. POLLACK:

Q. Right.

A. And extensive review would involve, you know, quite a few people at the FDA, which is one of the reasons that they don't like to make changes in specification or manufacturing processes. It is very concerning to them, and it consumes a great deal of resource and a great deal of analysis by quite a few people,

but I don't -- I can't give you the number.

Q. You're not aware of -- you've seen the label for the treprostinil products; right?

A. Yes, I have.

Q. Okay. Was there any label change made when the process for making treprostinil described in this letter was made?

MR. DELAFIELD: Objection. Vague. Relevance.

THE WITNESS: Label changes don't include process changes.

BY MR. POLLACK:

Q. Okay. Is there any -- is there anything on the label of the product indicating or any other public information indicating that the purity of the product changed?

A. FDA labels don't contain purity information.

Q. Is there any other kind of public announcement that the purity of treprostinil changed after this letter?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: The FDA, to my knowledge, does not put out public

announcements on changes in purity.

BY MR. POLLACK:

Q. This is all secret information; right?

A. This --

Q. The purity of this product?

MR. DELAFIELD: Objection. Vague. Calls for speculation.

THE WITNESS: This document would be, yes.

BY MR. POLLACK:

Q. Well, do you know is there any other document that has purity information that you know of that is public?

A. There are many, but not having to do with the FDA and NDAs. So when you purchase a compound for a study from some chemical supply company, they have purity on there.

Q. Sure. Sure.

A. But so there are lots of purities you can find on the Internet and then when you purchase material. But in an NDA, no, that information is not subject to announcements, inclusion in labels. It's not -- not done.

Q. This is all secret, in fact, which

is why it's stamped "Protective Order Material"?

MR. DELAFIELD: Objection. Lacks foundation. Calls for speculation.

THE WITNESS: Well, I don't know who stamped that, but I assume this document is confidential.

BY MR. POLLACK:

Q. Right. I'm not allowed to show this to SteadyMed or anyone else who's outside of this room who's not under the protective order; correct?

MR. DELAFIELD: Same objections. Asked and answered.

THE WITNESS: I would assume that's true.

BY MR. POLLACK:

Q. Yeah. And that would also be true of this validation report, VAL-00131?

MR. DELAFIELD: Objection.

BY MR. POLLACK:

Q. That would also be confidential?

MR. DELAFIELD: Objection. Lacks foundation. Calls for speculation.

THE WITNESS: That's Table 5 and

I would assume that would be confidential as well.

BY MR. POLLACK:

Q. Right. Now, it says that the impurities are not carried through, and that's the impurities in treprostinil diethanolamine salt; is that right?

A. Well, I'm going to have to read it again. Where are you referring?

Q. Yes. The same paragraph.

A. Same paragraph.

Q. This is on page 2 of Ruffolo Exhibit 5.

A. (Reviewing document).

Q. And do you see -- this is the penultimate sentence and it says:

"These impurities are not carried through to the final API, treprostinil as described below."

Do you see that?

A. I see that.

Q. Okay.

A. I need to -- I need to read a little bit more, I think.

Q. Sure. Let me ask you a question

and that way you can read more and try to find the answer to my -- to my question.

That sentence, that's referring to performing the optional step (d) in claim 9?

MR. DELAFIELD: Objection. Calls for speculation. Mischaracterizes the document.

THE WITNESS: (Reviewing document). Okay. So could you repeat the question?

BY MR. POLLACK:

Q. Yes. So my question is: That sentence which reads "These impurities are not carried through to the final API, treprostinil as described below," that sentence refers to carrying out step (d) of claim 9, the optional step?

MR. DELAFIELD: Same objections.

THE WITNESS: Yes, I believe they're talking about the free acid, in which case it would include step (d), which wouldn't be optional.

BY MR. POLLACK:

Q. Right. So if step (d) was not carried out, there's a number of impurities

that would still be left in the tri- -- in the treprostinil diethanolamine salt; is that fair?

MR. DELAFIELD: Objection. Calls for speculation. Lack of foundation.

THE WITNESS: There would be impurities in any product, you know, that's part of the product.

BY MR. POLLACK:

Q. Sure. But there are impurities that are removed by step (d) in making treprostinil that are present in triethanol -- in treprostinil triethanol --

A. Ethanolamine.

Q. Let me start again.

There are impurities that are removed by optional step (d) that are present in treprostinil diethanolamine salt that is a result of carrying the process through step (c)?

MR. DELAFIELD: Objection. Calls for speculation. Lacks of foundation. Asked and answered.

THE WITNESS: There are impurities in any compound and that would include this. As I recall, in the Walsh

document, the impurities were very low.

BY MR. POLLACK:

Q. Yes, but there are impurities in triethanolamine -- in treprostinil diethanolamine salt that are not -- that are removed by step (d) and, therefore, not in the treprostinil free acid?

MR. DELAFIELD: Objection. Lacks foundation. Calls for speculation. Asked and answered.

THE WITNESS: I'd like to look at the -- at the Walsh document before I answer that because that -- that will help me.

BY MR. POLLACK:

Q. Okay. Without looking at the Walsh document, you're not able to answer?

A. I don't have it memorized. I'm sorry.

Q. Okay. But, I mean, reading the text here, you're not able to conclude that there are impurities that were removed by carrying out step (d) --

MR. DELAFIELD: Objection.

BY MR. POLLACK:

Q. -- based on the sentence that's written here?

A. There is not enough information here for me -- for me to make that kind of a conclusion without looking at the -- at Table 5, for example, and -- and other sources.

Q. And if I gave you the Walsh declaration, would you be able to answer my question?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: If I had the -- the table in the Walsh declaration, I could tell you whether there are differences in -- in the impurity profile.

BY MR. POLLACK:

Q. Okay. Let me ask you.

Do you know whether step (d) removes impurities from treprostinil diethanolamine salt?

MR. DELAFIELD: Objection. Calls for speculation. Lack of foundation.

THE WITNESS: And, you know, again, I'm here to talk about long-felt need, but I can deal with that question with

the Walsh declaration where there is a comparison between the diethanolamine salt and the free acid made by the new process.

BY MR. POLLACK:

Q. Okay. As you sit here now, you don't know whether step (d) removes impurities from the treprostinil diethanolamine salt?

MR. DELAFIELD: Objection. Vague. Calls for speculation. Asked and answered.

THE WITNESS: I can guess, which would be speculation, but I can answer if I see the Walsh document.

BY MR. POLLACK:

Q. Okay. Well, you're an expert and so part of the things you do is give opinions.

What is your opinion --

MR. DELAFIELD: Same objections.

BY MR. POLLACK:

Q. -- on whether or not -- let me finish my question -- on whether or not step (d) removes impurities from the diethanolamine salt?

MR. DELAFIELD: Same objections. Outside the scope of his declaration.

THE WITNESS: I am an expert, but I don't have an eidetic memory, and I can look at the Walsh document, which I reviewed a number of times, and answer your question very simply if -- if you give me that document.

BY MR. POLLACK:

Q. Okay. Without that document, you don't have an opinion on whether or not step (d) removes impurities from treprostinil diethanolamine salt?

A. As I said, I don't --

MR. DELAFIELD: Objection. Asked and answered. Vague. Outside the scope of his declaration. Calls for speculation.

THE WITNESS: I don't remember. I'm sorry.

BY MR. POLLACK:

Q. Okay. I need -- I need -- I'm actually asking if you have an opinion, not whether you remember anything.

Do you have an opinion one way or the other?

MR. DELAFIELD: Same objection.

Asked and answered six times now.

THE WITNESS: The -- I would not like to rely on my opinion. I'd like to rely on data. That's what scientists do. I mean, you've asked me a scientific question and I can do it if you -- if I have access to --

BY MR. POLLACK:

Q. Right. Right. The reason I'm asking you is: Do you have an opinion regarding how the purity of treprostinil diethanolamine salt differs from the purity of any prior art treprostinil diethanolamine salt?

If you don't, that's fine. I was just wondering if that's something you're giving an opinion on.

A. That's --

MR. DELAFIELD: Objection. Asked and answered.

THE WITNESS: And I'm sorry, could you ask it again?

BY MR. POLLACK:

Q. Sure. Do you have an opinion on whether the treprostinil diethanolamine salt made in accordance with claim 9 differs from

prior treprostinil diethanolamine salts?

MR. DELAFIELD: Objection.

Vague.

THE WITNESS: For the

diethanolamine salt, I don't remember and I

need to look at -- at the data for

diethanolamine salt.

BY MR. POLLACK:

Q. Well, let me ask you. You have in

front of you your declaration.

Do you express in your declaration

an opinion -- and feel free to look through

it -- regarding whether or not there was a

long-felt need due to a difference in impurity

between the claim 9's patented treprostinil

diethanolamine salt and prior art treprostinil

diethanolamine salt?

MR. DELAFIELD: Objection.

Vague and compound.

THE WITNESS: The -- my comments

on long-felt need are based on the FDA's

desire to have purity improved, even in an

already pure compound, as far as possible

and practical. So that would apply to the

marketed products free acid and

diethanolamine salt.

BY MR. POLLACK:

Q. Do you have any opinion then that's specific to anything unique to treprostinil diethanolamine salt?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: The -- Dr. Walsh has made a -- I recall, I'd like to see the report to be certain -- has made a judgment that the '393 process produced a more pure diethanolamine salt, but I'd like to see the document.

BY MR. POLLACK:

Q. Yeah. Okay. I'm just asking you, though: Did you express that opinion in your declaration?

A. Which opinion? I'm sorry.

Q. That the tri- -- the treprostinil diethanolamine salt is purer made by the patent as opposed to the prior art.

MR. DELAFIELD: Same objections. Asked and answered.

THE WITNESS: The diethanolamine salt is the penultimate compound to the free

acid. Most of my comments refer to the free acid. I don't recall what I've said about the diethanolamine salt. So I -- that's -- that's what I remember.

BY MR. POLLACK:

Q. Okay. And feel free to look at your declaration. Can you look through and see if you made any comments about the treprostinil diethanolamine salt?

A. (Reviewing document).

Q. Let me refine my question.

Can you see if you made any comments in your declaration about the -- either the nature of the impurities or the amount of impurities in the treprostinil diethanolamine salt?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: Okay. Can I? Can I?

BY MR. POLLACK:

Q. Yes, please.

A. I can read it? (Reviewing document).

Could I make a note on here?

Q. Yeah.

A. Am I allowed to make a note?

(Marking). (Reviewing document).

Q. We need to just --

A. I'm almost --

Q. -- change the tape.

A. Oh.

Q. We can stay on the record as far as our court reporter is concerned.

A. Okay.

Q. But I don't think we need video of just him reading.

A. Okay.

MR. POLLACK: Yes, change the tape.

THE VIDEOGRAPHER: The time is 11:36 a.m. This completes Media Unit No. 1. We are off the record. Okay. I'm sorry for the delay.

The time is 11:37 a.m. This begins Media Unit No. 2. We're on the record. Please proceed, counsel.

BY MR. POLLACK:

Q. Do you need the question read back?

A. Yeah, I'm sorry for the delay and

if you could indulge me --

Q. No, that's fine.

A. -- by reading the question back please.

Q. No problem.

Can you see if you made any comments in your declaration about the nature of the impurities or the amount of impurities in treprostinil diethanolamine salt?

A. There are several references to treprostinil that -- and the patent that don't specify the salt or the diethanolamine and -- and that would include, therefore, both.

Q. Can you show me where?

A. Yes.

Q. Where you're referring to?

A. On paragraph 38, the last sentence.

"This desirable goal is one of the objects of the invention of the '393 patent with respect to the new preparation of treprostinil with a higher level of purity."

Q. Uh-huh. I'm sorry. Here at 38 it just says "treprostinil."

Does it say anything about treprostinil diethanolamine salt?

MR. DELAFIELD: Objection.
Vague.
THE WITNESS: As I said, because I didn't specify free acid or diethanolamine salt and I'm referring to the patent where both are produced, it would refer to both.
BY MR. POLLACK:
Q. Well, let me ask you something then. Can you go back to the patent --
A. Sure.
Q. -- for a second?
A. Yeah.
Q. Keep your declaration in front of you.
Let's take a look at -- did you ever look at claim 13?
A. Yes, I have.
Q. Okay. And in that claim, it says:
"The product of claim 9, wherein the base B in step (c) is selected from a group consisting of" and then there's "ammonia, N-methyl-glucamine, procaine, tromethamine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine."
Do you see that?

A. Yes, I do.

Q. Okay. Are you saying when you say "treprostinil" in the patent, does that include treprostinil ammonia salt?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: Those are not marketed products and, as I said, because I'm dealing with long-felt need, I would only be considering marketed products.

And, in fact, as I get further along in here with other examples, you'll see I even refer to "product" which would only be the free acid and the diethanolamine salt.

BY MR. POLLACK:

Q. Okay. So you're not -- in regard to, for example, claim 13, you're not commenting on any long-felt need for treprostinil ammonia salt, treprostinil N-methyl-glucamine salt, treprostinil procaine salt, etc.?

MR. DELAFIELD: Objection. Asked and answered and vague.

THE WITNESS: As I mentioned

earlier back in earlier questioning, I'm only commenting on the products because, in my opinion, a long-felt need wouldn't involve a salt that is not being developed or marketed or on the market.

So I'm referring to, with respect to long-felt need, to the marketed products, which is really what the FDA is concerned about.

MR. DELAFIELD: I just wanted to interrupt for a second. Lunch is here.

MR. POLLACK: Oh.

MR. DELAFIELD: Just whenever you guys are ready. So we can keep going or --

THE WITNESS: I can go all day.

BY MR. POLLACK:

Q. Okay.

A. Whatever you want. Whatever you like.

Q. No, that's fine with me.

A. It's up to you.

Q. Let me ask you, for example, about claim 12. You see there where it talks about the potassium hydroxide base?

A. Yes, I see that.

Q. Okay. Are you commenting at all about a long-felt need in regard to claim 12?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: Step (b) is the hydrolysis of the cyano nitrile.

So could you repeat the question?

BY MR. POLLACK:

Q. Yeah. Are you -- are you opining on a long-felt need in regard to claim 12?

MR. DELAFIELD: Objection. Vague. Asked and answered.

THE WITNESS: I -- again, I don't believe that the process of -- the product of step (b) is what? What is the product of step -- of step (b) in claim 12?

BY MR. POLLACK:

Q. You are the -- you are the expert. So let me ask you that.

What is -- do you know what the product of step (b) is?

A. Well --

MR. DELAFIELD: Objection.

Mischaracterizes the document and vague.

THE WITNESS: -- I said I was here to talk about long-felt need, and I'd like to know what that product is. And can you point to the chemical structure of the product for me? I could, you know, I guess I could work back.

BY MR. POLLACK:

Q. Yeah, I'm not trying to get you to form an opinion now.

I was wondering if you had expressed an opinion regarding the long-felt need of claim 12. Is that something you intend to do?

A. Well, claim 12 --

MR. DELAFIELD: Objection. Asked and answered.

THE WITNESS: -- is referring to a product from claim 9 that's been reactive with a base in step (b) of potassium hydroxide, and I'd just like to know which one of those and I suppose I could work it back.

BY MR. POLLACK:

Q. You've reviewed the patent; right?

A. Oh, of course, yes.

Q. Yeah. Okay. Okay. So if you look at column 10?

A. Okay. I'm sorry. I can -- I just worked it back.

Q. Okay.

A. And I will tell you what I believe the product is, and on the assumption that I have that right and only on that assumption, I'll then try to answer your question.

The claim 12 reads:

The product of claim 9, which is the cyano nitrile, wherein the base step is -- where the base in step (b) is potassium hydroxide.

So as I look at the chemical reaction or the chemical structures, that would result in a potassium salt of the free acid and that, to my knowledge, is not a product.

And so I think, as I recall your question -- it was a while ago since I had to work -- since I worked back -- you asked if that would be the subject of long-felt need, and I would answer no, because it's not a marketed product and the FDA wouldn't --

wouldn't have an opinion about it.

Q. Okay. So you're not offering an opinion about the long-felt need for -- for claim 12?

MR. DELAFIELD: Objection. Mischaracterizes his testimony. Asked and answered.

THE WITNESS: Actually, I thought I did offer an opinion that the FDA would not have a concern about a long-felt need for a salt form that was not an approved product, and potassium salt is not an approved product.

BY MR. POLLACK:

Q. Okay. So you have an opinion and your opinion is there isn't a long-felt need for claim 12?

MR. DELAFIELD: The same objections.

THE WITNESS: There is not a long-felt need for the potassium salt formed from claim 12 because it's not a product, if I got this structure correct, which I believe I do.

BY MR. POLLACK:

Q. Okay. And what about for claim 11? It has to do with the alkylating agent.

A. Okay.

Q. Do you have a need for long-felt claim 11, and if -- and if so, what is it?

A. Yes, I do have an opinion. That one --

MR. DELAFIELD: Same objections.

THE WITNESS: That one is easier for me in that I know what the product is, and the product is the cyano nitrile, and the FDA would not have any concern about the cyano nitrile in terms of long-felt need because it's not a marketed product.

BY MR. POLLACK:

Q. And just to make sure I'm understanding, is it then your opinion that there's no long-felt need for -- with respect to claim 11?

MR. DELAFIELD: Objection. Mischaracterizes the document and asked and answered.

THE WITNESS: The product of claim 11, which is not a marketed product and therefore not being given to patients,

the FDA would not have a long-felt need for that. They -- it wouldn't fall on their radar screen.

BY MR. POLLACK:

Q. So I'm trying to sort of get a yes or a no here. So I'm asking a yes or no question.

Am I correct that, in your view, there's no long-felt need for the product of claim 11?

MR. DELAFIELD: Objection. Mischaracterizes the document and testimony. Asked and answered.

THE WITNESS: Again, the product of claim 11 is the cyano nitrile, which is not a marketed product, and the FDA wouldn't have any long-felt need.

BY MR. POLLACK:

Q. Okay. Was that a yes or a no to my question?

MR. DELAFIELD: Same objections.

THE WITNESS: It was the answer to your question. Some questions you can't answer yes or no, and I'm saying that --

BY MR. POLLACK:

Q. Okay.

A. -- because it's not a marketed product, there wouldn't be on the FDA's concern a need for -- a long-felt need with respect to that product.

Q. Let me go down to claim 16. You see that one where it says:

"The product of claim 9, wherein the process does not include purifying the compound of formula (VI) produced in step (a)."

Do you see that?

A. Yes, I see that.

Q. Would there be a long-felt need with respect to claim 16?

A. I can write on this?

Q. Yeah.

A. (Reviewing document).

I don't believe that question has an answer. It's elimination of a step and -- and so elimination of a step I don't believe would have a long-felt need. Unless --

Q. Okay.

A. Unless you can tell me if I've misinterpreted that and that claim 16 refers to a specific compound, either the free acid or

the diethanolamine salt.

Q. Let me ask you then about claim 17, which talks about, again, the ammonia and then methyl-glucamine.

A. Yes.

Q. Are you opining regarding a long-felt need regarding claim 17?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: (Reviewing document). So it's my interpretation of claim 17, if I have this correct, that one of those bases, diethanolamine, would produce the diethanolamine salt and because that is a product, only that one product resulting from that one salt would have a long-felt need.

BY MR. POLLACK:

Q. Okay. And the other products, the ammonia, the glucamine, the procaine, those wouldn't have a long-felt need?

A. They're not marketed products and would not have a long-felt need by the FDA.

Q. And same question for claim 19. Are you opining on whether there's a long-felt

need for claim 19?

MR. DELAFIELD: Same objections.

BY MR. POLLACK:

Q. Why don't we do 19 and, in fact, 19 and 20 are somewhat similar, so why don't we do those together.

MR. DELAFIELD: Objection.

BY MR. POLLACK:

Q. Unless you feel otherwise --

MR. DELAFIELD: Objection. Compound and vague.

BY MR. POLLACK:

Q. -- that they're different.

A. I'd prefer to do one at a time. It will keep my --

Q. Okay.

A. -- mind more clear on what I'm answering. (Reviewing document).

If I understand the claim correctly, that derives from claim 1, which as we discussed earlier, has many, many, many compounds and I couldn't quantitate it, but there are a good many compounds.

And I believe it would only apply to one of those high number of compounds that

was reacted only with the diethanolamine to produce diethanolamine salt, which is a marketed product, and, therefore, there would be a long-felt need.

Q. And what about with respect to claim 20? Are you opining that there is a long-felt need for claim 20?

A. (Reviewing document).

So if I understand that claim correctly, that results -- that refers to a specific compound which, when reacted with diethanolamine, would form the diethanolamine salt, a marketed product, and that would, of course, fall within the scope of what I defined as a long-felt need.

Q. Okay. But the claim would also include the ammonia, glucamine, procaine salts. Am I correct you're not giving an opinion that the other members of that list of salts have a long-felt need?

A. The only one that I would say there was a long-felt need would be the diethanolamine salt.

Q. Now, let me just go to claim 22, and in claim 22, there's an extra thing that

after step (d) is done, so we formed the treprostinil acid --

A. Yes.

Q. -- is that fair?

A. That's -- that's my understanding, yes.

Q. After that is done, the product is converted to an unidentified pharmaceutically acceptable salt; is that a fair characterization?

MR. DELAFIELD: Objection. Mischaracterizes the document. Calls for speculation.

THE WITNESS: (Reviewing document). I'm sorry. Could you repeat that question? I think it doesn't make sense --

BY MR. POLLACK:

Q. Sure.

A. -- to me.

Q. After step (d) is performed --

A. Yes.

Q. -- in claim 22 --

A. Right.

Q. -- the treprostinil acid is

converted into a pharmaceutically acceptable salt.

Is that a fair interpretation of claim 22?

MR. DELAFIELD: Same objections.

THE WITNESS: As I understand it, no.

BY MR. POLLACK:

Q. Okay. How do you understand it?

A. But as I recall, step (d) generates the free acid, which can't be a salt because it's a free acid.

Q. Right.

A. So that free acid -- what confused me is you said "salt" and there is --

Q. Do you see the word "salt" in claim 22?

A. Oh, I'm sorry. I'm sorry. I was looking at claim 1.

Q. Yeah.

A. Claim 21. I apologize.

Q. Oh, okay. Yes. No, no. 22. I skipped over one.

A. I'm sorry.

Q. I didn't mean to throw you off.

A. I thought we were working down.

MR. DELAFIELD: Same objections.

THE WITNESS: My mistake.

(Reviewing document).

Okay. So, again, as I read the claim and if I understand it correctly, we're taking the product of claim 1, which is the free acid, and reacting it with a pharmaceutically acceptable salt, and there are no specified salts there.

So for that particular step, without specifying any salt, and I don't know if they're including diethanolamine in that, I can't say whether it would or wouldn't have a long-felt need. I don't know. They don't specify the salt. So I don't know what they're making.

BY MR. POLLACK:

Q. Can you take a look at the front of the --

A. Sure.

Q. -- '393 patent, Ruffolo 4?

A. Yes.

Q. And do you see there's a number 60 on the left and it says "Provisional

Application"? Do you see that on the left-hand column?

A. Oh, 60. Yes, I do see that.

Q. Okay. And do you see there's a provisional application filed on December 12, 2007?

MR. DELAFIELD: Objection. Mischaracterizes the document.

THE WITNESS: Yes, I do see that.

BY MR. POLLACK:

Q. Okay. Did you review the provisional application?

A. The '232 patent?

Q. Yes. The application. Well, it's an application --

A. Application.

Q. -- number, yeah.

A. I'd have to look at my -- at -- at the documents to -- to tell. I mean, I don't -- I don't know if I did. I may, I may not have.

Q. Okay. It is your understanding, though, that this application was -- applications leading to this patent were first

filed at the end of 2007?

MR. DELAFIELD: Objection.

Lacks foundation.

THE WITNESS: I know there were prior applications. I don't recall the dates. I think 2007 is a date that I do remember but, you know, I don't remember if that's the reason.

BY MR. POLLACK:

Q. Okay. Well, let me ask you.

In -- as you see, there's a bunch of filing dates on here. 2007, 2008, and 2012. Do you see that?

There's one at line 22.

A. I see 2008.

Q. Uh-huh.

A. 2007. I see 2012 at 65. At line 65. I see those.

Q. Yes.

A. Yeah. Okay.

Q. 2012 at -- at line 22 you mean?

MR. DELAFIELD: Objection.

Vague.

THE WITNESS: Oh, I see. Line 22. I was looking at the November 8th date.

Okay.

BY MR. POLLACK:

Q. I'm just talking about the dates of --

A. Filings?

Q. -- when things are filed you see.

A. Okay. I see that.

Q. Can you identify for me, can you name three people who felt there was a long-felt need for either treprostinil or treprostinil diethanolamine salt that was purer in any of 2008 -- 7, 2008 or 2012?

MR. DELAFIELD: Objection.

THE WITNESS: Can I look at --

MR. DELAFIELD: Vague.

THE WITNESS: Can I look at those patents? Or those filings?

BY MR. POLLACK:

Q. Well, why do you need to look at the filings?

A. I'd like to see who was on them and -- and maybe I'm not understanding your question. I'm sorry. Could you repeat that, please?

Q. Yeah. Let me -- let me rephrase it

then.

Other than the inventors, can you identify three people anytime between 2007 -- well, we'll do it this way -- anytime before 2012. Let me start my question again.

Can you identify for me at least three people other than the inventors prior to 2012 who expressed a long-felt need for a purer treprostinil or treprostinil diethanolamine salt?

MR. DELAFIELD: Objection. Vague. Calls for speculation.

THE WITNESS: The people who express the need -- the long-felt need for products with greater purity typically are the people at the FDA for a variety of products, and in particular those that are exquisitely potent and used chronically, and in that general sense it would be people at the FDA. And I can name three of those but...

BY MR. POLLACK:

Q. All right. Let's start with that.

Why don't you name for me the three people who prior to 2012 expressed a general

need for lower impurities that you know of.

MR. DELAFIELD: Same objection. Relevance.

THE WITNESS: Janet Woodcock, Norm Stockbridge, John -- Bob Temple.

BY MR. POLLACK:

Q. And how do you know that they expressed that general need prior to 2012?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: Because they are senior FDA executives and managers. They are involved in NDA decisions, and as I mentioned earlier, the FDA typically has the desire to have the highest purity possible and practical.

And they would have that -- they would have that desire, as well as the author on the letter from the FDA to UTC. That person would also have the -- and there are many others at the FDA, but those are names that -- that I -- that come to mind.

BY MR. POLLACK:

Q. Okay. But I think they were what you expressed -- I know you said that in your

declaration as well -- is that they would seek a high purity that's practical; is that fair?

MR. DELAFIELD: Objection. Mischaracterizes his testimony.

THE WITNESS: It's not just practical, it's possible and practical. They have to weigh both of those.

BY MR. POLLACK:

Q. Okay. But practical is part of the consideration?

A. It is part --

MR. DELAFIELD: Same objection.

THE WITNESS: -- of the consideration.

BY MR. POLLACK:

Q. Now, let me ask you if you could identify three people other than the inventors prior to 2012 who expressed a particular desire for greater purity particular to the drugs treprostinil or treprostinil diethanolamine salt.

MR. DELAFIELD: Objection. Vague. Relevance.

THE WITNESS: I don't know any employees at UTC and so I can't name any.

BY MR. POLLACK:

Q. As far as you know, United Therapeutics has never announced to the public that there was a change in the purity of its Remodulin product?

MR. DELAFIELD: Objection. Vague. Calls for speculation.

THE WITNESS: Not to my knowledge I don't. I don't know.

BY MR. POLLACK:

Q. You didn't ask to see anything like that, did you?

A. No, I did not.

Q. Okay. Why not?

A. I didn't believe that it was relevant to me. I was commenting on long-felt need and typically from the standpoint of regulators who always express that opinion.

Q. By the way, when you were at -- when you were director of R&D at Wyeth and SmithKline, was there another department at those -- those companies called the regulatory department?

A. Oh, yes, of course.

Q. Okay. And that department, was

that under your supervision or did it have a separate --

A. At --

Q. -- group?

A. At SmithKline, which is now GSK, it was under a separate division. At Wyeth, it reported to me.

Q. Would you agree, though, that the people in the regulatory group would know more about FDA regulatory requirements than the people in the R&D group?

MR. DELAFIELD: Objection. Vague. Calls for speculation. Lacks foundation.

THE WITNESS: So if your question is, would people in regulatory affairs know more than the scientists in the laboratory about what the FDA wants?

BY MR. POLLACK:

Q. Yeah.

A. The answer would be yes, they would.

Q. Okay.

A. And that's referring to the people in the laboratory.

Q. Right.
A. The scientists.
Q. Right.
A. Okay.
Q. Well, what about yourself? Would the people in the regulatory affairs group know more about what the FDA wanted in regard to impurities than -- than you would?
MR. DELAFIELD: Same objections.
THE WITNESS: Maybe not. I spent a lot of time walking the halls of the FDA and -- and regulatory -- regulatory positions are something that I've been invited to lecture on quite frequently, including to the FDA, and I consult with respect to regulatory positions to most large pharmaceutical companies and many mid-size.
So I don't believe everyone in regulatory affairs would know more than me. I'm sure some do, but I wouldn't agree that all of them or even the majority of them do.
BY MR. POLLACK:
Q. Okay. In forming your opinion today, though, did you -- other than the

attorneys, did you speak with anyone else to gain knowledge or other assistance in creating your declaration?

A. No, I did not.

Q. Okay. Did you speak to Professor Williams? I know you read his declaration; correct?

A. I read his declaration.

Q. Did you speak with him --

A. No.

Q. -- in regard to your -- let me finish my question.

A. I'm sorry.

Q. Did you speak with Professor Williams in regard to forming the opinions in your declaration?

A. No, I did not.

Q. Did you have an opportunity to ask Professor Williams questions about his declaration?

A. I guess I would have had an opportunity if I asked, but I didn't ask.

Q. Any reason why not?

A. Well, with respect to regulatory affairs, there isn't anything that Dr. Williams

could have told me or taught me about regulatory affairs.

Q. Okay. You do, though, refer to Dr. Williams' declaration in your -- in your declaration?

A. Oh, yes, in other capacities. I thought you were referring still to regulatory affairs.

Q. No, just in general.

A. Oh, I'm sorry.

Yes, I did refer to his -- his document.

Q. Okay. On those issues where you referred to his document, did you get an opportunity to ask him any questions about those issues?

A. I didn't ask him any questions.

Q. Okay. Any reason why not?

A. I didn't believe I needed to.

Q. Okay. Did you check or review any of the data that Dr. Williams was relying upon?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: I reviewed, I think, all of the data that he relied upon,

and I did some calculations based on his data, which appear in my report.

BY MR. POLLACK:

Q. Let's -- let's take a look at that. I think that's in paragraph 70; is that right?

A. I'll have to check. (Reviewing document).

Q. I'm sorry. It's in paragraph 67. Is that the calculation you're referring to at paragraph 67?

A. (Reviewing document). Yes, that's correct. This is what I was referring to.

Q. Are there any other calculations in your declaration?

A. I don't think so, but I don't --

Q. Yeah, I didn't see any.

A. -- recall with certainty.

Q. I was just checking.

A. Yeah, I don't think so.

Q. Okay. Explain to me. What was the calculation you did in paragraph 67?

A. I calculated the percentage reduction in total impurities based on the

analysis that Dr. Williams did on the treprostinil free acid by the former process and by the '393 process.

Q. Let me ask you.

Is what you did -- this number .9545, where did that come from? Did that just come from Dr. Williams?

A. Yes, that came from his table.

Q. Okay. Did you calculate that number independently yourself?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: No, I did not calculate that myself.

BY MR. POLLACK:

Q. Okay. Did you go through the individual, you know, purity numbers that -- from the raw data that he reviewed and check those?

A. I reviewed every Certificate of Analysis that was provided to me on the former process and the '393 process, and I reviewed every single one of them and took notes on almost every one of them.

Q. Did you calculate any of the

averages or standard deviations or anything like that?

A. No, I did not.

Q. Okay. So you're relying on Dr. Williams' --

A. Yes.

Q. -- calculation?

A. I'm relying on his calculation.

Q. Okay. And what about the number .2936? Did you just take that from Dr. Williams?

A. Yes, I took that from Dr. Williams' calculation.

Q. Okay. You didn't calculate any averages or standard deviations?

A. No, I did not.

Q. So am I correct, is the calculation that you did is you just subtract .2936 from .9545?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: No.

BY MR. POLLACK:

Q. Well, what did you do?

A. I divided .2936 by 9545 and

multiplied by 100 and then subtracted 1 to get the percentage reduction.

Q. Okay. That's the only calculation you did?

A. Yes.

Q. Okay.

A. I'm sorry. I didn't subtract that. Yes, I did subtract that from 1, yeah, to get the percentage reduction.

Q. And other than that, you didn't do any -- any other calculations?

MR. DELAFIELD: Objection. Asked and answered.

THE WITNESS: I didn't do -- I believe I did a calculation of the absolute percent. It's not in my document, and I forget what number I got. It was something close to [redacted] percent.

BY MR. POLLACK:

Q. What do you mean by the "absolute percent"?

A. That's dealing with the purity of the -- the free acid.

Q. Can you explain to me how that calculation is done?

A. Well, you decide -- divide the one by the other and multiply by 100, and I don't remember what I got, but it's something between a [redacted] percent and [redacted] percent.

Q. Okay. You said you divide one by the other.

What's the first one?

A. The first one --

MR. DELAFIELD: Objection. Vague.

THE WITNESS: -- would be the higher purity by the lower purity and then multiply by 100.

BY MR. POLLACK:

Q. The higher purity of what?

A. Of the free acid.

Q. When you say the "higher purity," are you referring to the purity of treprostinil made according to the '393 process?

A. That's correct.

Q. Okay. And there you're using the percentage. When you say the "higher purity" --

A. Yes.

Q. -- do you mean 1 minus .2936?

MR. DELAFIELD: Objection.

BY MR. POLLACK:

Q. Is that what you were referring to?

MR. DELAFIELD: Vague.

THE WITNESS: Yes.

BY MR. POLLACK:

Q. Okay. Okay. So you -- you took 1 minus .2936 and you divided that by 1 minus .9545?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: The other way around.

BY MR. POLLACK:

Q. Okay. I'm sorry.

You took 1 minus .94 -- 9545 and divided by 1 minus .2936?

A. Yes.

MR. DELAFIELD: Same objection.

THE WITNESS: Yes. Well, let me see. I just did it on the back of an envelope, so I don't remember.

No. I -- 1 minus -- yes. 1 minus .2936 divided by 1 minus .9545 multiplied by 100 to get the percent higher

level of purity.

BY MR. POLLACK:

Q. All right. What number did you get?

A. I don't remember. It was -- it was close to [redacted] percent, between a [redacted] and [redacted] percent.

Q. Between a [redacted] and [redacted] percent?

A. Between [redacted] -- yeah, [redacted] and [redacted] percent, something in that range.

Q. Okay. And why didn't you include that calculation in your report?

A. Oh, I just it did for my own interest. This was the number I wanted, the reduction in purity. Because the point I'm making here is that the FDA would certainly take a [redacted] percent reduction in purity -- in impurity level as being very significant, something they would like to see.

Q. Okay. Now, you're aware that the -- I think you are -- that there's a patent called the Moriarty -- not a patent, there's a paper in the Journal of Organic Chemistry that we've called the Moriarty paper.

You're aware of that; right?

A. Yes, I am aware of that.

MR. DELAFIELD: Objection.

Vague.

BY MR. POLLACK:

Q. And you're aware that in that paper they reported a purity of 99.7 percent?

A. I --

MR. DELAFIELD: Same objection.

Lacks foundation.

THE WITNESS: I believe that's what they reported at the -- in the very last sentence.

BY MR. POLLACK:

Q. Yeah, and that's -- that's the prior art Moriarty process in this case?

A. Yes, that's my understanding.

MR. DELAFIELD: Same objection.

Lacks foundation.

BY MR. POLLACK:

Q. Let me ask you.

If Dr. Williams made a mistake in his calculations and the set of data that he was relying on showed a purity of 99.7 percent for the Moriarty process, how would that change your opinion?

MR. DELAFIELD: Objection. Vague. Calls for speculation. Lacks foundation.

THE WITNESS: It wouldn't change my opinion.

BY MR. POLLACK:

Q. So even if the prior art was 99.7?

A. It wouldn't change --

MR. DELAFIELD: Same objections.

THE WITNESS: -- my opinion.

BY MR. POLLACK:

Q. So you're saying even -- even if there was a 99.7 percent purity level in the -- in the prior art, there would still be a long-felt need?

A. That 99.7 from Moriarty?

Q. Right, from Moriarty.

A. Yeah, that wouldn't change my -- my opinion.

Q. Okay. So even if all of the -- prior to the patent all of the treprostinil that United Therapeutics was selling had a purity of 99.7 percent, you still feel there would be a long-felt need for --

A. No, that's not what I was saying.

Q. Okay. Explain it to me.

MR. DELAFIELD: Objection. Lacks foundation. Calls for speculation.

THE WITNESS: I know how Dr. Williams did his analysis. He was pretty clear. And the purities that he got were based on total -- total --

BY MR. POLLACK:

Q. Related impurities?

A. -- total related -- total related impurities, and I know how that's done.

Q. Uh-huh.

A. Nowhere could I find in the Moriarty paper, which I looked very hard for, how his purity was measured, whether it was against a reference standard or whether it was against a -- or whether it was done by total related impurities.

And so you can't compare unless they're apples and apples and there that number 99.7 percent didn't mean anything to me because I couldn't tell how he did the analysis. You will get different results with a reference standard versus total related impurities.

Q. No, the FDA, though, requires that

United Therapeutics, and everyone else, reports total purity by HPLC analysis; is that correct?

MR. DELAFIELD: Objection. Lacks foundation. Calls for speculation.

THE WITNESS: There are options to use. They do happen to like the HPLC, but there are other analyses that are permissible.

And, of course, you have to run them by the FDA as part of your discussions, convince them of the reliability of that assay, show them the standard deviation, the relative standard deviation of the assay, the limit of quantitation, the limit of detection, and if they are convinced, you can use other assays.

BY MR. POLLACK:

Q. Okay. But in the case of treprostinil, United Therapeutics is submitting the HPLC assay analysis?

A. Yes, they are --

Q. Okay.

A. -- in the case of treprostinil.

Q. And that's not done by taking total related impurities?

MR. DELAFIELD: Objection. Mischaracterizes the documents and his testimony.

BY MR. POLLACK:

Q. Correct?

A. That's correct.

Q. Yeah. Okay.

A. They -- they do both, but the purity level by HPLC is what is required.

Q. Right. Actually --

A. Yes.

Q. -- you said they did both, but, in fact, they never total up the total related purities and subtract that from 100, do they?

MR. DELAFIELD: Objection. Lack of foundation. Calls for speculation.

THE WITNESS: No, because that's not a preferred analysis by the FDA. They want a reference standard and that's the HPLC.

BY MR. POLLACK:

Q. Right. And do you -- do you recall that the Moriarty reference he describes using an HPLC and a UV detector?

A. Yes.

MR. DELAFIELD: Objection.
Lacks foundation.
BY MR. POLLACK:
Q. Okay. Okay. Why are you then saying you don't -- you're not sure whether or not he used HPLC in a reference standard?
A. Well, H --
MR. DELAFIELD: Objection.
Lacks foundation.
THE WITNESS: -- HPLC is used for total related substances, too, but he didn't indicate whether he compared peak heights, which would be total related substances, or a reference standard, which would be the quantitation preferred by the FDA in their certificates of analysis, the release specs.
So I couldn't tell what Moriarty used, and I looked for it to see whether that was a number, a comparable number that I could use to compare apples to apples to -- to Dr. Williams.
BY MR. POLLACK:
Q. Let me ask you this.
Moriarty doesn't report anywhere

what the total related impurities are; right?

MR. DELAFIELD: Objection. Mischaracterizes the document.

THE WITNESS: I don't know.

BY MR. POLLACK:

Q. I mean, in the -- in the Journal of Organic Chemistry paper, he doesn't report it?

A. I don't know. He doesn't say what he did.

Q. Yeah. I'm saying, in the paper, he doesn't report the total related impurities?

MR. DELAFIELD: Objection. Lacks foundation. Mischaracterizes the document.

THE WITNESS: If he did his analysis by peak height comparison, he reported the total related impurities, and if he did it by HPLC, it was the HPLC quantitative assay. I don't know what he did.

BY MR. POLLACK:

Q. Yes, that's what I want to ask you.

I'm asking if he reports what the related impurities are.

A. I don't know.

MR. DELAFIELD: Same objections.

THE WITNESS: He may and he may not. Depends how he did the assay, and he doesn't say.

BY MR. POLLACK:

Q. Yes. I'm asking if in the paper he reports what the related impurities are, in other words, identifying them, saying anything about them.

MR. DELAFIELD: Same objections. Asked and answered. Asked and answered.

THE WITNESS: He doesn't report what it is he's measuring, whether it's total related impurities or a quantitative HPLC assay, and the results are different.

BY MR. POLLACK:

Q. Yeah. Maybe we're misunderstanding each other.

In the Journal of Organic Chemistry paper, does Moriarty say, here's some of the impurities that are present in treprostinil?

MR. DELAFIELD: Objection. Same objections. Asked and answered.

THE WITNESS: I don't recall. I'd have to go review the paper.

BY MR. POLLACK:

Q. You're aware that Moriarty is associated with United Therapeutics that that's their patent?

A. Yes, of course.

Q. Did you ask United Therapeutics, hey, can you tell me how Moriarty did this analysis?

A. No, I did not ask.

Q. Take a look at the '393 patent. Can you show me in the '393 patent where they report what the impurities are in treprostinil or any other compound?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: So they report purities in -- I don't see a table number -- in column 14 at the bottom, and those are HPLC area under the curve. So those are reference standards.

In table -- on column 16, they report a purity and -- and because that is the process that they submitted to the FDA for approval, that has to be an HPLC quantitative assay with a reference

standard.

BY MR. POLLACK:

Q. Uh-huh.

A. And in claim 2 -- I'm sorry -- claim 2 and claim 10, that is total related substances.

Q. Why do you say that if every other place in the patent it reports HPLC assay analysis?

A. Because it's my understanding that the document that was submitted by Dr. Walsh to the Patent Office was the last document before approval and that convinced the agency to approve this patent and the claims, and he did total related substances.

Q. So you're saying we should look at what Dr. Walsh says, not what's written in the patent?

MR. DELAFIELD: Objection. Calls for speculation.

BY MR. POLLACK:

Q. That is your opinion?

A. No, that's not my opinion.

Q. Well, then, why aren't we looking at the HPLC analysis in the patent?

A. That's not in the claim. I think, actually, you should look at all of them, but what's in the claim was done by a different method, total related substances.

Q. So you see the words "total related substances" in the claim?

A. No, I don't. As I said, I reviewed Dr. Walsh's analysis and that was submitted just before approval, as I understand, and there were no further actions taken before the decision. And so it makes sense to me that because he reported total related substances that the claims, which is what was in dispute -- dispute, referred to total related substances.

Q. Okay. You'd agree with me that within the patent itself, those are all HPLC analyses that are reported?

MR. DELAFIELD: Objection. Lacks foundation. Calls for speculation.

THE WITNESS: It's my judgment based on the description of area under the curve and the HPLC assay, as well as the fact that example 6 refers to the process that was approved by the agency, which is an

HPLC quantitative assay involving a reference standard, that that is what was used.

BY MR. POLLACK:

Q. And by "that" you mean HPLC analysis?

A. Yes.

MR. DELAFIELD: Same objections.

THE WITNESS: When you get to a point, I'd like to use the restroom. I don't need lunch if you don't want, but I do -- would like to use the restroom.

BY MR. POLLACK:

Q. Do you want to break? It's up to you. Do you want to break for lunch now?

A. It doesn't matter to me. Whatever you want to do.

MR. DELAFIELD: Yeah, it's already 12:30.

MR. POLLACK: You guys want to break for lunch? That's fine.

MR. DELAFIELD: Sure.

THE VIDEOGRAPHER: The time is 12:34 p.m. This completes Media Unit No. 2. We're off the record.

(Whereupon, at 12:34 p.m., a luncheon recess was taken.)

AFTERNOON SESSION

(1:23 p.m.)

ROBERT R. RUFFOLO, JR., PHD

called for continued examination and, having been previously duly sworn, was examined and testified further as follows:

EXAMINATION (CONTINUED)

THE VIDEOGRAPHER: The time is 1:23 p.m. This begins Media Unit No. 3. We're on the record. Please proceed, counsel.

BY MR. POLLACK:

Q. Welcome back, Dr. Ruffolo.

A. Thank you.

Q. Was lunch good?

A. Yes.

Q. Okay. You didn't discuss your testimony with counsel during lunch, did you?

A. No, we didn't.

Q. I'd like to turn to paragraph 32 of your declaration that is Exhibit 3.

A. Okay.

Q. And you can read -- you can read all paragraph 32, but I want to focus on page 15 at the top of the page. You have a

statement there that reads:

"For example, if the actual purity of an API is 99.4 percent and the lowest limit of purity in the Drug Specification of the Certificate of Analysis is 99.5 percent, the entire batch of API must be rejected."

Do you see that?

A. Yes, I do.

Q. Okay. So let me see if I -- if I understand this.

By the way, do you agree with that statement still?

A. Yes. As an example, yes.

Q. Okay. So, for example, let's say I have a Certificate of Analysis and it says the HPLC analysis is 99.6.

A. Okay.

Q. Okay. Would that drug be sold to the public?

MR. DELAFIELD: Objection. Vague. Calls for speculation.

THE WITNESS: That depends on what the specification was.

BY MR. POLLACK:

Q. Oh, I'm sorry. I was using --

A. Oh, in my example.

Q. -- your example. In your example.

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

Q. Yeah. So using your example.

A. Okay. Yeah.

Q. Let's say I had a drug which its HPLC analysis shows --

A. Yes.

Q. -- it had a Certificate of Analysis by HPLC of 99.6 percent.

Would the FDA allow the company to sell that batch to the public?

MR. DELAFIELD: Objection. Vague. Calls for speculation.

THE WITNESS: So if it was 99.6 and the specification was 99.5, yes, that would be allowed to be approved. I don't know if it could be sold to the public. That depends on many other steps because that API would go into that a drug product, and that has its own specs. So that would determine.

BY MR. POLLACK:

Q. Sure.

A. But it could move on in the manufacturing --

Q. It could move on in process?

A. -- in the manufacturing process.

Q. What if I had an API -- what does API stand for?

A. Active pharmaceutical ingredient.

Q. If I had an active pharmaceutical ingredient which had, just like your example, Certificate of Analysis, the specification is 99.5 percent. So let's say I had a batch and it had an HPLC assay analysis of 99.5 percent.

Could that move on in the process?

MR. DELAFIELD: Objection. Vague. Relevance. Calls for speculation.

THE WITNESS: Yes, that could move on if that 99.5 was the specification. Yes.

BY MR. POLLACK:

Q. Okay. Now, you're aware the limit for treprostinil that we're dealing with in this case is 98 percent; is that right?

MR. DELAFIELD: Objection. Calls for speculation. Lacks foundation. Vague.

THE WITNESS: That is the current lower limit.

BY MR. POLLACK:

Q. Okay. So if I have a batch, let's say I have a -- I make a batch of treprostinil and it -- I measure its HPLC assay and it's 99 percent.

Do you have my assumptions?

A. Uh-huh.

Q. Can that batch of treprostinil move on in the process?

MR. DELAFIELD: Same objections.

THE WITNESS: Assuming all of the other specifications were met, yes, that could move on.

BY MR. POLLACK:

Q. Okay. And I make another batch of treprostinil API and I measure its HPLC analysis and it's [redacted] percent.

Could that batch move on in the process?

MR. DELAFIELD: Same objections.

THE WITNESS: Yes, with that current level spec, that could move on.

BY MR. POLLACK:

Q. Okay. Based on your experience in the industry, if a company like United Therapeutics made a batch that was [redacted] percent on the HPLC analysis, it would be the normal expectation that the company would then move that batch into the rest of the process?

A. Yes.

MR. DELAFIELD: Objection. Relevance. Vague. Calls for speculation.

THE WITNESS: Yes, they could do that.

BY MR. POLLACK:

Q. Okay.

A. If they -- if they chose to.

Q. Now, Dr. Williams opined that certain batches that he looked at had an average HPLC analysis -- I'm sorry, I'm incorrect -- an average purity based on subtracting related impurities of 99 percent.

Is that -- is that what you recall?

MR. DELAFIELD: Objection.

BY MR. POLLACK:

Q. Approximately 99 percent --

MR. DELAFIELD: Objection. Vague.

BY MR. POLLACK:

Q. -- for the Moriarty batches?

A. Oh, for the --

MR. DELAFIELD: Objection. Vague. Mischaracterizes document.

THE WITNESS: I would have to look again at those tables, but it was something close to that. I don't remember the number.

BY MR. POLLACK:

Q. Okay. Yeah. I'm not trying to --

A. Yeah.

Q. -- trying to trick you here. If you look at where we were --

A. No, I understand. I just don't remember --

Q. Yeah.

A. -- the number.

Q. Remember we were -- we were looking --

A. Yeah.

Q. -- at your paragraph 67?

A. Yeah. Yeah. Okay.

Okay.

Q. And maybe I misunderstood, but I

think here you refer to Dr. Williams' declaration and his Table 1?

A. Yes.

Q. Do you see that?

A. I did, yes.

Q. And I think what I'm supposed to conclude here is that the -- well, what am what am I supposed to conclude about the typical purity of the Moriarty process, if anything, from your -- your paragraph 67?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: That the average relevant impurities are higher in the Moriarty process compared to the '393 process.

BY MR. POLLACK:

Q. Okay. Is there anything I'm supposed to conclude about what the average purity on the scale from zero to 100 percent is of API made by the Moriarty process?

MR. DELAFIELD: Objection. Vague. Calls for speculation.

THE WITNESS: Oh, I can't answer that because there will be variability.

There will be some high, some low, and I haven't analyzed how many would fall below spec. So I don't know.

BY MR. POLLACK:

Q. Okay. Well, let me ask you this. This number .945. If I subtract that number from 1 and multiply by 100 --

A. Uh-huh.

Q. -- right, I get approximately 99 percent; is that fair?

A. About, yes.

MR. DELAFIELD: Objection.

BY MR. POLLACK:

Q. Okay.

MR. DELAFIELD: Mischaracterizes the document.

BY MR. POLLACK:

Q. Would you -- in your view is -- does that characterize the average purity of products made by the Moriarty process?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: I believe that the analysis done by Dr. Williams gives a answer to the question that the Moriarty process

produces product that is less pure than the '393. And your question is?

BY MR. POLLACK:

Q. Okay. I was wondering if it gives an answer to the question of what the average purity was in the Moriarty process.

MR. DELAFIELD: Objection. Vague.

THE WITNESS: I think it gives a relative purity compared to the '393 process because, remember, it depends on how you do the analysis, whether it's against a reference standard or against total related product.

This I know was done against a reference standard, and so it gives an idea of average purity that one would expect with one process to another because you're comparing apples to apples in this case. And I think that's a fair comment what I said and --

BY MR. POLLACK:

Q. Okay. Let me just make sure you didn't --

A. Yeah.

Q. -- you didn't make an error here because you just said you know this was done by an HPLC analysis, but here it says total related substances in your paragraph 67.

A. Oh, I'm sorry. I'm sorry. I take that back.

The comparison is still valid because it's apples to apples total related substances. I apologize. But so it's apples to apples. The same relative purity is comparable. You can compare one to another, and it's higher with '393 than with Moriarty.

So I take it back. But you're right. It's total related substances.

Q. Okay. Based on this, are we able to say anything about how the HPLC analysis compares --

MR. DELAFIELD: Objection. Vague.

BY MR. POLLACK:

Q. -- for Moriarty versus '393 process?

MR. DELAFIELD: Objection. Vague. Calls for speculation. Outside the scope of his report.

THE WITNESS: Okay. I have not seen that comparison done on -- on HPLC quantitative assay against reference standard. I did look at all of those certificate of release forms where that's done, but I didn't do an analysis.

BY MR. POLLACK:

Q. Okay.

A. But the analysis that Dr. Williams did, because it's apples to apples, gives a good comparison of one process to the other, but I can't relate that to an FDA release spec that's done by different analysis to a reference standard. That's -- that's what I'm trying to say.

Q. Okay. Okay. I understand.

Okay. So what you're saying here in effect is, look, the '393 patent does another purification step on top of Moriarty, so the purity is going to be higher?

A. I'm not --

MR. DELAFIELD: Objection. Vague.

THE WITNESS: I'm not -- I wouldn't agree with that statement.

BY MR. POLLACK:

Q. Why not?

A. Because it takes away a purity -- a purification process of the -- of the nitrile. The Moriarty process -- excuse me -- involves purification of the nitrile --

Q. Okay.

A. -- and that's not done with -- with '393.

Q. Let's talk -- let's -- you said it wasn't done in '393. If we could go back to the '393. You got it there?

A. The patent? Yes. Yes.

Q. Okay. Very good. And then that is in this proceeding, our deposition, Ruffolo Deposition Exhibit 4.

If you turn to claim 16, you'd see there's a --

A. Claim 16.

Q. That's in column 20.

A. Yes.

Q. You see there's a step that says "does not include purifying the compound in formula (VI)."

And formula (VI) is the nitrile;

correct?

MR. DELAFIELD: Objection. Vague. Calls for speculation.

THE WITNESS: (Reviewing document). Yes, it says that the compounded formula (VI) does not include that purifying -- that purity step.

BY MR. POLLACK:

Q. Okay. So that's in claim 16?

A. That's in claim 16.

Q. Right. So then presumably the other claims you could include the purification of the nitrile.

MR. DELAFIELD: Objection.

BY MR. POLLACK:

Q. Is that your understanding?

MR. DELAFIELD: Objection. Vague. Lacks foundation. Calls for speculation.

THE WITNESS: That's not my understanding. The process that is the subject of this patent, which is, I think, referenced -- referenced in the claim 1 and claim 9, is referring to a process, which as I understand is the '393 process, which

doesn't have purification of the nitrile.

BY MR. POLLACK:

Q. Okay. I'm not -- I may be asking you something that's a little too legal, but do you have an understanding -- let me step back.

Do you have any patents?

A. I have a couple of patents, yes.

Q. Okay. Do you have any understanding of how patent claims work?

A. I have a -- compared to somebody like you -- a relatively low understanding of how patent claims work. I'm not totally ignorant on the subject, but I have some knowledge, but it's certainly nothing that I've devoted a great deal of time to.

Q. Are you familiar with the following concept? When a -- when a claim says "comprising" and it has a process comprising, that means the claim is met. If the steps of the claim are performed, plus in addition, because it says "comprising," it also includes processes which have additional steps that that's allowed, that's part of the claim as well.

MR. DELAFIELD: Objection.

Vague. Calls for a legal conclusion.

THE WITNESS: Yeah, that's getting a little bit beyond my -- my --

BY MR. POLLACK:

Q. Okay.

A. -- relative understanding.

Q. Yeah, I'm not asking you if that's right.

A. Yeah.

Q. I was just wondering if you knew about that.

A. Not -- not really.

Q. Oh, okay.

A. Not -- no. Again, I'm not a lawyer -- an attorney and -- and that is beyond my level of expertise.

Q. Okay.

A. So I'm sorry.

Q. Okay. Let me just ask you. Just going back to claim 16 where it said "wherein the process does not include purifying" the nitrile.

What was your understanding of how claim 16 was different from claim 9?

MR. DELAFIELD: Objection.

Vague.

THE WITNESS: Well, I -- because claim 9 says it's wherein the product is prepared by the process comprising, and that I understand is the '393 process, which doesn't have a purification step for the nitrile, I -- looks like claim 16 is reaffirming that. That's all I can say.

BY MR. POLLACK:

Q. Okay. So one of the -- one of the differences between the Moriarty process and what I call the '393 process -- that's what you call it in your declaration; right?

A. Yes, I think so.

Q. Is that in the '393 process, this purification step is -- of the nitrile has been removed?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: That's my understanding, yes.

BY MR. POLLACK:

Q. Yeah. Okay. Are there other -- in addition, there's a further purification step at the end where they make the diethanolamine

salt in the treprostinil that -- that United Therapeutics makes by the '393 process; is that your understanding?

MR. DELAFIELD: Objection. Vague. Lacks foundation.

THE WITNESS: It's my understanding that that crystallization was done, and it did result in an increase in the level of purity and a decrease in the level of impurities, which is what Dr. Williams analyzed.

BY MR. POLLACK:

Q. Other than that crystallization and the change in the purification of nitrile, did you identify any other differences between how United Therapeutics made treprostinil according to the Moriarty process and treprostinil according to what we're calling here the '393 process?

MR. DELAFIELD: Objection. Vague. Outside the scope of his declaration.

THE WITNESS: I would suggest that the formation of the diethanolamine salt as the step immediately before the

crystallization was part of the purification based on my -- on my review of -- of the documents.

BY MR. POLLACK:

Q. Now, you said that was a purification by crystallization; is that right?

MR. DELAFIELD: Objection. Vague. Mischaracterizes testimony.

THE WITNESS: That's the step (d), which is reacting the salt formed in step (c) with an acid to form the compound of formula IV, which is treprostinil free acid.

BY MR. POLLACK:

Q. That's called a crystallization?

A. That --

MR. DELAFIELD: Same objection.

THE WITNESS: -- to me would be a crystallization.

BY MR. POLLACK:

Q. Let me ask you.

Have -- have you seen crystallization used before to purify compounds?

A. Oh, yes. Yes, I have.

Q. How often?

MR. DELAFIELD: Objection. Vague. Calls for speculation.

THE WITNESS: It's a process that's used not uncommonly to purify final product of the reaction.

BY MR. POLLACK:

Q. Wasn't this -- isn't crystallization unique to the '393 patent?

MR. DELAFIELD: Objection. Vague and ambiguous.

THE WITNESS: The crystallization, as I understand it, is not what's unique to the patent. It's the result of that crystallization that resulted in a different product with a higher purity and lower levels of impurity.

BY MR. POLLACK:

Q. How long has crystallization been around as a method of purification?

MR. DELAFIELD: Objection. Vague. Relevance. Outside the scope of his report.

THE WITNESS: I don't know how long it's been around.

BY MR. POLLACK:

Q. Before 2007?

A. Oh, yes.

MR. DELAFIELD: Same objections.

THE WITNESS: Yes.

BY MR. POLLACK:

Q. Did you learn about it when you were in college at the university?

MR. DELAFIELD: Same objections.

THE WITNESS: Yes, I did.

BY MR. POLLACK:

Q. What course did you -- in what course did you learn about that?

MR. DELAFIELD: Same objections.

THE WITNESS: The inorganic chemistry, organic chemistry, physical chemistry, medicinal chemistry, pharmaceutical chemistry, analytical chemistry. Maybe some others.

BY MR. POLLACK:

Q. And when did you go to college?

A. In 1968 I started. In 1968.

Q. And when did you graduate?

A. I graduated with my BS in pharmacy in '73 and then my Ph.D. from the same

institution three or four years later.

Q. What school was that?

A. The Ohio State University, Football Capital of the World.

Q. Yeah. (Laugh).

And those courses you described taking where they talked about purification with crystallization, did you take those when you were an undergraduate or a graduate?

MR. DELAFIELD: Objection. Relevance.

BY MR. POLLACK:

Q. Or both?

A. Both.

Q. Okay. Okay. But you're an expert on or at least you have a lot of knowledge about stereochemistry; right?

A. Yes.

Q. Okay.

A. Yes.

Q. Okay. But I think it's the case -- is it the case that crystallization was not used to separate stereoisomers before 2007?

MR. DELAFIELD: Objection. Relevance. Vague. Calls for speculation.

THE WITNESS: Crystallization is often used to step -- separate stereoisomers. You have to conversion it to diastereomers by reacting with an optically active salt.

BY MR. POLLACK:

Q. Okay. But that wouldn't -- that technique of using crystallization to separate stereoisomers, that wouldn't apply to enantiomers, would it?

MR. DELAFIELD: Same objections. Outside the scope of his report.

THE WITNESS: To just the plain enantiomers?

BY MR. POLLACK:

Q. Yes.

MR. DELAFIELD: Same objections.

THE WITNESS: The same enantiomers -- crystallization of the same enantiomers wouldn't -- wouldn't separate them.

BY MR. POLLACK:

Q. I'm sorry. I didn't mean same enantiomers. I meant, you know, the two-direction, yeah.

A. The diastereomers -- excuse me.

MR. DELAFIELD: Same objections.

THE WITNESS: The enantiomers, dextro and levo --

BY MR. POLLACK:

Q. Right.

A. -- would not be separated alone by crystallization without first reaction with an optically active compound to produce diastereomers which then would be crystallized.

Q. Okay. All right. But how far back does doing that process you just described, how far back does that go?

MR. DELAFIELD: Objection. Relevance. Vague. Outside the scope of his report.

THE WITNESS: Decades.

BY MR. POLLACK:

Q. Before 2007?

A. Oh, yes.

MR. DELAFIELD: Same objections.

BY MR. POLLACK:

Q. Let me ask you some hypotheticals.

Suppose the -- just for this argument, for argument, suppose the Moriarty

process produced treprostinil and we had a batch of treprostinil made by the Moriarty product -- process and it had a 99 percent HPLC analysis purity.

Would United Therapeutics be allowed to send that Moriarty process treprostinil through the rest of the process and out to the public based on the current treprostinil specification?

MR. DELAFIELD: Objection. Vague. Calls for speculation. Lacks foundation.

THE WITNESS: They would be permitted to move it down the manufacturing process, and if subsequent specifications were met, then it could go out to the public.

BY MR. POLLACK:

Q. By "subsequent specifications," you're referring to specifications for the drug product?

A. Correct.

MR. DELAFIELD: Same -- same objections.

BY MR. POLLACK:

Q. They wouldn't measure the purity of the API again later in the process?

MR. DELAFIELD: Same objections.

BY MR. POLLACK:

Q. Once it's been formulated for a drug product?

MR. DELAFIELD: Same objections.

THE WITNESS: If the formulation had other components added to it, the API would not be tested again, but sometimes the API does just become the final product, so...

BY MR. POLLACK:

Q. Do you know in the case of treprostinil, does it just become the final product or does it need to be turned into a formulation?

MR. DELAFIELD: Objection. Relevance. Lacks foundation.

THE WITNESS: It needs to be turned into a formulation. I don't know what else is in the formulation, though.

BY MR. POLLACK:

Q. Let's suppose that the Moriarty process -- this is a hypothetical, this is my

assumption -- produces treprostinil on an HPLC analysis purity of [redacted] percent plus or minus [redacted] on the standard deviation. All right? So it might be [redacted]. It might be [redacted], but basically that's the range you're in.

In your opinion, would there be a reason for further purification?

MR. DELAFIELD: Objection. Vague. Calls for speculation. Outside the scope of his report.

THE WITNESS: [redacted] -- what did you say?

BY MR. POLLACK:

Q. [redacted] plus or minus [redacted].

A. As a standard deviation, that doesn't mean -- standard deviation doesn't mean you add 2 and subtract 2.

Q. Sure. But it does mean that -- what is it? -- 67 percent of the samples will fall between those limits?

A. It means that --

MR. DELAFIELD: Objection. Lacks foundation. Vague. Calls for speculation.

THE WITNESS: It means that the

95 percent confidence limit would be approximately plus or minus [redacted].

BY MR. POLLACK:

Q. [redacted]?

A. Standard --

Q. [redacted] or [redacted]?

A. [redacted].

Q. [redacted]?

A. Standard deviation is not plus or minus the actual number. Standard deviation is a statistical assessment of the variability, and when you have a standard deviation of 2, you calculate a 95 percent confidence limit which is multiplied by --

Q. I'm sorry. I said [redacted] plus or minus [redacted]. You may have misheard me.

A. Oh, I didn't hear the [redacted] if that's what you said.

Q. The point. Yeah, I'm sorry.

MR. DELAFIELD: Same objections.

THE WITNESS: And the same calculations still -- still you do. It's not plus or minus [redacted]. It would be plus or minus something like [redacted].

BY MR. POLLACK:

Q. And that would be 95 percent of the samples?

A. That would be -- would fall in --

MR. DELAFIELD: Same objections.

THE WITNESS: -- in that range.

BY MR. POLLACK:

Q. Okay. So 95 percent of the -- of the samples would fall between [redacted] and [redacted]; is that fair?

MR. DELAFIELD: Objection. Vague. Lacks foundation. Calls for speculation.

THE WITNESS: I forget what number you gave me for the medium purity.

BY MR. POLLACK:

Q. Ah, okay. Let me write it down [redacted].

A. Okay.

Q. And I'm doing a standard deviation of plus or minus [redacted] in my hypothetical.

And my question is whether that means that 95 percent of the samples would fall between [redacted] and [redacted].

MR. DELAFIELD: Objection. Vague. Calls for speculation. Lacks

foundation.

THE WITNESS: Approximately because I did an approximate calculation of confidence limit but...

BY MR. POLLACK:

Q. Okay. So let me just look back at your paragraph 32 for a second in your declaration, so we don't get confused then.

A. I'm sorry. Paragraph?

Q. 32.

A. Okay.

Q. And so you say here -- this is on page 14. I'm looking at your third sentence, and here you say:

"Although the FDA provides no absolute level of purity required for any drug, based on my experience of approximately 40 years in the pharmaceutical industry interacting with the FDA on regulatory issues, it is commonly assumed that, with rare exception, licensed drugs will have purities in excess of 99%, and often significantly higher."

Did I read that correctly?

A. Yes, you did.

Q. Okay. And you still agree with

that statement?

A. Yes, I do.

Q. Okay. If the Moriarty process is producing [redacted] plus or minus [redacted], wouldn't it meet the standard you just described there in paragraph 32?

MR. DELAFIELD: Objection. Vague. Calls for speculation. Mischaracterizes the document.

THE WITNESS: That's -- that's not a standard. That's -- that's what's commonly occurred. A standard is what's in the spec, what's in the specification of the Certificate of Analysis.

BY MR. POLLACK:

Q. Okay.

A. So that's really what matters.

Q. Right. Okay. Fair enough. And what's in the specification is 98 percent; right?

A. Correct. The lower limit now is 98 percent, yes.

Q. Right. So material made by the Moriarty process, if it has the limits that I just gave of [redacted] plus or minus [redacted], it will 95

percent of the time meet the spec?

MR. DELAFIELD: Objection. Calls for speculation. Lacks foundation.

THE WITNESS: Based on those, that number and the standard deviation, in my approximate calculation of 90 percent -- 95 percent confidence limits, yes, which is from --

BY MR. POLLACK:

Q. Right. In fact, if we pulled it out to 99 percent confidence limits, we would probably still meet the 98 percent specs?

MR. DELAFIELD: Same objections and outside the scope of his report.

THE WITNESS: Yeah, I can't do that calculation in my head.

BY MR. POLLACK:

Q. Okay.

A. So I don't know what the 99 percent confidence limits will be.

Q. They're going to be greater than 99 percent given my numbers; right?

MR. DELAFIELD: Same objections.

THE WITNESS: I don't know. I'd have to do the calculations and I can't do

that one in my head.

BY MR. POLLACK:

Q. Okay. But as you said here, based on your 40 years of experience, if you're in excess of 99 percent, it's not a rule, but as a kind of a sort of rule of thumb or best guess, better than 99 percent is probably going to be fine with the FDA; right?

MR. DELAFIELD: Objection. Mischaracterizes the document.

THE WITNESS: No, I wouldn't say that. The rule of thumb would be what's provided in the FDA guidances and, of course, they're guidances. So the FDA can and often does --

BY MR. POLLACK:

Q. Sure.

A. -- tighten them up above 99 percent. That's why I said "in excess of" and so it's what they agree with the manufacturer will be the specification for release.

Q. Right. But before you get to the FDA, when you were at Wyeth or GSK, your team would have to assess based on the purities you were getting what FDA would probably accept;

correct?

A. And --

MR. DELAFIELD: Objection. Vague.

THE WITNESS: And we would -- we would look at the guidance to give us an idea, but it's never a guarantee until the FDA -- until you sit down and discuss with the FDA.

They look at the data. They look at your analysis. They look at the -- the equipment that you're using. They look at the level of detection and, more importantly, the level of quantitation. And it's through that discussion and negotiation that you end up with a specification.

BY MR. POLLACK:

Q. Right. Fair enough. But when your team was working on drug approvals, if you saw, you know, a better than 99 percent, did that give you some confidence that yes, we can go to the FDA and see where that discussion goes?

MR. DELAFIELD: Objection. Vague. Relevance.

THE WITNESS: That depends on

when. 20 years ago, yes, I would think that our teams would go to the FDA with that. I don't believe we'd probably do that now on most drugs, but on some drugs we would go to 99 or maybe even lower.

BY MR. POLLACK:

Q. What about 10 years ago? Would you -- would you go with 99?

MR. DELAFIELD: Same objections.

THE WITNESS: I mean, the -- the criteria get tougher as time goes on and even today, depending on the drug, the FDA, if, for example, if it's a natural product with a very difficult extraction, they go to levels of 85 percent purity. Depends on the drug, the disease.

It's not a property of the drug itself. It's a property of the drug, the disease, the patients, whether there are alternate therapies and how serious a disease is, and those really go into determining what the specification will be in terms of purity.

BY MR. POLLACK:

Q. Okay. I assume in that analysis

the more serious a disease, the lower purity the FDA will accept?

MR. DELAFIELD: Objection. Relevance. Calls for speculation. Outside the scope of his report.

THE WITNESS: It's not that simple. There are serious diseases that have many good therapeutic options, and they may not --

BY MR. POLLACK:

Q. Sure.

A. -- go to that. So that's why I said, it's a very complex dynamic and that's why they issue guidelines and not regulation on these purities. And as you know, there are lots of guidelines on -- from the ICH and the FDA on purity.

Q. Sure. I'm just trying to understand how the guidelines work.

And so for a disease where there isn't or there aren't therapeutic options, is -- is the FDA a little more forgiving about impurities?

MR. DELAFIELD: Objection. Vague. Calls for speculation and outside

the scope of his report.

THE WITNESS: If the disease is very serious, there are few therapeutic options, or if the therapeutic options aren't very good and the FDA believes this is a drug patients should have and you can't get purity to a level that is typically found in guidance, they may relax that standard after negotiation.

But I can tell you, I've seen serious diseases, like cancer, where the FDA wouldn't budge. So it depends on a number of factors, and they take all those things into consideration that I mentioned, including your ability to manufacture a medically necessary drug, and they weigh that.

In addition to what I said earlier, how potent the drug is, which means it has a potent pharmacophore, and whether it's acute use or chronic use. And chronic use with a potent pharmacophore gets greater scrutiny.

So it's a very complicated analysis and assessment that they do which

is why it's the result of often multiple discussions and they -- the amount of data they demand to see before they make that final decision or accept your final recommendation is quite a bit.

BY MR. POLLACK:

Q. Do you know what disease treprostinil treats?

A. Yes.

Q. What disease is that?

A. Pulmonary arterial hypertension.

Q. Is that a serious disease?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: I consider that a very serious disease.

BY MR. POLLACK:

Q. Are there a lot of treatment options for pulmonary arterial hypertension?

MR. DELAFIELD: Objection. Vague. Outside the scope of his report.

THE WITNESS: There aren't many and they're not particularly effective. So it is a serious disease.

BY MR. POLLACK:

Q. What about treprostinil? Is it effective for pulmonary arterial hypertension?

MR. DELAFIELD: Same objections.

THE WITNESS: It is effective. It met the negotiated endpoints that the FDA required for approval in this disease.

BY MR. POLLACK:

Q. But people still die anyway of pulmonary arterial hypertension even on treprostinil?

A. They're --

MR. DELAFIELD: Objection. Vague. Calls for speculation. Lacks foundation.

THE WITNESS: Very sadly, yes.

BY MR. POLLACK:

Q. But in 2007, other than treprostinil, there weren't many treatment options for patients with pulmonary arterial hypertension?

MR. DELAFIELD: Same objections.

THE WITNESS: Not very many.

BY MR. POLLACK:

Q. Now, if treprostinil had a purity prior to 2007 of [redacted] percent on average, would

you agree with me that there's not a lot of leeway there to go up? I mean, it's only [redacted] percent?

MR. DELAFIELD: Objection. Calls for speculation. Mischaracterizes documents and vague.

THE WITNESS: If a single lot -- because that's all you can be talking about a single lot -- was [redacted], that's a -- depending on the assay and if it's the -- the reference standard assay HPLC, it -- it actually could be further away from 100 percent than [redacted] because you're basing it on a reference standard, which is not going to be 100 percent.

BY MR. POLLACK:

Q. Well, if the reference standard is not 100 percent, that raises the number; right?

MR. DELAFIELD: Objection. Vague. Calls for speculation. Lacks foundation.

THE WITNESS: No. What I said was that that [redacted] percent would be further removed -- [redacted] percent would be further removed from 100 percent. It would be less

than [redacted] percent from 100 because the reference standard is less than 100. So it would be [redacted] percent of the reference standard, and the reference standard is not 100.

BY MR. POLLACK:

Q. Right. Okay. And actually that, we've been talking about reference standards.

Reference standards are just a standard, a known error, in all HPLC assay processes?

MR. DELAFIELD: Objection. Lacks foundation. Vague.

THE WITNESS: It's not a known error. A reference standard has a known purity.

BY MR. POLLACK:

Q. Okay. But scientists were well aware about this issue of reference standards and that the value you get in an HPLC assay analysis, one of the sources of error in all HPLC analysis was reference standard?

MR. DELAFIELD: Objection. Vague. Lacks foundation.

THE WITNESS: That's not a

source of error. That's inherent in the assay, and it's related to the reference standard and not the equipment or the procedure relevant to the reference standard.

BY MR. POLLACK:

Q. You're saying the reference standard is not part of the HPLC procedure?

MR. DELAFIELD: Objection. Vague. Lacks foundation.

THE WITNESS: No, because you can do total related substances on an HPLC and that's not a reference standard procedure.

MR. POLLACK: I'm going to mark as Ruffolo Deposition Exhibit 6 a document formerly called UT Exhibit 2035.

(Document marked for identification purposes as Ruffolo Exhibit 6.)

THE WITNESS: Thank you.

BY MR. POLLACK:

Q. And Ruffolo Exhibit 6, is that one of the documents you relied on in your declaration?

A. Yes, it is.

Q. What is Ruffolo Exhibit 6?

A. The -- it's a guide to reviewers of primarily CMC sections of NDAs on chromatographic procedures of different types.

Q. Can you just very briefly explain what a CMC is?

A. Oh, the chemical, manufacturing and control section of a -- of an NDA. It's a very large and major portion of an NDA.

Q. Right. Very briefly, can you explain what's in the chemistry, manufacturers and control section of a New Drug Application?

MR. DELAFIELD: Objection. Relevance. It's outside the scope of his declaration.

THE WITNESS: I'll do the best I can, but it won't be 100 percent.

It will be the chemical synthesis, the purification procedures, the short-term stability, long-term stability, purity, melting point, the packaging, stability of the packaging, stability of the API, stability of the drug product. Many other things.

And, importantly, the validation of every single assay done on every single part of everything that I just mentioned and the ones I didn't mention, including the equipment and processes for cleaning equipment, cleaning rooms, cleaning. It's a very detailed document.

BY MR. POLLACK:

Q. Descriptions of all the factories and the equipment in the factories?

A. Descriptions and validation --

MR. DELAFIELD: Objection.

THE WITNESS: -- processes used for everything that comes in contact with that drug and every analysis done on that drug.

BY MR. POLLACK:

Q. You mentioned melting point as one of the things that's included in the CMC section.

Why do they have melting point in there?

MR. DELAFIELD: Objection. Vague. Relevance. Outside the scope of his report.

THE WITNESS: Melting point is used as a measure of identity of a compound.

BY MR. POLLACK:

Q. How does that work?

MR. DELAFIELD: Same objections.

THE WITNESS: The FDA wants to be sure that the compound that you say you've made is, in fact, the compound you say you've made, and so they include certain spectral analyses. It could be IR, infrared. It could be Raman spectroscopy. It could be UV and -- and melting points.

Those are characteristics of compounds that help the FDA confirm that what you've said you've made you've actually made.

BY MR. POLLACK:

Q. Okay. Do you know if the melting point is affected by the purity of the compound?

MR. DELAFIELD: Objection. Relevance. Calls for speculation. Outside the scope of his report.

THE WITNESS: There is a relationship to purity and -- between purity

and melting point and it's not an absolute relationship but also crystal form, polymorphs, amorphous forms, solvents, crystallization of solvents, crystallization procedure, all of those and other things affect melting point.

BY MR. POLLACK:

Q. Okay. Let me just ask you.

If I have two solids that are the same crystal form of the same drug and they have different melting points, is there a way to compare their purity based on the melting points?

MR. DELAFIELD: Objection. Vague. Calls for speculation. Outside the scope of his report.

THE WITNESS: As I said, melting point has a relationship to purity, but melting point isn't purity. The FDA doesn't accept melting point as a measure of purity.

BY MR. POLLACK:

Q. Sure.

A. And your question was, if you had a drug with a higher melting point is it more pure?

Q. Well, I said, they're the same crystal form.

A. Same crystal?

MR. DELAFIELD: Same objections.

BY MR. POLLACK:

Q. Yeah.

A. Yeah, in the same crystal form? Perhaps, perhaps not.

Q. What's the relationship -- you said there's relationship between melting point and purity?

A. Yes.

Q. What's the relationship?

MR. DELAFIELD: Same objections.

THE WITNESS: Often higher melting points have higher purities, but that's not necessarily the case. And when I reviewed all of the -- the Certificate of Analysis sheets on the specs, you can see many examples where higher levels of purity didn't have a higher melting point.

BY MR. POLLACK:

Q. You didn't put an opinion in your declaration on that, though; correct?

A. No. As I said, my -- my task was

to deal on long-felt need and so I didn't comment on that.

Q. Okay.

A. But if I had, I would have commented in the way I've told you and which, in fact, I believe is consistent with Dr. Williams' assessments with melting point.

Q. You can look at Exhibit 6, Ruffolo Exhibit 6. If you could turn to page 12.

And you reviewed this exhibit in detail, right, before creating your opinion?

A. Yes, I did.

Q. Okay. You said first paragraph, that first full paragraph, it says "With UVD detectors."

A. I'm sorry. I don't -- I don't see that. I must -- I'm on page 12.

Q. Page 12.

A. Oh, there are two page 12s.

Q. Ah, I'm sorry. Yes. I'm looking at the one that's sort of typed at the bottom.

A. Okay. I have it. Okay.

Q. I think it also says --

A. I'm sorry.

Q. -- page 9 in the smaller.

A. Yeah, I see it.

Q. No, you're right.

A. Yeah.

Q. There's two -- there's two different numbers on there so it's confusing.

A. Yeah. Okay.

Q. So it's the one that says P.12.

A. I see that. Okay.

Q. And you see there's a first full paragraph that says "With UV detectors."

Is it -- well, let me ask you. UV detectors. Those are the kind of detectors that are used in HPLC assay analysis?

A. Oh.

MR. DELAFIELD: Objection. Outside the scope of his report. Vague. Calls for speculation.

THE WITNESS: Lots of different types of detectors can be used with almost any spectra -- spectra photographic.

BY MR. POLLACK:

Q. Sure.

A. So it's one of them.

Q. For example, in Moriarty, Moriarty used a UV detection?

A. Are you saying --

MR. DELAFIELD: Same objections.

THE WITNESS: I don't remember that.

MR. POLLACK: I got to do my own work now.

I'm going to mark as Ruffolo Deposition Exhibit 7 a document formerly known as Exhibit 1004. It's an article from the Journal of Organic Chemistry by Moriarty and others.

(Document marked for identification purposes as Ruffolo Exhibit 7.)

THE WITNESS: Thank you.

BY MR. POLLACK:

Q. And this is what we've been referring to as the Moriarty article?

A. Yes.

Q. And I think if you turn to the very last page, it says -- I'm going to create ambiguity here, but the one that says page 13 in the bottom right-hand corner.

A. I see it, yes.

Q. It's also known as 1902.

A. Okay.

Q. Page 1902 from the original article.

Looking at page 1902, also known as page 13, does Moriarty report there on the purity of treprostinil that he made according to the Moriarty process?

MR. DELAFIELD: Objection. Vague. Calls for speculation. Outside the scope of his report.

THE WITNESS: So you're referring to what? I'm sorry.

BY MR. POLLACK:

Q. I just asked: Does he report on the purity of treprostinil made by the Moriarty process?

MR. DELAFIELD: Same objections.

THE WITNESS: There is a purity of 99.7 percent listed.

BY MR. POLLACK:

Q. Okay. And does he say there that it was done by HPLC?

MR. DELAFIELD: Same objections.

THE WITNESS: It says it was done by HPLC.

BY MR. POLLACK:

Q. Okay. And prior to that, does he -- does he indicate that UV was used?

MR. DELAFIELD: Same objections.

THE WITNESS: Prior to that. Can -- can you --

BY MR. POLLACK:

Q. Just before the words "HPLC." I'm not -- I'm not trying to --

A. Where HPLC is methanol --

MR. DELAFIELD: Same objections.

THE WITNESS: -- 217 nanometers.

BY MR. POLLACK:

Q. You see the words "UV" before that?

A. No.

MR. DELAFIELD: Same objections.

BY MR. POLLACK:

Q. No, you don't?

A. Oh, UV. I see. Yes, I'm sorry.

Q. Okay.

A. Yeah.

Q. Based on your review, can you tell me whether or not he used UV detection for HPLC?

A. Yes.

MR. DELAFIELD: Same objections.

THE WITNESS: It appears he did.

BY MR. POLLACK:

Q. Okay. Let me ask you.

The analyses that United Therapeutics did for HPLC analysis, do you know whether they used UV detectors?

MR. DELAFIELD: Objection. Vague. Calls for speculation.

THE WITNESS: I'd have to, just as with Moriarty, I'd have to -- I'd have to go back and check.

BY MR. POLLACK:

Q. Okay. You didn't look into that?

MR. DELAFIELD: Same objections.

THE WITNESS: I probably did. I don't remember. It would be common to do that, but I don't -- I don't remember.

BY MR. POLLACK:

Q. What about in the '393 patent? Do you know whether they used UV detection?

MR. DELAFIELD: Objection. Vague. Outside the scope of his report.

THE WITNESS: (Reviewing document). Unless you see it listed

someplace, I don't see it, but I'm, you know, I could read the whole thing to find out, and I don't know if it says.

BY MR. POLLACK:

Q. Yeah, I haven't seen it. I was just wondering --

A. I don't -- I don't know.

Q. -- if you had any knowledge.

A. I don't know.

Q. Okay. What about when United Therapeutics looks at total related impurities? Do you know whether they're using UV detection for those impurities?

MR. DELAFIELD: Objection. Vague. Calls for speculation. Outside the scope of his report.

THE WITNESS: I don't know. That will be in the CMC section, but I don't recall.

BY MR. POLLACK:

Q. But it would be fairly typical to use UV as a detection?

A. It would --

MR. DELAFIELD: Objection. Vague. Calls for speculation.

Mischaracterizes his testimony.

THE WITNESS: It would be -- it would be common --

BY MR. POLLACK:

Q. Yeah.

A. -- to do that.

Q. Let me ask you if the following sentence from Exhibit 6 is one you can agree with.

"With UV detectors" --

A. I'm sorry. Exhibit?

Q. And this is on page 12. Yeah.

A. Oh, oh, that's the same document. Okay.

Q. Yeah. This is the Reviewer Guidance --

A. Yeah, got it.

Q. -- Validation of Chromatographic Methods.

A. Okay.

Q. Just to make things clear, this comes from the Center For Drug Evaluation and Research?

A. Yes.

Q. That's a branch of the United

States Food and Drug Administration?

A. Yes, that's CEDR, part of the FDA.

Q. Right. They're the ones who actually decide drug approvals within the FDA?

MR. DELAFIELD: Objection. Calls for speculation.

THE WITNESS: For small molecules and, yes, for those types of drugs, yes.

BY MR. POLLACK:

Q. Right. And treprostinil is a small molecule. It's not a biomolecule?

A. Correct.

MR. DELAFIELD: Objection. Vague.

BY MR. POLLACK:

Q. So the CEDR, these are the kinds of people, this is a group that would approve a drug like treprostinil?

A. I --

MR. DELAFIELD: Objection. Vague.

THE WITNESS: I assume --

MR. DELAFIELD: Lacks foundation.

THE WITNESS: I assume treprostinil went through CEDR.

BY MR. POLLACK:

Q. Well, I think you earlier were referring to an NDA rather than a BLA based on that?

A. That's -- that's correct.

Q. Does that indicate that, therefore, it went through CEDR?

MR. DELAFIELD: Same objections.

THE WITNESS: It can -- when a drug is used with a device, as this one, it can go through the device division, too. I don't know if it did. I have no -- no reason to believe it, but I don't know.

BY MR. POLLACK:

Q. Okay. So CEDR says here on page 12 of the document, and by that I mean the P.12:

"With UV detectors, it is difficult to assure the detection precision of low level compounds due to potential gradual loss of sensitivity of detector lamps with age or noise level variation by detector manufacturer."

Do you agree with that statement?

A. I agree with that statement, but in

the CMC section, as I said, all instrumentation has to be validated and go through, and these are things that would be specified to assure the FDA that this isn't happening.

The F -- that's why they're giving this guidance to their reviewers to make sure that that is in there. You couldn't use an old lamp. You couldn't use a device -- a machine with a high noise level because that will affect what they care about, which is the level of quantitation and level of detection.

Q. Okay. But noise level is something that really is only a problem when you're trying to detect very small amounts of signal in materials?

MR. DELAFIELD: Objection. Vague. Lacks foundation. Outside the scope of his report.

THE WITNESS: Not -- not only. It depends on the signal from -- the magnitude of the signal from even the agent you're looking at. If it doesn't give a very powerful signal, then the inherent noise could affect that, too.

BY MR. POLLACK:

Q. Sure. But if I have a sample where, you know, [redacted] percent of it is my drug and [redacted] percent of it is an impurity, it's more likely I'm going to have noise problems with the [redacted] percent rather than the [redacted], is that generally the case?

MR. DELAFIELD: Objection. Vague. Calls for speculation. Lacks foundation.

THE WITNESS: That would generally be the case.

BY MR. POLLACK:

Q. And then one of the other things they say here. It's kind of interesting. Going a couple sentences later.

A. Uh-huh.

Q. It says:

"With no reference standard for given impurity or means to assure detectability, extraneous peaks could disappear and appear."

Do you agree with that statement?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: Yes, that's why

the FDA on these types of analyses for release specifications have reference standards so that that doesn't happen.

BY MR. POLLACK:

Q. Right. So reference standards, they're actually preferred in doing HPLC analysis?

MR. DELAFIELD: Objection. Vague. Calls for speculation. Lacks foundation.

THE WITNESS: They are preferred and almost always insisted on by the FDA.

BY MR. POLLACK:

Q. Okay. Let's go back to Ruffolo Exhibit 5, and that's the letter that used to be known as Exhibit 2006, from United Therapeutics to Norman Stockbridge dated January 2, 2009.

A. Exhibit 5?

Q. Exhibit 5.

A. Yeah, I have that.

Q. I want to look at a statement that United Therapeutics made to the FDA.

If you look on page 3, if you look at the second full paragraph, the third

paragraph on the page, beginning with the words "In conclusion."

Do you see where I am?

A. Yes, I do.

Q. Okay. It says:

"In conclusion, the lots of treprostinil API produced by the new process in Silver Spring are of the same high quality impurity as the commercial lots of API produced by the existing process at the Chicago facility."

Did I read that correctly?

A. Yes, you did.

Q. Okay. And I'm correct that the commercial lots of API produced by the existing process of the Chicago facility, that refers to what we've -- we've been calling the [redacted]?

MR. DELAFIELD: Objection. Calls for speculation.

THE WITNESS: I'm sorry. Could you repeat that?

BY MR. POLLACK:

Q. Yes. The -- where it says here the commercial lots of active pharmaceutical

ingredient produced by the "[redacted]" at the Chicago facility, that refers to what we've been calling the [redacted]?

MR. DELAFIELD: Same objection.

THE WITNESS: Yes.

BY MR. POLLACK:

Q. Okay. And the "[redacted]" in the Silver Spring facility, that refers to the process we've been calling the [redacted]?

A. Yes, that's my understanding.

Q. Okay. And what the -- what United Therapeutics is representing to the FDA here is that the treprostinil made by the '393 process has the same quality and purity as API made by the Moriarty process; isn't that what this says?

MR. DELAFIELD: Objection. Mischaracterizes --

BY MR. POLLACK:

Q. In simpler English?

A. Yeah.

MR. DELAFIELD: Mischaracterizes this document.

THE WITNESS: It says same high purity. They both could have high purity

and -- and it's pretty clear from the analyses that I've seen that the purity of '393 process is higher than Moriarty, but that doesn't mean that they're both not highly, highly pure.

BY MR. POLLACK:

Q. Okay. They're not making a representation here in this conclusion that the [redacted] process is superior to the -- the [redacted], that is, the '393 process is superior to the Moriarty process in that sentence?

MR. DELAFIELD: Objection. Mischaracterizes the document.

THE WITNESS: There are no purity levels given and I don't know when the -- the recognition for the high level of purity was made, but also I don't think that changes the fact that both could be high purity. One is higher than the other.

BY MR. POLLACK:

Q. Okay. Now, let me turn to some of the other representations they made.

If you can go to page 6.

A. Yes.

Q. And you're going to need to look at page 5 as well because, unfortunately, they didn't repeat the headings of the table.

A. Okay.

Q. Okay. So let me go through the headings on page 5. So the first column is labeled "Test."

Do you see that?

A. Yes.

Q. Okay. And that refers to whatever test or category is described underneath --

A. Uh-huh.

Q. -- is that fair?

A. Yes.

Q. Okay. And the second column is called "Currently Approved Specification"?

A. Yes.

Q. Okay. And that refers to the Moriarty process?

A. That's correct.

Q. And the third column is called -- is called "Proposed New Specification"?

A. Yes.

Q. Okay. And that refers to the '393 process?

A. That's correct.

Q. And if we go to page 6, under the Test column -- and feel free if you want to write these column headings on top. If you remember, that's fine.

A. Okay.

Q. So the first column, the Test column, you see it has a chromatographic purity HPLC.

Do you see that row?

A. Yes, I do.

Q. Okay. And then in that row is a set of named impurities?

A. Yes, I see.

Q. Okay. And these were the purities that -- the impurities that United Therapeutics was able to see in its HPLC instrument?

MR. DELAFIELD: Objection. Mischaracterizes the document.

THE WITNESS: These are the specifications for those purities. The minimum specifications for allowable levels of these impurities in -- in the product.

BY MR. POLLACK:

Q. Right. Right.

A. The API. API.

Q. I'm just -- I'm just saying, yeah, before we get to the spec part.

A. Yeah.

Q. Just in the Test column, that's a list of the impurities that United Therapeutics saw on their particular HPLC column?

MR. DELAFIELD: Objection. Vague. Mischaracterizes the document.

THE WITNESS: Those are the average characteristic impurities that you see in their analysis.

BY MR. POLLACK:

Q. Yeah. Okay. And if an impurity for some reason doesn't separate out on their particular HPLC column, we wouldn't see that impurity listed here?

MR. DELAFIELD: Same objections. Calls for speculation.

THE WITNESS: I'm not sure I agree. Could you repeat that?

BY MR. POLLACK:

Q. Sure. If an impurity doesn't separate out from the other ingredients in the particular HPLC column material that they

selected, we wouldn't see that impurity listed here?

MR. DELAFIELD: Same objections.

THE WITNESS: That's not true.

BY MR. POLLACK:

Q. That's not true?

A. No.

Q. Okay. So you're saying HPLC can separate all impurities from other impurities --

MR. DELAFIELD: Objection.

BY MR. POLLACK:

Q. -- regardless of what column is used?

MR. DELAFIELD: Objection. Mischaracterizes testimony.

THE WITNESS: No.

MR. DELAFIELD: Calls for speculation.

THE WITNESS: The FDA requires that you actually conclude that there are not two superimposing peaks, and so they have an assurance of that in the CMC part of the document as part of all of that validation that I mentioned earlier.

BY MR. POLLACK:

Q. What if an impurity comes out at about the same retention time as the API itself?

MR. DELAFIELD: Objection.

BY MR. POLLACK:

Q. Would they be able to separate that?

MR. DELAFIELD: Objection. Vague. Calls for speculation. Lacks foundation.

THE WITNESS: The FDA would force you to use a different column with a different bedding that did separate them. The FDA will insist that you confirm that there are no overlapping peaks.

BY MR. POLLACK:

Q. Even if you don't know if the impurity is there, they would do that?

MR. DELAFIELD: Same objections.

THE WITNESS: You actually have to go look. So when you report a peak, you have to assure them that there are not -- that there's only one material there under that peak. And there are various tests you

can do to show them, and you do have to show them that. That's part of the validation for using the technique.

BY MR. POLLACK:

Q. Do you know whether that was done for treprostinil?

MR. DELAFIELD: Same objections.

THE WITNESS: I don't know. If they had two drugs under one peak, it would have been done. It would be required.

BY MR. POLLACK:

Q. But for treprostinil you don't know?

MR. DELAFIELD: Same objections.

THE WITNESS: I don't know, but because I don't recall the -- that part of the CMC, but I do know that United Therapeutics would have to show them that there are not two peaks occurring at the same retention time with one masking the other.

And you have to show that by convincing evidence, and there are ways to do that and that's part of the validation of the assay that the FDA requires that United

Therapeutics would have had to have been done.

BY MR. POLLACK:

Q. Okay. You haven't reviewed, though, the CMC other than this letter?

A. I reviewed -- no, that's not true. I reviewed quite a bit of the CMC, but I didn't review it all. It would be too much for a single person to review.

Q. You didn't attach the CMC to your declaration?

A. No, I did not attach the CMC to my declaration.

Q. Okay. That's not listed in your materials you reviewed in your -- in the paragraph you have on that in your declaration?

MR. DELAFIELD: Objection. Mischaracterizes declaration.

THE WITNESS: I don't -- I don't recall if there are CMC sections in my declaration, but I have reviewed parts of the CMC as part of those documents that I mentioned that were sent to me by counsel.

BY MR. POLLACK:

Q. Which -- which parts did you

review?

MR. DELAFIELD: Objection.

Relevance.

THE WITNESS: I reviewed the Certificates of Analysis and I reviewed the injectable NDA component showing how those analyses were done and the calculations that were used. And there was, I think, an ND -- annual NDA update or something like that that I reviewed. So I did review components of the CMC.

MR. POLLACK: Counsel, I'm going to request that production of all sections of the CMC and any other documents that Dr. Ruffolo reviewed that haven't been produced so far.

MR. DELAFIELD: I believe we've produced everything. I think he's only been shown things that we've produced, so...

BY MR. POLLACK:

Q. So the sections of the CMC you're referring to, were those ones that Dr. Williams relied upon?

MR. DELAFIELD: Objection.

Calls for speculation.

THE WITNESS: I think you have to ask Dr. Williams that. I don't know what he -- what he did, what he looked at.

MR. POLLACK: Counsel, are there any documents that he reviewed that were not attached as exhibits provided to the PTAB?

MR. DELAFIELD: No, we haven't reviewed anything other than what's been an exhibit.

MR. POLLACK: What's been an exhibit to PTAB?

MR. DELAFIELD: Yeah.

BY MR. POLLACK:

Q. Okay. All right. Let's take a look at these.

MR. DELAFIELD: One thing. He mentioned that he reviewed the label. I don't think the label is an exhibit. So the label for treprostinil.

MR. POLLACK: Okay.

MR. DELAFIELD: All right.

MR. POLLACK: Would be the only?

MR. DELAFIELD: Yeah.

MR. POLLACK: If you could produce the label that he reviewed then.

MR. DELAFIELD: Okay. We'll take it under advisement.

BY MR. POLLACK:

Q. So let's look at the second column.

A. Yes.

Q. And the second column, that is specifications --

A. Yes.

Q. -- for each of the impurities for the Moriarty process; is that correct?

A. Yes, that's correct.

Q. Okay. And the third -- third column, those are specifications for impurities for the '393 process; correct?

A. That's correct.

Q. Okay. And am I also correct that the specification for the impurities in the Moriarty process are identical for every single impurity to the specifications for the '393 process?

A. Yes.

MR. DELAFIELD: Objection. Vague.

THE WITNESS: The specification limits are the same for both processes.

BY MR. POLLACK:

Q. Do you know whether on this document United Therapeutics listed every impurity for which a peak was observed?

MR. DELAFIELD: Objection. Vague. Calls for speculation.

THE WITNESS: I'm sorry. Would you repeat that?

BY MR. POLLACK:

Q. Yeah. Do you know whether on this document United Therapeutics listed every impurity for which a peak was observed?

MR. DELAFIELD: Same objections.

THE WITNESS: They do list unidentified impurities, which are peaks, and if the level of that impurity rose to a level of requiring identification, it would have been identified. That would have been a requirement.

BY MR. POLLACK:

Q. Right. Now, the final sum there at the bottom, it says "total related substances"?

A. Yes, I see that.

Q. Okay. What is it -- why does it use the term "related"? Are there unrelated

substances?

MR. DELAFIELD: Objection.

Vague.

THE WITNESS: I don't -- I don't recall the exact definition of total related substances. I would have to go research that. Remember, this is not something I prepared for.

BY MR. POLLACK:

Q. Sure.

A. This is, you know, here mainly for -- for the -- for the need. So I'd have to go -- I'd have to go look up and see exactly what the regulatory definition of that is.

Q. Okay. You didn't look into that as part of your opinion?

A. No, I didn't look into -- into that.

Q. Okay. Now, the names of some of these substances are a little, I think, funny. There's one called 1AU90.

A. Yes.

Q. What is that?

MR. DELAFIELD: Objection.

Outside the scope of his report.

THE WITNESS: Somebody would have to show me the chemical structure on that.

BY MR. POLLACK:

Q. Well, this -- do you think anyone knows the chemical structure of that?

A. Oh, yes.

Q. You do?

MR. DELAFIELD: Objection. Argumentative.

THE WITNESS: The -- if it rose to the level of reporting threshold, it would have to be reported.

BY MR. POLLACK:

Q. Sure. What's the reporting threshold?

A. Well, .05 and -- and .1 would be the identification threshold and they would have to identify it.

Q. If it's greater than .1?

A. Yeah.

Q. Yeah. Do you know if any of these which have just code names have a greater than .1?

A. Oh, I -- I don't know.

Q. Okay. Do you know whether 1AU90 was identified by United Therapeutics?

MR. DELAFIELD: Objection. Vague. Outside the scope of his report.

THE WITNESS: I don't know. You're, again, asking me questions outside of what I prepared for.

BY MR. POLLACK:

Q. I mean, this is one of the documents you are heavily relying on. That's why I'm asking you.

MR. DELAFIELD: Same objections.

THE WITNESS: Yes, but you're asking me questions that are not related to unfelt need. So --

BY MR. POLLACK:

Q. Your unfelt need has to do with purity; correct?

A. It has to do with increases in purity.

Q. Right. Okay.

A. Yeah.

Q. So I'm asking about the impurities here.

A. Yeah.

Q. Okay.

MR. DELAFIELD: Objection. Outside the scope of his report here.

BY MR. POLLACK:

Q. Outside the group of us here, who are privileged to see this, do you think any member of the public knows what 1AU90 is?

MR. DELAFIELD: Objection. Calls for speculation. Argumentative.

THE WITNESS: I don't know, but I would assume not, but that's just an assumption.

BY MR. POLLACK:

Q. By the way, do you have -- do you have any reason to believe that in 2007 -- that's when this patent was filed, two years before this document was created -- do you have any evidence that United Therapeutics had any idea what impurities were in treprostinil made by the '393 process?

A. Before?

MR. DELAFIELD: Objection.

BY MR. POLLACK:

Q. Before 2009. In 2007 where the '393 patent was filed -- first filed.

MR. DELAFIELD: Objection. Vague. Calls for speculation.

THE WITNESS: Because I reviewed all of the -- the lot specifications on the Certificate of Analysis, these were present before 2007 as well as after.

BY MR. POLLACK:

Q. Okay. In the '393 patent, is there any mention of what impurities are present or any of these names or similar names?

A. Can I refer to the patent?

Q. Please.

A. (Reviewing document).

Okay. Can you repeat the question, please?

Q. Is there any evidence in the '393 patent regarding what impurities were in the treprostinil made in the '393 patent?

MR. DELAFIELD: Objection. Vague. Calls for speculation. Outside the scope of his report.

THE WITNESS: I didn't see this list reproduced there.

BY MR. POLLACK:

Q. Okay. Was -- was there any kind of

list of what impurities were in the treprostinil made in the '393 patent?

MR. DELAFIELD: Same objections.

BY MR. POLLACK:

Q. In the patent itself?

A. Without reading the whole thing, I see primarily purities of the parent compound, which is what I believe the invention is related to. And -- and so I see comparisons between the old process and new process with purities, but -- but I don't see, unless I've missed it, I don't see the impurities.

Q. Right. All that information -- all the information in the '393 patent is related to the parent compound?

A. The overall purity of the parent compound.

Q. Right. And that compound is, well, treprostinil or one of those other compounds that are -- that are in there, the diethanolamine salt or the other ones that are in the claim?

MR. DELAFIELD: Objection. Compound.

THE WITNESS: The -- yes.

BY MR. POLLACK:

Q. I want to go back to your paragraph 32. There's something else there I was confused about. It's on page 14 of your declaration.

A. Okay. I have it.

Q. And that's Ruffolo Exhibit 3.

If you go about halfway down the page, it says:

"There is so much concern with the purity of drug substance and drug product that the highest level of purity possible should be achieved, even if that means changing the synthetic method as has been done in the '393 patent."

Do you see that?

A. Yes, I see that.

Q. Okay. And then in -- this is what confuses me.

In paragraph 57 -- it's on page 27 of your declaration -- you say in the last sentence:

"My personal experience has been that when considering the safety and toxicology profiles of impurities, it is often more

efficient to reduce the levels of impurities in the drug substance by altering or changing the synthetic method."

Do you see that?

A. Yes, I do.

Q. Okay. So here you're saying change the synthetic method but in 32 --

A. I'm saying exactly the same thing.

Q. Same thing. Okay. Oh, I see what confused me.

But then you say "as has been done in the '393 patent."

So I guess what I was wondering is: How has the synthetic method changed in the -- in the '393 patent?

A. The number of steps was reduced. The purification of the nitrile was taken out. The starting material was changed. The efficiency of the system was increased. The purity, of course, was increased. Fewer solvents were used.

And there's a list of -- in the patent, which I could probably find, of things that were changed and improved by the process.

Q. Yeah. Can you find me that list?

A. (Reviewing document).

On column 5 about line 36 or 37.

"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."

Q. Okay. Yeah. I didn't see any list there of some of the changes that you described, like the elimination of the purification of the nitrile or --

A. I just said that. It's in that

paragraph. They -- they specifically state:

"For example, the purification by common chromatography is eliminated."

That's for the nitrile.

Q. Oh, okay. Thanks. Thanks for clarifying that.

A. Yeah.

Q. And eliminating that purification of the nitrile, how does that affect the purity of the treprostinil?

MR. DELAFIELD: Objection. Calls for speculation. Outside the scope of his declaration.

THE WITNESS: I don't know how that affects the purity. I'd have to -- have to look into that, but it certainly is related to the efficiency and the -- the faster speed of the reaction, easier to operate, and -- and be more economical. That's -- that's quite significant.

BY MR. POLLACK:

Q. What about the change in solvents? How does that -- does that affect the purity?

MR. DELAFIELD: Same objections.

THE WITNESS: I give a similar

answer.

I can't tell what the solvent impact would be on the purity level, but it would certainly be relevant to the easier to operate, the greener, the faster component and, you know, so that's what that would be relevant to.

BY MR. POLLACK:

Q. Okay. Let me ask you, though, changing the solvents. That's something that you're not sure how much it does it, but it's something that might affect the purity?

MR. DELAFIELD: Objection. Calls for speculation. Outside the scope of his report. Vague.

THE WITNESS: I don't know.

BY MR. POLLACK:

Q. Okay.

A. It might, it might not.

Q. It might or it might not; is that right?

A. Yes, that's what I said. I'm sorry.

Q. Yeah, okay. That's fine. My hearing is going. (Laugh).

A. No. It happens to all of us.

Q. And the same for eliminating the purification of the nitrile. That might or might not affect the purity?

MR. DELAFIELD: Same objections.

THE WITNESS: I -- I don't know. That's what you asked, I think, two or three questions ago. I don't -- I don't know. I haven't seen that assessment done.

BY MR. POLLACK:

Q. Okay. But it could. It's a possibility?

MR. DELAFIELD: Same objections.

THE WITNESS: I don't know.

MR. POLLACK: Okay. I'm going to mark as Ruffolo Deposition Exhibit 8 a document formerly known as UT Exhibit 2047. It's the "Guidance for Industry on Non-Penicillin Beta-Lactam Drugs."

(Document marked for identification purposes as Ruffolo Exhibit 8.)

THE WITNESS: Thank you.

MR. POLLACK: And I'm going to mark one more exhibit while we're at it.

This will be Ruffolo Deposition Exhibit 9 formerly known as UT Exhibit 2048.

(Document marked for identification purposes as Ruffolo Exhibit 9.)

BY MR. POLLACK:

Q. And Ruffolo Exhibit 9 is an article called "Clinical Pharmacology of Human Insulin."

Are these, Dr. Ruffolo, these two documents that you relied upon in writing your declaration?

A. Yes, they are.

Q. All right. Starting with Exhibit 8, the non-penicillin beta-lactam drugs?

A. Uh-huh. Yes.

Q. Why did you rely on this document?

A. In putting together my -- my report, which relates to the importance of high purity and some of the risks of having impurities even in highly pure drugs, I gave examples that are known so that that -- and these are widely known examples -- that confirm that some impurities that one wouldn't even anticipate could be extremely risky and present

high risk to patients.

Q. What's this example?

A. This example?

Q. Yes. I'm sorry.

A. The --

Q. What is the example in Ruffolo Deposition Exhibit 8?

A. So in -- when I first started my career, penicillins and beta-lactams in general, which would include cephalosporins, were manufactured by, for example, my first company Lilly, which was the worldwide leader in antibiotics at the time, but they made many other drugs.

And as part of the CMC section in an NDA, you have to show how you cleaned the room, sterilized the equipment, and -- and, you know, run into basically an aseptic room when you manufacture another drug so there's not cross-contamination.

With respect to penicillins, even when you do that, penicillins just by being airborne can contaminate other products you make in the same building. And what was learned was that that minute contamination,

which you can't even quantify it's so low, produced allergic reactions ranging from very minor to very severe anaphylaxis, resulting in death, and because beta-lactams in general are so highly sensitizing to the immune systems of some people. And this is just what might be existing in a cleaned laboratory in the air.

So the FDA first, and then other agencies following shortly thereafter, mandated that you couldn't make a penicillin even in the same building, no matter how much you cleaned that building. You couldn't manufacture any other drug except another penicillin in a building and, of course, you can imagine the difficulty that creates to have a solely dedicated building only for penicillins and you have all these other drugs you manufacture.

And so that's what this guideline is. It was the regulators and ultimately the global regulators and, as you can see, the ICH that -- that -- that mandated completely different facilities had to be used. And it -- and so those are very, very low levels of contamination that you, as I say, you can't measure.

And it even got so significant that when we ordered AP -- starting materials, for example, for other companies, we always had to ask, are there rooms different from penicillin? Because they're not making a drug. They're just making an intermediate.

And then, finally, many of these companies that supply intermediates and starting materials would even advertise themselves as non-penicillin producing companies. So that's an example of how dangerous a safe drug, penicillin, can be as a contaminant.

Q. Right. In fact, for beta-lactams, those companies that are still making them, they require interlocks right into the buildings?

A. Now they've made a concession. They went from completely different buildings, totally separate buildings, and now with improvements in air handling, filtration systems, if you have in one building rooms with completely different ventilation systems that are physically isolated and separate, you now can do it in the same building, but that's

rarely done.

People still use separate buildings, but you have to have -- again, they relaxed the requirement. You can do it in the same building but completely different -- your interlocking systems that have absolutely no chance of crossover and that even includes air intake, so...

Q. Right. And the workers have to actually change their clothes as they go in and out?

A. Yeah. Well, they have to do that that anyway, no matter -- no matter what. When you walk into a plant that makes any drug, not just penicillin, the workers have to go through pressure locks, change their clothes, and then go through other double door pressure locks. There are several double door pressure locks to get into any manufacturing facility.

Q. To get into the United States?

A. That's correct.

Q. I don't want to scare you, but you haven't seen what it's like in India, but that's another day.

A. But in India, you know -- well,

okay. Okay.

Q. (Laugh).

A. So that's -- that's what that's about.

Q. Right. Because beta-lactams, those are drugs that come from a biological source?

MR. DELAFIELD: Objection. Lacks foundation.

THE WITNESS: Most are synthetic now and don't come from a biologic source.

BY MR. POLLACK:

Q. Right. But initially there was a biologic source?

A. Well --

MR. DELAFIELD: Same objection.

THE WITNESS: -- way back penicillin was isolated. The pharmacophore that I discussed earlier was isolated, and you would put different decoration on it to change it into different antibiotics with different spectra. Now they're synthetic. They're entirely synthetic and have been for many, many years.

BY MR. POLLACK:

Q. Treprostinil, though, as far as you

know, there isn't a compound like penicillin that requires that kind of isolation in the manufacture of treprostinil; is that fair?

MR. DELAFIELD: Objection. Vague. Lacks foundation.

THE WITNESS: Well, I don't know what I don't know and there are unidentified peaks, as we've discussed earlier, and -- and as we also talked about, there could be peaks below level of detection of a -- of an HPLC. And I don't know what those are.

I have no reason to believe it would be this, but the point of this in my document was to highlight that even very safe impurities can be dangerous because penicillin is clearly a safe drug. You give --

BY MR. POLLACK:

Q. Not for me but maybe for others. (Laugh).

A. Yes, that's unfortunate, but it is very safe. You give now -- when I worked in Children's Hospital, they used to give 5 million units. The first people to get penicillin in World War II got 10,000 units.

So it's a very safe drug, but as a contaminant that you can't even detect, it can be very dangerous.

Q. For those who are allergic?

A. For those who are allergic.

Q. And looking at your second exhibit here, Exhibit Ruffolo 9.

A. Uh-huh.

Q. This is about insulin?

A. Yes.

Q. Okay. And insulin is a bio -- it's a biodrug; right? It's not a small molecule?

MR. DELAFIELD: Objection. Calls for speculation. Lack of foundation.

THE WITNESS: Insulin is a biologic. It's a large molecule.

BY MR. POLLACK:

Q. And for insulin, the concern, I understand, is the E. coli bacteria?

A. It wasn't the bacteria. It was residual impurities from the bacteria in which the insulin was made.

Q. Referring to antigens from the -- from the bacteria?

A. They would --

MR. DELAFIELD: Objection. Vague.

THE WITNESS: They would or could be antigens, and it was a very high purified -- highly purified product.

MR. DELAFIELD: Counsel, I hate to interrupt.

MR. POLLACK: No.

MR. DELAFIELD: Do you mind if we take a break? He has to catch a flight and I wouldn't mind going to the bathroom.

MR. POLLACK: Yeah. Okay. Yeah. No problem like that.

THE VIDEOGRAPHER: The time is 3:13 p.m. This completes Media Unit No. 3. We are off the record.

(Recess - 3:14 p.m. - 3:21 p.m.)

(Mr. Maebius no longer present.)

THE VIDEOGRAPHER: The time is 3:21 p.m. This begins Media Unit No. 4. We're on the record. Please proceed, counsel.

BY MR. POLLACK:

Q. Okay. We were talking about Ruffolo Deposition Exhibit 9 before the break.

A. Yes.

Q. This is about the biomolecule insulin?

A. That's correct.

Q. Correct. And the concern here was about certain antigens from E. coli that could end up in the insulin?

A. Yes, that's correct.

Q. And that's because E. coli were involved in the production of the -- of the insulin?

A. Yeah. Yes, they were.

Q. In manufacturing treprostinil, am I correct there are no biological agents that are used in manufacturing treprostinil?

MR. DELAFIELD: Objection. Vague. Lacks foundation.

THE WITNESS: This, again, was an example of trace contaminants that can be potentially dangerous. But if you do look in the manufacturing process of treprostinil and you look into the specifications, example listed right here in the 2009 letter in the specifications that were sent to the FDA showing an increase in the level of --

of purity, you can see that they were looking at endotoxins, which can only come from bacteria, as well as total aerobic count, total yeast count, E. coli, Salmonella, pseudomonas, staphyloncus.

So these are -- the reason they're here is they can cause the same kind of allergic reaction that we saw with human insulin.

BY MR. POLLACK:

Q. Well, these are all lists, if you look at the microbial limits, right, these you would see for any drug? These are all lists of microbes that cause disease; right?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: Well --

MR. DELAFIELD: Mischaracterizes the document.

BY MR. POLLACK:

Q. Staph?

A. E. coli is the same as in the example I gave.

Q. Sure.

A. And so it was given as an example

of how a trace contaminant from a microbe can produce adverse events, and that's the same logic in the specification for treprostinil and many other drugs.

Q. Sure. But treprostinil is not made from biologic agents of any kind?

MR. DELAFIELD: Objection. Vague. Lacks foundation.

THE WITNESS: No, it is not made from a bio -- a cell.

BY MR. POLLACK:

Q. Right. And the concern here on page 6 where it says "microbial limits," that's about the sterility of the facilities, something we -- one always looks at?

MR. DELAFIELD: I'm sorry. Page 6 of what?

MR. POLLACK: Yeah. Page 6 of -- you are right -- Deposition Exhibit 5 formerly known as Exhibit 2006 on page 6.

BY MR. POLLACK:

Q. The microbial limits on this document have to do with the sterility of the facilities; isn't that correct?

MR. DELAFIELD: Objection.

Mischaracterizes the document. Lacks foundation.

THE WITNESS: Yeah, or airborne contaminants, as we discussed, with -- with non- -- with penicillins. They could come in through any process.

In fact, in the ICH guidelines on purity, they specifically point out that every single step of every single drug can introduce contaminants and impurities, including every single instrument or vessel. So that's why it's important.

BY MR. POLLACK:

Q. Okay. But looking at this document, there's nothing on here about penicillin or other beta-lactam antibiotics on Ruffolo Deposition Exhibit 5?

A. No, and they weren't intended to. As I said, the examples I gave for contaminants was to show that contaminants that you didn't know were there or you believed were safe or that were there in extremely low and undetectable levels can have significant effects that lead to serious adverse effects. So that's really what these were about.

Q. Right.

A. And that's also what these numbers in the table on page 6 are related to. They could be introduced the same way. Trace penicillin contaminants can be introduced into a product.

But the examples that I gave that you just cite in these last two exhibits was just to show the significance and why the FDA is so concerned about contaminants and why there is an unfelt need to increase purity.

Q. Let me ask you.

Both of these exhibits, Deposition Exhibit 8 and Exhibit 9, these are examples of contaminants, as you called it, that affect the immune system; correct?

MR. DELAFIELD: Objection. Calls for speculation. Vague.

BY MR. POLLACK:

Q. These are contaminants that create an immune response. That's why they're a problem?

MR. DELAFIELD: Same objections.

THE WITNESS: In the case of penicillin, it's a sensitization of the

immune system after penicillin acts as a hapten binding to a protein.

BY MR. POLLACK:

Q. And let me try to put that in simpler English.

A. Oh.

Q. Some people are allergic to penicillin?

A. That's -- okay.

Q. Is that right?

A. That's -- that's correct.

Q. Right. And it sets off their immune system?

A. Yeah. Yes.

Q. Okay.

A. But you can be allergic to anything, and as you look at FDA labels for virtually any drugs, one of the precautions is don't take if you're allergic to any of the components in it. So that that's a very common occurrence.

Q. But penicillin it is agreed that a fair percentage of the population is allergic to, while other drugs it's a little more rare?

MR. DELAFIELD: Objection.

Lacks foundation. Vague.

THE WITNESS: It's -- it's not that necessarily that the allergic reaction is more rare with other drugs. It can be less severe. So there's a difference between the frequency of allergic and the severity and that's, of course, penicillin and contaminants.

BY MR. POLLACK:

Q. And similarly with the -- with the E. coli antigens, that's an issue also involving the immune system in Deposition Exhibit 9?

A. Yes. That would be antigens that would -- antigens that would cause an immune response.

Q. Let me ask you.

Looking at the -- let's go back to -- I guess we were already looking at it -- Ruffolo Deposition Exhibit 5 at page 6.

A. Okay. Yes.

Q. Do you know if any of these listed chromatographic impurities have any adverse effects in humans?

MR. DELAFIELD: Objection.

Vague.

BY MR. POLLACK:

Q. And if so, what are they?

MR. DELAFIELD: Same objections.

THE WITNESS: I don't know.

What I can tell you is that if you review the FDA label, there are a host of adverse effects produced or observed in patients who are taking treprostinil.

BY MR. POLLACK:

Q. Sure.

A. And --

Q. But they're taking purified treprostinil?

A. Well, the purified treprostinil still has impurities, and if it's made by the '393 process, it has fewer of them, but there's still some there and including those maybe you don't see.

And the -- I lost my train of thought when you asked that second question. What was the question you asked for?

Q. Yes. I was asking about the effects of any of these listed impurities. What were those?

MR. DELAFIELD: Same objections.

THE WITNESS: Oh, yes, I remember my point.

In the FDA label, there are adverse events, serious adverse events listed, and the FDA breaks them down into two categories.

One that's -- one category are those adverse events that are related to the pharmacology or an extension of the pharmacology of treprostinil, which would be prostaglandin-like activity, and the others don't have an attributable cause.

BY MR. POLLACK:

Q. Does that mean they could be due to the treprostinil itself?

A. Or they -- it could be due to the treprostinil itself or it could be due to a contaminant or it could be due to something else, but the FDA never really knows. They only know what they think is due to the extension of the pharmacology, and it's based on that that they have this desire for impurities to be as low as possible and practical.

Q. Did you review -- in forming your opinion on the effect of impurities, did you review adverse event reports for treprostinil for the Remodulin product sold by United Therapeutics?

A. I reviewed the adverse events in the label, and -- and those include adverse events observed in clinical trials and also after market. So that that's what I reviewed.

Q. Okay. But did you review individual adverse event reports that were provided to the FDA?

A. No, I didn't review that section of the NDA.

Q. Okay. Do you know whether there were any changes in the adverse event reports after United Therapeutics changed its process of making treprostinil?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: That would be a very difficult thing to do and is rarely done. Most adverse events occur at a low level and the possibility of seeing a difference statistically -- and the FDA --

the FDA would only -- only change a label based on data that solid -- is very low and that's the case with any process change or even any increase in purity.

So you wouldn't expect to see that, and at the time you file a change in manufacturing, for example, to give you a decrease in purity, you would not have that information because you don't repeat clinical trials. You repeat and you do studies to match purity standards and release specifications.

BY MR. POLLACK:

Q. Okay. But as far as you know, from the adverse events reports, there's nothing indicating that there was some change in adverse events over time?

MR. DELAFIELD: Objection. Asked and answered.

THE WITNESS: Nobody would know that, and I didn't review the adverse events reports -- adverse event reports.

BY MR. POLLACK:

Q. Go back to your declaration, Ruffolo Deposition Exhibit 3.

A. Okay.

Q. If you could turn to paragraph 70.

A. Okay.

Q. And I'm looking on page 35. Near the end of that paragraph, you say here:

"Additionally, as shown by the 175 batch records, the average purity of the treprostinil product prepared by the process of the '393 patent is 99.71% while the average purity of the Moriarty product is 99.05%."

Do you see that?

A. Yes, I do.

Q. Where did those two numbers come from?

A. Those would have come from Dr. Williams.

Q. Okay. That's not something you calculated?

A. No.

Q. Okay.

A. I didn't calculate that.

Q. And then it says in the next sentence:

"Thus, the average purity of the treprostinil product prepared by the process of

the '393 patent has a 0.7% higher average purity than the Moriarty product."

How did you determine that?

A. That I also believe was from Dr. Williams.

Q. Okay. Do you know where that .7 percent number came from?

A. I believe it came from -- I don't remember. It came either from his analysis or from his declaration.

Q. Okay.

A. I'm not sure.

Q. I guess I was wondering: Do you know if that came from taking 99.71 and subtracting the 99.05?

A. That's -- that's what I believe he did.

Q. Okay.

A. Yes.

Q. You're not certain, though, but that's what you think he did?

A. Yes, that's what I believe he did.

Q. In view -- in your view, is that a correct way to compare the purity?

A. Because he compared apples to

apples and had the same -- compared the same analyses on total related substances, yes, I think that's a valid assessment of the difference.

Q. Earlier you and I were talking about standard deviation --

A. Uh-huh.

Q. -- and confidence intervals.

Do you remember that?

A. Yes, I do.

Q. Okay. What role does standard deviation and confidence intervals play in making the comparison between the two purities?

MR. DELAFIELD: Objection. Vague. Relevance. Outside the scope of his report.

THE WITNESS: Any measurement of means can have associated with it a standard error or standard deviation and from which you can calculate a confidence interval and -- and that would be used to show a statistically significant difference between two pools of numbers.

BY MR. POLLACK:

Q. You may recall this as well.

There's no standard deviation reported by Dr. Williams for these averages.

If the confidence interval significantly overlapped, how would that affect your conclusion about the differences between the purity?

MR. DELAFIELD: Objection. Vague. Calls for speculation. Relevance. Outside the scope of his report.

THE WITNESS: It wouldn't change my interpretation because there would still be a numerically higher number level of purity with the Moriarty process -- with the -- excuse me -- '393 process and that also translated to a -- what did I have? -- [redacted] some odd percent reduction in impurities, and that's a number that is impressive and regulators would like to see.

BY MR. POLLACK:

Q. That reduction you just described, the [redacted] some percent, that's based on these two numbers here, isn't it?

A. Yes.

Q. Okay. And earlier in one of your -- in your answer just two answers ago,

you used the word "statistical significance" I believe?

A. Yes.

Q. What were you referring to?

A. Numbers can differ and when they differ by what's called a statistical significance that's assuming a 95 percent probability, that's called statistical significance, and when they don't, it's called a trend.

Q. If you only see a trend, what conclusions can you draw from the difference between numbers that are only a trend, as you called it?

MR. DELAFIELD: Objection. Vague. Relevance. Calls for speculation and outside the scope of his report.

THE WITNESS: The trends that are not statistically significant don't mean that they're not real. I think the more important part is based on these data, the FDA agreed to change the specification for purity from a mean of 99 percent to a mean of 100 percent, resulting in a higher quality product.

BY MR. POLLACK:

Q. Actually, didn't they change the specification from 98 percent to 102?

A. That's --

MR. DELAFIELD: Objection. Vague. Mischaracterizes the document.

THE WITNESS: That's the range. I was talking about the mean centered around that.

BY MR. POLLACK:

Q. Okay.

A. But we can talk about both because the answer is the same.

If you have a mean purity of 99 percent that they move up to 100, that's a higher quality product. If you take the lower level of 97 percent and move it up to 98 percent, which is what the FDA did.

Q. Right. Did the FDA do that or did United Therapeutics do that?

A. Oh, United Therapeutics made the request and the FDA, which doesn't have to do it and they don't make changes that they don't believe are -- are not important. The FDA approved, agreed and approved those changes to

the FDA's standard. It met their long-felt need, and they made that change.

Q. The FDA made that change or United Therapeutics made that change?

A. United Therapeutics --

MR. DELAFIELD: Objection. Vague.

THE WITNESS: -- can't make a change. They can only propose a change. Only the FDA can make a change.

BY MR. POLLACK:

Q. At the time that United Therapeutics was making an -- making an amendment to their application, they were asking to move, factories, correct from Chicago to Silver Spring?

MR. DELAFIELD: Objection. Lacks foundation.

THE WITNESS: I don't recall the timing. I think the document, the letter suggests that they were about the same time.

BY MR. POLLACK:

Q. Actually, the letter is about the change --

A. Yeah. Okay.

Q. -- of the factory from Chicago to Silver Spring; correct?

A. I think so, yes.

Q. Yes. And the letter is also about the -- that's a major change, by the way, moving from one factory to another; right?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: That is considered a major change.

BY MR. POLLACK:

Q. Yes. And in addition, they -- the people at United Therapeutics decided that they would change what [redacted] were used for the process; right?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: United Therapeutics decided to change the process, and as part of that change in process, they also changed the [redacted].

BY MR. POLLACK:

Q. Right. Now, changing [redacted] has nothing to do with what's discussed in the '393 patent; correct?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: Sorry. Could you say that again, please?

BY MR. POLLACK:

Q. Yeah. A change in [redacted] that has nothing to do with what's discussed in the '393 patent?

A. The '393 patent describes a change in process from a more lengthy process to a much abbreviated process, and as part of that process, the starting material changed from whatever it was in Moriarty many, many, many steps earlier to the benzindene triol.

So, yes, both the process and the starting material did change, and that's the subject of the patent.

Q. The [redacted] change, though, was not; right? In the patent, they describe making the product from other materials, correct, not from benzindene triol?

MR. DELAFIELD: Objection. Vague. Mischaracterizes the document.

THE WITNESS: It's my understanding that the starting material of

the '393 process in the patent is the benzindene triol.

BY MR. POLLACK:

Q. The patent describe -- doesn't describe using materials to make the benzindene triol as well?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: When I -- when I look at the process, for example, in Example 1, it looks to me like the starting material is benzindene triol. That's one of the four compounds that occur in the entire process and that to me seems very different than the Moriarty process.

BY MR. POLLACK:

Q. The Moriarty process doesn't go through benzindene triol?

MR. DELAFIELD: Objection. Calls for speculation.

THE WITNESS: Your question --

MR. DELAFIELD: Lack of foundation.

THE WITNESS: -- was the starting material, and the starting material

in the Moriarty process is not the benzindene triol. It's something many, many steps earlier.

BY MR. POLLACK:

Q. And if we look at the '393 patent at column 7?

A. Yes.

Q. There's a formula there 10.

Do you see that?

A. Formula?

Q. It's in column 10. It says "X." There's an X and under that it's X11. It's around line 20.

A. Oh, I see. Yes, I see that.

Q. Isn't that the starting material for the process described in the '393 patent?

MR. DELAFIELD: Objection. Vague. Outside the scope of his report. Lacks foundation.

THE WITNESS: When I look at the steps that they're talking about -- steps A, B, C, and D -- they start at the benzindene triol, not at compound X.

BY MR. POLLACK:

Q. Sure. So you're saying the claims

only claim that part of the process; correct?

A. Yes.

MR. DELAFIELD: Objection. Vague.

THE WITNESS: And I, you know, again, am not a lawyer.

BY MR. POLLACK:

Q. Right.

A. I wasn't prepared for this, but it looks to me like the process that they're patenting is starting at benzindene triol and ending with treprostinil free acid.

Q. Okay. You understand that in the patent it describes the process as starting from compound 10?

MR. DELAFIELD: Objection. Vague. Lacks foundation.

THE WITNESS: That's not my understanding. I see that they're referring to that reaction from another patent and I -- that to me doesn't look like the starting material for this process, nor is it what they told the FDA was their new process.

The new process started with benzindene triol, which is a major change,

and then, of course, the [redacted] of that [redacted], which was going to be [redacted] and none of that involves this material.

BY MR. POLLACK:

Q. Right.

A. Compound X.

Q. And one of the issues is, it's going to be [redacted]. So now the United Therapeutics doesn't have [redacted] over how some [redacted] is [redacted] the [redacted] [redacted]; correct?

MR. DELAFIELD: Objection. Vague. Calls for speculation. Lacks foundation.

THE WITNESS: No, that's not correct.

BY MR. POLLACK:

Q. Okay. Explain to me.

A. In the letter where the -- the 2009 letter where UTC is requesting this change in process as well as a change in [redacted], both of which are major changes, the FDA is so concerned about purity, as we've said all day, that they were worried about the

purity of the [redacted] and carryover of any impurities into the final product. It's a major change. That's a very difficult question.

And the response you can see shows that the [redacted] of the [redacted] was subject to specifications that were put in place by the [redacted] that matched [redacted] specifications for [redacted].

So they did have [redacted] over that [redacted] and that's basically what the FDA was asking and that's what satisfied the FDA and allowed them to start this new process starting benzindene triol.

Q. Right. But United Therapeutics is not -- they're getting a [redacted] from that [redacted], but they're [redacted]; is that fair?

MR. DELAFIELD: Objection.

BY MR. POLLACK:

Q. Of the [redacted]?

MR. DELAFIELD: Objection. Vague. Calls for speculation. Lacks foundation. Outside the scope of his

report.

THE WITNESS: It's been my experience that when a late-stage [redacted] is [redacted] and [redacted] we actually place somebody at that [redacted] to make sure that the [redacted], which as it turns out happened to be [redacted] by definition.

So it's not as if the material is [redacted], [redacted], and then just put into a reaction. The material [redacted] the [redacted], the [redacted] at the site where you [redacted] it, and then the first thing you do when you [redacted] the [redacted] is [redacted] the [redacted] in-house as well.

BY MR. POLLACK:

Q. By the way, do you know whether the [redacted] United Therapeutics' [redacted], do you know whether or not they used the process described in [redacted]?

MR. DELAFIELD: Same objections.

THE WITNESS: Again, I wasn't prepared to go into detail on that and it's not something I was asked to comment about,

but in that letter, they -- UTC indicates that the process is -- I don't remember -- either the same or virtually the same.

BY MR. POLLACK:

Q. Okay. Do you know where that is in the letter?

A. I can find it.

Q. Is that the bottom -- bottom of the first page that you're referring to?

A. (Reviewing document).

Yes, beginning on the bottom of page 1 and extending through about the first third of page 2.

Q. Okay. So I'm right. I think I'm right. One of the things that needs to get -- one of the changes that needs to get approved here as a major amendment is that the [redacted] is now being [redacted] from a [redacted] called [redacted] or [redacted] called [redacted]; is that right?

A. Yes.

Q. Okay. And so the FDA is approving all of these changes; right? The change in factory, the change -- and the change in [redacted] and the change in crystallization in

the process?

A. And process and starting material, yes.

Q. So there's a large number of changes in here instead of three changes, big changes?

MR. DELAFIELD: Objection. Mischaracterizes the document.

THE WITNESS: There were -- these are considered major changes, and so UTC had to go through all of the documentation necessary to satisfy the FDA because this is a major concern of the FDA because of ultimately quality of the material produced and purity.

And, again, in the three questions raised by the FDA, two of them had to deal with purity.

BY MR. POLLACK:

Q. Right. One of those had to do with the purity of the benzindene triol; right?

A. One of those was the purity of the benzindene triol and the concern by the FDA of the carry-through of any impurities in the benzindene triol to the final product. That's

how concerned they are about purity and contaminants.

Q. Right.

A. And they were obviously satisfied by the fact that the process were the same and the release specs remained the same for [redacted], and then also the fact that there was a higher level of purity by this new process. That was considered significant enough by the FDA to allow a change to the drug specification.

Q. You keep saying the FDA considered it significant enough.

Can you show me where in the letter they said they thought it was significant?

A. No, it doesn't say that in the letter. The fact that they approved it when they don't like to make changes unless they're considered important. You can't simply change it yourself.

And when you submit this change for approval, it involves a great, great, great deal of analysis by the FDA. It takes a long time, a lot of people and, again, they have to balance that between their desire to increase

purity and their belief that you can make this product consistently so that there are no drug shortages.

Q. And that last reason, the drug shortages, that's why they allow, for example, a purity of 98 percent?

MR. DELAFIELD: Objection. Calls for speculation. Lacks foundation.

THE WITNESS: The -- the FDA, again because of their strong desire to have the highest levels of purity as possible, and I keep saying practical, the practical part is to make sure that they get the highest level of purity, which they obviously we're happy with.

They made -- they approved the change, but they would not have approved that if they thought the company couldn't make the material or that a subsequent company, after the drug loses its patent, couldn't make that material, which would result in drug shortages.

BY MR. POLLACK:

Q. But, in fact, all the material made under the [redacted] process, at least all the

material we've seen, met the 98 percent standard, didn't it?

MR. DELAFIELD: Objection. Calls for speculation. Lacks foundation.

THE WITNESS: Well, all of the batches, I don't know whether they all met that. I'd have to go look at the data. I don't know what the variability was and, you know, I reviewed 170 something Certificates of Analysis. I don't remember if any did or didn't. So I don't know.

BY MR. POLLACK:

Q. Okay. I'll represent to you that all of the ones made under the [redacted] process made the 98 percent level.

MR. DELAFIELD: Same objections.

BY MR. POLLACK:

Q. Given that, how does that affect your opinion?

A. That doesn't change my opinion at all. Because when the FDA agrees to allow a mean range to center from 99 to 100 percent and a lower level from 97 to 98 percent, they are assured of having a higher quality product than would have been allowed under the other

guidelines, and that makes them feel good. That's what they shoot for. That's their -- it's an unfelt need or the -- I'm blanking on the words. That's what their need is. That's what they desire.

MR. POLLACK: Let's -- let's take a break for 10 minutes. I want to look at --

THE WITNESS: Okay.

MR. POLLACK: -- what other things we want to ask you?

THE WITNESS: Sure. Okay.

MR. POLLACK: Why don't you guys out.

THE WITNESS: Yeah, I'll leave.

THE VIDEOGRAPHER: The time is 4:03 p.m. We're going off the record.

(Recess - 4:03 p.m. - 4:21 p.m.)

(Document marked for identification purposes as Ruffolo Exhibit 10.)

THE VIDEOGRAPHER: The time is 4:21 p.m. We're back on the record. Please proceed, counsel.

MR. POLLACK: Okay.

BY MR. POLLACK:

Q. Welcome back.

A. Thank you.

Q. I've already marked as Ruffolo Deposition Exhibit 10 a letter from the Department of Health and Human Services, the FDA -- Food and Drug Administration to United Therapeutics Corporation, Dean Bunce, Executive Vice President of Regulatory Affairs and Compliance, dated March 10, 2014 regarding the drug Remodulin.

A. Thank you.

Q. Let me just ask you first. Am I correct that this is a -- that Deposition Exhibit 10 is a letter from the FDA to United Therapeutics Corporation?

A. Yes, it is.

Q. Okay. And the letter is dated March 10, 2014?

MR. DELAFIELD: Objection. And I object to this exhibit that it hasn't been submitted to the Patent Office yet and it's beyond the scope of his declaration. And relevance.

THE WITNESS: The -- you asked

about the date?

BY MR. POLLACK:

Q. The date, yeah.

A. But, you know, this is a problem with -- and I've had it with many FDA documents. It can't find the date. I see a stamped date. I don't know whether that's when it was received. So I don't -- I don't know anything. I can't confirm the date.

Q. Okay. You haven't seen that kind of stamp on all of the FDA's official documents?

A. No.

Q. No? Okay.

A. No.

Q. Remodulin. You see the name Remodulin?

A. Yes.

Q. Okay. That's the -- that's United Therapeutics treprostinil product?

A. Yes.

Q. Yes? Okay.

And now you haven't reviewed this letter before; is that -- is that correct?

A. No, I've never seen this.

Q. Okay. But you see this is a letter responding to a citizen's petition? You see that in the first sentence?

MR. DELAFIELD: Objection. Vague. Relevance. Beyond the scope of his declaration.

THE WITNESS: (Reviewing document). I see that it says it's a citizen's petition.

BY MR. POLLACK:

Q. Okay. It's a letter responding to a citizen's --

A. Yeah.

Q. -- petition; right?

A. Yeah.

Q. And it's a citizen's petition that was filed by United Therapeutics?

MR. DELAFIELD: Objection. Relevance. Beyond the scope of his declaration.

THE WITNESS: I don't -- I don't know.

BY MR. POLLACK:

Q. Well, it says there; right?

"This letter responds to a

citizen's petition submitted to the FDA by United Therapeutics Corp."

Did I read that correctly?

A. You -- yes, you did.

Q. Okay. Do you have any reason to believe it's -- that United Therapeutics Corp. did not file a citizen's petition?

A. I don't know.

MR. DELAFIELD: Objection.

THE WITNESS: Did they?

MR. DELAFIELD: I'd just like to enter a standing objection for any questions relating to this regarding relevance and that it's outside the scope of his declaration.

THE WITNESS: And I, you know, I don't know what United Therapeutics did. You know, I guess if they're responding to it, they probably did, but I don't -- I don't know. I have no idea what this is about.

BY MR. POLLACK:

Q. Okay. You know -- do you know what a citizen's petition is?

MR. DELAFIELD: Objection.

Outside the scope of his testimony and lacks foundation.

THE WITNESS: I've heard -- I've heard the word a number of times. I actually don't really know what it means.

BY MR. POLLACK:

Q. Okay.

A. It's -- despite my experience, I don't -- I never had to deal with one. So I really don't know what -- exactly what it is.

Q. Okay. I mean, I assume when you were at Wyeth they did file citizen's petitions with the FDA?

MR. DELAFIELD: Objection. Lacks foundation. Vague.

THE WITNESS: I assume they did. Again, I'm familiar with the words, but I'm not familiar with what it is --

BY MR. POLLACK:

Q. Okay.

A. -- and what was done with them.

Q. Okay. Are you aware that a citizen's petition is part of the -- a process of challenging regulatory approvals at the FDA?

MR. DELAFIELD: Objection.

Lacks foundation. Same objections as before.

THE WITNESS: I was not familiar with that. I haven't seen many of them, and I don't know --

BY MR. POLLACK:

Q. Okay.

A. -- what that is.

Q. So this goes beyond your regulatory expertise?

A. This?

Q. Citizen's petitions.

A. Citizen's? Yes, I would say this goes beyond my regulatory expertise.

Q. Okay. If you could turn to -- indulge me and turn to page 8 of Ruffolo Deposition Exhibit 10.

A. Oh.

Q. This one.

A. Oh, oh, oh. I'm sorry.

Q. If you could turn to page 8.

A. 8. Okay. (Pause). Okay.

Q. Let me ask you this first.

Are you aware that -- are you -- are you aware of what the Orange Book is?

MR. DELAFIELD: Objection. Relevance. Outside the scope of his declaration.

THE WITNESS: I have heard of the Orange Book. I have a little bit of knowledge, but I -- it's not something that I've paid a lot of attention to. So it's -- I put that in the same category of -- of the citizen's petition.

Most of my regulatory experience focuses on regulations, guidelines, approval, and -- and that goes not just for the FDA, but the three major agencies in the world, EMA and PMDA.

And I know the Orange Book has something to do with patents, but as I said, I'm not a patent lawyer and I don't really follow that very much. So that also is beyond my area of expertise in regulatory.

BY MR. POLLACK:

Q. Okay. But let me ask you this.

Were you aware that in filing a New Drug Application, the drug companies that you worked for are required to file a list of patents that covered the drug in the New Drug

Application?

MR. DELAFIELD: Same objections.

THE WITNESS: I am aware of that.

BY MR. POLLACK:

Q. Okay. And were you aware that those patents would then get listed in something called the Orange Book, which today is just a website?

MR. DELAFIELD: The same objections.

THE WITNESS: I was not aware of that.

BY MR. POLLACK:

Q. Okay. But you're aware that patents are filed with New Drug Applications?

MR. DELAFIELD: Same objections.

THE WITNESS: Yes, I was.

BY MR. POLLACK:

Q. Okay. And are you aware regarding whether or not United Therapeutics filed any patents with the FDA in their NDA for Remodulin?

MR. DELAFIELD: Objection. Relevance. Outside the scope of his

declaration.

THE WITNESS: Not -- not -- no, I don't know that. Again, as I said, I was focused on -- on need and -- and I haven't had a chance to look at this, think about this. And even if I did, this falls outside my area of expertise.

BY MR. POLLACK:

Q. Let me ask you this.

Have you compared the claims of the '393 patent to United Therapeutics' Remodulin product?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: I'm sorry?

BY MR. POLLACK:

Q. Yes. Have you compared the patent claims in the '393 patent to United Therapeutics' Remodulin product?

MR. DELAFIELD: Same objection.

THE WITNESS: You have to clarify. Compare what and how?

BY MR. POLLACK:

Q. Oh, okay. So by that I mean, did you go through, say, claim 9, compare the

element -- do you know what the elements of a claim are?

A. Sorry.

Q. Okay.

A. I'm not a patent attorney. I...

Q. Did you compare the language in claim 9 to United Therapeutics' treprostinil product?

MR. DELAFIELD: Same objection.

THE WITNESS: Still I don't know how -- what you mean "compare." Compare to what?

BY MR. POLLACK:

Q. I'll see if I can make it simpler.

Did you analyze claim 9 and determine whether it covers United Therapeutics' Remodulin product?

MR. DELAFIELD: Same objection.

THE WITNESS: I -- again, I'm still not quite sure what you mean but, you know, that wasn't what I was asked to do, and I don't believe I did make any comparison like that.

BY MR. POLLACK:

Q. Do you know if anyone else in this

case made that comparison?

A. No.

MR. DELAFIELD: Same objection.

THE WITNESS: I haven't spoken to anyone outside of Mr. Delafield.

BY MR. POLLACK:

Q. Okay. All right. If we can turn back to page 8 in Ruffolo Deposition Exhibit 10.

A. Yes.

Q. And as you'll see here, the issue is whether a generic treprostinil injection product can emit material that's on the Remodulin label and, in particular, the use of something called a "high pH glycine diluent."

Do you see that?

MR. DELAFIELD: Objection. Outside the scope of his declaration. Lacks foundation.

THE WITNESS: I mean, I can't interpret that. I'd have -- even if I had read this, I may not be able to interpret it. But is there a section you would like me to read?

BY MR. POLLACK:

Q. Why don't you feel free to read this section starting from the word "Discussion" on the page before.

A. "Discussion." Oh.

Q. Yep.

A. (Reviewing document). Okay.

Q. Have you read enough or you want to read more?

A. I don't know. It depends on your question.

Q. Okay. Fair enough.

Do you understand from this that United Therapeutics was allowed by the agency to add to their label for Remodulin (treprostinil) information about using a high pH glycine diluent to reduce the risk of BSIs?

MR. DELAFIELD: Objection. Mischaracterizes the document. Relevance. Outside the scope of his declaration.

THE WITNESS: No, I wasn't aware of that. The section I read didn't define BSIs and, again, I focused on long-felt need with respect to purity and I -- and impurities and I didn't see anything here related to any of that.

So I really don't know what this letter is in response to and I don't understand. Here we're talking about drug product and that wasn't the focus of my review. It was on --

BY MR. POLLACK:

Q. Uh-huh.

A. It was on contaminants and impurities in the synthesis of API. So I'm sorry. I don't even know how to respond.

Q. Yeah. I'm not going to ask you about BSIs and whether that's true or anything else.

A. Yeah.

Q. I just wanted to know is, you know, based on the letter, is it -- is it the case that the FDA had allowed United Therapeutics to add to their label information about the use of high pH glycine diluent?

MR. DELAFIELD: Objection. Relevance. Calls for speculation. Mischaracterizes the document and outside the scope of his declaration.

THE WITNESS: And what was your question?

BY MR. POLLACK:

Q. Yeah. I was just asking whether or not United Therapeutics was allowed by the FDA to add information about the use of a high pH glycine diluent, whatever that may be, to their -- to their label.

MR. DELAFIELD: Same objections.

THE WITNESS: I don't know anything about that at all, and reading a couple of paragraphs on this letter that don't even define some of the abbreviations used, I can't -- I can't do anything with this. This doesn't mean anything to me.

BY MR. POLLACK:

Q. Well, do you see -- let's take a look at the second full paragraph on page 8.

A. The which? The --

Q. The one beginning with "More the point." "More to the point." I want to a take a look at the second sentence. Do you see there it says:

"When we approve the addition of this information to Remodulin's label in September 2013."

Do you see where I'm reading?

A. Yes, I do.

Q. Okay. Reading that, am I correct that the FDA approved adding certain information to Remodulin -- that's the same product we've been talking about -- to the labeling of Remodulin; is that fair?

MR. DELAFIELD: Same objections.

THE WITNESS: I guess so. I don't know.

BY MR. POLLACK:

Q. Okay. That's what the letter says; right?

A. That's --

MR. DELAFIELD: Same objection.

BY MR. POLLACK:

Q. I know you don't know independently, but in the letter that's what it says?

MR. DELAFIELD: Same objection.

THE WITNESS: That's what, two sentences out of a 10-page letter I never saw before that's related to something I didn't prepare for. It doesn't mean anything to me.

BY MR. POLLACK:

Q. Okay.

A. In fact, the only thing that means anything to me is the signature of Janet Woodcock, who's a good friend of mine.

Q. Okay. That's the same Janet Woodcock --

A. Yes.

Q. -- that you refer to in your declaration?

A. Correct.

Q. She's the author of this letter?

A. She's the signatory of this letter.

Q. Letter is issued with her approval; correct?

A. That's correct.

Q. Okay. And if we go back to page 8?

A. Okay.

Q. Okay. In Janet Woodcock's letter, she says "We" and by 'we' she's referring to the FDA?

MR. DELAFIELD: Objection. Calls for speculation. Lacks foundation. Relevance. Outside the scope of his declaration.

THE WITNESS: Which "we"? "We

did not take these acts"?

BY MR. POLLACK:

Q. Yes, or we did -- all of the "we's." "We approved." "We did so in the interest."

That's referring to the FDA; right?

MR. DELAFIELD: Same objections.

THE WITNESS: I guess so. I suppose she would.

BY MR. POLLACK:

Q. Right? It's a letter from the FDA; is that fair?

A. Yeah.

MR. DELAFIELD: Same objections.

BY MR. POLLACK:

Q. Okay. And it says here --

A. I should point out.

Q. Uh-huh.

A. Letters come from the FDA that don't represent the entire FDA opinion. During the entire NDA process, you get letters from the FDA. That's -- that's a --

Q. Yeah. This is an official response to a citizen's petition?

MR. DELAFIELD: Same objection.

THE WITNESS: Again, I don't know.

BY MR. POLLACK:

Q. You don't know what those are?

A. Yeah. I'm sorry.

Q. Okay. And they say here they made a label change; right?

They did so in the interest of "providing healthcare providers with up-to-date information on the use of high glycine diluents and not out of the concern that the administration of IV treprostinil with a neutral diluent should always be avoided because it poses a risk to patients. The agency had been concerned about the safety of neutral diluents" -- I'm sorry.

"If the agency had been concerned about the safety of neutral diluents, it could have revised the labeling to require the use of high pH glycine diluents only and taken steps to raise awareness about the effect that choice of diluent has on the risk of BSIs."

Now, in the case of the changes that we're talking about here that were approved by the FDA, the manufacturing changes,

those changes don't even appear on the label; correct?

MR. DELAFIELD: Same objections.

THE WITNESS: That's correct.

BY MR. POLLACK:

Q. Right. Here we're talking about changes that were approved by the agency that do appear on the label; correct?

MR. DELAFIELD: Same objections.

THE WITNESS: I don't know. I don't remember it from the label. I reviewed the label. I don't remember this.

BY MR. POLLACK:

Q. Okay. But here the agency is saying, just because we approved it on the label, that doesn't mean we endorsed your statements about the effect of these high pH glycine diluents; isn't that what they're saying?

MR. DELAFIELD: Objection. Vague. Mischaracterizes the document. Relevance. Lacks foundation. Outside the scope of his declaration.

THE WITNESS: To be honest, I don't know what the agency is saying here.

You know, I'm sorry. In a 10-page letter, looking at a couple of paragraphs, I don't know what they mean. I don't know what they're referring to. I don't know what their intent is. And this is an area that I have not been involved with before.

BY MR. POLLACK:

Q. Okay. Well, you said you had some regulatory expertise.

Based on your regulatory expertise, can you explain what's being described here?

MR. DELAFIELD: Same objections. Asked and answered.

THE WITNESS: I said I had a great deal of regulatory expertise. But I also said that I didn't know everything about regulatory affairs and that there were people in regulatory affairs that knew more than me and many who knew less, but this is something that I have not had to deal with.

And this is -- again, I don't know what this is.

BY MR. POLLACK:

Q. Okay. I'm only asking this because earlier I believe you stated the opinion that

by approving United Therapeutics' changes from 97 to 98 percent, the FDA was endorsing that as a change in purity. And you seem to have the expertise to opine on that or that was your view that there was an endorsement, or maybe I misunderstood you.

And yet here you're not able to tell me whether the FDA considers an approval, as they did here, to be an endorsement.

A. They --

MR. DELAFIELD: Objection. Mischaracterizes testimony. Relevance and outside the scope of his declaration.

THE WITNESS: The area I testified to before I've had a great deal of experience in at every level with the FDA.

BY MR. POLLACK:

Q. Uh-huh.

A. This I have not had any experience and I know for -- I know that the FDA does not like to make changes in specifications unless they believe they are significant. I don't know what Janet is saying about whatever label -- labeling change she's talking about.

Q. Well, you said earlier that you had

reviewed the label?

A. I did review the label, yeah.

Q. Okay. If you reviewed the label, you saw a discussion about what diluents should be used with Remodulin?

MR. DELAFIELD: Objection. Lacks foundation.

THE WITNESS: It --

MR. DELAFIELD: Outside the scope of his declaration. Relevance.

THE WITNESS: Well, and because it was outside the scope, it's not an area that I would have focused on. I focused on other parts of the label, and I do know a good deal about labeling negotiations as far as NDA approval.

This in citizen's petition I don't -- is an area that I have not been involved with, not focused on, and I don't have the experience in. What I testified to I have great deal of experience in. Sorry.

BY MR. POLLACK:

Q. Yeah. Okay. But in regard to whether or not the FDA endorses statements made by applicants, what's your evidence of that?

MR. DELAFIELD: Objection. Mischaracterizes his testimony. Relevance.

THE WITNESS: The applicant can't make a change without the FDA's agreement and approval.

BY MR. POLLACK:

Q. Uh-huh.

A. And when they do that in the context of a specification, they wouldn't permit it if they didn't believe it was significant and important enough to do so.

I have no idea what this letter is talking about, and I don't even understand the argument that's being made here. Again, maybe if I studied this for a couple of days but, you know, this is not something I've seen or been involved with.

Q. Okay. But you don't have any statements, articles, documents, evidencing that the FDA endorses statements made by applicants merely because they approved the change?

MR. DELAFIELD: Objection. Vague. Asked and answered. Relevance.

THE WITNESS: The FDA doesn't

allow change unless they agreed with that change and approved that change. That's their job.

BY MR. POLLACK:

Q. Sure.

A. And with respect to specifications and release of batches and all of the pre-NDA work and NDA work, their approval is required and that approval is so important that it's what allows you to sell a new product. That's a big deal.

Q. Uh-huh.

A. So that acknowledgement by the FDA is important, it has a legal meaning, and it's not done trivially.

Q. Okay. I understand that.

A. So --

Q. But that's not what I asked you.

A. Well, but, again, I have no idea what you're asking me. I'm sorry.

Q. Oh. I was asking if you had any --

A. I can't say it in any other words.

Q. Sure. I was asking if you had any documentation regarding the statement you just made. Not -- not your -- not your opinion but

what -- do you have any documents with those statements on them from the FDA? Do you have any other written materials from anyone --

A. Well --

Q. -- supporting those statements?

MR. DELAFIELD: Same objections. Compound.

THE WITNESS: There are numerous documents that define the changes that we spoke about earlier, and I've referenced those, on how sponsors deal with the FDA and what the FDA requires.

So, yes, there are documents that lay out what the FDA requires.

And as I said earlier, the changes that were made by UTC with respect to the manufacturing process, the starting material, those are defined in FDA and ICH documents as major changes requiring validation, documentation, and ultimately approval by the FDA.

So, yeah, those documents exist, and I've cited them.

BY MR. POLLACK:

Q. Well, actually --

A. This is --

Q. Uh-huh.

A. You know, again, I don't even know what this is.

Q. This is just a document regarding the same product that we're talking about in this case; right?

MR. DELAFIELD: Objection. Argumentative.

THE WITNESS: Yeah. It's --

BY MR. POLLACK:

Q. Yeah. Okay.

A. I understand from the title it's the same product we're talking about, but I don't know what they're talking about.

Q. Okay. Looking back at Exhibit -- what was called Exhibit 2006, the letter from the --

A. Oh, yeah.

Q. -- from United Therapeutics to the FDA.

As we discussed earlier, there were two other major amendments that were made; right? One regarding the [redacted] of the product and one regarding the location of the

facility?

MR. DELAFIELD: Objection. Mischaracterizes the document.

THE WITNESS: Yes, that's correct.

BY MR. POLLACK:

Q. Okay. Given that those -- those two were changes requiring major amendments in the first place, how do we know that changing the spec from 97 to 98 was also a major amendment? Is there any indication that they considered that to be a major amendment?

A. Sure.

MR. DELAFIELD: Objection. Compound. Vague.

BY MR. POLLACK:

Q. What's the indication?

A. You -- the documents that I've cited consider those changes to be amendment. They specifically address changes in specifications.

Q. Can you -- can you show me where it says that a change in purity from 97 to 98 percent is considered a major amendment?

A. They wouldn't have listed something

as a change in purity from 97 to 98 percent. That's not what guidelines do. They talk about changes in specifications, which that would -- would be.

Q. Okay. Can you show me where they say a change -- in the documents you've cited -- a change increasing the minimum HPLC assay purity is a major amendment?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: The increasing the stringency of a -- of a specification is not a major amendment. What is a major amendment was the change in the process, the change in the starting material. Those are major changes, and those major changes resulted in an increase in purity that the FDA ultimately approved.

MR. POLLACK: I'm going to mark as Ruffolo Deposition Exhibit 11.

(Document marked for identification purposes as Ruffolo Exhibit 11.)

THE WITNESS: Thank you.

BY MR. POLLACK:

Q. Ruffolo -- and Ruffolo 11 is a document entitled "Patent Owner Response to Petition."

A. Yes.

Q. Have you seen this document before?

A. Yes, I believe I have.

Q. Okay. When did you see this document?

A. I saw this maybe a year ago. Oh, I'm sorry. This is the response. This is not the --

Q. Yeah. I don't want to trick you or anything.

A. Right. Yeah.

Q. If you turn to the last page?

A. Yeah.

Q. You'll see it's dated July 6, 2016?

A. Oh, okay. Sorry. I would have read this in the last couple of weeks.

Q. Oh, okay. Were you involved at all in creating Ruffolo Deposition Exhibit 11?

A. No, I was not --

Q. Okay.

A. -- involved in the creation of this document.

Q. Okay. And had you read this document at any time before you wrote your final draft of your declaration?

A. I don't believe so because I believe my document was submitted on this day because it was the day before a family vacation where I had to finish mine. So I don't know if I could have read this in advance.

Q. Okay. Let me ask you.

Did you read any prior drafts of Ruffolo Deposition Exhibit 11?

A. Oh. No.

Q. Okay.

A. No.

Q. So Ruffolo Deposition Exhibit 11 you first read in preparation for today's deposition?

A. Yes, that's correct.

Q. Okay. Was there anything in Ruffolo Deposition Exhibit 11 that you disagreed with?

A. Could you be more specific?

Q. Well, did you see any mistakes or -- let me start with that. Did you see any mistakes in Ruffolo Deposition Exhibit 11?

A. Not that I recall.

Q. Okay. Did you see opinions or statements that you thought were maybe just slightly inaccurate?

A. Can you be more specific on whose opinions you're talking about?

Q. Yeah. Any of the opinions that were written in here by -- this was submitted -- this was submitted by United Therapeutics.

A. I understand.

Q. Okay.

A. Yeah.

Q. Were any of the statements in here -- I assume this was -- these were written by United Therapeutics attorneys.

Were there any statements in this document that you looked at and said, well, I don't know if I completely agree with --

A. Okay.

Q. -- that statement?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: This document, as I recall, quotes some opinions from -- from either Dr. Winkler or from the -- the Board,

that Board.

BY MR. POLLACK:

Q. The Board? The Board that's -- that's hearing this case?

A. Many of those I wouldn't have agreed with.

Q. Okay.

A. Obviously the opinions that relate to mine --

Q. Uh-huh.

A. -- my declaration and the opinions that relate to Dr. Williams' declaration I do agree with.

Q. Okay. So there was nothing -- there were no statements in here that United Therapeutics was advancing that you thought, I don't -- I don't completely with that?

A. Not that I recall.

MR. DELAFIELD: Objection. Asked and answered.

BY MR. POLLACK:

Q. Let me just -- I just wanted to check one thing with you.

If you turn to page 34?

A. Okay.

Q. At the top of the page, this is under a heading that says "The '393 Patent Product is Structurally and Functionally Distinct from Moriarty's Product."

A. Yes, I see that.

Q. Okay. Do you know what that means?

A. I believe I do.

Q. What -- what does it mean?

A. "Structurally different" I believe means a difference in the chemical that was produced as a result of the reaction, and "functionally" I believe means the clinical or perhaps patient significance. That's -- that's my understanding.

Q. Is there a difference between the approved Moriarty treprostinil product that was shown clinically that's different from the '393 product?

MR. DELAFIELD: Objection. Vague. Compound. Outside the scope of his declaration.

THE WITNESS: Not -- not to my knowledge.

BY MR. POLLACK:

Q. And you said that -- we were

mentioning structurally.

Is there a difference between the structure of treprostinil as made by the Moriarty product and the structure of treprostinil as made by the '393 patent?

A. Yeah. As I -- as I indicated, structure to me represents the result of the chemical reaction, and the purity of the material produced by '393 is higher and the levels of all but one of the impurities are lower in the '393 process compared to Moriarty.

Q. Let me ask you a hypothetical.

If the -- here you point out that the difference in purity is .7 percent; right?

A. That's --

MR. DELAFIELD: Objection. Vague.

THE WITNESS: That's -- yes, that's from my declaration.

BY MR. POLLACK:

Q. Okay. Is that a fair characterization of your declaration that's made on page 34? A .7 percent difference in average purity?

A. Yes, I believe it is.

Q. Okay. And in your view, is that being used to show that the '393 product is structurally different from the Moriarty product?

A. Yes, in that it contains two-thirds less impurity than the Moriarty process.

Q. Okay. Let me ask you.

If instead of .7 percent difference, what if the difference was [redacted] percent? Would that still be a structural difference, in your view?

MR. DELAFIELD: Objection. Calls for speculation. Outside the scope of his declaration.

THE WITNESS: If it was [redacted], that would represent about a [redacted] percent reduction. Yeah, that -- that would be important to me.

BY MR. POLLACK:

Q. Okay. What about a [redacted] percent difference? Would that be a structural difference, in your view?

MR. DELAFIELD: Same objections.

THE WITNESS: That would be about a [redacted] percent -- would be, yeah, [redacted]

percent reduction in overall impurities. Maybe. I don't know. I'd have to think about that.

BY MR. POLLACK:

Q. Okay. What if it were a [redacted] percent difference in impurity? Would that -- between the '393 and treprostinil product, would that be a structural difference, in your view?

MR. DELAFIELD: Same objections.

THE WITNESS: Well, certainly if I have to think about [redacted], I'd have to think about [redacted], and I haven't thought about that.

BY MR. POLLACK:

Q. Do you -- you're giving an opinion that .7 is a structural difference.

I'm trying to figure out where is that borderline between structural difference and one that's not a structural difference.

MR. DELAFIELD: Same objections.

THE WITNESS: I don't know, but I do believe that a [redacted] percent reduction in -- in purity is. I don't know what the cutoff is at the low end, but I'm confident that [redacted] percent reduction in purity is.

BY MR. POLLACK:

Q. Okay. Are there -- is there a number that I could give you that you would agree that that would be too small a difference to make a structural difference?

MR. DELAFIELD: Objection. Relevance. Outside the scope. Lacks foundation.

THE WITNESS: You know, not -- if you're asking me can I set the lower limit?

BY MR. POLLACK:

Q. Yeah.

A. I'm telling you, I'd have to think about that. I haven't thought about that, and I don't know off the top of my head what it would be.

Q. In your view, is there no lower limit?

MR. DELAFIELD: Objection. Asked and answered.

THE WITNESS: There is a lower limit to everything. I just don't know where it is off the top of my head.

BY MR. POLLACK:

Q. You haven't thought of that?

A. No.

MR. DELAFIELD: Same objections.

BY MR. POLLACK:

Q. What if there were no difference in the average purity for the Moriarty process and the '393 process? How would your [redacted] change then?

MR. DELAFIELD: Objection. Vague. Calls for speculation.

THE WITNESS: Well, first off, there isn't no difference. There is a difference in the purity of treprostinil that's higher and a difference in the overall level of impurities that are lower in the '393 process. So the hypothetical doesn't mean anything to me.

BY MR. POLLACK:

Q. I understand, but I'm asking you to give an opinion based on my hypothetical and you're here as an expert. So --

MR. DELAFIELD: Same objections.

BY MR. POLLACK:

Q. -- I'd like to you do that.

A. So if you're asking me are two

identical preparations?

Q. Uh-huh.

A. Is there a difference between two identical preparations?

Q. Well, they're two different processes; right?

A. Well --

Q. But let's say they give around the same average purity.

A. Then there could be a difference depending on which contaminant -- which contaminants are or aren't different, which ones are elevated or which are lower, and I wouldn't know that in a hypothetical example.

Q. How come you don't know that?

MR. DELAFIELD: Objection.

THE WITNESS: Because I can't --

MR. DELAFIELD: Calls for speculation.

THE WITNESS: Because I can't make it up.

BY MR. POLLACK:

Q. Okay.

A. You're asking me to make up information that doesn't exist and I -- that's

not how I think.

Q. So, in your opinion, it's not just a difference in purity, but also the exact identity of each of those impurities that --

A. Sure.

Q. -- matters to the claim?

A. Sure.

MR. DELAFIELD: Objection. Calls for speculation.

BY MR. POLLACK:

Q. Okay.

A. Absolutely. Absolutely. It's what I referred to as the -- the characteristic impurities.

Just to give you an example. If two processes that were different and had exactly the same purity, but one of them had a very high level of one single impurity. It would be very high that made up all of that impurity, and the other one had much lower levels. You bet that would make a difference.

Q. Right. Wouldn't that depend on the FDA, the guidelines, how --

A. Of course.

Q. Whether or not that impurity

mattered? So it may make no difference at all; isn't that right?

MR. DELAFIELD: Objection. Vague. Incomplete hypothetical. Calls for speculation.

THE WITNESS: You know, if the purity was [redacted] percent and that [redacted] percent was all one single peak, that would get a great deal of attention by all those groups you said: the FDA, the reviewers, and including the company itself.

BY MR. POLLACK:

Q. All right. But that's not the case for the Moriarty process?

MR. DELAFIELD: Same objections.

THE WITNESS: The Moriarty process doesn't fit your hypothetical example where you ask me to make up data.

BY MR. POLLACK:

Q. Uh-huh.

A. The Moriarty process produces [redacted] plus fold increase in impurities compared to '393 and that I'm more comfortable with because that's real and not made up.

Q. Okay. Yeah, but I'm just asking

that weren't real, you know, how far would your opinion go?

MR. DELAFIELD: Objection. Calls for speculation. Outside his expert evaluation.

THE WITNESS: Well, I mean, as I said, I can't off the top of my head think of that.

But in the example that you gave me where you required me to make up data, which is something scientists don't really do well, at least not good scientists -- we go on real information like this .7 percent data, you know -- I have difficulty answering that question.

And I gave you an example of made-up data that you requested where it would make a big deal, a big difference but, I mean, I guess you can ask me to make up data all day long and I could come up with lots of silly examples where it would make a difference. And I'm happy to do that if you like. It's just not something I do for a living.

BY MR. POLLACK:

Q. All right. No further questions.

A. Thank you.

MR. DELAFIELD: I have no questions.

MR. POLLACK: Thanks so much for your time.

THE WITNESS: Thank you. Thank you.

THE VIDEOGRAPHER: The time is 5:11 p.m. This concludes today's audiovisual deposition of Dr. Robert R. Ruffolo. We're off the record.

(Off the stenographic record.)

THE REPORTER: Mr. Delafield, do you wish a copy of the transcript?

MR. DELAFIELD: Yes, if I could get it expedited.

MR. POLLACK: I need it expedited.

THE REPORTER: What time frame?

MR. POLLACK: Three days.

THE REPORTER: Do you wish a rough?

MR. DELAFIELD: I want one.

MR. POLLACK: Sure. Yeah, I'll

get a rough, too.

MR. DELAFIELD: If I could get expedited, both the rough and final.

THE REPORTER: When do you want the final?

MR. DELAFIELD: When can I get it?

THE REPORTER: Three days.

MR. DELAFIELD: Okay. If that's the quickest, yes.

(Signature having not been waived, the taking of the deposition concluded at 5:11 p.m.)

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DECLARATION UNDER PENALTY OF PERJURY

I declare under penalty of perjury that I have read the entire transcript of my Deposition taken in the captioned matter or the same has been read to me, and the same is true and accurate, save and except for changes and/or corrections, if any, as indicated by me on the DEPOSITION ERRATA SHEET hereof, with the understanding that I offer these changes as if still under oath.

Signed on the _____ day of _____, 2016.

_____

ROBERT R. RUFFOLO, JR., PHD

CERTIFICATE OF REPORTER

DISTRICT OF COLUMBIA)

I, DENISE D. VICKERY, CRR/RMR and Notary Public, hereby certify the witness was by me first duly sworn to testify to the truth; that the foregoing deposition was taken at the time and place stated herein; and that the said deposition was recorded stenographically by me and thereafter reduced to printing under my direction; that said deposition is a true record of the testimony given by said witness.

I certify the inspection, reading and signing of said deposition were NOT waived by counsel for the respective parties and by the witness; and that I am not a relative or employee of any of the parties, or a relative or employee of either counsel, and I am in no way interested directly or indirectly in this action.

Denise D. Vickery, CRR/RMR

My Commission expires February 14, 2018

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ERRATA SHEET

Page No. 8 Line No. 4 Change to: "and" to "am"

Page No. 10 Line No. 9 Change to: "Trandolapril" To "Trandilapril"

Page No. 10 Line No. 10 Change to: "Trandolapril" To "Trandilapril"

Page No. 10 Line No. 11 Change to: "Trandolapril" To "Trandilapril"

Page No. 83 Line No. 21 Change to: "Their" To "There are"

Page No. 113 Line No. 19 Change to: "reactive" To "reacted"

Page No. 142 Line No. 15 Change to: "purity" To "impurity"

Page No. 142 Line No. 17 Change to: "purity" To "impurity"

Page No. 164 Line No. 24 Change to: "a" to "an"

Page No. 204 Line No. 20 Change to: "Spectra photographic" To "Spectrophotometric"

Page No. 245 Line No. 3 Change to: "for" To "from"

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ERRATA SHEET

Page No. 261 Line No. 7-8 Change to: "a decrease" To "an increase" (mispoke)

Page No. 284 Line No. 6 Change to: "It" To "I"

Page No. 318 Line No. 25 Change to: "purity" To "impurity"

Page No. 320 Line No. 12 Change to: "no" To "any"

Page No. 323 Line No. 7 Change to: "90" To "99"

Page No. ____ Line No. ____ Change to: ____

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DECLARATION UNDER PENALTY OF PERJURY

I declare under penalty of perjury that I have read the entire transcript of my Deposition taken in the captioned matter or the same has been read to me, and the same is true and accurate, save and except for changes and/or corrections, if any, as indicated by me on the DEPOSITION ERRATA SHEET hereof, with the understanding that I offer these changes as if still under oath.

Signed on the 1st day of September, 2016.

ROBERT R. RUFFOLO, JR., PHD

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UT Ex. 2058
SteadyMed v. United Therapeutics
IPR2016-00006

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

STEADYMED LTD.,

Petitioner,

vs.

UNITED THERAPEUTICS CORPORATION,

Patent Owner.

Case IPR2016-000006 (Patent 8,497,393)

VIDEOTAPED DEPOSITION OF ROBERT M. WILLIAMS, PH.D.

Friday, August 26, 2016

9:30 a.m.

12235 El Camino Real

San Diego, California

Reported by:

Harry Alan Palter

CSR No. 7708, Certified LiveNote Reporter

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San Diego, California

Friday, August 26, 2016; 9:30 a.m.

THE VIDEOGRAPHER: Good morning. We are on the record. This is the videotaped deposition of Robert M. Williams, Ph.D., in the matter of SteadyMed, Ltd., vs. United Therapeutics Corporation.

This deposition is taking place at 12235 El Camino Real, Suite 200, San Diego, California 92130, on August 26, 2016, at 9:30 A.M.

My name is Kory Ross. I'm the videographer with U.S. Legal Support. Video and audio recording will be taking place unless all counsel agree to go off the record.

Would all present please identify themselves, beginning with the witness.

THE WITNESS: Robert M. Williams.

MR. POLLACK: Stuart E. Pollack, DLA Piper, LLP U.S., on behalf of SteadyMed, Ltd., the petitioner. I'm joined with Maya Choksi from the same law firm.

MS. HASPER: Katherine Hasper of Wilson, Sonsini, Goodrich & Rosati, on behalf of United

Therapeutics and the witness.

MR. MAEBIUS: And Steve Maebius from Foley & Lardner on behalf of patent owner.

THE VIDEOGRAPHER: Thank you, Counsel.

The certified court reporter is Harry Palter.

Will you please swear in the witness.

ROBERT M. WILLIAMS, PH.D.,

having been duly administered an oath in accordance with the California Code of Civil Procedure Section 2094, was examined and testified as follows:

EXAMINATION

BY MR. POLLACK:

Q Good morning, Dr. Williams.

A Good morning, Counselor.

Q Just as a formality to start today, could you state your name for the record and your current position.

A Robert M. Williams, university distinguished professor at Colorado State University.

Q Okay. Now, I know you've been deposed before; correct?

A Yes.

Q How many times have you been deposed?

A I don't know the exact number. It's somewhere around 17, 15 -- 16, 17, somewhere in there. I lost count, actually.

Q Okay. Were all of those patent cases?

A Yes.

Q And how many of those cases were for United Therapeutics?

A Let me see. Three. I think this would be my third deposition with United Therapeutics. But I'd have to -- I can check -- check. It may be three or four. I don't remember. I think it's for sure three.

Q Okay. But you understand all the rules of depositions at this point?

A Yes.

Q Okay. And there's no reason today that you can't give your best testimony?

A No.

Q All right.

MR. POLLACK: I'm going to mark as Williams Deposition Exhibit 1 the Petitioner's

Notice of Deposition.

(Exhibit 1 marked)

BY MR. POLLACK:

Q And Dr. Williams, are you here today in response to Petitioner's Notice of Deposition of Robert M. Williams, Ph.D.?

A Yes, that's my understanding.

Q So you've done two other depositions for United Therapeutics. Did both of those cases also involve treprostinil?

A Yes.

Q And those were two cases in New Jersey involving generic challenges to United Therapeutics Remodulin product?

A Yes.

Q Do you remember the names of the two defendants in those cases?

A Sandoz in the first case, which went to trial, and then Teva.

Q Okay. And the type of case is still ongoing?

A I believe so.

Q Have you submitted an expert report or Declaration in the Teva case?

A Yes.

Q And have you -- and you've been deposed already in that Teva case?
A Yes.
Q Did your expert Declaration or deposition concern the '393 patent at all?
A Yes.
Q Okay. Did you opine on the validity or invalidity of the '393 patent in that case?
A No.
Q Okay. What did you opine on?
A Claim construction.
Q Okay. And what were the issues regarding claim construction in that case?
MS. HASPER: Objection. Relevance.
THE WITNESS: I don't -- I don't recall off the top of my head.
BY MR. POLLACK:
Q Okay. Were they similar to the claim construction issues in the current IPR?
A I believe there was some overlap, yes.
Q Which ones were an overlap?
A Again, I'd have to go back and look at my Declaration.
Q You don't recall --
A It's -- I don't recall exactly.

Q Okay.

A I don't want to give an inaccurate answer.

Q Absolutely.

Do you recall if there was any discussion of the meaning of the term "product" in the '393 case with either -- with Teva?

MS. HASPER: Objection. Relevance.

You may answer to the extent it doesn't reveal privilege.

THE WITNESS: Again, my -- I haven't looked at that material for awhile, so I'm hesitant to give an answer right now.

BY MR. POLLACK:

Q You're not sure?

A I'm not 100 percent sure.

Q Okay. What about the word "comprising"? Was there any issue about the meaning of the word "comprising" in the '393 case?

MS. HASPER: Same objection.

THE WITNESS: I'd have to give the same answer. I don't exactly recall.

BY MR. POLLACK:

Q Well, do you know did you -- whether there was an issue or not, did you make any comments

or provide any opinions regarding the meaning of the word "comprising" in the Teva case?

MS. HASPER: Same objection.

THE WITNESS: I didn't hear you, Katherine?

MS. HASPER: Same objection.

THE WITNESS: And your question again was? Did I give --

BY MR. POLLACK:

Q Did you give any opinion of any form regarding the meaning of the term "comprising" in the Teva case regardless of what the -- ultimate issue was?

A I'd need to refresh my recollection by looking at the Declaration I submitted.

Q You don't recall as you sit here?

A I don't recall.

Q And do you know whether the Declaration you submitted, whether it was -- whether it was stamped "confidential"?

A I believe so.

MR. POLLACK: Counsel, to the extent it's available, we'd like to get a copy of his Declaration from the Teva case.

MS. HASPER: I'll look into it for you.

BY MR. POLLACK:

Q And are you also involved in certain other generic challenges to the Remodulin product, also pending the District of New Jersey?

A I know that there's a case now that I've been retained for involving Watson Laboratories.

Q Any others?

MS. HASPER: Objection. Privilege.

To the extent that you can answer without revealing attorney-client communications or confidential information, you may do so.

THE WITNESS: Not that I'm aware of.

BY MR. POLLACK:

Q Not that you're aware of? Okay.

And in the Watson case, have you submitted any opinions or formed any opinions in that case?

A Not yet.

Q Not yet? Do you know what the issues are in the Watson case?

MS. HASPER: Again, objection. Privilege.

I caution the witness not to answer to the extent that doing so would reveal privileged information.

THE WITNESS: That's at a very early stage, so I haven't done any --

BY MR. POLLACK:

Q You haven't done anything?

A No.

Q Okay. About how many hours in total have you worked on cases for United Therapeutics at this point?

MS. HASPER: Objection.

Mr. Pollack, this is -- you're asking about how much time he's spent either on his own with counsel working on --

MR. POLLACK: Okay. Stop the speaking objections now; all right?

MS. HASPER: I'm trying to explain that you're asking a line of questions which assumes --

MR. POLLACK: Okay. Just -- just say your objection.

(Indiscernible crosstalk)

THE WITNESS: Excuse me, Counselor?

BY MR. POLLACK:

Q Yes. How many hours have you worked on cases for United Therapeutics?

MS. HASPER: Objection. I instruct the witness not to answer to the extent doing so will

reveal privileged information.

THE WITNESS: I have no idea.

BY MR. POLLACK:

Q Well, more than a hundred?

MS. HASPER: Objection. Privileged.

THE WITNESS: I don't know.

MR. POLLACK: Are you instructing him not to answer?

MS. HASPER: The objection -- so I'm going to give you a standing instruction to this entire line of questioning, that to the extent Mr. Pollack asks you about privileged information, including your communications with counsel for United Therapeutics, that we request you not answer.

MR. POLLACK: I'm not asking about his communications.

BY MR. POLLACK:

Q About how much income have you received so far from United Therapeutics working on their cases?

MS. HASPER: Objection. Relevance. Prejudicial.

THE WITNESS: I don't recall.

BY MR. POLLACK:

Q Over $100,000?

MS. HASPER: Objection. Relevance. Prejudicial.

THE WITNESS: I'd have to go look at my invoices.

BY MR. POLLACK:

Q Over $50,000?

MS. HASPER: Objection. Relevance. Prejudicial.

THE WITNESS: Likely.

BY MR. POLLACK:

Q Likely over 50 -- between 50 and 100? Is that fair?

MS. HASPER: Objection. Relevance. Prejudicial.

THE WITNESS: I don't know.

BY MR. POLLACK:

Q It could be over hundred?

MS. HASPER: Objection. Relevance. Prejudicial. Asked and answered.

BY MR. POLLACK:

Q It could be over a hundred thousand dollars?

A I'm thinking I'd have to go look.

MS. HASPER: Objection. Relevance, privilege, asked and answered.

THE WITNESS: I'd have to look.
BY MR. POLLACK:
Q You'd have to look.
I'm asking if it's possible whether it was over a hundred thousand dollars?
MS. HASPER: Objection. Relevance. Privileged. Asked and answered.
THE WITNESS: I just remember I've been working on a lot of different cases at the same time.
BY MR. POLLACK:
Q Sure.
A I don't remember.
Q Sure.
What's your hourly rate?
A $650 an hour.
Q Okay. Have you worked over a hundred hours on United Therapeutics cases?
MS. HASPER: Same objection.
THE WITNESS: I'd have to give the same answer. I'd have to go back and look at my invoices. I don't -- I don't recall off the top of my head.
BY MR. POLLACK:
Q Okay. What about in this IPR? About how

many hours have you worked in this IPR?

MS. HASPER: Same objection.

THE WITNESS: I don't know.

BY MR. POLLACK:

Q No idea?

A No.

Q "No." More than 40 hours?

MS. HASPER: Same objection.

THE WITNESS: Again, I don't want to give an inaccurate answer, so I would need to look at my invoices.

BY MR. POLLACK:

Q I understand. But I'm asking just for an approximate answer. Is it more than 40 hours?

MS. HASPER: Same objection.

THE WITNESS: I don't know.

BY MR. POLLACK:

Q About how much have you invoiced for in this matter?

MS. HASPER: Same objection.

THE WITNESS: Between two and three invoices, so I'm not really sure.

BY MR. POLLACK:

Q Okay. About how much was this at each invoice?

A I do not recall.

MS. HASPER: Same objection.

BY MR. POLLACK:

Q Was each invoice larger than $50,000?

A No.

MS. HASPER: Same objection.

BY MR. POLLACK:

Q Were some of the invoices larger than $50,000?

A No, I don't think so.

Q You think all of them were below $50,000?

A Yes.

Q Okay. And there were about three invoices?

MS. HASPER: Same objection.

THE WITNESS: Again, I can't exactly recall.

BY MR. POLLACK:

Q Okay. Can you give --

A Because I'm working on other matters. Completely different matters, not for United Therapeutics. So --

Q Sure.

A I have a very accurate record on my computer, but I don't remember.

Q How many matters are you working on now?

MS. HASPER: Objection. Relevance.

THE WITNESS: Around nine right now.

BY MR. POLLACK:

Q Okay.

A I'm paid for about nine different matters.

Q All right. About how much do you earn a year doing matters?

MS. HASPER: Objection. Relevance.

THE WITNESS: Which -- what do you mean "a year"? It varies from year to year.

BY MR. POLLACK:

Q How about this year? How much in --

MS. HASPER: Same objection.

BY MR. POLLACK:

Q -- 2016 so far?

A I haven't tabulated that yet from my accountant. He's been buggin' me to give him numbers to him before September 15th. So I'll be doing that soon. I don't know.

Q Okay. Approximately how much?

A I don't know.

Q How about 2015? How much?

MS. HASPER: Same objection.

BY MR. POLLACK:

Q How much have you earned in 2015 on patent matters?

A It was somewhere around $800,000.

Q And what about 2014? A similar amount?

MS. HASPER: Same objection.

THE WITNESS: I don't recall.

BY MR. POLLACK:

Q Of that $800,000 last year, about how much of that was from United Therapeutics?

A I have no idea.

MS. HASPER: Same objection.

BY MR. POLLACK:

Q Would you say half of your time --

(Indiscernible crosstalk)

THE WITNESS: I have no idea.

BY MR. POLLACK:

Q No idea at all?

A No.

Q Okay.

MS. HASPER: I'll just repeat what got lost in the crosstalk was me saying, "Same objection." Also, "privilege."

BY MR. POLLACK:

Q Have you done work in other -- you

understand this is a proceeding called an "inter partes review"?

A Yes.

Q Have you done work in other inter partes reviews?

A Not yet, no.

Q This is your first one?

A Yes.

Q Okay. And how many cases have you testified at trial in?

A Four times.

Q Four times?

A Four different cases.

Q Okay. One of those was the Sandoz case?

A Yes.

Q That case didn't involve the '393 patent; is that right?

A No.

Q Okay. Are you involved also -- I think there's another Sandoz case involving the '393 patent? Are you involved in that one?

MS. HASPER: Objection. Foundation.

THE WITNESS: Not that I'm aware of.

BY MR. POLLACK:

Q No?

Okay. The Declaration?

MR. POLLACK: I'm going to mark as Williams Deposition Exhibit 2 the Declaration of Robert M. Williams, Ph.D., in support of patent owner response to petition.

(Exhibit 2 marked)

BY MR. POLLACK:

Q If you could just verify me that that's a fair and accurate copy of your Declaration?

A (Examining document) So this is -- yes. This is a copy of my Declaration as submitted.

Q Okay. Were there any mistakes in your Declaration that you discovered?

A Yes.

Q Okay. What are those mistakes?

A There is two minor mistakes. At paragraph 88, there's a typographical error. One, two, three, four -- fifth line down, middle, Exhibit 2034 should be Exhibit 2044.

Q Okay.

A And the second error is there is a small change to Exhibit B, entry --

Q I'm sorry, where are you?

A Exhibit B.

Q Okay.

A Page 50, the entry [redacted] was inadvertently a duplicate. So that -- that one entry needs to be crossed out.

Q Okay. Could you tell me what page we're looking at?

A 50.

Q And which entry is it?

A It's the -- I believe it's the [redacted] was inadvertently a duplicate of another -- another entry.

Q And that is the 17th one down?

A Yes. I think that's correct.

Q Okay. Other than those two corrections, are there any other corrections you want to make?

A Not that I have found.

Q Okay. Are all of your opinions in this matter -- are they all contained in your Declaration?

A Yes.

Q Okay. Who did the first draft of your expert Declaration?

A I actually made the draft of -- sort of the template of the first draft and, Counsel, Bobby Delafield, and I also worked with Katherine here. We went back-and-forth by e-mail assembling

different drafts as we went along, and discussed issues and --

Q What's Katherine's last name?

A Hasper.

Q All right. Anyone else you worked with at counsel?

MS. HASPER: You can answer to the extent it doesn't reveal privileged information.

THE WITNESS: I primarily worked with Bobby and Katherine, as I recall.

BY MR. POLLACK:

Q Who assembled the appendices "A" and "B"?

A Counsel did.

Q Did you have any questions about how counsel assembled Exhibits A and B -- or appendices "A" and "B"?

A What do you mean?

Q Did you ask them: How were these assembled?

A Yes. I worked with them, and there was underlying batch data that I was provided with, and I was able to cross-check that the entries were all accurate.

Q Okay. Who selected the particular batches that were chosen to the analyzed?

A These were -- I think these were requested by counsel from United Therapeutics.

Q Okay. You had nothing to do with the selection?

A Other than asking for as much batch data as was available.

Q Okay. Did you get all batch data that was available?

A I believe so.

Q Okay. Was there any batch data that you saw that's not included in appendices "A" and "B"?

A No.

Q Did you ask whether there was any other batch data that you could include?

A I did ask.

Q Okay. And what was the answer?

A That this was all they were able to find.

Q Okay. If we can go in your Declaration to paragraph 27.

Here in paragraph 27, you list some patent litigation matters that you were working on?

A Yes.

Q Is that right? Okay.

Are there -- it says here, "Process chemistry patent litigation." Are there other kinds

of litigation matters that you were working on that aren't in this list?

A Yes.

Q Okay. About how many other matters?

A So this lists, I believe, seven. And I've worked on somewhere around 27. So 20 other matters that -- that were not dealing with process chemistry issues.

Q Just briefly what were those other matters concerning?

A I would need to look at my list of -- of cases. I don't have a memory of all of 'em.

Q Sure. Do you have a recollection of some of them?

A I did a couple of cases on behalf of Apotex in Canada early on.

Q Apotex is a generic pharmaceutical company?

A Yes.

Let me see. I did a formulation case where I testified at trial on behalf of Hospira and Apotex against Sanofi-Aventis. That wasn't process chemistry. That was formulations. I've done a bunch of formulation cases.

Q I see on this list there are some cases

that name United Therapeutics.

A Hmm-hmm.

Q Okay. The first one lists United Therapeutics is United Therapeutics Corp. versus Sandoz. And there are two cases listed. Do you see that?

A Yes.

Q Is the first case the case that went to trial already?

A Yes.

Q Okay. And --

A I believe so.

Q And that case didn't involve the '393 patent?

A No.

Q Okay. And then there's a second case. Do you see that? 13-316?

A 13 --

Q It's in the same -- sorry. It's in the same phrase on page 11.

A That was -- I think that was a consolidated thing where there were two different -- there was a formulation patent and a process patent that were litigated at the trial --

Q Okay.

A -- as I recall.

Q And neither of them involved the '393 patent? Neither of those cases?

A No, I don't think so. No.

Q At the very bottom of the page, we see the words United Therapeutics starting?

A Yes.

Q And then it says, "versus Teva." That's the matter you're working on now?

A I believe that matter is over. I believe the parties settled.

Q Okay. Okay.

The matter in which you've given an expert on claim construction, that's a new Teva matter that's not listed here?

A Boy, I -- you know, just looking at the case numbers, I don't remember. I'd have to look at my -- at my records.

Q Okay. Looking here, you see this is a matter filed -- this Teva matter was filed in 2014. Is the matter you're working on now the one that was more recent?

A Well, as far as I -- as far as I can recall, the only two matters for UTC I'm working on right now is this one.

Q Right.
A The IPR matter.
Q Okay.
A And then the upcoming Watson case.
Q Okay. Okay. And you see it also lists here yet another matter for Sandoz?
A Oh, I'm sorry, the Sandoz one is the one I believe that settled. The Teva one might still be ongoing. I just don't recall. Nothing's happened in a while, so I don't remember.
Q Okay. Okay. And in addition to these, there's this Watson matter?
A Yes.
Q Are you working on any matters for United Therapeutics involving their -- the oral form of treprostinil?
MS. HASPER: Objection. Privilege.
THE WITNESS: Not that I can think of.
BY MR. POLLACK:
Q Okay. Nothing comes to mind?
A No.
Q Okay. When did you first get hired to work on this matter?
A I don't recall the exact date of -- when I signed my Retainer Agreement. I believe it was

either late -- late last year or early this year. I'm not exactly sure of the timing.

Q And when -- when do you actually start working substantively on the matter?

MS. HASPER: Objection. Privilege.

I instruct the witness not to answer to the extent doing so will reveal privileged communications with counsel.

THE WITNESS: I just don't recall.

BY MR. POLLACK:

Q Well, was it in the Spring? You start working on it in the Spring.

MS. HASPER: Same objection.

THE WITNESS: I don't remember.

BY MR. POLLACK:

Q Don't recall at all?

A No.

Q How about as late as Summer?

MS. HASPER: Same objection.

THE WITNESS: I was certainly working on it by the Summer, but I don't remember how early in the year or if there was anything late in 2015. I just don't remember.

BY MR. POLLACK:

Q Okay. Well, you recall -- you can look

at your Declaration. You filed that on or around July 6th. Do you recall that?

A This (Indicating)?

Q Yes.

A Yes. Okay.

Q Okay. So using that date, about how many months earlier did you start working on the IPR?

MS. HASPER: Objection. Privileged.

THE WITNESS: I just don't remember the timing.

BY MR. POLLACK:

Q Three months before?

MS. HASPER: Objection. Privileged.

THE WITNESS: Counsel, I said, "I don't remember."

BY MR. POLLACK:

Q Okay. But I'm trying to -- you know, could it have been six months before?

MS. HASPER: Objection. Privileged. Asked and answered.

THE WITNESS: I just don't recall the timing. I could easily look at my invoices.

MR. POLLACK: I'd like to request Dr. Williams's invoices in this matter.

MS. HASPER: I hear your request.

BY MR. POLLACK:

Q Okay. Do you think you started working on it substantively in late 2015?

MS. HASPER: Objection. Privileged. Asked and answered.

THE WITNESS: I -- I don't recall.

BY MR. POLLACK:

Q Nothing at all, whether --

A I just don't recall.

Q No idea?

How soon after you were retained did you start working on that?

MS. HASPER: Objection. Privileged. Asked and answered.

I instruct the witness --

MR. POLLACK: None of this is privileged. And your speaking objections are going so far. If this continues, I'm going to ask for a second deposition of him. Understood?

Go ahead.

THE WITNESS: I don't recall.

BY MR. POLLACK:

Q Okay. Other than your hourly rate, is there any other compensation you expect for working on this IPR?

A No. Other than the opportunity to play golf in Southern California tomorrow.

(Laughter)

BY MR. POLLACK:

Q Could you tell me about why you're playing golf in Southern California tomorrow?

A Because there's a great golf course near here that I like.

Q Oh, Okay.

A But United Therapeutics is not paying for it. I am.

Q How many -- how many matters have you worked with the law firm of Wilson Sonsini on?

MS. HASPER: Objection. Privileged.

This also refers -- it sounds like you're asking about case others than this case.

THE WITNESS: So give me your question one more time, please.

BY MR. POLLACK:

Q Sure. How many matters have you worked on with the Wilson Sonsini law firm?

A By "matters," do you mean litigation matters, because -- --

Q Any kind of matter.

A -- I was a cofounder of a biotechnology

company that used Wilson Sonsini's patent counsel.

Q Okay.

A That was microcide pharmaceuticals, and we use the Wilson Sonsini. So I have -- and that was their Palo Alto office.

Q Did they take -- in exchange for that legal work, did they take any kind of equity or any kind of compensation of that type?

A That, I don't remember. It was a long time ago.

Q Okay.

A It was the early '90s. I just don't remember. But I know Wilson Sonsini was patent counsel to Microcide.

Q Okay. How many other matters?

A Um, let me see.

MS. HASPER: Objection. I instruct the witness not to answer to the extent doing so would reveal any privileged information.

THE WITNESS: I have a current spinoff company that I founded and am president of in Fort Collins. And we have patent counsel from Wilson Sonsini who volunteered to work for free.

BY MR. POLLACK:

Q Really?

A Yeah.

Q Why did they do that?

A It's active-retirement-sort-of situation. So retired attorney who actually still is associated with Wilson Sonsini but wants to do something interesting instead of just playing golf, and skiing or something like that.

Q Okay.

A We were very lucky to get a very qualified attorney who's interested in our company and our technology.

Q Okay. All right. Anything else?

A I was retained to work on one other case that never materialized. So there was no -- no expert reports or anything. So I was retained, no invoices that I can recall, and the matter settled before anything happened.

Q Okay. Anything else?

A Not that I can think of.

Q Okay. I mean, other -- there's also a bunch of matters with United Therapeutics. Those were all the Wilson Sonsini firm?

A Yes.

Q Okay. And same set of questions for the Foley & Lardner firm. How often have you worked

with that firm?

A Who?

Q Do you know Mr. Maebius?

A Oh, I just met him for the first time yesterday.

Q Oh, okay. Okay.

Have you met anyone else from Mr. Maebius's firm?

A I don't think so.

Q Okay. And did you meet with Mr. Maebius yesterday to prepare for today's deposition?

A He came to the preparation that I was doing with Counselor Hasper.

Q Okay. Who else was at that preparation?

A One other attorney from UTC. Shaun -- I can't remember his last name.

Q Okay. Anyone else?

A No.

Q And other than yesterday, were there other meetings in -- that you had with counsel in preparation for today's deposition?

A No.

Q About how long did you meet with counsel yesterday?

A About nine hours.

Q And prior to yesterday's meeting with counsel, did you have telephone -- you know, meetings by telephone or other means of communication -- with counsel?

A A few with Counselor Delafield.

Q Okay. Other than Counselor Delafield, anyone else?

A No.

Q What else did you do to prepare for today's deposition?

A I reread lots of documents, patents, prior art, my own Declaration.

Q Did you search for prior art?

A Did I search for prior art?

I don't -- I don't recall.

Q You don't know, one way or the other?

A No, I don't know, one way or the other.

Q Okay. Did you search for any papers, articles, or documents that were relied upon in your Declaration?

A Well, I already had a vast amount of literature from the other cases. So I was already fairly familiar with a massive volume of literature and information relative to treprostinil. So --

Q Did any of the articles that were

attached to your Declaration -- let me rephrase.

Were all of the articles attached to your Declaration provided by counsel?

A I guess I'd need to look at my list of exhibits. I don't remember. I'd have to look --

Q Okay. If you look at paragraph 28 of your Declaration, there's a description of what you considered.

A Well, this isn't a list.

Q Well, that's the only list you provided, sir.

A Okay.

Q Let me ask you: It says there, "I have also reviewed a number of documents in this case, including all documents cited by SteadyMed and UTC, as well as the materials I have cited in the Declaration."

Other than those documents, were there any other documents not described in that sentence that you reviewed?

A No.

Q Okay. You say in the last sentence, "If I am provided additional information or documents in this proceeding, I may offer further opinions regarding the additional information."

Were you provided any additional information or documents?

A No.

Q Okay. And, therefore, you will not be, I assume, offering further opinions regarding any additional information?

A Not at this time.

Q Okay. Was there anything that you asked for from counsel that you wanted to review?

A I actually -- can I go back to a previous question you asked me?

Q Absolutely.

A You asked me if I -- if I did my own -- any literature searching?

Q Yes, yes.

A So I actually did pull up every single one of Dr. Winkler's publications.

Q Okay.

A I did that myself. And I provided all of those papers to counsel and looked through all of his papers.

Q Okay.

A So that was -- so I would consider that a literature search. It was actually a lot of work.

Q Okay. He's written a lot of papers;

right?

A That's all relative. Relative to me, no.

Q Okay.

A I've published maybe three or four times the number of papers of Dr. Winkler.

Q Okay.

A So it was actually, from my point of view, a modest amount. But it was still over a hundred papers, I think it was.

Q Yeah. You know Dr. Winkler; right?

A Yes, I do.

Q In fact, you're together in a network of experts; is that right?

A I wouldn't characterize it that way. Dr. Winkler has a -- an expert witness head-hunting firm called Cymedex, and he's contacted me at least a half a dozen times as a potential candidate to work on cases that came to his company. And none of them materialized in a retained engagement, but we've certainly talked on the phone. He's had my CV. He obviously thinks I'm a very good expert, so he's been trying to find, you know, an engagement for his company that uses me.

Q Okay. The two of you know each other; right?

A Oh, yes.
Q Yeah.
A Yeah. Organic chemistry is a small community.
Q Yeah. Would you say Dr. Winkler's a distinguished organic chemist?
A I think he's a very solid organic chemist.
Q How does "solid" differ from "distinguished"?
A So I would reserve the characterization "distinguished" to be with more accolades, national awards, and things like that, and I don't think he's quite hit that bar.
Q Okay. What about you? Have you hit that bar?
A Very fortunately, yes, I would say so. I got a major -- two major national ACS awards recently. I'm university distinguished professor, Colorado State University, which is a lifetime appointment, and there's only 12 in a campus of more than 1,200 faculty.
Q Okay.
A I don't mean to disparage Dr. Winkler. He's a very nice man, and he's a very good chemist.

Q Other than searching for Dr. Winkler's articles, do you recall any other documents that were provided solely by you for use in this proceeding?

A I provided counsel with some of my own papers.

Q And what did those papers concern? Why did you provide those?

A So I cited those in my Declaration that had to do with how I have used the word "product" in my own publications. And I also -- some of the papers from -- that I found from Dr. Winkler, how he also very, very -- in the very same way uses the word "product" in his own publications.

Q Okay.

A So we use the word the same way.

Q Other than those papers which were attached from you regarding the meaning of the word "product," was there anything else that you provided for use in this proceeding?

A Not that I can think, off the top of my head.

Q When counsel provided you with the data for appendices "A" and "B," who did the calculations based on those appendices?

A Counselor Hasper did.

Q You didn't do the calculations?

A No. But I checked them.

Q Okay. As I understand it, one of your main opinions here is that the product of the '393 patent has an average purity of [redacted] percent, while the product of the Moriarty patent has an average purity of 99.0 percent, approximately. Is that -- is that fair?

A There's more to it than that. Just the overall purity. There's also impurity -- significant impurity profile differences between the product of the two patented processes.

Q How are those different profiles significant?

A In what context?

Q Well, are any of those impurities known to be particularly harmful?

A Well, by "harmful," what do you mean "harmful"? In what context?

Q In any context.

A Well, I mean, in process chemistry, the goal is to try to get as pure an API as possible that is free of any type of extraneous impurities. And so sometimes, depending on the API material,

impurities may have deleterious biological consequences; sometimes they don't. Um --

BY MR. POLLACK:

Q Do any of the -- as far as you know, any of these particular impurities have deleterious biological consequences?

MS. HASPER: Objection. Beyond the scope of his expert Declaration.

THE WITNESS: I'm not a clinician, so I don't know.

BY MR. POLLACK:

Q You don't know?

A I don't know.

Q Okay. So other than the percentage of the impurities, if there's no knowledge about the biological deleterious effects of any of these impurities, what difference does it make which ones they are?

A So I think the stereoisomer impurities would be the ones that a process chemist would be particularly wary of. The dimer impurity and the ethyl and methyl ester impurities are hydrolyzable back to treprostinil to API.

So those are both -- I guess, operationally, you can recover, actually,

treprostinil from those impurities if you needed to. And, you know, in vivo, they can be hydrolyzed in treprostinil. So they're not going to have a deleterious effect, presumably.

Q But no one knows that?

A Not for -- not that I've seen.

MS. HASPER: Same objection.

BY MR. POLLACK:

Q Let me ask you this: If -- let's say the difference in impurities between the '393 patent and the Moriarty prior art patent was [redacted] for the '393 -- same number you're relying on -- and 99.5 for the Moriarty patent, how would that change your -- your opinion?

MS. HASPER: Objection. Foundation.

THE WITNESS: Well, there's a lot more to it than just the -- and you're talking about average --

BY MR. POLLACK:

Q Average. Yeah.

A -- over --

Q Yeah. I'll give you average.

A 50, 100 batches or something like this?

Q Sure.

A Again, it's not just a simple matter of

that one of the significant advantages of the '393 process is the elimination of chromatography, which from a process chemist point of view is exceedingly important because chromatography is expensive, it's time-consuming, it adds cost of goods, there's safety issues, waste issues. And eliminating that is a -- is always a very, very desirable goal.

So the '393 process allows for the elimination of chromatography in the preparation of the final drug substance. So that's very important.

Q I don't see that opinion expressed in your Declaration, though, sir.

A Hmmm?

Q That opinion is not expressed in your Declaration, is it?

A About the elimination of chromatography?

Q Yeah.

A I -- I think it's in there, and it's certainly in the patent. The patent talks about the advantages of the elimination of chromatography.

Q Okay. But in your opinion, you talk about the difference in the impurities; correct?

A Yes. I certainly spend quite a bit of time on the impurity profiles.

Q Right. Okay.

A The differences.

Q If the difference in the quantity of impurities was only [redacted] versus 99.5, how would that affect your opinion?

MS. HASPER: Objection.

THE WITNESS: I'd have to look at actual data and impurity profiles. You're asking me a hypothetical --

BY MR. POLLACK:

Q Yes.

A -- that I'm reticent to just give an opinion on without actually seeing what you're talking about.

Q Well, you gave an opinion on the difference between 99.0 and [redacted]. I'm trying to understand how your opinion changes when it's [redacted] versus 99.5.

A Again, I would need to see data and the way in which the two processes operate that rendered the material of those relative impurities.

Q So the 99.5 is the Moriarty process. Got it? And the [redacted] is the '393 process. How would your opinion change if those were the average results?

MS. HASPER: Objection. Asked and

answered.

THE WITNESS: So I would need to see the distribution of actual impurities, and I would also need to understand the process that resulted in those materials.

BY MR. POLLACK:

Q What would you need to understand about the process?

A Well, like the '393 process I just mentioned eliminates chromatography. So crystallization gets an incredibly pure salt.

Q Let me ask you this: The claims of the '393 patent, you're allowed to do chromatography and practice those claims; right?

A Yes.

Q Okay.

A But the patent enables you to eliminate that step.

Q Okay. But the claims would include that step; right?

A They can --

Q Yeah.

A -- but again, the process -- very important part of the process is that it enables you to eliminate that step.

Q The --

A We've been going almost an hour, and my 63-year-old bladder is not as robust as it used to be. So could we take a quick break?

MR. POLLACK: Absolutely. Absolutely.

THE VIDEOGRAPHER: We are off the record. The time is 10:18 A.M.

(Off the record)

THE VIDEOGRAPHER: We are back on the record. The time is 10:25 A.M.

BY MR. POLLACK:

Q Welcome back, Dr. Williams. I have -- we've already marked as Williams Deposition Exhibit 3 a patent -- U.S. Patent No. 8,497,393, the patent at issue in this proceeding.

(Exhibit 3 marked)

BY MR. POLLACK:

Q And I've marked as Williams Deposition Exhibit 4, U.S. Patent 6,765,117, the Moriarty patent, also known as Exhibit 1003 in the proceeding.

(Exhibit 4 marked)

BY MR. POLLACK:

Q If we could start with Deposition Exhibit 4.

This is the Moriarty patent; correct?

A Yes.

Q Okay. And you've -- you've reviewed that thoroughly for your opinion in this proceeding?

A Yes.

Q If you could turn to column -- columns 9 and 10. Do you see there's a compound toward the bottom -- a compound 14? Do you see that?

A Yes.

Q Okay. And there's a step where it's being turned into compound 15? Do you see that?

A Yes.

Q Okay. I wanted to compare that to the claims in Exhibit 3, the '393 patent. And what I want to know is whether or not that change from 14 to 15 -- is that what the '393 patent refers to as "step (a)"?

A Okay. Which page of the '393 patent?

Q The claims are -- they start at column 17 --

A Oh, I'm sorry.

Q -- and then they go through to column 21.

A (Examining document) Okay. So your question was, is the conversion of 14 to 15 step (a)? Is that your question?

Q That's correct. Yes.

A Yes.

Q Okay. And my next question is: The conversion from 15 to 16 in Exhibit 4, the '117 Moriarty patent, is that what is known as "step (b)" in the claims of the '393 patent?

A Yes.

Q And looking at Exhibit 4, the '117 patent, this is showing a scheme for making compounds of the type claimed in the '393 patent but by the Moriarty method. Is that -- is that fair?

A Yes.

Q Okay. On pages 9 and 10, compound 16, is that the final compound of the process? The Moriarty process.

A Structure 16?

Q Yes.

A So that would be true where R1 is H. M in brackets on both sides is 1. All three Ms are 1. That would be treprostinil.

Q Treprostinil. But the '393 patent has a lot of other compounds to the final products; right?

A Yes.

Q Okay. Would that be a structure of final products -- let me start again.

Would structure 16 in the Moriarty patent, Exhibit -- Deposition Exhibit 4 -- would structure 16 be a structure of final compounds made in, for example, claim 1 of the '393 patent?

A No, because there's an additional step in the '393 step (c).

Q The purification step?

A The contact and the product in step (b) with a base to form a salt, which is then optionally reactive with an acid to form the carboxylic acid 16.

Q Okay. Okay. So if you did step (1) all the way through step (d) -- where step (d) is optional, though, you would get a compound of 16?

A You said, step (1) through D? What do you mean?

Q Sorry. I may have misspoken, then.

If you performed claim 1 through step (d), you would get a compound of structure 16?

MS. HASPER: Objection. Mischaracterizes the document.

THE WITNESS: So --

BY MR. POLLACK:

Q I was just trying to understand your last answer, but --

A Okay. So --

Q -- we can move on.

A Structure 16, where I specify what the variables were, R1 and M, where R1 is H, and M is the number 1, that structure would then be treprostinil acid. And included in the Markush or the more generic formula shown in claim 1, you would get treprostinil after step (d).

Q Okay. So structure 16 would be included in the products would you get in claim 1 after step (d)?

MS. HASPER: Objection. Mischaracterizes the document.

THE WITNESS: So included in the formula 1S -- I think that's what you're referring to; right? In --

BY MR. POLLACK:

Q Yes. 1 --

A So in formula 1 -- 1S where the stereochemistry of the secondary hydroxyl group, there's a wavy line that has to be defined as down -- would be a dashed line. And then these other variables, Y1, W, M1, L1, R7 -- and I believe that -- I'm certain, actually, that the definitions they call out when you plug them in correctly reads

on the structure of treprostinil.

Q Okay. Okay. I didn't want to confuse you. And I may have confused you. I was actually referring to structure 1, which is -- just turn to the very beginning of the claim, claim 1; right? The structure -- structure Ss with the base; right?

A Wait. So you've lost me now.

Q Right.

A We're at column 17.

Q Yes.

A On the '393.

Q Yeah.

A And you're asking me to look at structure 1; right?

Q You can look at anything you want to. You referred to, just now, to structure 1S, and that shows the salt -- the base salt; right?

A Yes.

Q Okay.

A That's the salt.

Q Okay.

A And after D, you get to formula 1, the treprostinil acid.

Q Right.

A Acid.

Q And 16 would be included in formula 1?

MS. HASPER: Objection. Mischaracterizes the document.

BY MR. POLLACK:

Q The '117 patent?

A Well, the molecular structure of 16 reads onto formula 1 where the variables are defined appropriately --

Q Okay.

A -- which the claim calls out.

Q Okay. Looking at the -- looking at columns 9 and 10, which show how to make treprostinil in similar structures, do you see a chromatography step?

A Well, I can see a chromatography step in every step.

Q One could do it optionally?

A Yeah. And the way organic chemistry works is that when you're going through a synthesis of this complexity the first time, every intermediate product is typically isolated by chromatography to get an analytical sample and characterize it to get it as pure as possible for analytical purposes. And then as you go from small scale to large scale, one hopes to eliminate

chromatography steps, and you take Cree material on it or crystallize intermediates if they're crystalline.

Q Okay. But here on pages 9 and -- column 9 and 10, the '117 patent, it doesn't say anything about chromatography?

A Well, a person skilled in the art looking at this would understand that this is just a reaction scheme structure with no details. One would need to look at the actual experimental -- detailed experimental procedures for each step and see if any of these steps require chromatography.

Q Okay. But as Moriarty lays out the reaction here, chromatography may be optional, but he doesn't -- here on pages 9 and 10 -- columns 9 and 10 require chromatography; is that fair?

A Well, that's --

MS. HASPER: Objection. Asked and answered. Mischaracterizes the document.

THE WITNESS: There's not enough information here. Again, I just said this is a reaction scheme. One would need to look at the actual published procedures, the experimental -- the recipe, the detailed how to do each step.

///

BY MR. POLLACK:

Q Let me ask you this: The claims for the '117 patent -- the claims, which is in the back at columns 21 to 24 --

A Okay.

Q -- do the claims of the Moriarty patent require a chromatography step?

A No, I did not see the word "chromatography" in the claims. But I know that the reality of doing synthesis like this, it does entail chromatographic separation.

Q Okay. Could we go back to your Declaration? That's Exhibit 2. I'd like to turn to paragraph 98 of your Declaration. It's on page 33.

In the last two sentences, those appear to be the conclusion sentence of your paragraph. And it says there, "The treprostinil product of the '393 patent has an average purity of [redacted] percent, while the Moriarty product has an average purity of 99.05 percent. Thus, the treprostinil product of the '393 patent has an average purity that is .7 percent higher than that of Moriarty's."

Do you see -- did I read that correctly?

A Yes.

Q Why is that difference important to you?

A Well, that's -- that's one important difference. This is the overall average purity. And then inside those numbers are the actual characteristic impurity profiles that come along as a signature of the synthesis. And the '393 patent process allows for elimination or significant reduction of a significant number of those impurities. And that's important.

Q Well, what if the reduction in each of those impurities was only .02 percent? Why is that important?

MS. HASPER: Objection. Foundation.

THE WITNESS: So you're -- I'm trying to understand. This is a hypothetical question?

BY MR. POLLACK:

Q Hypothetical question.

A Okay. And so you're asking me if the difference between -- just re --

Q Just pick one impurity. Let's pick 1AU90. That's one of the impurities?

A Yes.

Q What is 1AU90?

A That's one of the stereoisomers.

Q Which one?

A There's 32 stereoisomers. I don't have

the structure memorized, but I recall that it's a [redacted] stereoisomer. I think --

Q Okay.

A -- but I'd have to check.

Q All right. Anything particularly significant about that stereoisomer?

A Well, it's a carboxylic acid like treprostinil. And so in terms of separating it from the desired molecule, treprostinil, that's a challenging impurity to remove, because it has very similar PKA. They're both carboxylic acids. They have the same molecular skeleton. They're just different in stereochemistry.

Q But biologically, is there any difference between 1AU90 and treprostinil?

MS. HASPER: Objection. Beyond the scope.

THE WITNESS: I don't know, but certainly treprostinil is the biologically active principal. And I'm not aware of any biological data on 1AU90. But there may be some, but I'm not a biologist.

BY MR. POLLACK:

Q That's not something you looked into?

A No.

Q You didn't speak to anyone else working on this case who looked into that?
A No.
Q Did you speak to any -- other than the attorneys, did you speak to anyone else in working on this case?
A No.
Q And are you familiar with a Dr. Ruffolo who submitted a Declaration in this case?
A I don't know him.
Q Okay. You never spoke to him?
A No.
Q Did you read his Declaration?
A Briefly and very recently.
Q Was that only in preparation for your deposition?
A No. So that was part of the big -- sort of master file that I saw, and I -- I briefly scanned through his -- his Declaration.
Q Let me ask you: Did you read his Declaration before you signed and completed your Declaration on July 6th?
A No.
Q Okay. So it was only after --
A Only after.

THE REPORTER: Try to pause a little bit, please.

THE WITNESS: I'm sorry.

BY MR. POLLACK:

Q We both have that habit.

THE REPORTER: Yes, do you.

THE WITNESS: I will try and speak much slower. Is that what you want?

THE REPORTER: Like that will happen.

BY MR. POLLACK:

Q Are you originally from New York?

A How did you guess?

Q I'm a New Yorker, also. So we're both fast-talkers.

A Huntington.

Q I'm Brooklyn, lucky you.

A But I hate the Yankees. Red Sox fan.

Q Oh, Mayor Bloomberg was; right?

Let me ask you -- you make this point about the [redacted] versus the 99.05. I'm really trying to understand, how far can the 99.05 number increase before that point is no longer that significant to your opinion?

A You know, I didn't -- I didn't do that analysis or consider -- consider that.

Q Understand. I'm asking you to just consider that now.

A I'd need to look at data -- impurity profiles and data.

Q Let's say the impurity profiles were all the same as we're seeing now, just the number has changed. So if the number is changed, and they change in such a way that we go from 99.05 to 99.5, how would that change your opinion?

MS. HASPER: Objection. Incomplete hypothetical. Beyond the scope.

THE WITNESS: Okay. So you're asking me, again, sort of a make-believe Moriarty series of batches that I've never seen. I haven't seen any such material. And Dr. Winkler didn't produce any Moriarty material batches, or he didn't do his own experiments to show that he would get that. But, again, I -- you know, I -- I'd -- I'd have to look at the data.

BY MR. POLLACK:

Q Let me ask you: What if -- what if the Moriarty batches -- the average value for the Moriarty batches was [redacted] -- the very same as your number there --

MS. HASPER: Same objection.

BY MR. POLLACK:

Q -- how would that change your opinion?

MS. HASPER: Same objection.

BY MR. POLLACK:

Q So no difference in the purity level.

MS. HASPER: Same objection.

THE WITNESS: Okay. So, again, I think your question's about overall impurity -- overall purity, [redacted] percent, which is total related substances, which is known, plus unknown impurities -- so it's just not a simple matter of overall purity. You also have to look at the impurity profiles, because that is the significant difference in the product between the '393 and the Moriarty process.

BY MR. POLLACK:

Q So you're saying even if the overall purity is the same, the distribution of those impurities -- which we don't know anything about in regard to their biological property -- but that really matters? That's your opinion?

A That's my understanding, that in product-by-process patents, the -- the new product by the new process has to have structural, functional differences. And impurity profiles are

structural differences.

Q Are there any functional differences, though, between a material -- a new material which has a impurity level -- or purity level of [redacted] and another material which has a purity level of, say, [redacted]?

MS. HASPER: Objection. Beyond the scope. Incomplete hypothetical.

THE WITNESS: I don't know. And, again, the -- you know, the -- really, the significant thing about the '393 process is the elimination of the chromatography. The way I view it, that's a functional difference. It reduces cost of goods, and solvent safety. So it's -- it's not a insignificant matter.

BY MR. POLLACK:

Q Let me ask you something: In the -- if you go to the '393 patent -- pick up Exhibit 3, again -- there's a claim 16. Do you see that claim?

A Yes.

Q It's in column 20.

A Yes.

Q Now, do you have any patents?

A Yes.

Q Okay. You understand how patent claims

work; correct?

A Generally.

Q Okay.

A I'm not a patent expert, but --

Q You know -- do you know what an independent and a dependent claim is?

A Yes.

Q Okay. What's your understanding of what a dependent claim is?

MS. HASPER: Objection to this, that it seeks a legal conclusion.

THE WITNESS: Well, generally, a dependent claim is -- follows an independent claim and typically narrows down the scope of the independent claim to a more -- some type of parameter.

BY MR. POLLACK:

Q It adds something the independent claim doesn't require; is that fair?

A Again, I'm not a lawyer. I don't know if that's ubiquitously true, but that sounds reasonable.

Q Is claim 16 -- is that a dependent claim?

A Yes. It's dependent from claim 9.

Q Okay. What is claim 16 adding?

MS. HASPER: Same objection.

THE WITNESS: So claim 16 says, "The product is claim" --

THE REPORTER: Speak up, please.

BY MR. POLLACK:

Q If you could read more slowly. He's got to type it all.

A "The product of claim 9 wherein the process does not include purifying the compound of formula VI produced in step (a), which is the nitrile."

Q What does that mean?

A So this is -- this claim is saying that you do -- you perform step (a) and then carry the nitrile through to the next step without doing a purification step, like a chromatography.

Q Okay. In your understanding, though, does that mean that claim 9 could be carried through with the chromatography?

A It could, but importantly, this patent and the process that's being used eliminates that.

Q Right. But claim 9 doesn't; right? Claim 9, you can do the chromatography.

A You could if you wanted to. It seems like a nonsensical thing to do when we know it works

really great without.

Q But claim 9 does include with the chromatography?

A It's agnostic as to chromatography; right? Doesn't say, one way or the other.

Q Sure. But claim 16 is very specific. That's done without the chromatography; right?

A Yes.

Q So that means claim 9 includes both with or without the chromatography; is that fair?

A Again, I'm not -- I'm not a patent lawyer, so I'm not sure that that is necessarily the way that's read.

Q What's your understanding?

A Yeah. It's -- I mean, it's silent on that issue. So --

Q And based on that, what do you conclude about whether chromatography is included in claim 9?

MS. HASPER: Objection to the extent it seeks legal conclusion.

THE WITNESS: So, you know, I think a person skilled in the art looking at this, again, would be informed by the specification and column 15, a real-world 5-kilogram example, says no column for that step. Whereas in the prior art process,

there's a purification column chromatography step.
So --
BY MR. POLLACK:
Q Let's take a look at claim 1.
Now, you'll agree with me that claim 1 also would include the chromatography; is that fair?
A I don't know if I would read in the requirement for chromatography. It doesn't say anything about it. It's also silent on that issue.
Q But it couldn't -- since it's silent and there's a claim that says, "Don't use chromatography," we could probably conclude that it does include chromatography, just on basic logic?
A Yeah. I suppose it could, but we -- again, the patent talks in several places about the advantage of elimination of the chromatography step.
Q Let me ask you: About how many compounds do you think there are in claim 1?
A Oh, lots. I don't know the -- I don't know the exact number.
Q Hundreds of thousands? At least?
A Very likely. But I'm not sure.
Q Okay. So for all of those hundreds of thousands of compounds, is there any information in the '393 patent about whether those hundreds of

thousands of compounds will be pure without chromatography?

A Well, the specification only deals with treprostinil itself so that's the -- I guess the important enabling example that's in the specification of the patent. But the patent teaches that if you applied this salt formation, crystallization, that -- in this structural family, one would have a reasonable expectation that you'd also be able to crystallize and purify just as was done for treprostinil.

Q Okay. You don't see any data in this patent, though, about the purity of any of these other thousands of compounds, do you?

A No. There's no data for the other compounds, but there is really great data for treprostinil.

Q Now, do you understand that claim 9 also includes treprostinil diethanolamine salt as a product?

A Yes.

Q Okay. And, in fact, if I don't carry out step (d), the optional step, and I use diethanolamine as my salt, I'm going to get treprostinil diethanolamine salts; correct?

A Yes.

Q If I don't carry out step (d), does the claim include chromatography?

A So your question is, if I do not carry out --

Q Let me rephrase my question.

If I don't carry out step (d), would it be necessary to use chromatography?

A If I -- so your question is, if you do not carry out step (d) --

Q Right.

A -- would it be necessary to use chromatography?

Q Correct.

A So I would say that you're forming a salt. And it's -- salts are perhaps the most obnoxious compounds to purify by chromatography. And it's very, very rare to, in fact, purify salts by chromatography. So the whole reason a person skilled in the art would form a salt in the first place is by trying to avoid chromatography, 'cause you can crystallize salt. Salts -- and particularly salts like this that are water soluble, that's the whole purpose of forming the salt.

Q Okay. However, if I carry out steps (a)

through (c), the claim 9 allows me to do chromatography if I so wish; correct?

A Chromatography at which step? A? I don't know where you're talking about.

Q At any of the steps.

A Well, could you, but the whole purpose of this invention is to eliminate the chromatography step.

Q Okay. By the way, you don't see in the claims where it says the invention is carried out without the chromatography step, other than the one claim, claim 16?

A No. But the spec also prominently talks about the elimination of chromatography.

Q Okay.

A And a process chemist really would zero in on that important advantage.

Q What can you tell me about the impurity profile of the thousands of compounds in claim 1?

MS. HASPER: Objection. Beyond the scope.

THE WITNESS: I could tell you about the impurity profile of one of the thousands of compounds in claim 1, treprostinil, because I have data on that.

BY MR. POLLACK:

Q Does any person of ordinary skill in the art or any person of any skill in the art know anything about the purity [sic] profile of the thousands of compounds in claim 1, other than treprostinil?

MS. HASPER: Objection. Beyond the scope.

THE WITNESS: Well, because all the structures that are called out under claim 1 have the same molecular framework as treprostinil, one would expect that the impurity profiles would very likely be similar in that you'd have to stereoisomeric impurities, and dimers, and esters, and the triol and so on.

It's very similar types of species would very likely be present, if you change the variables, like added a carbon atom to the side chain, or what have you.

BY MR. POLLACK:

Q But some of the species would be different; correct?

A What do you mean by "different"?

Q Some of the impurities would be ones not seen in treprostinil; correct?

MS. HASPER: Objection. Foundation.

THE WITNESS: Well, they would necessarily be different because you've already changed the structure. So -- so if you change even by one carbon atom, now longer -- you can't get the same exact impurities from treprostinil because you've already changed the molecular structure to a different molecule.

BY MR. POLLACK:

Q So all of those molecules would have different impurity profiles from treprostinil; is that fair?

MS. HASPER: Objection.

THE WITNESS: So -- I think -- I'm trying to give a good answer here, that you would have similar -- I guess you call them "homologous series of impurities," stereoisomeric impurities, that would almost certainly be similar. So they'd be the -- like 1AU90 could be 1AU90 prime for another compound, but it would be a similar stereoisomeric impurity, because they're made by the same kind of chemical steps.

BY MR. POLLACK:

Q You referred to 1AU90. Is that a name used in the literature?

A No. I think that's a UTC code number for -- for that.

Q It's a secret code number; right?

A I don't know if it's secret or not. I know that in Moriarty's GOC paper, he used UT-15 or something, which is the United Therapeutics code number. So that one wasn't secret. So I don't know if they're secret or not.

Q Right. UT-15 is the published name for treprostinil; correct?

A Yes.

Q Okay. But 1AU90, you've never seen that in the literature; correct?

A Not that I can recall.

Q Okay. None of the -- have you seen in the literature where any of these impurities are characterized?

A I don't recall.

Q What about in the '393 patent? Do you see any mention in Exhibit 3 of what impurities are present in any of the compounds in the '393 patent?

A No. I don't believe they're specifically called out.

MR. POLLACK: To make things a little easier for us, I'm going to mark as separate

exhibits your appendices to your Declaration. I'm going to mark Appendix A as Williams Deposition Exhibit 5.

(Exhibit 5 marked)

MR. POLLACK: And I'll mark Appendix B as Williams Deposition Exhibit 6.

(Exhibit 6 marked)

BY MR. POLLACK:

Q If you could just verify for me that Deposition Exhibits 5 and 6 are true and accurate copies of your appendices A and B, respectively?

A (Examining documents).

(Brief pause)

Okay. Appendix A is identical. And Appendix B is identical to the one submitted but does not have the one correction that we made at the beginning of the deposition.

Q Could you do me a favor? Could you take Exhibit 6 and make the correction on there by pen?

A Okay. I don't have a pen. Can I borrow yours?

And I think it was -- oh. I think it's this one. 11 -- wait. I think it's this one. Okay. So I've just crossed out that [redacted].

Q Okay. I'd like to turn to Exhibit 5.

That's Appendix A.

A Okay.

Q Okay. And I want to look at your Data Source column. Do you see you have a column that says, "Data Source"?

A Yes.

Q Okay. This is a column that counsel created for you -- right? -- and then you checked this?

A Yes.

Q Okay. So the first -- well, let's count 'em -- one, two, three, four, five, six, seven, eight, nine, ten -- the first ten entries are all solely from an exhibit called "Exhibit 2052." Do you see that?

A Yes.

Q Okay. And then after that, all of the entries are included in an exhibit called "2036" that you attached to your Declaration. Do you recall that?

A Well, no. I think it's 2053, page 19. And then Exhibit 2036. So there's two --

Q But those were identical; right?

A Okay.

Q The 2053 and 2036, did you check that,

that they were identical?

A I don't recall right now.

Q Okay. Let me say, I also misspoke as well.

If you look on page 44, there are two samples, UT-15-011001 and UT-15-020101, about four and five rows up from the bottom? Do you see where I'm reading?

A Hmm-hmm.

Q Okay. Those two were listed as -- wait. Did I -- I think I did -- as just being from 2053; is that correct?

A That's what it says, yeah.

Q Okay. But all of the other ones are in both 2053 and 2036; is that fair?

A Yes.

MR. POLLACK: Okay. If we can mark as Deposition Exhibit 7 what was formerly called "Exhibit 2036."

(Exhibit 7 marked)

BY MR. POLLACK:

Q Did you review in detail all of the Certificates of Analysis in Exhibit 2036?

A I laid my eyes on every page, and I cross-checked some of them in detail. I didn't look

at every number on every batch record.

Q Okay. You didn't compare each one to make sure it was correct on your table?

A I said I spot-checked them, and they all seemed fine.

Q Okay. By spot-checking, though, you didn't do every single one, you --

A I didn't do every single one. I just randomly picked and found no errors.

Q Okay. Did you calculate what the average purity was of the samples in Exhibit 2036?

A Well, counsel did the calculation. And that's the summary at the bottom.

Q That's all of the samples; right? That's 2036 and 2052 and 2053; correct?

A Yes.

Q Okay. Did you calculate just what it would sum up to in 2036?

A So, in other words, eliminating the 2052, the development batches is what you're asking?

Q Yes.

A No.

Q Why -- do you have an understanding why 2052 was added -- why the samples from 2052 were added to the samples from 2036?

A Yes, because we also added development batches for the '393 process. And we -- and I thought that the fairest comparison was to look at the development batches that were used in UTC's development of the Moriarty process and the development batches from the '393 as well. I thought that was the fairest comparison.

Q That was your idea or counsel's idea?

A We discussed it. I -- I don't remember if who -- who came up with the first idea, but we agreed this was a reasonable thing to do.

Q Okay. Guess what? Ms. Choksi did the calculation for us, so I'm going to provide that to you.

So I'm going to mark as Williams Deposition Exhibit 8 a chart of all of the purities and total related impurities from the Appendix A, Deposition Exhibit 5.

(Exhibit 8 marked)

BY MR. POLLACK:

Q And I'm also going to mark -- just so you can see how we created this -- I'm going to mark as Deposition Exhibit 9 a chart containing all samples, including the ones from 2052.

(Exhibit 9 marked)

BY MR. POLLACK:

Q What we've done here is, we've just marked in highlighting which ones are from 2052. And so what we've done here is, we've used all of the samples that you did, and we also used the HPLC analysis. Do you know what I mean by that?

A Why don't you explain.

Q Yeah. If you look at, for example, 2036, Deposition Exhibit 7 -- let's go to the third page of the document, the one that says, "Page 3 of 3." And on the bottom, it says -- well, it says, "Page 3" at the bottom center. Do you see where I'm looking?

A Hmm-hmm.

Q Okay. Now, do you see there's a -- it says, "Test," and there's a number, "Assay HPLC." Do you see that?

A Yes.

Q And do you see it says, "98.4"?

A Yes.

Q Okay. So what we've done on this chart is, we've put in all of those values as well. Do you see where it says, "Assay Purity"?

A Okay. Which --

Q You can pick either 8 or 9. The only

difference is, we highlighted the ones from 2052 on 9.

A Okay.

Q Okay. So do you understand what I mean by the HPLC assay?

A So this one corresponds to --

Q Let's see. This one here that we're looking at is lot UT15-99H001. Do you see that on Exhibit 2036?

A Yes. So that's entry 11; right?

Q That's correct.

A Okay.

Q Okay. Is that number recorded fairly?

A It appears to be.

Q Okay. And what we've done at the end is, we've taken -- we'll let you go through, electronically, these spreadsheets -- we've taken all the data you used, and we did an average, as did you, and we got 99.0 by both methods, whether you use the HPLC assay, or what I'm calling "implied purity" where you subtract the total related substances.

A Wait. What --

Q On the very last page of either document.

A Oh.

Q Do you see that?
A Yes.
Q Okay. That's the same number you got; correct? Appendix A.
A Yes. Basically the same.
Q Okay. Now what I'm going to mark as Deposition Exhibit 10 is the same document, except with the first ten samples, the ones that came from Exhibit 2052 removed.
(Exhibit 10 marked)
BY MR. POLLACK:
Q If you would verify for me that Exhibit 10 is the same as 8 or 9 except with the highlighted exhibit -- lots removed.
A Okay. That appears to be the case.
Q Okay. And then what we did is, we -- we did the same thing you did. We took the average, but we did it two ways. We did it with the HPLC assay --
A Hmm-hmm.
Q -- so taking each of those numbers from 2036. You understand what I'm referring to?
A Yes.
Q And we also did it the way you did it, subtracting the total related substances from 100.

A Yes.

Q Okay. If you look on page 5, there's the result of our average. Do you see that?

A Yes.

Q And do you see that the HPLC assay -- the average was [redacted]?

A I see that.

Q Okay. Instead of 99.0. Do you see that?

A Hmm-hmm.

Q And doing it your way, the way you prefer, the result was 99.5. Do you see that?

A What do you mean --

Q Subtracting the total related substances from 100, the average was 99.5.

A Okay.

Q Do you see that?

A I'm not sure what this implied impurity is. I don't -- I don't -- what's implied impurity?

Q So that's the language I'm using. If you want to call it "purity," that's fine. It is the 100 minus the total related substances.

A Okay.

Q How did you calculate the purity of each sample?

A Okay. So the total related substances is

the -- the sum of the known impurities plus the unknown impurities.

Q Is it?

A That's my understanding.

Q Well, let's take -- let's take, for example -- let's go to the top of page 44; all right? So there's all of the impurities, and that sum is .4. Do you see that in the right?

A Yes.

Q Okay. Now, do you get .4 when you add all those numbers up?

A I have to do the calculation. Can I use my phone --

Q Absolutely.

A -- here? (Using phone).

MS. HASPER: Counsel, while Dr. Williams does the math, may I ask a question to clarify something, perhaps to avoid an extraneous objection?

You introduced Exhibit 10 and said that the highlighted rows had been removed. I noticed highlighting on two rows. Is that merely a printing error, or is that --

MR. POLLACK: Those are just simply -- I'll point that out to him. Those are simply the highlighted two rows from Exhibit 2053. Different

exhibit.

MS. HASPER: They're not also in 2036?

MR. POLLACK: -36. Correct.

MS. HASPER: All right. Thank you.

THE WITNESS: So that line -- we're talking about the top line on the top of page 44?

BY MR. POLLACK:

Q Correct.

A Let me check this again. First time I got .55.

Q That's what I get. But please feel free to do it again.

A Okay. So it's -- I get .55, the addition of those.

Q Yes.

A Known -- and those are all known impurities, I believe.

Q Right. And then the total related substances is .4?

A So I believe the reason that the -- that the numbers don't add up is that the -- the -- where the amount of impurity was less than .05, a number of .05 was put. So it's -- it's estimated conservatively high. But the actual total, which comes from, I believe, these batch documents, is

what's in this column.4.

Q Right. But, in fact, what's in that column is not the sum of the known impurities listed in your prior columns; correct?

A Again, I just explained what -- is there any confusion to what I just said?

Q Yes.

A Hmmm?

Q Yes, there is. The -- you said earlier that the sum of total related substances was the sum of each of the known impurities; correct?

A And unknown impurities.

Q And unknown impurities.

A Yes.

Q Okay.

(Mr. Snader entered the deposition at 11:24 A.M.)

BY MR. POLLACK:

Q And here we see that summing those up, they don't equal the same number; correct?

A So maybe the place to go is the source document here. This is 20 -- so the source document at page 36 shows total related substances as .4 percent.

Q I see that.

A So that's -- that's -- where these numbers came from. They weren't from the linear addition here (Indicating).

Q Right.

A Yeah.

Q Okay. We're both agreed on that; right?

A Yeah.

Q Okay. And, actually, your way of putting in what the total related substances are for compounds that are not detected or ones which are less than .05, that's sort of arbitrary, isn't it?

A No. Arbitrary?

Q Well, you could have done instead of .05, you could have made it zero for example; right?

A Yeah. So I was conservative and estimated on the high side. So less than .05 could be .000001; okay?

Q And, actually, putting it on the high side, that makes the purity lower, doesn't it? It makes it seem like it's less pure than it actually is, doesn't it?

A Yes. And I did the same thing for the '393 process batches. So they -- so the same -- to be fair, that same conservative method was used to compare both.

Q Okay. Here's what I want to know: So when -- the batches 2036 all done by Magellan, even the ones from 2053, are included to make an average, the average value is either [redacted] percent pure for HPLC analysis or a total of .5 percent impurities by total related substances. What I want to know is, who, then, decided to go out and find ten other pieces of data to try to drag that number lower to 99?

A I sort of don't like the way you just characterized that, 'cause it sounds like this was done deliberately to make the Moriarty process look worse than it is. That's not really fair.

Q Really?

A So what we did was, we looked at development batches from the '393, and we also looked at development batches from Moriarty. And, you know, either way -- I mean, if you put them in or drop them out, the impurity profiles between the two processes are different; okay? So you can't just look at the overall total related substances purity; you have to look at the actual distribution of the impurities. Because the '393 process unexpectedly -- okay? -- because of the crystallization of the salt, removes stereoisomeric

impurities -- two of them completely -- and leaving only the very small amount of the enantiomer, which is [redacted].

Q Okay.

A So just doing these -- these overall impurity comparisons and percentages, I don't think is -- is valid.

Q But you actually submitted this to the Patent and Trademark Office and told them that that was one of the significant differences between Moriarty and the '393 process, that the purity was 99.0 versus [redacted], isn't that true?

A I didn't submit anything to the Patent and Trademark Office.

Q You understand this is your Declaration that you signed.

A Yes.

Q That was submitted to the Patent and Trademark Office. You understand that?

A I thought you were talking about the -- the batch records.

Q Well, those are submitted as well.

A Yeah.

Q You understand that --

///

(Indiscernible crosstalk)

THE WITNESS: I'm sorry. I don't understand where you're --

BY MR. POLLACK:

Q You understand your Declaration?

A Yeah.

Q That it was used as evidence at the Patent and Trademark Office in this proceeding. You understand that; right?

A Yes.

Q Okay. And in that Declaration, you represented to the Patent and Trademark Office that the difference between Moriarty -- one of the differences between Moriarty and the '393 patent was that Moriarty produced an average of only 99.0, while the '393 patent produced an average of [redacted]. You recall saying that; right?

A Yes.

Q Okay. And now what we're seeing is, if we take only the data, the two data sets, created by Magellan, one for the '393 and one for the Moriarty process, in fact, the numbers are [redacted] and [redacted].

A But, again, you're talking about the overall purity. You're not talking about impurity profile.

Q Sure. I understand. I'm not disagreeing with you on that. I'm just saying, you told the Patent Office that these two differed. And one of the ways they differed was one was 99.0 and the other was [redacted]. Now we see that both are [redacted]. How does that jive with acceptable scientific conduct?

A Well, the -- again, the '393 batches were produced without chromatography. So you could repurify and purify anything you want --

Q Of course.

A -- by chromatography to [redacted] percent if you wanted to --

Q Right.

A -- okay? -- but, you know, in large-scale manufacturing, that's not practical. It's not economical. It's not safe. It's not environmentally appropriate; okay? So -- but, again, I think the -- what I was focused on was looking at -- the -- the -- the structural differences between the impurities between the two processes is different. And that is not reflected in the overall purity, no matter however you want to eliminate batches, and cherry-pick batches or however you want to do that.

Q You'd agree with me somebody here

cherry-picked some batches, didn't they?

A No, I don't think so.

Q You don't think somebody added 10 batches to take the number down from [redacted] to 99.0?

A No. We -- my understanding is, we asked for -- these were all the batches we could find records for. And these were the same -- I think these are the same 56 batches that were used by Dr. Aristoff in the -- the Sandoz litigation.

THE VIDEOGRAPHER: Sorry to interrupt, we have five minutes of video left.

MR. POLLACK: Why don't we take a short break.

THE WITNESS: Sure.

MR. POLLACK: Whatever you want.

THE WITNESS: Yeah. 15 minutes? I need a bathroom break, anyway.

THE VIDEOGRAPHER: This ends Media No. 1 in the deposition of Robert M. Williams, Ph.D. The time is 11:32 A.M.

(Off the record)

THE VIDEOGRAPHER: This begins Media No. 2 in the deposition of Robert M. Williams, Ph.D. We are back on the record. The time is 11:53 A.M.

MR. SNADER: And this is Shaun Snader,

United Therapeutics Corporation, Washington, D.C., counsel for patent owner.

BY MR. POLLACK:

Q Welcome back, Dr. Williams.

A Hmm-hmm.

Q During the break, did you speak to counsel about this case, the deposition, or any -- any matter having to do with treprostinil?

A No. We talked about golf, hotels, and restaurants.

Q Okay. If you can go back to your Exhibit 2 -- that's your Declaration.

A Okay.

Q If you turn to paragraph 98, you see there, it says, "The treprostinil product of the '393 patent has an average purity of [redacted] percent, while the Moriarty product has an average purity of 99.05." Do you see that statement?

A I see that statement.

Q And then you say, "Thus, the treprostinil product of the '393 patent has an average purity that is .7 percent higher than that of Moriarty's." Do you see that statement?

A Yes, I do.

Q And you understand that those statements

were given to the Patent and Trademark Office -- right? -- in this proceeding?

A Yes.

Q Are those statements not important to your opinion?

A They're important. But if we also read above, I say, "It is clear the treprostinil product produced by the '393 patent process has a markedly different impurity profile than the treprostinil product of the Moriarty prior-art process and as such is physically distinct from the prior-art product."

So my opinion in total is important in paragraph 98, not just that one little aspect.

Q Okay. Although, I know that one little aspect is the -- what's called a "conclusory sentence"?

A I don't know if I would label that as the final conclusion.

Q Even though it follows the word, "Thus"? Begins with the word, "Thus"?

A Well, I sort of begin the paragraph, ". . . from these data." That's also -- I'm making a conclusion about the impurity profile. So I'm actually making two different important conclusions

in this paragraph. So the overall purity, and I think very significantly, the impurity profile, which is different. That's the structural difference.

Q But it seems like you made the impurity profile point in paragraph 97, isn't that right?

A Let me just read that.

Well, I talked about the differences in impurity -- I talked about salient features of the impurity profile for the '393 patent process in paragraph 97.

Q Now, you said that the statement about the [redacted] versus the 99.5 was also important. Why was it important to your opinion?

A Well, it shows that in addition -- in addition to the differences in impurity profile, the structural differences is also an overall purity difference.

Q And why didn't you think that was important?

A Well, because you're looking at various aspects of the product. The overall purity, as well as the detailed components of the impurities.

Q Yeah. So why was the overall purity important for distinguishing -- if it was -- for

distinguishing the '393 product from the Moriarty product?

A Well, the Moriarty product, again, involves a very time-consuming, expensive chromatography. And if that step weren't conducted, you'd get an even worse product. So you have to perform that step, which is very, very deleterious in so many ways, as we discussed earlier. And so you still want to have a high overall purity. But it's also important to recognize that there is a difference in the individual impurities between the two processes. And the data shows that so incredibly clearly.

Q Let me ask you -- you have a paragraph 103, if you go a couple pages later. And you see there, again, you talk about the difference in purity between Moriarty or Phares and the '393 patent. Do you see that?

A So this is with regard to the treprostinil diethanolamine salt?

Q Yes. The first sentence is, but further down, you say, "Regardless of the purity identified in Moriarty, a further analysis of all batches made by the Moriarty process up to the time of the reference itself, reveals an average purity of

99.05 percent, while the average purity of the '393 patent batches is [redacted]." Do you see that sentence?

A I see that.

Q Okay. And that's referring to the treprostinil free acid; correct?

A Um, so the -- the [redacted] percent, this is the 121 batches in the table that I have. And that includes some batches of just salt, but most of them are acid.

Q So you actually looked at both salt and acid in your analysis?

A Yes. And the salt is amazing. The salt is just stunningly pure.

Q Salt, in fact, is somehow purer than the free acid, isn't it?

A That's correct.

Q Even though the last acidification step hasn't been performed?

A On the salt.

MS. HASPER: Objection.

BY MR. POLLACK:

Q On the salt.

A Sorry.

Q Yes.

MS. HASPER: Objection. Mischaracterizes

the document.

THE WITNESS: Yeah. So at the salt stage, the step (d) has not been performed.

BY MR. POLLACK:

Q Right.

Why did you think it was important in this one paragraph -- 103 that's about the salt to point out the differences in the purity of 99.05 versus [redacted] in the prior art versus the patent?

A So you've already asked me this question and I've already given you have the answer. So you're asking me the same question over and over.

Q So what's the answer?

MS. HASPER: Objection. Asked and answered.

THE WITNESS: I told you that the overall purity is important, but I also looked at the individual components of the impurities. And they're different.

BY MR. POLLACK:

Q Okay. Since it is an important point that the overall purity is important, isn't it a problem for your opinion if data points were cherry-picked to try to bring the actual purity down from [redacted] to 99.0?

MS. HASPER: Objection. Mischaracterizes his testimony and the document.

THE WITNESS: No. So I -- I -- I don't like your question, because it's -- it's accusatory and mischaracterizes the analysis that I did that I thought was very fair. I included development batches for both the Moriarty process, and I also included development batches for the '393 process. So the development batches for the '393 are also poorer than the later commercial batches. And so by the same token, those numbers bring down the average purity of the '393 process. So I thought I was being very fair.

BY MR. POLLACK:

Q Oh, really? To bring it down when it's [redacted], even with those batches?

What did it bring it down from?

A Well, I didn't -- I didn't do the calculation to eliminate those. I included both. But if you did eliminate the development batches, it would certainly improve the overall purity of the '393 batches.

MR. POLLACK: I'm going to mark as Williams Deposition Exhibit 11 a document known as "Exhibit 2052" in the case, the UT-15 injection

drug-substance chemistry manufacturing and controls submission for an NDA No. 21-272.

(Exhibit 11 marked)

MS. HASPER: And just to let you know, my realtime has not been working since we came back from the break.

THE REPORTER: Off the record.

THE VIDEOGRAPHER: Off the record. The time is 12:03 P.M.

(Off the record)

THE VIDEOGRAPHER: We are back on the record. The time is 12:05 P.M.

BY MR. POLLACK:

Q All right, Dr. Williams, I've put in front of you the Exhibit 2052, which is the source of the ten additional data points you added to your analysis. Is this 2052 the document that you relied upon?

A (Examining document) Yes.

Q Okay. Now, if you would turn to what's called at the bottom of the document in the center, "Page 25"?

A Okay.

Q Are these the lots that you added to the analysis of the average purity of the Moriarty

process?

MS. HASPER: Objection. Mischaracterizes his testimony and the documents.

THE WITNESS: So I don't think I would agree with the way you phrased your question -- that I added these. I was given all of the data together.

BY MR. POLLACK:

Q By counsel?

A Yes.

Q Hmm-hmm.

A So there was no importing separately these batches to try and obfuscate the data.

Q Right. 'Cause counsel had already calculated the average value so that you just checked that calculation; correct?

A Yes. I checked the calculation, and we did the same thing for the '393 batches. We added -- the development batches were there to do a fair comparison.

Q When you did the check of the calculation, you didn't say: Hey, why are we adding that other exhibit? Let me see how these numbers come out if I just use the set that was presented as existent 2036.

MS. HASPER: Objection.

BY MR. POLLACK:

Q You didn't do that; right?

MS. HASPER: Objection. Mischaracterizes the document and the testimony.

THE WITNESS: So I didn't do a separate calculation. I certainly looked at the charts, the exhibits. And either way you slice it, if you want to include the development batches, or you want to exclude them, my opinion does not change; okay? Because with the -- with the -- the Moriarty process, you're starting with an inferior process.

So the development batches were not as nice as the development batches that you started with the '393, 'cause it's a better, distinct, process; okay? But even if you wanted to eliminate both of them either way, the impurity profiles are different. And the '393, no matter how you slice it, gives you a superior product, a different product.

BY MR. POLLACK:

Q Okay. But one part of your opinion -- and you definitely stated this a number of places in your Declaration -- was that the Moriarty process gave you 99.0 while the '393 process gave you [redacted];

right? That was one opinion that you stated?

A That's one aspect of my opinion.

Q It's one opinion that you stated?

A One aspect of my opinion.

Q Looking now and seeing that certain of the data points were added from these older development batches and that brought down the purity from [redacted] to 99.0, do you want to now remove just that one aspect of your opinion?

MS. HASPER: Objection. Mischaracterizes his testimony and the documents.

THE WITNESS: No, because, you know, the development batches are compared fairly to development batches between two processes; okay? So, again, we're looking at an average of many, many batches over time. And so what I did not do is, I did not cherry-pick a single batch from the '393 and compared it to a single batch of the Moriarty process. So I thought it was much more significant to look at the overall picture. And I think my report very fairly and accurately provides the overall picture with the exception of that one duplicate entry, which doesn't change the number very much.

///

BY MR. POLLACK:

Q Let's think about it this way: So 46 batches show an average value for the purity of [redacted]. And 10 batches bring that number down to 99.0.

Is it not true that, fairly, one should take the 46 rather than throwing in 10 outliers? Isn't that how science is done?

MS. HASPER: Objection. Mischaracterizes the documents.

THE WITNESS: No. I don't -- I don't agree.

BY MR. POLLACK:

Q Let's take a look at this page 25 that I asked you to look at in Exhibit 11. The dates of manufacture of these lots -- do you see them? There's a line that says, "Date of Manufacture."

A Okay.

Q The first two lots are dated in 19 -- they're both in 1986. My eyes are a little weak, but I think one's July 1986, and the other one is August 1986? Do you see that?

A Okay.

Q And then the next batches are all dated in -- their date of manufacture is either 1997 or

1998; correct?

A Yes.

MR. POLLACK: I'm going to mark as Williams Deposition Exhibit 12 a document known in this case as "Exhibit 1004," which is the Moriarty Journal of Organic Chemistry Article.

(Exhibit 12 marked)

BY MR. POLLACK:

Q And can you verify for me that Exhibit 12 is the Moriarty article that's prior art that we've been referring to in this deposition?

A Yes.

Q What's the date on the Moriarty article?

A 2004.

Q Okay. What date was it received by the journal?

A June 5th, 2003.

Q Okay. How many years after was this article published compared to when these lots were manufactured in -- sorry. Let me ask my question again.

How many years are there between the lots described in Exhibit 2052 and the Moriarty article?

MS. HASPER: Objection. Vague. Relevance.

THE WITNESS: So the earliest -- the earliest date is July of '86 to 2003. Is that -- is that the year-spread that you're asking me about?

BY MR. POLLACK:

Q Year-spread. Right. Okay.

Many of the lots are from 1998 and 1999?

A So there's the date of manufacture and date of testing.

Q I'm asking the date of manufacture.

A Yes.

Q Isn't that what's relevant here, date of manufacture?

A Relevant -- relevant to what?

Q Relevant to -- I'll withdraw that question.

Okay. So, for example, one of the lots you included -- and you're free to look at your chart -- is lot No. LRX97J01, made in October 1997. Do you see that?

A I see that.

Q Okay. That is seven years before the Moriarty article was published?

A Yes.

Q Okay. Let me ask you: There's two lots you didn't include in your analysis. They're the

two that are made by -- you see there's also a line that says "Manufacturer"; correct? On the top?

A Yes.

Q Okay. And -- by the way, none of these lots that are on page 25 were manufactured by United Therapeutics; correct?

A So I believe that Steroids and SynQuest are contract manufacturers that were making the drug for United Therapeutics.

Q Right. It wasn't made by United Therapeutics itself?

A I'm not really privy to the detailed relationship between United Therapeutics and its suppliers. But if a supplier is making the drug for UTC, I believe that UTC would be the -- you know, ultimately be the manufacturer.

Q Okay. Do you know who makes treprostinil now for United Therapeutics?

A I know that there's suppliers that -- different suppliers that make different -- do different parts of the synthesis, but I'm actually not sure of the whole picture of how -- who's contributing what pieces, what companies.

Q Okay. Now, you understand the first two lots were made by Upjohn back in the '80s; correct?

A Yes.

Q Okay. And you'll agree with me that it can't be the case that way back in the '80s, Upjohn was using the Moriarty process; correct?

A No. It's not possible.

Q Okay. Now, do you notice that there's a footnote -- it's a little hard to read the typeface is small -- it's footnote 4. Do you see that footnote 4?

A Yes.

Q Can you read footnote 4 for us into the record?

A "These lots were manufactured by Pharmacia and Upjohn using a slightly different route of synthesis."

Q In reading that, is it your understanding that what they mean by that is all the other lots here were made in a way that's only slightly different from the way Upjohn made treprostinil?

MS. HASPER: Objection. Calls for speculation.

THE WITNESS: Yeah. I don't know.

BY MR. POLLACK:

Q What's your understanding of what that says?

A What? Footnote 4?

Q Yeah. Footnote 4.

A So --

MS. HASPER: Objection. Relevance.

THE WITNESS: That these -- these two 1986 lots were made by Pharmacia and Upjohn using a different -- a slightly different route of synthesis.

BY MR. POLLACK:

Q Okay.

A That's what it says.

Q Sure. Okay. And is it your understanding that the other lots, then, were not made exactly the way Upjohn made them but a fairly similar process was used?

MS. HASPER: Objection.

THE WITNESS: You know, I don't know the details.

BY MR. POLLACK:

Q You don't know the details of how all these lots were made?

A No. I haven't seen the detailed batch records of what went into those lots.

Q Okay. So you don't know whether or not these lots were made by the '393 process, the

Moriarty process, the older Aristoff process; is that right?

MS. HASPER: Objection. Mischaracterizes testimony and the documents.

THE WITNESS: Um, you know, I -- I'd have to investigate further. I don't know.

BY MR. POLLACK:

Q Right. You -- you don't know if any of these are from the Moriarty process?

A Um --

Q At least not the ones on page 25?

A So the Moriarty paper came out in 2003.

Q 2004 it came out.

A Well, yes. Yeah. The paper was published in 2004, but the technology had been put together as easily as early as 2003.

Q Okay.

A So I don't think it's possible that any of these could have been made by Moriarty process just based on the dates.

Q And yet these are the ten additional samples that you added to your analysis that brought the value down from [redacted] to 99.0; correct?

MS. HASPER: Objection. The testimony -- mischaracterizes testimony and the documents.

THE WITNESS: So I -- I guess I don't know.

BY MR. POLLACK:

Q Well, do you want to compare the lot numbers here to the lot numbers on -- if you take the exhibit that has the yellow highlighting -- that's our Exhibit 9 -- this one here (Indicating). Or you can compare it to your appendix. Either one.

A (Examining documents) So it begins with 9 -- 97J01.

Q Right. That's the third -- third column?

A Yes.

Q And that's on your -- that is on one of the ones you analyzed on your -- on your chart?

A Yes.

Q Okay. And LRX99801, you analyzed that one, too?

A Yes. That's the second entry. And then BO-1. And then they go to -- the next one is UT, but it's -- oh, that's -- yeah. So they're just in sequential order.

Q Okay. And each of these lots were just -- we were just reviewing, you're not sure what method was used to make any of these. You haven't seen the batch sheets?

A I haven't seen the batch sheets.

Q Does that -- looking at this data now, are you prepared to change your opinion about whether or not the Moriarty method, in fact, gives a [redacted] percent purity just like the '393 patent?

A No.

And you keep asking me the same question 30 different ways, and I already told you: If you wanted to throw out all the development batches from both processes and both analyses, fine --

Q Okay.

A -- that doesn't change the differences in impurity profile. And it also is not going to change the overall fact that the '393 process gives an overall higher purity than Moriarty.

So, you know, fine. Scratch out those 10 entries if you want to. It doesn't change my opinion.

Q Okay. You understand if we scratch out those 10 entries, we're going to get [redacted] for impurity --

A We're still never going to change the impurity profile.

Q I understand. I'm just talking about the one -- you said twice, at least -- I think much more

than twice -- in your opinion that the purity profile between Moriarty and the '39 -- I'm sorry -- that the purity level between the '393 patent and Moriarty were different -- let me start my question again.

You've said -- now seeing, at least twice -- and I think there were some more times -- in your Declaration that the -- an important point is that the purity level between Moriarty and the '393 patent is different, and it's different by 99.0 versus [redacted]. I just want to focus on that one opinion, nothing else.

A Okay.

Q Do you want to retract that opinion now, having seen this information at this deposition?

MS. HASPER: Objection. Asked and answered.

THE WITNESS: No.

BY MR. POLLACK:

Q No? Why not?

A Because, you know, even if the -- you eliminate these development batches, the overall purity for both processes goes up, but Moriarty's never going to catch the '393 purity.

Q Okay.

A So no matter how you want to add or eliminate data, the -- the important -- the really important thing that these spreadsheets show of these -- from these batch records is that the Moriarty process does not provide, on average, a purer material than the '393, and the impurity profiles are distinctly different. And it was unexpected that you would be able to eliminate, for example, two to three stereoisomeric impurities entirely.

Q Okay. You said it doesn't provide -- the Moriarty process doesn't provide on average a higher purity than the '393. But let me ask you another direction. Does the '393 process significantly provide a higher purity than the Moriarty process?

MS. HASPER: Objection. Asked and answered.

THE WITNESS: Yes, on average, that is definitely the case. That's what the data shows.

BY MR. POLLACK:

Q Did you include standard deviation -- you know what standard deviation is; right?

A Yes.

Q And I notice you didn't calculate any standard deviations for your average, isn't that

true?

A That is true. I did not. That's not the sort of thing anyone would do.

Q Isn't that the standard scientific method?

A It may be for some sciences, but organic chemistry and even process chemistry, you know, it's very rarely, in my experience, done.

And, you know, if you wanted to put instead deviations, I didn't calculate that. You know, I don't think it's going to change the picture. The impurity profiles are different, and the '393 process produces a superior product.

Q I'm going to -- and we'll provide this spreadsheet electronically to counsel -- but for you for now --

MS. HASPER: Is there a way I can see the spreadsheet?

MR. POLLACK: You can go look over his shoulder. That's perfectly fine.

BY MR. POLLACK:

Q We have calculated the averages and the standard deviations for all of the samples, excluding 2052. And I've given you the spreadsheet there.

You know how to use Excel; right?

A Yes.

Q Okay. So I've given you the Excel spreadsheet there. You're free to play with it and verify we did everything correctly. You'll see the standard deviations are recorded there; right?

A I see them.

Q Okay. And those were calculated using the standard Excel method. And you see that for the HPLC assay, I believe it's .6 is the standard deviation? Do you see that?

A I see that.

Q And .24, the total impurities.

A I see that.

Q Okay. Let's start with the .6.

If the standard deviation -- if it's [redacted], plus or minus .6, is there any value that the '393 patent purity could have that would be statistically different from [redacted], plus or minus .6?

MS. HASPER: Objection. Beyond the scope.

THE WITNESS: So, Counsel, I know that your focus is on this overall average purity, but my opinion is not on this average overall purity in isolation; it's the overall purity in combination

with the impurity profile. And I can't separate those two, because they're inseparable from the reality of how this drug is made and what the characteristics of the product are.

BY MR. POLLACK:

Q Okay. Yeah. I'm not trying to attack the whole of your opinion. You can keep the impurity profile part. I'm trying to understand the other prong -- the total impurities level. Is that -- you've said it's important to your opinion. So I'm now exploring why it's important to your opinion. And now seeing that that value really doesn't change much, how does removing that one leg change your opinion?

A It doesn't.

Q Okay. And should we -- since your opinion is fine without that one leg -- without the purity comparison, should we just eliminate the purity comparison from your opinion and just rely on the difference in impurity profile?

MS. HASPER: Objection. Mischaracterizes his testimony.

THE WITNESS: No.

BY MR. POLLACK:

Q Why not?

A Because, even if you eliminate these development batches, the -- the overall purity of the '393 product that is being manufactured on a commercial scale is still better than what UTC was getting with the Moriarty process. And significantly, we've eliminated chromatography, and the impurity profiles themselves are distinct.

Q You understand that the two purity-level values hardly change. You understand that -- right? -- between the Moriarty process and the '393 process?

A I don't agree.

Q Why not?

A Well, again, if -- even if we're going to chop off the tops of both of those Exhibit A and B charts, the overall -- the overall purities are still different.

Q Let me ask you something: Did you notice that the HPLC assay analysis of the -- all of the samples, excluding those ten that were made by method -- you're not even sure what method was used -- just including those, did you notice that the value was [redacted] and that that's the same value reported in the Moriarty prior art? Did you notice that?

A For the single batch made in the Moriarty paper?

Q Yes. Yes.

A Yeah. So that's not in my opinion representative.

Q Well, having now seen 56 batches that average [redacted], doesn't that show that, in fact, the [redacted] number is quite representative is? Isn't that so?

MS. HASPER: Objection. Objection. Mischaracterizes the documents.

THE WITNESS: Ask me your question one more time, please?

BY MR. POLLACK:

Q Sure. Having seen 56 samples now which came to an average of [redacted] for the purity level -- and comparing that to the [redacted] number that Moriarty reported, doesn't that show that Moriarty's value, in fact, was representative?

MS. HASPER: Objection. Same objection.

THE WITNESS: No. So 56 batches give 99.1 percent.

BY MR. POLLACK:

Q I'm sorry. 46 batches -- I apologize.

Having seen now that 46 batches give a

value of [redacted], isn't that consistent with the [redacted] value reported by Moriarty in the prior art?

A So those -- they're the same number.

MS. HASPER: Objection.

THE WITNESS: Sorry.

MS. HASPER: Objection. Mischaracterizes the document.

THE WITNESS: So, you know, I'm not really sure -- so you're referring to in here --

BY MR. POLLACK:

Q Yes.

A -- [redacted] percent of, apparently, recrystallized treprostinil in the JOC paper; right?

Q Yes.

A That's the number you're referring to; right?

Q Yes. That's the number that Moriarty reports; correct?

A Right.

Q That is on, for the record, if we look at -- let's call it page 13 of the exhibit -- page 1902 of the original article. The right-hand column, and it's just above where it says, "Acknowledgement"; right?

A Yes.

Q Is that where we're looking?

And there, it refers to a purity of [redacted] percent, and that is for the compound treprostinil, which was also known as UT-15; correct?

A Yes.

Q Okay. And that number, [redacted], is consistent with the [redacted] we see for the average of 46 samples; correct?

MS. HASPER: Objection. Mischaracterizes the document.

THE WITNESS: So -- okay. So, you know, even if those numbers are the same, if you eliminate development batches from the '393, that number goes up. And I -- again, the data in the '393 chart is very conservative because less than [redacted] was put in as [redacted] -- as [redacted]. So it's actually much purer.

BY MR. POLLACK:

Q What's much purer?

A The '393 product.

Q Well, the same is true for the Moriarty product.

A No. So you've -- you might max out if you do your own type of cherry-picking of eliminating these early development batches, but the

'393 data, again -- all of those -- all of those percentages are going to be improved if you eliminate those -- whatever it was -- number of development batches that were also -- that I also included for the '393.

Q Oh, what if I represent to you that actually that's not the case that they won't be improved?

A Okay. But, again, you can look at the impurity profiles, and there is -- 1AU90 appears in only one batch and 2AU90 only appears in one batch and the rest of them have zero. You cannot say the same for any -- any -- for the Moriarty on average. So the -- there's only two batches: [redacted] and [redacted]. Those are the only two batches where the stereoisomeric impurities appear. And then if you scan down the column 0000000 -- all the way down.

So that crystallization step completely obliterates those two stereoisomeric impurities. And a person skilled in the art couldn't have predicted that. And the triol, t-r-i-o-l, also was completely obliterated.

Q And did you look at -- if you look at Appendix A -- and Appendix A, that's the Moriarty

method; right?

A I'll give you your computer back.

MS. HASPER: Could I just ask counsel -- since you've been showing him an electronic document, can we get that in electronic form immediately?

MR. POLLACK: We will provide it after the --

MS. HASPER: Perhaps before lunch?

No, I'd like it before the deposition is over, please.

MR. POLLACK: I don't know if we'll be able to do that.

MS. HASPER: Well, I'm going to insist on it.

MR. POLLACK: I heard what you said.

BY MR. POLLACK:

Q Sir, take a look at Appendix A.

A Okay.

Q And if you look at 1AU90 starting below the ten lots -- the first ten lots on your chart, you notice they're all zeros.

A Okay. Which entry?

Q Let's start on page 43.

A Okay.

Q Okay. And let's start below where -- below the 2052s that you used; okay? So look at Data Source and get to the line that's below the 2052s.

A Okay.

Q Okay? Do you see a bunch of zeros for 1AU90?

A Yes. And I see [redacted] for 2AU90.

Q Right. But those are [redacted] you put in because it said less than [redacted]; right? That's why they're all [redacted]?

A Some of them may be actually [redacted]. [redacted] or --

Q Or less?

A Or less.

Q Okay.

A But they're detectable.

Q Okay. But, similarly, though, even under Moriarty 1AU90, barely detectable, in most cases?

A Okay. But the profiles are still different, on average.

Q I'm going to mark --

A So I'm -- I need a nature break, and maybe this is a good time for lunch, perhaps?

MR. POLLACK: It's up to you.

THE WITNESS: Yeah. And it's gotten warmer in here.

MS. HASPER: Yes, it has.

THE WITNESS: Maybe we can adjust the thermostat again?

MS. HASPER: Why don't we go ahead and go off the record, and maybe we can adjust the environmentals.

THE VIDEOGRAPHER: We are off the record. The time is 12:38 P.M.

(Luncheon recess taken at 12:38 P.M.)

* * *

A F T E R N O O N S E S S I O N

Commenced at 1:34 P.M.

THE VIDEOGRAPHER: We are back on the record. The time is 1:34 P.M.

EXAMINATION (Resumed)

BY MR. POLLACK:

Q Welcome back from lunch, Dr. Williams.

A Thank you.

Q Over lunch, did you have a chance to review the spreadsheet of the 46 data points in Excel form?

A No.

Q Okay. You didn't look at that at all?

A No. I ate lunch.

Q Okay. That was it. Okay.

I'm going to mark as -- let me just do one more, sort of, housekeeping thing. I think what we'll do is, we'll mark the spreadsheet in electronic form which we've now sent to United Therapeutics' counsel, and we've now e-mailed it to the court reporter as well.

MR. POLLACK: We'll mark that as Williams Deposition Exhibit 13 so it exists on the record.

(Exhibit 13 marked)

MR. POLLACK: Now, I'm going to mark as Williams Deposition Exhibit 14 a document currently called on the record "Exhibit 2006."

(Exhibit 14 marked)

BY MR. POLLACK:

Q Exhibit 2006, also known as "Williams Deposition Exhibit 14," appears to be a letter from United Therapeutics to the FDA, dated January 2nd, 2009.

Dr. Williams; is that correct? Is that what this is?

MS. HASPER: Objection. Beyond the scope.

THE WITNESS: Wait. What are you asking me?

BY MR. POLLACK:

Q I'm asking you if Williams Deposition Exhibit 14 is a letter from United Therapeutics to the FDA, dated January 2nd, 2009.

A That's the date, and it's on United Therapeutics letterhead, and it's addressed to the Division of Cardiovascular and Renal Products -- FDA, yes.

Q Is my answer -- is the answer "yes"?

A Yes.

Q Okay. And this is one of the documents you relied upon in forming your opinion?

A I looked at a lot of documents. I believe I've seen this before.

Q If you turn to page 3 of the document -- no, let me step back.

Let me ask you: Do you know what this letter is about?

A I have to refresh my memory. I don't remember --

Q Okay.

A -- just by looking at the face page.

Q Let me ask you -- if you don't remember, you can just tell me.

If we go to page 3, you see there's a paragraph that begins, "In conclusion . . ."

A I'd like to read the letter --

Q Absolutely.

A -- to just familiarize myself with the content if you don't mind.

Q I don't mind.

A (Examining document) Okay. I've had a chance to review the document.

Q Okay. Was this a documented you used in

forming your opinion?

A Yes. I -- I remember looking to this. This is the change in the spec for the API.

Q Okay. So if we turn to page 3, Exhibit 14, you see there's a paragraph that says, "In conclusion . . .," just above the bolding? Do you see that?

A Yes.

Q And the conclusion says, "In conclusion, the lots of treprostinil API" -- that means "active pharmaceutical ingredient"; is that right?

A Yes.

Q "In conclusion, the lots of treprostinil active pharmaceutical ingredient produced by the new process in Silver Spring are of the same high-quality impurity as the commercial lots of API produced by the existing process at the Chicago facility."

Did I read that correctly?

A That's what it says.

Q Okay. Do you have any reason to disagree with that statement?

A No.

Q Okay. And when it says here, "the new process in Silver Spring," that's a process that now

includes the '393 process, is that your understanding?

A That's correct. Yes.

Q And the -- in that process, the quality and purity are being compared to the existing process at the Chicago facility. Do you see that?

A Yes.

Q Okay. And the existing processes at the Chicago facility, that was done using the Moriarty process; is that correct?

A I believe that's correct. That's what I've been told.

Q Okay. Go down just a couple paragraphs. There's a paragraph that begins with the word, "During." Do you see that?

A Yes.

Q And it says, "During the initial analytical method validation for the treprostinil assay, the results indicated that there is about 2 percent variability in the assay." Did I read that correctly?

A That's what it says.

Q Okay. Do you have any reason to disagree with that statement?

A No.

Q Okay. When referring to the treprostinil assay, that's the HPLC assay of how pure the treprostinil is?

A I don't know for certain. It doesn't say, "HPLC assay."

Q What's your understanding?

A That sounds reasonable, but I can't be certain.

Q Well, did you review this document in forming your opinion; correct?

A Yeah.

Q Okay. And when you read that, did you wonder what it was referring to?

A Not in that context, no.

Q Maybe I can help you. Let's go to page 6. And do you see there, it says, "Assay HPLC"? Do you see that row?

A Yes.

Q Okay. And do you see it refers to certain numbers --

A Yes.

Q -- in the next two rows -- columns? Yes?

A Yes.

Q Okay. Looking at page 6 and then looking back at page 3, reading those sections, can you now

conclude for me that the 2 percent variability in the assay refers to the HPLC assay?

A Yeah. I believe that's what they're talking about.

Q And so what this sentence on page 3 says is that the HPLC assay analysis for treprostinil has a plus or minus 2 percent variability; is that fair?

A So variability -- but -- I don't think that's accuracy -- variability.

Q Am I correct that what that means is that the HPLC assay analysis can only be controlled such that the outcome falls somewhere between plus or minus 2 percent of the desired amount?

A Yeah, I'm not sure about that. I mean, HPLC is an extremely sensitive technique, and you can detect levels of impurities at much, much lower than 2 percent.

Q Let me ask you: Are you an expert at analytical chemistry?

A I have a lot of expertise in analytical chemistry, yes.

Q What's your expertise in analytical chemistry?

A I have extensive experience with NMR -- nuclear magnetic resonance spectroscopy -- infrared

spectroscopy, HPLC, thin-layer chromatography, mass spectrometry, ultraviolet spectroscopy, X ray crystallography.

Q Okay. And you've used all those techniques?

A Yes.

Q Okay. But your research area is not analytical chemistry; is that fair?

A I wouldn't say it that way. My research area relies, on a daily basis, on analytical technologies and instrumentation.

Q Sure.

A So I can't -- my laboratory can't function without daily routine access to all the techniques I just enumerated.

Q Sure. But your specialty is not the design, development, construction of analytical instruments; is that fair?

A I have not designed analytical instruments. But for my entire career as a chemist, I have been using extensively all these analytical instruments, including with my own hands.

Q Let me ask you: Did you take analytical chemistry in graduate school?

A I actually didn't take any courses in

graduate school.

Q Okay. Even for the master's?

A Hmmm?

Q Even for the master's portion of your graduate school?

A So my master's degree, the way it works at MIT when you get a Ph.D. degree, you automatically get a master's degree. It wasn't like a separate thesis. I sat in on a lot of courses, but I didn't actually take any courses in graduate school.

Q Did you sit in on analytical chemistry?

A No.

Q Did you take analytical chemistry in college?

A Yes.

And I also taught graduate level spectroscopy courses when I started my independent career at Colorado State University. So I have also taught mass spec and NMR and HPLC to graduate students.

Q Okay. That course didn't include HPLC?

A The course I taught was mostly centered on spectroscopy. We did talk a little bit about HPLC, but I also teach my own graduate students

about HPLC.

Q Okay. And as part of your teaching of HPLC, do you discuss error analysis of the HPLC instrument?

A Yes, because sometimes we have to report very accurate data based on HPLC. So, yes, HPLC is much, much more sensitive than NMR.

Q I think one of the things you say in your Declaration, though is that -- let me ask you this: Is there in your view any preference for using HPLC assay analysis where you measure the peak of the substance of interest versus measuring the total related impurities?

A I didn't quite follow your question.

Q Yeah. In determining the purity of a substance, which technique is better? Using the HPLC peak of the substance of interest or using a sum of the peaks of the impurities?

A I really am sorry. I'm not following your question. It doesn't make sense to me.

Q Let me break it down, then.

The HPLC assay analysis described here -- that's an analysis in which the area under the curve for -- in this case, treprostinil, but for any other substance as well -- is compared to a reference

standard; is that fair?

A Yes.

Q Okay. And that's one technique of determining the purity of a substance; right?

A Yes.

Q Now, something else that you did in your Declaration, I believe, is you looked at a table of total related substances; correct?

A Yes.

Q And you subtracted those from 100 to get the purity analysis; right?

A Yes.

Q Okay. Which of those two techniques is preferable?

A Well, I think you need to do both. In fact, in my own research, I don't rely exclusively on HPLC. I always ask my students to corroborate through NMR as well, because some compounds are invisible by HPLC if they don't have a chromophore, if you're using a UV detector.

Q Right.

A So it's -- but for industrial process validation, you know, the assumption is that the analytical group who has established the protocols and methods is already thoroughly vetted and

confirmed and verified that the analytical technique that's going to be use San Diego reliable and sensitive within a given set of parameters for a given type of compound and impurities.

Q Right. But there could be some compounds -- some impurities in there that don't have a chromophore and wouldn't be seen in a particular HPLC analysis?

A That's possible, yes.

Q Okay. And you said you would do both. Is there any preference for one or the other, or they're both equal?

A Well, HPLC is typically faster, particularly if you have it set up in a -- you know, a robotic auto-sampler type of thing.

So NMR takes more time. You gotta prepare the samples, you have to get the spectrometer, and you have to look at everything in the spectrum. But in my own research, I insist that my students use every technique available to figure out what's in that product mixed or purified product.

Q Now, let me also ask you, though -- so I can do HPLC and just look at the peak for the substance of interest, say, treprostinil or

something else.

A Hmm-hmm.

Q Or I could look at the total related substances. And I think you said it's probably best to do both. Is there a preference, though, for total related substances or for the looking at the larger peak?

MS. HASPER: Objection. Asked and answered.

THE WITNESS: Okay. I'm not sure about this preference issue. I mean, it's important to understand -- like for batches -- you know, commercial batches of treprostinil with what the individual impurities are and how pure the main component is, and so there's impurities that are known, we know exactly what -- like the enantiomer where that --

BY MR. POLLACK:

Q Right.

A -- peak is and that type of thing, as well as unidentified impurities -- these other things that are there that you're not sure exactly what that is.

Q Okay.

A May be a mixture of things.

Q Okay. Now, in your Declaration -- and you may have misunderstood -- I thought there was some criticism of the use of reference standards. Did I misinterpret?

A You want to point me to where you think I've got a criticism?

Q Let me just ask you first: Do you have any criticism of reference standards?

A In general or specifically with respect to this matter?

Q Both.

A Well, it's important -- I mean, the reference standard itself has to be a highly purified material, and there's no such thing anywhere on this planet of something that's 100.0 percent pure.

So no matter how many times you recrystallize or do chromatography over and over again, you can approach 100 percent, but you can never get there.

So the goal is to try and have as pure a reference standard as possible, and then you measure against that, if you can ascertain what the purity of the reference standard is.

Q And that's an initial that's inherent in

all HPLC measurements; is that right?

A Yes.

Q And that's true, even if you're measuring the total related substances, you need to use a reference standard, isn't that correct?

A Well, I think -- the reference standard is the same reference standard, and they're just measuring area under the curves of other peaks. And that's added to the known ones.

Q Okay. They're not using reference standards for each impurity?

A I don't believe so, no. I mean, they know what each -- they use reference standards because they've identified for example where 1AU90 -- what the retention time is that so they know where that comes.

Q Right.

A For the known ones.

Q They would use a reference standard for the known ones?

A Well, they know where that is. I don't know -- I do not believe that they separately calibrate the small peak for, like, 1AU90 against the reference standard for 1AU90. It's a single reference standard for treprostinil.

Q Okay.

A Otherwise, it would just take too long.

Counselor, I apologize. The coffee here after lunch just came --

MR. POLLACK: No problem.

THE VIDEOGRAPHER: Going off the record, the time is 2:00 P.M.

(Off the record)

THE VIDEOGRAPHER: We are back on the record. The time is 2:03 P.M.

MS. HASPER: Mr. Pollack, just before you begin, I'd like to interject a posthumous objection to the introduction of the electronic document that was introduced as Exhibit 13. It's just irregular to introduce an electronic copy of something, rather than a printed copy.

MR. POLLACK: I believe we did provide a printed copy as well, which was --

MS. HASPER: Are you saying that what you introduced as Exhibit 13 was identical to what you printed out and provided as a printed copy?

MR. POLLACK: Yes. The information is identical.

MS. HASPER: Could you show me which of the other exhibits is the same as --

MR. POLLACK: We can do that off the record at some other time.

MS. HASPER: Okay. Until I have that, then I will let the objection stand. I may retract it later.

BY MR. POLLACK:

Q If you could go to -- back to an exhibit we had looked at before -- it's Exhibit 11. It's this giant book here that is also known as "Exhibit 2052."

If you could turn to -- there's a lot of numbers, I know, on these pages, but there's a P.43 at the bottom of the page.

A Okay.

Q Okay. Do you see on that page it has an explanation of total related substance equals some of all reported peaks except UT-15? Do you see that?

A Yes.

Q Okay. And what I was trying to understand here is, when it says, "reported peaks," those are peaks of the known and identified substances; is that right?

A My understanding was that total related substances includes known plus unknown.

Q Where did you get your understanding?

A I don't remember what document. I know that we -- I discussed this several times with -- with counsel, and we referred to documents. I can't remember off the top of my head which one confirmed that, but that was my understanding, anyway.

Q And that was your understanding from counsel?

A Yes.

Q Okay. Looking here, can you tell whether -- from this definition whether unidentified substances are included?

A So reported peaks is not, to me, synonymous with known species. So there could be a peak that's reported, but -- it has a certain height and area under the curve. And --

Q Okay.

A So I'm not really sure what you're asking me.

Q Yeah. I was asking you whether this indicated that it was only those peaks which were identified with a code number or other kind of name.

A No. So I believe at the -- the batch records themselves show separately the known impurities, and then unknown impurities, and then

total related substances. They're broken out separately.

Q Right. Right. Right. Earlier, though, remember we went through those numbers, and we weren't able to sum them to the number which was the total related substances? Do you recall that?

A Yes.

Q Okay.

A But I -- I explained that that's because they come from two different types of -- and that the .05 was less than .05 and the actual total related substances gives the net amount of other things besides UT-15.

Q Okay. Do you know how the less than .05s were handled?

A Well, the less than .05s were given a value in my chart of .05. So rounded up, essentially.

Q Right. I'm asking you how -- United Therapeutics, or whoever else, was compiling that data, how did they handle it?

A Well, they're reported just like that. It's less than .05. So it was detectable, but then the sum of those end up -- my understanding is, the sum of those all end up in the total related

substances value. So known plus unknown.

Q But if one's not detected or .05, how is that handled by UT or whoever was reporting the values?

MS. HASPER: Objection. Asked and answered.

THE WITNESS: You're -- I think I just explained exactly the answer to your question.

BY MR. POLLACK:

Q What was the answer? Maybe I didn't follow it.

MS. HASPER: Same objection.

THE WITNESS: I said, so if you look in the batch records themselves, they split out the individual known impurities and the unknown impurities; okay? And so the ones that are -- record a value of less than .05 percent in the summary that I gave were given a value of .05.

So that's erring on the high side -- okay? -- 'cause it could be .00001 percent, but the total related substances value, then, would have built in, you know, say one peak was .0003 -- okay? -- so it wouldn't be added in as .05. It comes just through the standard protocols that they have for -- for measuring this.

BY MR. POLLACK:

Q So you're saying even though they don't report a value, they have some value for these very, very small peaks in your view?

A Yeah. Of course, there's a value. They're visible in the chromatogram. And the computer, you know, measures the area under the curve, and you get a -- you know, this total related substances number.

Q Okay. And that -- even for peaks that are so small that there's a signal to noise problem? Those are included?

A I can't speak to signal to noise. I don't -- you know -- you know, I'm sure this has all been vetted in their validation procedures for that.

Q Okay. I mean, did you speak to anyone or --

A No.

Q -- look into --

A No.

Q Let me ask my question again: Did you speak to anyone or look into how United Therapeutics determined those values?

A No.

Q Okay.

A No. I took these -- this data -- I mean, these are all things that are produced to the FDA, and they have to be validated, and confirmed and -- so I didn't question the veracity or authenticity, accuracy, because these are, you know, important documents.

Q Let me ask you -- if you go back to Exhibit 2006, also known now as "Williams Deposition Exhibit 14" --

A Okay.

Q -- if you could turn to page 6. You see it says, "Assay HPLC"; right?

A Yes.

Q Okay. And in the right-hand column, they've set a standard for that; right? It says, "not less than 98 percent and not more than 102 percent"?

A Yes.

Q Okay. So if I have a batch and I run an HPLC assay on the batch, and the purity comes out as 98.0 percent -- by the way, that's done by -- let me make sure I understand.

These assay HPLCs, those are done by taking the area under the curve for the treprostinil and comparing that to the standard?

A I believe so, yes.

Q Okay. So if I have -- if I make a batch of treprostinil, and I measure its HPLC assay, and I get 98.05 percent, that batch passes the FDA specification; right?

A Yes.

Q I can sell that batch to the public?

A That's my understanding, yes.

Q Okay. In fact, as far as the FDA is concerned, any batch that has a purity better than 98 percent -- so long as it meets these other specifications -- that batch can be sold to the public; right?

MS. HASPER: Objection. Beyond the scope.

THE WITNESS: Well, I'm not an FDA expert, but my understanding is, it has to be between 98 percent and 102 percent.

BY MR. POLLACK:

Q Fair enough.

But if it's between those numbers, then it can be sold to the public?

MS. HASPER: Same objection.

THE WITNESS: As far as I know, but I'm not an FDA expert.

BY MR. POLLACK:

Q You've done a lot of ANDA litigation? Do you know what I mean by, "ANDA litigation"?

A Yes. "Abbreviated New Drug Application." The Hatch-Waxman Act.

Q And that's where a generic company tries to sell a copy of something very similar?

A Yes.

Q And the ANDA litigation you've been involved in, including some for treprostinil; right?

A Yes.

Q The ANDA filer, they report a purity as well -- right? -- for their API?

A I believe so.

MS. HASPER: Objection. Beyond the scope.

THE WITNESS: I believe so. That's what I've seen previously.

BY MR. POLLACK:

Q Okay. Have you seen that in your other litigations?

A I have.

Q Yeah. Okay.

And they need to meet the same purity specifications for their active pharmaceutical

ingredient that the brand name does; right?

MS. HASPER: Same objection.

BY MR. POLLACK:

Q Is that your understanding?

A So, again, I'm not an FDA expert, but I know that the generic also has to meet some target specification. I don't know if it's the same as the branded drug or not in every case.

Q Okay. In your experience, when you've done your ANDA cases, have you seen that the generic company meets the same purity specification as the brand name?

MS. HASPER: Same objection.

THE WITNESS: You know, I just don't -- I just don't recall, because in the ANDA cases that I have worked on, this is all prelaunch, end of product, so they have a proposed product and a proposed spec. So I don't know what happens at -- you know, after, when they're actually selling, if they, you know, start to sell their product.

BY MR. POLLACK:

Q Although, they've created a -- a batch which they provide to the FDA. You've seen that; right?

A Yes.

Q Okay. And they've made purity measurements of their batches in order to try to gain approval of their ANDA?

MS. HASPER: Same objection.

THE WITNESS: I think that's generally how it works, yeah.

BY MR. POLLACK:

Q Okay. And they've done an HPLC assay purity analysis of their active pharmaceutical ingredient. You've seen that; right?

MS. HASPER: Objection. Scope. Relevance.

THE WITNESS: Perhaps, if that's the assay that's used for that particular drug. I would assume they would be doing the same thing. But I suppose there could be other types of assays.

BY MR. POLLACK:

Q Okay. What about for treprostinil? Did companies like Sandoz, or Watson or Teva, did they submit an HPLC assay analysis for their active pharmaceutical ingredient?

MS. HASPER: Objection. Scope. Relevance.

I advise the witness not to answer if it would reveal privileged or confidential information.

THE WITNESS: I actually don't recall.
BY MR. POLLACK:
Q Okay. Let me ask you this: When a generic company is measuring the purity of their active pharmaceutical ingredient by HPLC assay analysis, they, too, need to use a reference standard; right?
MS. HASPER: Same objection.
THE WITNESS: I presume they also have to do that as well to validate their Assay Purity to the FDA.
BY MR. POLLACK:
Q And when they're doing that with their reference standard, they don't have access to the brand-name company's reference standard; right? They have to create their own?
MS. HASPER: Same objection.
THE WITNESS: I actually don't know.
BY MR. POLLACK:
Q Okay. No idea?
A I have no idea.
Q Okay.
MR. POLLACK: I'm going to mark as Williams Deposition Exhibit 15, an article by Terence L. Threlfall titled, "Analysis of Organic

Polymorphs," a review that appeared in "The Analyst," October 1995.

(Exhibit 15 marked)

BY MR. POLLACK:

Q Let me ask you: Are you familiar with Terry Threlfall?

A I don't recall. I think I've seen this before.

Q Okay.

A Are you going to tell me that I cited it in my Declaration?

Q No, I'm not. I'll tell you that you have not.

A I actually don't recognize this.

Q Okay. Do you know Dr. Threlfall?

A No.

Q Okay. I want to turn to -- if you look on the first page, 2435 and going over to 2436, there's a discussion there about how to name polymorphs.

What are polymorphs, if you could --

A Actually, polymorphs are different crystalline forms of solid compounds. They adopt different crystal-lattice configurations.

Q Do you consider yourself an expert on

crystal forms of organic molecules?

A No.

Q But you're -- you've heard of this phenomenon before?

A Yes, yes.

Q So, Dr. Threlfall discusses here, there's no clear choice on how to designate polymorphs. And one of the suggestions he has is numbering, based on order of discovery. Were you familiar with that system for naming polymorphs?

MS. HASPER: Objection. Beyond the scope.

THE WITNESS: No.

BY MR. POLLACK:

Q No? Okay.

You've never seen polymorphs named "Form 1," "Form 2," "Form 3"?

A I have.

Q Are you aware that's usually based on the order of discovery?

A I have no idea.

MS. HASPER: Same objection.

BY MR. POLLACK:

Q Okay. Now, further down, he has some other suggestions. If we go on to 2436, top of the

page, he says -- the second sentence, "The addition of a melting or upper transition point to a Roman numeral is possibly the best compromise, although care must be taken to distinguish the melting point of the polymorph and that of the transformed product."

Do you see where I'm reading?

A Yes.

Q Okay. Did I read that correctly?

A That's what it says.

Q Am I correct that one of the ways of naming polymorphs that's been proposed is to name them by assigning their -- the melting point in addition to a Roman numeral?

MS. HASPER: Objection. Scope. Relevance.

THE WITNESS: Yeah. So I'm not a polymorph expert. So --

BY MR. POLLACK:

Q Well, why do you think they do that?

Why do you think they append a melting point to each polymorph?

MS. HASPER: Same objection.

THE WITNESS: Well, certainly, that's a physical characteristic of an individual solid form.

BY MR. POLLACK:

Q The melting point is something that's unique to that particular solid form?

MS. HASPER: Same objection. Also speculation.

THE WITNESS: Yes. But I know enough about crystallization that melting points are highly dependent upon the solvent that was used, the conditions that the crystals were grown under, time, scale. There's lots of variability in that. And I've run into this many, many times over the years in my own research.

BY MR. POLLACK:

Q Okay. But those conditions create different polymorphs, isn't that the issue?

A No. It could be the same --

MS. HASPER: Same objection.

THE WITNESS: It could be the same polymorph, but depending on how the crystal was grown, there's lots of -- you know, I've consulted on this issue. Inclusion of solvent can sometimes affect melting ranges and things like this.

BY MR. POLLACK:

Q Well, if there's solvent in it, then it's known as a "solvate"; right?

A Not necessarily.

Q Why not?

A Solvates are different. Solvates are actually -- for example, hydrates are solvates where there's a certain number of water molecules that will be noncovalently associated with a molecule in the crystal lattice. And sometimes these can be highly well-defined numbers like a trihydrate. So every molecule -- say a treprostinil trihydrate, each one would have three molecules of water associated with it. And sometimes there is a range that, you know, it's not exactly 3; it's 3.6. Okay.

Q You know, we're talking about -- in this proceeding, we're talking about treprostinil diethanolamine salt Form B. You'll agree with me that they've verified that that salt is neither a hydrate nor a solvate in the Phares reference; right?

MS. HASPER: Objection.

THE WITNESS: I don't recall. I'd have to look at --

BY MR. POLLACK:

Q Do you want to look at it?

A Sure.

Q You could have "Exhibit 1005" as it was

called.

MR. POLLACK: I'm going to mark as Williams Deposition Exhibit 16 a document currently known in the case as "Exhibit 1005," also known as the "Phares," P-h-a-r-e-s, "reference."

(Exhibit 16 marked)

BY MR. POLLACK:

Q In order to make this a little bit easier for you, the discussion of the characterization of treprostinil diethanolamine salts starts on what's called "Page 90" in the bottom right-hand corner of the document. It's page 87 in the original pagination.

A (Examining document) Okay. I've looked at the paragraph on that page 90, or 87.

Q Okay. If you could move on to the section on Form B, which starts at the bottom of --

A I'm sorry.

Q -- 87 and goes onto 88. I particularly wanted to focus on moisture sorption/desorption data and thermal data, but feel free to read all of it.

A (Examining document) Okay. I've read that.

Q Okay. Based on what you've read here, can you tell whether or not the Form B described

here is a hydrate solvate or is otherwise wet with solvent?

A Well, in contrast to Form A, where it specifically says -- indicated the material is not solvated, they don't make such an affirmative statement with Form B. But I'm not a polymorph expert, so -- you know, I'm -- I wouldn't be certain.

Q Okay. So you don't understand what it says there about the minimum weight loss. That's not an indication to you that there's -- no water was contained in the crystal?

A Well, it's certainly hydroscopic. Absorbs water.

Q Hmm-hmm. Okay. But this information here, can you tell from that -- the fact that water is not desorbing? Does that indicate to you -- and I recognize you're not a crystal-form expert, but does it indicate to you that it's not a solvate, or is this outside of your area?

A It's really outside of my area.

Q Okay. And what about -- you see there it says -- do you know what a "TG" is? It says, "A TG shows minimum weight loss up to 100 degrees C."

A I've seen that acronym before. I don't

remember off the top of my head exactly what it means.

Q Have you ever seen the acronym "TGA" as it's sometimes referred to?

A Is that "thermographic metric analysis"? Yeah.

Q Yes. Are you familiar with how that technique is used with polymorphs?

A Not intimately, no.

Q Okay. You're not aware that technique is sometimes used to show that there's a solvent or solvate in a -- in a polymorph?

MS. HASPER: Objection. Asked and answered. Scope.

THE WITNESS: Yeah. I mean, I'm not very familiar with the technique, so --

BY MR. POLLACK:

Q Okay. Fair enough.

If we could go back just quickly in the Threlfall article.

You know, never mind.

A Okay.

MR. POLLACK: I'm going to mark as Exhibit Williams Deposition Exhibit 17 an excerpt from the book "Solid-State Chemistry of Drugs," by

Steven R. Byrn, Ralph R. Pfeiffer and Joseph G. Stowell.

(Exhibit 17 marked)

BY MR. POLLACK:

Q And, no, this wasn't attached to your report.

Have you either seen or read this book, ever, before?

A No.

Q Okay. Do you know any of the authors?

A No.

Q Okay. Are there any textbooks on the solid-state form of drugs that you have read?

A Not that I can think off the top of my head, no.

Q Okay. Turn to the first page of this document. This is Chapter 10 on polymorphs. Let me just ask you about the second sentence which says that, "Compounds that crystallize as polymorphs can show a wide range of different physical and chemical properties, including different melting points and spectral properties."

I just want to know if you agree with that sentence or have any reason to disagree with it?

MS. HASPER: Objection. Scope.

THE WITNESS: I don't have any reason to disagree.

BY MR. POLLACK:

Q Okay. Do you agree with it?

A I have no reason to disagree.

Q Okay. One of the things that characterizes a polymorph is its melting point. It's one of the things that uniquely identifies a polymorph; is that right?

MS. HASPER: Objection. Scope. Asked and answered.

THE WITNESS: Again, based on my limited understanding that this can be quite dependent on conditions, the solvent that was used, the scale.

BY MR. POLLACK:

Q If you look a little further down on page 143, there's a second paragraph. This, again, talks about how polymorphs are made. Do you see -- or named. Do you see that?

A Yes.

Q Okay. And they point out there's no standard numbering systems for polymorphs; right?

A That's what it says.

Q Okay. And if you go down about three,

four, five sentences, there's a sentence beginning with the word, "It." Do you see that sentence?

It says, "It has been suggested . . ."?

A Yes.

Q Okay. And I'll read it into the record.

"It has been suggested that polymorphs be numbered consecutively in the order of their stability at room temperature or by their melting point."

Did I read that correctly?

A That's what it says.

Q Okay. And so what he's proposing here is that a polymorph would be identified by its melting point. Do you see any place where he says: And it needs to be further identified by what solvent was used?

MS. HASPER: Objection. Relevance.

THE WITNESS: No, but I guess I'd have to read a lot more on -- on this -- in this article. It may be discussed later.

BY MR. POLLACK:

Q Okay. Well, this is a -- I'll represent to you, it's not discussed later. But this is the second time we've seen a proposal that polymorphs be named by their melting point; right? You saw that

in the Threlfall article as well?

A Okay. Yes. That's what it says.

Q And Threlfall also, he doesn't suggest: Oh, it needs to be named also by what solvent was used -- right?

A I didn't see that mentioned, no.

Q While we're getting that out, could you go back to the patent for me.

A The patent? Which patent?

Q The patent. The '393 patent, Exhibit 1001, now known as "Williams Deposition Exhibit 3."

A Okay.

Q And I'd like to turn to what's called "Page 8" in this exhibit. It's column 12 of the patent. And if you look in that column in the paragraph starting -- two paragraphs starting around line 35, you see it refers to, "Polymorph B of the treprostinil diethanolamine salt"; right?

A What line?

Q I'm sorry. Line 40 -- it starts around line 42 and continues down the page.

A Okay.

Q Okay. Now, that polymorph B, that's the same polymorph B that's referred to in Exhibit 1005,

the Williams Deposition Exhibit 16, the Phares reference?

A I can't be certain they're the same, 'cause Phares doesn't tell us where the treprostinil comes from.

Q It's the same polymorph, though; is that fair?

A Well, that's what it's called, "polymorph B."

Q Okay. They're both polymorph Bs; right?

A That's what they're called.

Q Do you have any reason to believe that they're different?

A Well, I certainly know where polymorph B in the patent comes from. In Phares, they do not identify the source of the treprostinil.

Q Yeah. I'm not asking about how it was made or other differences. I'm just asking in regards to what crystal form it is.

Are both of these the same crystal form, the crystal form of treprostinil diethanolamine salt in the '393 patent and the crystal form in the Phares prior art reference, which are both called Form B? Are they the same crystal form?

A I can't be 100 percent certain. This

melts at 104, and I think the Phares melts the 107. So I'm not certain.

Q Okay. Now, the Phares reference, that's -- that's a patent application written by people at United Therapeutics; right?

A Yes.

Q Okay. Did you ask anyone at United Therapeutics: Hey, do you have information about that particular Form B that you made in the Phares patent?

A No.

Q But you knew they -- if anyone had that information, it would be United Therapeutics; right?

A Presumably.

Q Right. You don't think I'm going to have that information; right?

A No.

Q Right. And if they were different -- right? -- if the Form B in the Phares reference and the Form B in the '393 patent -- if they were different, don't you think that your counsel would have given you documents showing that they were different crystal forms?

A All I know is what's stated in the documents.

Q That you received.
A Yes.
Q And you didn't ask for any further information on this issue?
A No. No. I didn't think there was a need to.
Q So we were looking at the patent, Exhibit 1001, also known as "Williams Deposition Exhibit 3." I want to go to the next paragraph that begins with, "At this stage . . ."
Do you see that paragraph? In column 12.
A Okay. Column 12 and -- where -- okay.
Q It's about line 53.
A Hmm-hmm.
Q I'll read it into the record so we know where we are?
A Okay.
Q It says, "At this stage, if the melting point of the treprostinil diethanolamine salt is more than 104 degrees C, it was considered polymorph B."
Did I read that correctly?
A That's what it says.
Q Okay. So if you're in the '393 patent, they are identifying whether a treprostinil

diethanolamine salt is Form B by its melting point; right?

A Yes.

Q Okay. And if the melting point is greater than 104, that indicates that it must be the Form B; correct?

A Your question again?

Q Let's just put it this way: The melting point is a signature for Form B.

A It's one characteristic, physical property, yes.

Q They're not just saying it's one characteristic property; they're saying it is the property which tells you it's Form B. Isn't that what that sentence says?

A Well, its X ray defraction pattern is going to be much more diagnostic.

Q Okay. I'm just asking: What does this sentence say?

A Well, it says, "At this stage if melting point of the treprostinil diethanolamine salt is more than 104 degrees, it was considered polymorph B." That's what it says.

Q Okay. Let me ask you this: The people at United Therapeutics, they know how to take PXRDs;

right?

MS. HASPER: Objection. Speculation.

THE WITNESS: I'm not sure if they do that in in-house, or if they contract that out to another lab that has deep expertise in this or not. I don't know if they do it in-house or not. I don't know.

BY MR. POLLACK:

Q Okay. They have access to the technique; right?

A Sure.

Q We saw in the Phares reference, they have a PXRD for Form B; right?

A Yes.

Q So presumably, they did a PXRD of what they did here in the '393 patent, Exhibit 1001; right?

MS. HASPER: Same objection.

THE WITNESS: You're asking me presumably they did a PXRD?

BY MR. POLLACK:

Q Yeah.

A I don't know if there was data on that or not in here.

Q There's no data in here.

Let me ask it to you this way: Do you think that the people at United Therapeutics would have reported that this is Form B without do doing a PXRD? Is that your opinion?

A I don't have an opinion.

Q One way or the other?

Okay. I mean, the people at United Therapeutics, they're not amateurs at these techniques; right?

MS. HASPER: Objection. Scope.

BY MR. POLLACK:

Q You don't know?

A I don't know.

Q Okay.

A We've been going for another an hour, could we possibly have a break?

THE VIDEOGRAPHER: This ends media No. 2 in the deposition of Robert M. Williams, Ph.D. We're off the record at 2:45 P.M.

(Off the record)

THE VIDEOGRAPHER: This begins Media No. 3 in the deposition of Robert M. Williams, Ph.D. We are back on the record. The time is 2:57 P.M.

MR. POLLACK: I'm going to mark as Williams Deposition Exhibit 18, a Guidance for

Industry from the FDA titled, "ANDAs: Pharmaceutical Solid Polymorphism."

(Exhibit 18 marked)

BY MR. POLLACK:

Q I'm going to represent to you, this wasn't attached to your report. But I'm wondering if you've reviewed this document in the past in the course of your various ANDA litigations or consulting?

A Not that I can recall.

Q Okay. This is -- well, can you explain to me what is -- what this document is?

A No.

Q Okay.

A I've never seen it before.

Q Sure. Do you know what a Guidance for Industry is -- I mean -- from the FDA?

A I've seen FDA guidance things. These are things the FDA puts out to help pharmaceutical companies jump through all the hoops with the FDA to get approval.

Q Okay. And I'm right -- this one is about pharmaceutical solid polymorphism?

MS. HASPER: Objection.

THE WITNESS: That's what it says.

MS. HASPER: Scope.

BY MR. POLLACK:

Q Okay. And in simple language, that's about different crystal forms of drugs; right?

MS. HASPER: Same objection.

THE WITNESS: Yes.

BY MR. POLLACK:

Q Okay.

MS. HASPER: Counsel, if I could clarify: You said this was a -- Exhibit 18. I thought the previous exhibit was 18.

THE REPORTER: No, the last one was 17.

MS. HASPER: Thank you. I'll correct that, then.

BY MR. POLLACK:

Q Let me ask you: Are you familiar with any guidances from either the FDA or -- are you familiar with the ICH?

A I'm trying to remember what the acronym stands for. I don't remember now.

Q Okay.

A But, yes, I've seen -- I've seen each before. I was trying to remember what the acronym is.

Q Have you looked at any either ICH or FDA

documents concerning polymorphism in the past?

MS. HASPER: Objection. Relevance. Scope.

THE WITNESS: Not that I can think of.

BY MR. POLLACK:

Q Okay. Let me ask you just to turn to page 9 of Exhibit 18. You see here this is a -- a guidance setting forth specifications for polymorphs in drug substances for solid, oral, and suspension dosage-form products.

And you see that in the first square, the question is: Is there a polymorph specification in the USP -- the USP -- that's the United States Pharmacopeia?

A Pharmacopeia.

Q What is the United States Pharmacopeia?

A Oh, it's a compendium of drug substances that is indexed and catalogued by this organization.

Q Okay. And the organization which is known as the "USP"; is that right?

A I think so, yes.

Q The USP puts in specifications for each drug substance, including things like purity, crystal form, melting point -- is that your understanding?

A I don't recall off the top of my head exactly what data's in there.
Q Okay. You've used the USP; right?
A I have.
Q Okay. What do you recall from your use of it? What that -- what is in there?
A It's been a while since I looked at one, so I don't exactly remember.
Q Okay. About how long did you look at one?
A I don't remember.
Q More than a year ago?
A Well, you know, my father was a pharmacist, and he has a whole bunch of old ones that we just had to move from one place to another. I looked at those, but those are ancient.
Q Okay. Have you ever looked at the U.S. -- you understand there will be a USP monograph for treprostinil?
A Yeah.
Q And there's also one for treprostinil diethanolamine salt; correct?
A I guess so. I'll take your representation.
Q Okay. You haven't looked?

A No.

Q Okay. Now, you see here, one of the things that the FDA asks the ANDA applicant to do is to look if there's a polymorph specification in the USP, and then it says, for example, "melting point." Do you see that?

A Yeah, I see that.

MS. HASPER: Objection. Scope.

BY MR. POLLACK:

Q So melting point is one of the things the FDA calls out. In fact, it's the only thing in here that they give as an example as associated with a polymorph. Do you see that?

MS. HASPER: Same objection.

THE WITNESS: It says, "example." "For example."

BY MR. POLLACK:

Q There's other things; right?

A Certainly.

Q Right. But melting point is the one that they gave in this document?

A As an example.

MS. HASPER: Same objection.

BY MR. POLLACK:

Q Because melting point is something that

uniquely identifies a polymorph; right?

MS. HASPER: Same objection. Mischaracterizes the underlying document.

THE WITNESS: I would not necessarily agree with that.

MR. POLLACK: Let me mark as Williams Deposition Exhibit 19 a document that's been called "Exhibit 2030" in this case. It's an article by -- rather than try to say the name, it's an article that appeared in the International Journal of Pharmaceutics in 2006.

(Exhibit 19 marked)

BY MR. POLLACK:

Q Let me ask you: Is Williams Deposition Exhibit 19 an article you relied upon in your Declaration?

A Yes.

Q Okay. Do you have any idea how to pronounce the author's first name?

A "Adhiyaman."

Q Okay. We'll call this the Adhiyaman article?

A Okay.

Q Okay. Now, in the Adhiyaman article, we see -- I think my understanding of this -- or at

least of your opinion of it -- is that there are a number of crystals of certain chemical called "dipyridamole"? Is that a decent pronunciation of it, or how would you pronounce that?

A "Dipyridamole."

Q Okay. And they're all made in different solvents; is that fair?

A Yes.

Q Okay. And each of them has a different PXRD pattern; is that fair?

A I think that's what they're illustrating in the article, yes.

Q Okay. Isn't it correct that a different PXRD pattern means that the crystal has a different three-dimensional structure in a solid form?

A Yes.

Q Okay. So each of these is really a different crystal form of the same drug; is that fair?

A I think that's fair.

Q Okay. So what we learned about in this article is sometimes when you use different solvents, you get different crystal forms of the same drug; right?

A Yes.

Q Okay. So there's nothing in here saying that two crystals that have the same crystal form and same PXRD structure made from different solvents are different?

MS. HASPER: Objection. Mischaracterizes the document.

THE WITNESS: Please state your question one more time?

BY MR. POLLACK:

Q Sure. Sure.

So there are no -- let me make the following clear: There are no examples in Williams Deposition Exhibit 19 of two crystals having the same PXRD pattern but which are different crystal forms.

A You'll have to ask me that one more time.

Q Sure. There are no examples in Williams Deposition Exhibit 19 of two crystals, made with different solvents, having the same PXRD pattern but different -- but are different crystal forms?

A I'm not sure I can come to that conclusion.

And what I did cite from this article is that the conclusion, which I quoted in my Declaration, and it's also based on my experience of

crystallizing the same compound on different days from different solvents under slightly different conditions, you can get a different melting point. And it depends on the scale and lots of things.

Q Okay. But could you get a different melting point because you've gotten a different crystal form. Isn't that the issue?

A Not necessarily.

Q So your testimony today is, I can have -- let me ask you this: If I have two crystals that have the same PXRD pattern, can I get two different melting points?

A Yes.

Q Okay. And what is the reason for that in your opinion?

MS. HASPER: Objection. Scope.

THE WITNESS: So the way these melting points, which are done typically today with this differential scanning calorimetry, the melting ranges can depend on the rate of heating, the sample size, and even the individual instrument that's used. There can be variability.

BY MR. POLLACK:

Q Sure. You're saying there can be errors in the measurement?

A Yes.

Q Fair enough. Okay.

But assuming that the appropriate scan rate is used and appropriate sample size is used and all of those things are the case, will two crystals which have the same PXRD pattern have the same melting point?

A I don't know if that's ubiquitously true. I wouldn't agree with that.

Q Do you not know, or do you formally disagree with that?

A I disagree.

Q Okay. Do you have any -- is there anything in this article that supports your opinion?

A Well, the conclusion is that -- it says right here, "In conclusion, it can be said that the crystallization conditions" --

Q Read that slowly.

A Sorry.

"In conclusion, it can be said that the crystallization conditions and the medium used have a major effect on dipyridamole crystals habit modification under ambient conditions. The crystals showed significant changes in the shape, size, melting points, dissolution rate, XRD patterns and

DSC curves."

And I quoted that in my --

Q But here, they pointed out they all had different XRD patterns, right?

A Okay.

Q Right?

And, in fact, that's what the data shows in here. They all had different XRD patterns?

A Hmm-hmm.

Q Right. I'm asking about two crystals having the same XRD pattern.

A So in my own research, we do a lot of x-ray crystallography. And I work pretty closely with an expert crystallographer, Orrin Anderson. And we've had crystals that had the exact same XRD pattern that were produced on different days that had slightly different melting points. So I've seen this myself.

Q Okay.

A So what you're trying to say is just simply not ubiquitously true.

Q Okay. Do you have any literature or any papers -- other than your own personal anecdotal experience, do you have any scientific literature or papers that support that opinion?

A I'm sure I could find it if I was asked to, but that was based on my own experience.

Q Okay.

A And that's -- it happened not just once. It's happened numerous times.

Q Okay. But as part of this proceeding, you didn't look for any papers that supported that opinion?

A Well, I think the main point here is that you can't compare the polymorph form and Phares to what's in the '393. That was the main underlying theme here.

Q Right. But your opinion on that was based on the idea that the same polymorph could have two different melting points; correct?

MS. HASPER: Objection. Mischaracterizes the document and the testimony.

THE WITNESS: I mean, what's characterized is the same polymorph -- or what's called -- but there wasn't enough information to ascertain that that was the case.

BY MR. POLLACK:

Q The people who called it the same polymorph, that's United Therapeutics?

A Okay.

Q The people you're working for; right?
A That doesn't mean they're infallible.
Q Okay. It wasn't -- it wasn't me; right?
A No.
Q It wasn't Dr. Winkler?
A No.
Q No?
And -- okay. You think maybe they made a mistake in identifying the polymorphs?
MS. HASPER: Objection. Mischaracterizes -- testimony.
THE WITNESS: Yeah. I was addressing Dr. Winkler's analysis.
BY MR. POLLACK:
Q That's not what I asked you.
I said, do you think they made a mistake in identifying the polymorphs of each of those papers? United Therapeutics made a mistake?
MS. HASPER: Objection. Mischaracterizes testimony. Asked and answered.
THE WITNESS: I cannot be 100 percent certain.
BY MR. POLLACK:
Q Okay. You didn't do anything to investigate whether they made a mistake in

identifying those two polymorphs?

A No. I just have the documents as they read.

Q And the documents called both of those "polymorphs Form B"?

A Yes. Made under different conditions, and Phares doesn't provide any information on solvent that was used, scale, source of the treprostinil, and so on. So it's just not enough there.

Q You know, you've brought up the term "scale" several times in this deposition. Looking back at Exhibit 1001, is there anything --

A What's Exhibit 1001?

Q Exhibit 1001 is the '393 patent. It's also known as "Williams Deposition Exhibit 3."

A Okay.

Q I'd like you to look at claims in the '393 patent. Do you see anything in there that says what scale the reaction is being carried out at?

A No.

Q Okay. So the reaction covers any scale; right?

A Certainly.

Q Could be bench; laboratory reaction, like

Moriarty did in his Journal of Organic Chemistry article?

A Yes.

Q That could be included -- and it could be a large clinical batch; correct?

A Yes.

Q Okay. Let me go back to the Phares reference, Exhibit 1005, known as "Williams Deposition Exhibit 16." If you could turn to page 42. And we have a lot of page 42s here, so let me be a little more specific.

Page 42 in the lower right-hand corner of the document, original page 40 of the reference --

A Yes. I'm there.

Q Okay. -- I was wondering if you could help me understand some of the chemistry in -- you see there's a synthesis at the top of page; right?

A Yes.

Q Okay. Here's what I was not fully understanding: There's -- if you go to this synthesis scheme, there's a structure on the lower right-hand corner in the scheme. And next to it, there's an arrow, and there's a letter "L" above it. Do you see that?

A Yes.

Q Okay. And now, what's -- to the right of the arrow with the letter "L," that's the mirror image of the -- some of the compounds that are shown in claim 9 of the '393 patent; is that right?

A So which -- which structures are you asking me to compare?

Q Yeah. Let's take a look at -- there's a structure called "5" in claim 9.

A Okay. That's the so-called "benzindine triol."

Q Hmm-hmm. And is that structure and claim 5 -- is that the mirror image of the structure on page 42 also known as "40," in the lower right-hand corner?

A That would be 11-B where R is H. That would be the mirror image of the benzindine triol.

Q Okay. Thanks.

And then in step (l), if you look down in the paragraph, it tells you what step (l) is. And step (l) seems to have two parts to it; is that fair?

There's a little (i) and then a two little (ii) part?

A Yes.

Q Okay. Those are two separate steps in

(l); right?

A Yes.

Q Okay. And the first step -- the letter -- single (i) step where it says, "CL," "CH2," "CN," and then it says "K2," "CO3" -- is that the -- is that the alkylating step like is done in step (a) of claim 9, except for the mirror-image compound?

A Yes.

Q Okay. And then there's a step where it says "KOHCH30H reflux 83 percent." Is that the hydrolyzing step of -- which is called "step (b)" in the '393 patent being applied to the mirror-image compound?

A Yes.

Q Okay. So what we see here is there's an alkylating step (a) and a hydrolyzing step (b) on page 42 of the Phares reference.

A Yes.

MR. POLLACK: I'm going to mark as Williams Deposition Exhibit 20 an excerpt from Exhibit 1002, and it's a small section from that exhibit which was the prosecution history. And it's called the "Declaration of David Walsh."

(Exhibit 20 marked)

BY MR. POLLACK:

Q You've reviewed this document in preparation for this deposition and for -- in preparing your Declaration; correct?

A Yes.

Q I think we discussed earlier that according to this document -- if we turn to the document called "Page 348" in the lower right-hand corner. I think we discussed earlier how for the treprostinil diethanolamine salt, that's what's presented at the top of the page -- the salt?

A Yes.

Q Okay. And then below that is the free acid?

A Yes.

Q Okay. And we see in the free acid, the impurities are 0.2 percent; right? Total related substances.

A No.

Q Oh, I'm sorry. What is the impurities by HPLC for total related substances for the treprostinil free acid on the Walsh Declaration?

A Oh, you were asking me about the salt, which is .1 pertinence.

Q I'm sorry. Misspoke, then. I was not --

okay.

Want to do the salt first or the free acid?

A You're asking the questions.

Q Okay.

A You pick the order.

Q All right. Let's do the free acid.

A Okay.

Q Am I correct that the total related substances for the free acid is 0.2 percent?

A Yes.

Q And for the treprostinil diethanolamine salt, the total related substances is 0.1 percent?

A Yes.

Q Okay. So, in fact, there are -- well, let me ask you this: The treprostinil free acid, it's made the same way as the diethanolamine salt, except step (d) is then executed; is that correct?

A That's correct.

Q Okay. And so when step (d) was executed, the amount of total related substances actually increased; correct?

A Yes.

Q And, in fact, the spec, even, for treprostinil free acid made using the step (d) is

actually set to not more than 3 percent. Do you see that?

A Yes.

Q And for the salt, the level of impurities is set to only not more than 1-1/2 percent. Do we see that?

A Yes.

Q So carrying out an additional step, step (d), on the treprostinil diethanolamine salt actually increases the impurity level of the product; right?

MS. HASPER: Objection. Mischaracterizes the document.

THE WITNESS: So what's going on here -- this is actually fairly easy to understand.

BY MR. POLLACK:

Q Okay.

A -- is that the salt, which is incredibly pure. Seven to eight impurities is not present. The only thing that's detectable is an tiny amount of the enantiomer 3AU90. All the others have been eliminated. And when you treat the salt with acid, the impurities that now come back are the two dimers: 750W93, 751W93; and the ethyl ester.

And that's because those are formed by

acid-catalyzed self-condensation to make the two dimers, and the tiny residual amount of ethanol that was used to recrystallize the diethanolamine salt forms a small amount of the ethyl ester.

Q Okay. If you could turn to -- we had an exhibit we were looking at before, Williams Deposition Exhibit 14. That was a letter from the FDA.

A Okay. I've got the letter.

Q If you could turn to the second page of the letter, the one that says "2" in the center at the bottom. If you look -- you see there's a bullet point in the middle of the page?

A Yes.

Q Okay. And in that first paragraph there, they say, "Historically at our Chicago facility, UT15C intermediate is not a compound that was used during the conversion of [redacted] to treprostinil." Did I read that correctly?

A That's what it says.

Q And UT15C intermediate, that's a code name for treprostinil diethanolamine salt. You know that; right?

A Okay. I actually -- I don't remember that that's the code name. Here in this -- Walsh

Declaration it's called "UTW-11-0327." So --

Q You're not familiar with the code name "UT15C" from the documents?

A I mean I didn't -- I saw UT15C. I was real -- I focused more on the more explanatory names like benzindine triol, the diethanolamine salt.

Q Maybe this next sentence will help you recall what UT15C was. It says, "This new process was necessary for the production of our UTC15C API" -- "API" stands for "active pharmaceutical ingredient"?

A Yes.

Q -- "for investigational oral formulation."

Are you aware of that United Therapeutics sells an oral treprostinil diethanolamine salt drug?

A Yes.

Q Okay. Reading this now, does that refresh your recollection that UT15C is treprostinil diethanolamine salt?

A Yeah.

Q Okay.

A That's fine.

Q Okay. Now, it says here that, "The data in table 5 from the validation report" -- which

apparently has a number, [redacted] -- "showed several impurities detected at low levels, below the ICH identification limit of [redacted] percent. These impurities are not carried through to the final API treprostinil as described below."

Did I read that correctly?

A That's what it says.

Q So here, what they're saying is, there's a bunch of impurities in treprostinil diethanolamine salt. And those ones are not carried forward to the free acid. Did you see that?

A Okay. I see that.

Q Okay. I'm not mischaracterizing that -- right? -- that's what they're saying?

A That's what it says.

Q Okay. And so, in fact, here, what they're telling the FDA is, the treprostinil free acid is cleaned of all these impurities by the acid step, and yet Walsh's Declaration doesn't list these impurities and claims that the diethanolamine salt is purer than the free acid.

Do you see that?

MS. HASPER: Objection. Mischaracterizes the documents.

THE WITNESS: So in Walsh's Declaration,

there are unidentified impurities. So -- so I can only assume that that's what this is referring to.

BY MR. POLLACK:

Q Here, it shows that there are several impurities. Do you see that?

A Well, it says --

MS. HASPER: Objection. Vague.

Where are you referring to?

THE WITNESS: I'm sorry.

BY MR. POLLACK:

Q In page 2.

A Yeah. So in the Walsh Declaration, it says, "unidentified impurities," plural.

Q Right.

A Okay.

Q Hmm-hmm.

A And so there's 0.7 percent of those. And then in the acid, those are not detected.

Q Yeah. Except here, you notice how here it says they're below the ICH identification limit of 0.1. That doesn't say they're below the .05 identification limit where you don't have to report them; right?

MS. HASPER: Objection. Mischaracterizes the documents.

THE WITNESS: Okay. I haven't thought about this. You know, I haven't --

BY MR. POLLACK:

Q That's why I'm asking you to think about it now.

A Okay.

MS. HASPER: Objection. Beyond the scope of his report.

THE WITNESS: You know, I'd have to think about this deeply and figure out what the significance, if any, of that is.

BY MR. POLLACK:

Q Okay. You agree with me they're saying here -- reading this sentence fairly, that there are a number of impurities that are above the .05 level but below the .01 level which are in the salt, and those are being cleaned out by the acidification process.

MS. HASPER: Objection. Mischaracterizes the --

BY MR. POLLACK:

Q That's what they're saying to you; right?

MS. HASPER: Objection. Mischaracterizes the documents.

THE WITNESS: So I'd have to think about

this, but I -- I actually -- anyway, I'd have to think about it.

BY MR. POLLACK:

Q What were you going to say?

A I'd need more time to consider.

Q You agree with me there appears to be some contradiction here between what Walsh is presenting and what is being presented to the FDA in Exhibit 2006?

MS. HASPER: Objection. Mischaracterizes the testimony and the documents. Also asked and answered.

THE WITNESS: Yeah. I wouldn't -- I -- I don't have an opinion on that. So --

BY MR. POLLACK:

Q You have no opinion, one way or the other?

A I have no opinion.

Q This isn't something you looked at in forming your opinion for this case?

A No.

Q Let me ask you: What kinds of impurities that would be in the diethanolamine salt would be cleaned out by the acidification step?

MS. HASPER: Objection. Foundation.

THE WITNESS: You know, I could only speculate what would be reasonable to a person skilled in the art, since the diethanolamine salt -- the only basic species is diethanolamine. Diethanolamine may also come with some other basic impurities: Maybe ethanolamine, triethanolamine.

So I'm always speculating.

I have no data, but it's possible that those are basic impurities that are removed when you proteinate the salt because you also get rid of diethanolamine. So it would make sense that molecules like that would also disappear.

BY MR. POLLACK:

Q And I'm correct if we look on Walsh or Williams Deposition Exhibit 20 here, on page 348 as it's styled in the bottom right-hand corner, those kinds of impurities were not included on the list for the treprostinil diethanolamine salt?

A I'm not -- I didn't follow you. I'm sorry, counselor.

Q The kind of impurities you just described that could be cleaned out by the acid, those impurities are not on the list that Walsh presented of impurities for the diethanolamine salt.

MS. HASPER: Objection. Mischaracterizes

the document.

THE WITNESS: Well, those presumably could be unidentified impurities, because there's .07 percent that are in the salt that are not detected in -- or there's -- there's "ND" for unidentified impurities in the final acid. So --

BY MR. POLLACK:

Q If we have, let's say, just two impurities that are above the .05 nonreporting level for ICH, that already gets us to above .1 -- right? -- .1 and above in total unidentified impurities?

A I'm not quite following your question. Just --

Q Here, it refers to the -- I'm sorry.

Here it refers to, there are some impurities in 2006 that are referred to. And it says it shows several impurities. Not one, but several impurities.

Let's imagine there's just two for this hypothetical. At low levels, they're below the ICH identification limit of .1 -- or presumably, if they were below the .05 level -- right? -- for ICH -- in which case, you don't even have to discuss them -- that would have been mentioned.

So there are several impurities that are

below .1 but above .05. If we just have two of those, that's already going to put us greater than point .07 that you referred to in the Walsh Declaration; right?

MS. HASPER: Objection. Mischaracterizes the documents.

THE WITNESS: So since I don't know what they are, how many unidentified impurities are in that number of .07 percent, I can't say anything.

BY MR. POLLACK:

Q All right.

A I'd only be guessing, and I don't want to guess.

Q Okay. Okay.

But -- seem a little strange to you that Walsh doesn't mention this to the Patent Office in providing this Declaration that there are other impurities?

MS. HASPER: Objection. Mischaracterizes the document. Beyond the scope.

THE WITNESS: You know, I have no idea what was inside Dr. Walsh's mind and what the actual exchange was between him and the Patent Office. You know, these are individual batches that he represented as being representative.

And I think that is fair, because the analysis that I did on 121 batches of treprostinil made by the '393 are as good, if not significantly better, than these. So it's consistent. I don't think he's hiding anything. I don't think there's anything sinister going on here.

BY MR. POLLACK:

Q I mean, earlier, we were talking about the one Moriarty batch, and you were complaining that that [redacted] batch was not representative, even though it was the one that Moriarty presented in his paper. Now you're saying one batch from Walsh is representative?

A Well -- that's what he represented to the FDA, and the data I've looked at corroborates that.

Q Well, we saw earlier -- right? -- there's a [redacted] percent that's corroborated by 46 samples; right?

MS. HASPER: Objection. Mischaracterizes the document.

THE WITNESS: I mean, I haven't done the comparison. You threw, like, a spreadsheet in front of me and --

BY MR. POLLACK:

Q Do you want to do it now? We can go

through the spreadsheet, and you can check that every number is correct.

A I'll -- you're asking the questions. Not me.

Q Okay. Let's do that now. We'll put up the spreadsheet, and you can go through it and verify that each number is correct. Is that fair?

Okay.

THE REPORTER: Let's go off the record.

THE VIDEOGRAPHER: We're off the record. The time it 3:37 P.M.

(Off the record)

THE VIDEOGRAPHER: We are back on the record the. The time is 3:55 P.M.

BY MR. POLLACK:

Q Welcome back, Dr. Williams.

Before the break, we were -- you had asked to see the spreadsheet regarding the 46 values for purity from the Certificates of Analysis that we averaged and took a standard deviation of. What we've put in front of you is what's been previously marked as "Williams Deposition Exhibit 13." It's an electronic copy of the documents we were showing you before.

And you can feel free to manipulate them

on the computer, examine them, and compare them to the data you reported in your Declaration in Appendix A or any other place and verify that the calculation is correct.

MS. HASPER: Objection. Mischaracterizes the testimony.

Also, I've previously lodged an objection to the use of this electronic exhibit. I'm going to maintain that objection at this time.

And also, if counsel would permit, I'll enter a standing objection to the entire line of questioning regarding this exhibit so I don't have to keep making it.

MR. POLLACK: That's fine.

MS. HASPER: All right.

THE WITNESS: And, actually, I didn't ask to see this again.

BY MR. POLLACK:

Q Okay. You did not ask to see that again?

A I did not.

Q Let me ask you: Do -- so I had asked you -- do you trust that these calculations are correct?

A I haven't had a chance to look through them. So, no, I don't trust them.

Q Okay. Well, now you have a chance to look through them. Why don't you take a look through them and see if you trust the calculation.

A Can I use this -- so these supposedly correspond to entries on Exhibit A.

Q That's correct.

A Is that right?

Q Yes. Except we've removed the first ten as we've discussed.

A Okay. So we started there. Okay.

First of all, I'm -- I have not seen "implied impurity." That was nowhere in my charts.

Q Okay. You have seen "total related substances," though?

A Yes.

Q Okay. You'd agree with me that the -- whether you like the phrase "implied purity" or not, based on total related substances, the purity for each sample is determined by taking 100 and subtracting total related substances?

A Yes.

Q Okay.

A So this first one has a -- what the results are -- that 1.0 -- that's 1 percent -- that was in the second to last column of this; right?

Q Yes.

A And so your implied impurity is 100 minus 1, so 99. That's what that second --

Q Correct.

A -- entry means?

Q Yes.

A And that's the source document.

Q Is there another name, other than "implied purity," that you would like to use?

A Not -- no. I don't have any other fancy name for this.

Q Okay. That calculation was done correctly; right?

A Yeah. So Assay Purity -- where did that number come from?

Q That is from the original Certificate of Analysis.

A Ah. So where are those?

Q That is Exhibit 2036, which is among your --

A Is it this big, thick thing?

MR. POLLACK: Did we mark it already?

MS. HASPER: Yeah.

MR. POLLACK: Yeah. I'll give you the number in a second.

It's Williams Deposition Exhibit 7.

THE WITNESS: You don't have -- do you have a printout of this?

BY MR. POLLACK:

Q So we have --

A Making life much easier for me. Actually, with these glasses on, these are my -- not my computer glasses. These are my driving glasses.

Q A printout of the spreadsheet?

A Yeah.

Q Yes. We have --

THE REPORTER: Would this help (Indicating)?

BY MR. POLLACK:

Q If you look, there's a Deposition Exhibit 10 in your documents. Williams Deposition Exhibit 10.

A That's what this is?

So what's missing from this spreadsheet that you prepared are the individual impurities.

Q You didn't rely on the individual impurities either -- right? -- for this calculation? You used the total related substances; correct?

A For which calculation are you talking about?

Q For your calculation of the average purity.

A Oh, right. That was total related substances. But I relied on the individual impurities for my opinion that the '393 product is distinct and more pure and different.

Q I understand that. But here we're just looking at the calculation. I just want you to verify for me that the calculation we've done of the average purity is correct.

A 2036 -- okay. (Mumbling).

THE REPORTER: Sir, please don't mumble.

THE WITNESS: Okay. I'm sorry. I'm just going through this, one entry at a time.

(Brief pause while witness works with exhibit)

BY MR. POLLACK:

Q Dr. Williams, those two we haven't given you that exhibit yet -- why don't you finish the --

A The yellow? Okay.

Q Yeah. When you finish, we'll give you those two as well.

A Okay.

(Brief pause)

MS. HASPER: Counsel, while Dr. Williams

is still looking at the document, I'd like to take the time to make this statement on the record that, previously, you made the representation that the electronic document was the same as the printouts that had been provided earlier and marked as Exhibits 8 through 10; is that correct?

MR. POLLACK: Yes.

MS. HASPER: Okay. Having reviewed at least Exhibit 10, I see several -- at least a few changes -- differences between the electronic version that you provided to me and the document.

So I'm going to be maintaining my objection to the entirety of Exhibit 13.

THE WITNESS: So I did all the ones from here. 2036.

BY MR. POLLACK:

Q And you have two more to check; right?

A I think there were four -- four.

Q Which ones do you still want to check?

A So there's 20101, 20201, and 20302 and 20303 -- oh, wait. The -- oh, these, I can get from here. I'm sorry.

Q Okay.

A Two, yeah. Let me pull these off here while I've got this document open.

Q Yeah.

(Brief pause)

A Okay. Just the remaining two.

MR. POLLACK: Okay. We're going to mark as Williams Deposition Exhibit 21 a document known in the case as "Exhibit 2053."

(Exhibit 21 marked)

BY MR. POLLACK:

Q Dr. Williams, is this the Exhibit 2053 you relied on in listing batch data in your Appendix A?

A Yes.

(Brief pause)

All right. So I've finished checking them.

Q Okay. Let the record reflect you spent more than 30 minutes checking them.

A Okay.

Q Okay. And you checked every single data point; right?

A I did.

Q Okay. You didn't spot-check them. This is a check of every single point?

A Right. Yes.

Q Okay. What -- did you see any mistakes

or differences?

A Yes.

Q Okay. Which ones did you see?

A So entry No. 16, which was UT lot -- UT15-000901. And the discrepancy apparently comes from the actual batch record from Exhibit 2036, has total related substances at .5, and thus the -- your implied purity is 99.5 instead of 100. And I think it's because on the other document -- which was a summary at page 19 --

Q 2053?

A Right. -- 2053 at page 19 for that lot 901, it's listed as .05 percent. So this is probably a typo (Indicating); and this is probably accurate (Indicating), the original source document.

Q Let's -- take a look at the entry on here for -- this is lot -- which one? UT15-00901?

A Yes.

Q Okay. Let's just take a look at -- you're referring to this number here, the .1 (Indicating)?

A Yes.

Q Okay. If we look there, do you see up there at the top of the screen that says, ".05"?

A Well, I actually -- my -- I can't see

that.

Q You can look -- why don't you take a look up there on the big screen.

A Okay.

Q Can you see it there?

A Yeah.

Q Okay. And so you see that on Excel, we set the number -- the digits with one decimal place -- right? -- on the printout?

A Okay. So where you got that from was Exhibit 2053, but the source document for that shows that it's 0.5.

Q 0.5 or 0.05?

A 0.5.

Q Oh.

A While you're checking that, could I take a short break?

MR. POLLACK: Sure.

THE VIDEOGRAPHER: We are off the record. The time is 4:44 P.M.

(Off the record)

THE VIDEOGRAPHER: We are back on the record. The time is 4:48 P.M.

MR. POLLACK: Okay.

///

BY MR. POLLACK:

Q So we just -- you just said that entry 16 should be changed to .5; is that right?

A Yeah, I believe that's correct.

Q Okay. So should we change that here, this being the spreadsheet and see what we get? Is that fair?

MS. HASPER: I'm just going to reiterate my standing objection to this entire line of questioning using this document.

MR. POLLACK: Okay.

BY MR. POLLACK:

Q So now it says, ".5"; right? Fair enough?

A Okay.

Q Okay.

A You have to change the number below it.

Q Oh, okay. There you go.

All right. Any other changes?

A Yes.

Q Okay.

A So I found for entry 33 --

Q Okay.

A -- UT15-020202 --

Q Okay.

A -- what was reflected -- I was looking at the 2036 document. Let me double-check that.

Page 62, 63. The total related substances is 0.2 percent.

Q And what does it say on this document?

A 0.6. Again, that may be --

Q Row 33, you're saying?

A Yes.

Q Okay.

A I didn't cross-check to this bigger spreadsheet, which is maybe where that number came from. So that's -- yeah. So the .6 is on here (Indicating).

Q Okay. So we should change that number, too, from .6 -- do we know which one is correct? Whether it's 2036 or 2053?

A Well, it's -- I think -- this is a summary spreadsheet. So I -- I think it's probably better to rely on the Certificate of Analysis.

Q Okay. So you're saying, this value, I should change from .6 to .2?

A Yes.

Q Do you want to look on the screen?

Okay. Shall I do that?

Any other changes?

A Yes. I also found errors on entry 43, UT15-030401.

Q Okay.

A And --

Q Okay. What should the value be in your view?

A On the 2053 document, it has .5.

Q Okay.

A And on the Certificate of Analysis, it's .6.

Q Okay. Shall we change that one to .6? Row 43? By the way, so far, all these errors are due to taking numbers from 2053 instead of 2036; is that right?

A That seems to be the case.

Q Is that change that I made, is that now correct? If you want to look up at the screen.

A The assay purity is 100.1 instead of 100.3.

Q For 43? Let me check -- verify with you making that change. Is it correct now?

A Yes.

Q Okay.

A And entry 55, UT-15031201 -- the Assay Purity is 100.5, and it says 100.4.

Q Okay. So do you want to do this change, or do you want me to do it?

A You operate the computer.

Q Okay. So that's row 55? If you look on the screen with me, can you just verify that I'm making this change correctly?

A Yes.

Q Okay. Okay. All right. Were there any other changes?

A Not -- not that I could find.

Q Okay. Now -- so now we've made all those changes to the spreadsheet.

Can you verify for me what -- that the average and standard deviation were calculated correctly? We can show you here how that's done. The average.

A Right. It says, "[redacted]."

Q Do you see up in the calculation section how that's calculated up at the top?

A Yeah. It's just summed and averaged in Excel.

Q Is that the correct way to do it?

A Yeah.

Q Okay. Do you have any issues, then, with this calculation now that we've made the corrections

you pointed out?

A No.

Q Okay. So you'd agree with me that the -- for the HPLC assay, the value of [redacted] for the average is correct?

A Appears to be.

Q Any qualms or disagreements about it?

A No.

Q Okay. And just checking the -- just want to make sure I've calculated the standard deviation correctly. You see the calculation formula up there?

A Yes.

Q Okay. Is that a correct way to calculate the standard deviation in Excel?

A I'm not familiar, because I don't do that, so --

Q Okay. You haven't used that function, standard deviation, in Excel?

A No. I just don't do that in my normal course of work. So --

Q Okay. Okay. Any reason to doubt that that's the standard deviation?

A No.

Q Okay. So now that we've -- now that

you've checked every single data point and looked at the calculations, you agree with me that this calculation of the purity is fair and accurate?

A The overall purity. But this does not reflect impurity profile.

Q Yeah. I understand. I'm just talking about the overall -- the level of purity.

A Yes.

Q We don't have anything even in this chart about the impurity profile; correct?

A That's right.

Q Okay. And so it is correct that for the samples from Exhibits 2036 and 2033, the 46 samples, the average level of purity was [redacted] percent for the samples made under the Moriarty process?

A Yes.

Q Okay. That [redacted] value, that is consistent with the value that Moriarty reports in his Journal of Organic Chemistry article?

A They're the same numbers.

Q Turn back to your Declaration. I'd like you to turn to paragraph 63 in there. That's Williams Deposition Exhibit 2. And I think here you're giving an opinion on the meaning of the word "product"; is that right?

A Yes. In the context of the '393 patent.

Q And you submitted some articles that you wrote where you used the term "product"; is that correct?

A Yes.

Q Okay. None of those articles are anything to do with treprostinil and everything else in the '393 patent?

A No. Different molecules.

MR. POLLACK: I'm going to mark as Williams Deposition Exhibit 22 a document attached to Dr. Williams's Declaration that was known as "UT Exhibit 2028."

It's an article by Dr. Williams in the Journal of Organic Chemistry entitled, "Synthetic Studies on Et-743, Assembly of the Pentacyclic Core and a Formal Total Synthesis."

(Exhibit 22 marked)

BY MR. POLLACK:

Q Now, this is one of the articles that you rely upon for your use of the term "product"; correct?

A Yes.

Q And I believe the use of the term "product" that you rely on is on the very first page

of Williams Deposition Exhibit 22. And it reads: "The scarcity of a natural product from marine sources renders Et-743 an important target for synthesis."

Is that the sentence you were relying on?

A That's what I quoted in the Declaration.

Q And so then what it's referring to -- "marine sources," what does that refer to?

A So Et-743 comes from a marine tuna kit, and there's a microbial consortium that is a symbiotic host in the tuna kit that biosynthesizes this molecule. So this natural product is the product of a biosynthetic series of chemical reactions.

Q Okay. This is, though, a -- this is a product that's produced by a biological source; correct?

A Yes.

Q All right. It's not a -- it's not a chemical reaction; this is a biological reaction; correct?

A They're still reactions, so it's the product of, ultimately, chemical-bond formation. So it's still understood by a person skilled in the art of a product of chemical reactions.

Q Okay. But they're distinguishing marine sources from other kinds of sources here; right? You are, actually.

A Yes. That because it comes from a marine source, it's very expensive and very difficult to isolate sufficient quantities of this molecule from a natural source for clinical use.

Q Right. And what you're proposing in here is, you can create this molecule from a chemical reaction?

A Yes. And that's what we did.

Q Yeah. So in this article, the word "products" is used a little more broadly than the typical, or your claim, that it's only the product of chemical reaction, isn't that so?

A No.

Q No? That's not your view?

A No.

Q No?

So here where it distinguishes getting the product from marine sources and instead says that the product can be gotten from chemical sources, that's not distinguishing?

A Well, the use of the word "product" is still the result of chemical reactions that produce

that molecular entity, whether it be biochemical reactions or laboratory chemical reactions.

Q Let me ask you this: A can of tuna fish -- that's a product from chemical reactions, ultimately; right? At least the way you're using it.

A No. A can of tuna fish is a much different substance. I wouldn't make the equation between a can of tuna fish and the product of a chemical reaction.

Q Okay. But you've heard a can of tuna fish referred to as a "product"; right?

A Yeah. They put salt, and oil, and other things in there. You know.

Q So that wouldn't be a legitimate use of the word "product" there, would it?

A Well, "product" can be used in -- in different contexts; okay? Just like the word "compound" can be used in different contexts in chemistry.

Q Okay. But the word "product" is broad enough -- right? -- to encompass all kinds of products?

A It depends on the context.

Q It can encompass biological products.

A As I just said, it depends on the context in which the word's being used. In the context of the '393 patent, it's very clear that the word "product" is the result of chemical reactions.

Q You know, I was wondering about that, because you say here in your Declaration -- could you turn to paragraph 30 in your Declaration?

A (Complies).

Q Now, here, you say, "I have also been informed by counsel that the claims of the '393 patent are product-by-process claims."

You wrote that; right?

A Yes.

Q Okay. And in that phrase there where it says, "product-by-process claims," that's not referring to necessarily a chemical reaction; right? That's a legal phrase there.

A Yes. But a person skilled in the art, you know, who would want to understand what a product by process is, we're talking about in this case a chemical process. Chemical reactions that produce the product.

Q Yes, but this -- well, let's go on in your paragraph.

"I have also been informed by counsel

that when evaluating the validity of a patent claim, the 'product'" -- and "product"'s in quotes; right?

A Hmm-hmm.

Q This is defining what a product is -- right? -- for this purpose?

A Yes.

Q That's why it's in quotes; right?

A Yes.

Q Yes.

"The product of product-by-process claims must include structural and/or functional differences over the prior art, even if they are not explicitly claimed."

I read that correctly?

A Yes.

Q That's a different definition of "product" than your chemical reaction, isn't it?

A No.

MS. HASPER: Objection. Mischaracterizes the document.

BY MR. POLLACK:

Q No? Now, do you see the word "chemical reaction" in that phrase?

A No. But it's -- we're still talking about a chemical process. That's what this patent's

about.

Q But this paragraph's not talking about a chemical process -- paragraph 30?

MS. HASPER: Objection. Mischaracterizes the witness's testimony and the document.

THE WITNESS: It is, because I'm talking about the claims of the '393 patent are product-by-process claims. So when the word "product" is used in the '393 patent, we're talking about the result of the chemical reactions, the chemical process that's described in the patent and claimed in the patent.

BY MR. POLLACK:

Q Let me ask you this: Do you know this -- do you know that a product-by-process claim is invalidated by a product made by other processes? Did you know that's the law?

MS. HASPER: Same objection. Also seeks a legal conclusion.

THE WITNESS: I'm not a lawyer.

BY MR. POLLACK:

Q Did you know that?

A I'm not a lawyer, and I'm, you know --

Q I'm not asking if you're a lawyer. I'm asking if you know it. If you don't know it, just

say you don't know it.

MS. HASPER: Same objections.

THE WITNESS: Well, when I was instructed by counsel, was that -- and there are many product-by-process patents out there that are valid. I've been involved in other litigation. And if the product over the prior art has structural and functional differences that are unique, then you can still get a product-by-process patent on an already known substance.

BY MR. POLLACK:

Q Okay. But what I asked you was: Do you understand -- right? -- that a product-by-process claim is invalidated by any product that's the same as the product claimed, regardless of what process is used?

Did you know that was the law?

MS. HASPER: Same objection. Also asked and answered.

THE WITNESS: So, again, my understanding is that if the product of the new process can be shown to have structural and functional differences over the prior art product, it's patentable.

BY MR. POLLACK:

Q Hmm-hmm. I understand that. I was just

asking if you understood this other thing -- okay? -- which is in my question. Listen to my question; okay?

My question is: Did you understand that under the law of product-by-process claims, any product, regardless of what process it's made from, will invalidate a product-by-process claim, so long as the products are the same?

Did you understand that? Yes or no?

MS. HASPER: Same objections.

THE WITNESS: Yeah. My understanding is, the products can be shown to be identical. That's not the case here.

BY MR. POLLACK:

Q Okay. But if the products are identical, regardless of process, it will invalidate the claims; is that fair?

MS. HASPER: Same objection.

BY MR. POLLACK:

Q Is that your understanding?

A So I'm not a lawyer, and I'm not going to come to a legal conclusion.

Q Yeah. I'm just asking what your understanding is.

A I've already told you my understanding.

Q What is it?

MS. HASPER: Same objection.

THE WITNESS: Would you like to reread my answer into the record?

BY MR. POLLACK:

Q Sir, you need to answer my question.

A I did. I already answered it twice.

Q No. I'm asking you to answer it now.

MS. HASPER: Same objection.

THE WITNESS: Okay. My understanding is that a product-by-process patent is valid if the new process produces a product that's structurally and functionally different than the prior art product. That's my understanding.

BY MR. POLLACK:

Q Okay. I'm asking you, though, about what will invalidate a product-by-process claim; okay? So listen to my question.

Is it your understanding that a product that is the same as the product made by the claimed process in the prior art will invalidate the claim, regardless of what process was used to make that product?

Is that your understanding?

MS. HASPER: Same objection.

THE WITNESS: I do understand that.
BY MR. POLLACK:
Q Okay. And so that -- that's the legal definition of "product" in "product by process"; right? What we just discussed?
A Wait. Ask me that again. What was that?
Q Yeah. That description you just gave, that's a legal definition of "product" in the phrase "product by process"; right?
MS. HASPER: Objection. Calls for a legal conclusion.
THE WITNESS: And what was the definition again?
BY MR. POLLACK:
Q Oh, that a prior product will invalidate a product in a product-by-process claim, if it's the same, regardless of which process is used?
MS. HASPER: Objection. Calls for a legal conclusion. Mischaracterizes testimony.
THE WITNESS: I mean, I've heard that. But, again, my understanding with regard to this matter is that if the product has structural and functional differences over the prior art, the process patent can be valid.
///

BY MR. POLLACK:

Q Yeah. Okay. But you'd agree with me that legal definition is different than the definition you typically use in your papers and elsewhere; is that correct?

MS. HASPER: Same objection.

THE WITNESS: The legal definition of the word "product" or --

BY MR. POLLACK:

Q Yeah, of the word "product."

MS. HASPER: Calls for a legal conclusion.

THE WITNESS: I think this is very context-dependent again.

BY MR. POLLACK:

Q Well, when you're using the word "product" -- and I think you told me it's the product of a chemical reaction; right? Is that correct?

A Yeah. When I'm -- when I'm doing organic chemistry, and synthesizing molecules and doing reactions, there's a reactant and then a product. And the product is the result of the chemical reactions used to assemble that molecule, the product.

Q Right. You don't use that term "product" to refer to: Oh, well, I can have a product that's done by a different chemical reaction -- you wouldn't call that the same product?

MS. HASPER: Objection. Mischaracterizes testimony.

THE WITNESS: You've now lost me on -- I'm really not following you.

BY MR. POLLACK:

Q If you made a product using a different chemical reaction, would you consider that to be the same product as you used the term "product"?

A Your question is not clear to me.

Q What's unclear about it?

A Well, I just don't understand it. So perhaps you need to ask me a better question.

Q Why don't you tell me what you don't understand, sir.

A Your question just didn't make sense to me. I didn't follow it.

Q Which word didn't you understand?

MS. HASPER: Objection. Mischaracterizes the witness's request for clarification.

THE WITNESS: You want to read the question back, perhaps?

MR. POLLACK: Yes. Why don't you read the question back.

THE WITNESS: Since you're apparently not willing to rephrase it so I can understand what you're trying to ask me.

(Record read by the reporter as follows:)

"QUESTION: If you made a product using a different chemical reaction, would you consider that to be the same product as you used the term 'product'?"

THE WITNESS: Okay. So my understanding as a chemist is that -- you know, so my laboratory synthesized this marine natural product, Ecteinascidin-743, and another laboratory synthesized the same molecule by a completely different set of reactions.

BY MR. POLLACK:

Q Okay.

A And chemists would be able to draw the structure and say: Oh, the target -- the desired target molecule is this structure.

Q Okay.

A But we also understand that, because

different chemical processes, reactions were used to make those, that the product that my lab got is going to be distinct from the product that another lab gets because of characteristic impurities that come along as a result of the different reactions that were used, the different starting materials, intermediates, and so on, of the two different processes.

Q You're saying, if we looked at another paper by one of your colleagues making the same chemical, they would describe that as a different product?

A No. Chemists -- you know, in the art, another paper making the same molecule would say: And the final product Ecteinascidin-743 was purified by blah, blah, blah.

They wouldn't call it a different name. They'd say, you know: The product Et-743.

But inside the understanding is that you know that because a different type of chemistry, different types of reactions were used, that the impurities that come necessarily with any -- anything in chemistry -- there's no such thing as 100.0 percent pure anything -- okay -- in chemistry. Everything has some impurities.

And so in chemical synthesis, there are going to be signature impurities that come as like a fingerprint -- a unique fingerprint of that process that was used to make that particular molecular entity; okay.

So even though two papers may say the same phrase, you know, "The product Et-743," "The product Et-743," that does not mean they're exactly the same, because they were made differently, and their impurities would be made differently.

THE VIDEOGRAPHER: Counsel, three minutes to go on this media.

MR. POLLACK: Oh, three minutes? Why don't we take a break.

THE VIDEOGRAPHER: This ends Media No. 3 in the deposition of Robert M. Williams, Ph.D. we're off the record. The time is 5:16 P.M.

(Off the record)

THE VIDEOGRAPHER: This begins Media No. 4 in the deposition of Robert M. Williams, Ph.D. We're back on the record. The time is 5:24 P.M.

BY MR. POLLACK:

Q Go back to your Declaration, Exhibit 2. If you could turn to page 13, paragraph 34. There, you record Dr. Winkler's opinion about a person of

ordinary skill in the art?

A Yes.

Q Okay. I don't know if you were told this, but the other expert for United Therapeutics, Dr. Ruffolo -- he believed that a higher level of ordinary skill in the art would be more appropriate. If you like, I can show you his deposition or just read to you what he said?

A A higher level than --

Q Than Dr. Winkler.

A Than Dr. Winkler's?

Q Yes. Do you agree?

A Well, I don't recall what his -- Dr. Ruffolo's definition was.

Q Let me tell you his definition. If you want to see his deposition, I can give you that as well.

A His deposition or his Declaration?

Q His deposition. This was in his deposition.

Did you read his deposition?

A No.

Q Okay. Would you like to see the deposition, or would you like to just hear it from me and let me know if you agree with what he said?

A Okay. You can go ahead and read it.

Q Okay. He said that he considers the patent to be a complex chemistry, and he would have changed what Dr. Winkler wrote to be a Ph.D., he would not -- he would take out the master's degree. And he also said -- so would set the level higher.

And he also said that the number of years of experience -- he would add several years of experience in the pharmaceutical industry on top of the Ph.D.

I was just wondering if you agreed with that or had a different opinion?

A Well, it sounds substantially very similar to both Dr. Winkler and my definition. Dr. Winkler says, a master's degree, or a Ph.D. degree, or closely related field.

Q Hmm-hmm.

A Alternatively, a person of ordinary skill would include an individual with a bachelor's degree, and at least five years of practical experience, medicinal or organic chemistry.

And my opinion wouldn't change if I adopted Dr. Winkler's or Dr. Ruffolo's that you just read to me. And I think the one I said was also very appropriate.

Q Okay. I mean, do you agree with Dr. Ruffolo that it should be set higher; it shouldn't include the master's or the bachelor's?

A I don't necessarily agree, because I also said, alternatively, the POSA may have had a lesser degree in one of those fields with correspondingly more experience.

Q Okay.

A So I also allowed for less than a doctorate.

Q Okay.

A So I think we're all more or less in the same level of skill.

Q All right. I only ask you because Dr. Ruffolo seemed very concerned about this; that the level was too low, and I was wondering if you agreed or not?

A Perhaps he misunderstood what Dr. Winkler wrote.

Q Okay. I'd like to have you pull out, again, the Phares reference.

MS. HASPER: Counsel, can you remind us what number that was?

MR. POLLACK: I will. The Phares reference which used to be called "Exhibit 1005" is

now Williams Deposition Exhibit 16.

BY MR. POLLACK:

Q And while you're searching for that, can you also find Williams Deposition Exhibit 12, the Moriarty reference.

Do you have -- do you have Deposition Exhibits 12 and 16 in front of you?

A I do.

Q Okay. So the Phares reference, that was published in 2005; is that right?

A Yeah, 27 January 2005.

Q Okay. And the Moriarty reference, Deposition Exhibit 12, it was published in 2004; correct?

A Yes.

Q Okay. So am I right that at the time that the Phares reference was published, a person of ordinary skill in the art would have been familiar with the Moriarty reference?

A Yes. It was already published.

Q And am I right that at that time in 2005, it was understood that the Moriarty reference was the best way at that time to make treprostinil; is that fair?

A Yes. I think that's correct. I would

agree.

Q Okay. So a person of ordinary skill in the art in 2005 reading the Phares reference, that person would know the best way to make treprostinil is the Moriarty method, Exhibit 12; right? Is that fair?

A I think that's fair.

Q Okay. So a person of ordinary skill in the art, if they wanted to make treprostinil diethanolamine salt in 2005, following the Phares method, their best way of doing that would have been to follow Moriarty Deposition Exhibit 12; is that fair?

A Well, it's interesting that the Phares reference doesn't reference Moriarty.

Q Okay. That's not what I asked you.

Would a person of ordinary skill in the art, familiar with Exhibit 12 and Exhibit 16 -- would they follow the Moriarty reference? Would that be the best way to do it?

A Well, it was certainly in the literature. The Phares reference actually references two other ways to make treprostinil that are significantly inferior in my opinion.

Q Inferior to Moriarty, even?

A Yes.

Q Yes. And a person of ordinary skill in the art would have known in 2005 that those other methods were inferior to Moriarty; is that fair?

A I guess -- we're assuming that the person of ordinary skill had done a detailed analysis of all the different ones.

Q Yes?

A And that's the end of my sentence.

Q Oh, okay.

Well, I mean, did people who were, you know, doing research on treprostinil at that time, do you think they would have read a paper in the Journal of Organic Chemistry?

A Sure. It's a very well-known journal.

Q It's one of the most prestigious; right?

A Yes.

Q I mean, you have grad student; right? When you tell 'em to go out and synthesize stuff, they do a basic literature research; right?

A Sure.

Q You don't think would have missed this article in the Journal of Organic Chemistry; right?

A No.

Q Okay. So a person of ordinary skill in

the art -- they're similar to graduate students or some of the other people you've taught; correct?

MS. HASPER: Objection. Mischaracterizes testimony.

BY MR. POLLACK:

Q Is that fair?

A What was the question again, please?

Q Your graduate students or some of the other students you've taught, they have a level similar to a person of ordinary skill in the art; is that fair?

MS. HASPER: Objection. Mischaracterizes testimony.

THE WITNESS: I guess it depends on what year graduate student. First-year graduate students, I would consider to be below the level of ordinary skill. And a 5th- or 6th-year graduate student would probably meet the minimum bar. They don't have a Ph.D. yet.

BY MR. POLLACK:

Q Let's take one of those 5th-, 6th-year graduate students. You would of expect them if you assigned them to make treprostinil, they would find the Moriarty reference; right?

A It's easy to find.

Q And you would assume that they would follow this Moriarty reference the best way to make treprostinil if you asked them to make treprostinil diethanolamine salt in 2005; right?

MS. HASPER: Objection.

THE WITNESS: Well, I would certainly want to go over all the options in the literature before I started spending time in chemical grant money on them to do that.

BY MR. POLLACK:

Q Okay. Right. But what method would you have advised in 2005 to your graduate students?

A What? If I -- if I --

MS. HASPER: Objection.

THE WITNESS: -- needed to make treprostinil in 2005?

BY MR. POLLACK:

Q Yes.

A I certainly would have picked Moriarty paper.

Q Yeah. And would you say that your 5th-, 6th-year graduate students, they'd be somewhat capable of making that conclusion, as well, that they would use the Moriarty paper?

A Possibly.

Q Possibly?

At least the ones who are actually getting their Ph.D.s, would they be able to get the Moriarty paper?

MS. HASPER: Objection.

THE WITNESS: You never know what a graduate student is going to come up with, as their favorite way of doing something.

BY MR. POLLACK:

Q But, you know, on average, a typical person of ordinary skill in the art, typical graduate student, they would have found the Moriarty paper and used that technique to make treprostinil in 2005?

MS. HASPER: Objection.

THE WITNESS: It was in the literature. It wasn't buried in some obscure journal. So, sure, it was available.

BY MR. POLLACK:

Q That was a "yes" to my question, I think?

A Yes.

Q Okay. I want to talk a little bit about the Kawakami reference. You recall that reference; right?

A Yes.

Q Why don't we mark the Kawakami reference.

THE REPORTER: 23.

MR. POLLACK: I'd like to mark two exhibits. Exhibit 23 is going to be the original Kawakami reference in Japanese, just so you can check the figures. That's what's known as "Exhibit 1006" in the proceeding.

(Exhibit 23 marked)

MR. POLLACK: And Exhibit 1007 is an English translation of the Kawakami reference.

THE REPORTER: And that's Exhibit 24.

MR. POLLACK: 24. Yes. And that's Exhibit 24.

(Exhibit 24 marked)

MS. HASPER: And is what you've handed me 26 -- 23 or 24?

MR. POLLACK: That's 24. And the Japanese is 23.

BY MR. POLLACK:

Q And Exhibits 23 and 24 are the Kawakami reference discussed in your Declaration?

A Yes.

Q Okay. And then I'm going to mark as Exhibit 25, a pair of drawings that we made of the compound in the Kawakami reference -- the preferred

compound, and treprostinil. I just want you to review them and make sure the drawings are okay.

MR. POLLACK: This will be Exhibit 25.

(Exhibit 25 marked)

BY MR. POLLACK:

Q So feel free to use, you know, Moriarty or any other reference you like and the Kawakami reference.

And can you verify for me that these are fair and accurate drawings of treprostinil and Kawakami.

A (Examining documents) Well, treprostinil is definitely correct.

Q Okay.

A The structural rendering you have for Kawakami does not show the stereochemistry of the bicyclic portion.

Q Okay. But other than that, is it correct?

A Yes. That's one of the two geometrical isomers described in Kawakami.

Q Okay. And other than I didn't show on here that the ring is below the page -- the upper five-member ring-- this is a correct drawing of the structure of the Kawakami compound?

A Yes.

Q Okay. So earlier, you and I were discussing the meaning of the term "product." Do you recall that discussion?

A Yes.

Q Okay. And I think we were talking about how other chemists use the term "product." Do you remember that?

A Yes.

Q Okay. And you said: Well, you know, chemists might make a product by a different process from yours -- from let's say the product you made in your exhibit. And in their papers, they would say: Oh, yes. We made the product Ecteinascidin -- right?

A Ecteinascidin.

Q They might say that they made the product Ecteinascidin-743, but they may have used a different process; is that right?

A Yes.

Q Okay. So in chemists' ordinary use of the term "product," is it fair to say that when they're using it in papers and other places, they often don't point out that the impurities or other things are different, because the process was

different in using the term "product"?

A I don't agree with what you said.

Q Why not?

A Because chemists use the word "product" in two different contexts, routinely.

Q Okay.

A There's a molecular structural context; okay? So if I said to one of my students, "Show me the product of this reaction on my blackboard."

And they'd write a structure like Ecteinascidin-743; okay?

Q Okay.

A And if I said, "Bring me a sample of the product that you just made in the lab," they would bring me a bottle, a flask, a vial of a real-world substance that, hopefully, contains mostly what we were trying to make, and it would also have its characteristic impurities.

So there's the molecular structural context, and then there's the real-world substance context of the word "product." And chemists know what you're talking about when you use the word "product" in those two different contexts.

Q Okay. Let me ask you: In the '393 patent, do you see any place where the '393 patent

says: I'm going to define the word "product" for this patent?

Do you see that anywhere in there?

A I don't recall it being defined, other than its plain, ordinary meaning as it's understood, as I just explained.

Q Did you see anything in the prosecution history where the term "product" was defined?

A I don't recall. Prosecution history is huge. I don't remember everything in there.

Q As you sit here now, you don't recall --

A I don't recall if that was -- that came up.

Q If it's okay, we're going to take a break for a couple minutes.

A Okay.

THE VIDEOGRAPHER: We're off the record. The time is 5:42 P.M.

(Off the record)

THE VIDEOGRAPHER: We are back on the record. The time is 6:04 P.M.

BY MR. POLLACK:

Q Dr. Williams, since the deposition started today, have you had any discussions with counsel regarding, you know, the substance of this

case, or this deposition, or anything about treprostinil or about any redirect testimony with -- with counsel?

A No.

MR. POLLACK: All right. Other than that, no further questions. Thank you for your time.

EXAMINATION

BY MS. HASPER:

Q All right. On redirect, Dr. Williams, you noted earlier today when looking at some of the exhibits that were introduced by Mr. Pollack an error in Appendix B of your report; is that correct?

A Yes.

Q And have you previously asked counsel to correct this error and create updated versions of Appendix B?

A Yes. We did that this morning.

Q Yes. And I'm going to hand what I guess --

THE REPORTER: 26.

MS. HASPER: I'm going to hand to be marked as Exhibit 26 a corrected version of both Appendix B and the summary chart table from

paragraph 94 of Dr. Williams's report.

(Exhibit 26 marked)

BY MS. HASPER:

Q Dr. Williams, if you take a look at this for a moment, is this the corrected version of Appendix B and the summary chart from paragraph 94 of your Declaration that you instructed counsel to prepare and approved before this deposition?

A (Examining document) Sorry. I'm just checking against my -- yes. This is the correct -- the corrected one.

Q And just for the record, the difference between Appendix B in this document and Appendix B, as it appears with your report, is the omission of batch or sample [redacted]; is that correct?

A That's correct.

Q And that slightly changes the averages on both the -- for a few of the values on both the chart in Appendix B and the summary chart in paragraph 94 of your Declaration; is that correct?

A Yes.

Q And can you just note what those changes are and we can just look at the summary chart from paragraph 94 so you can note what the changes are.

A Okay. So these are the '393 patent

process impurities one, two, three -- fourth column from the left, the number changed from 0.0642 to 0.0643.

And three more columns over, the ethyl ester changed from 0.1207 to 0.1208. And then the total related substances changed from 0.2936 to 0.2944.

Q Thank you, Dr. Williams.

And just to confirm, for both Appendix B and Appendix A, those were created using all of the batches or samples of treprostinil that you were able to find?

A Yes.

Q And there was no selection or additional searching for particular type of batches that you're aware of?

MR. POLLACK: Objection. Leading.

THE WITNESS: No.

BY MS. HASPER:

Q If you can please get back out the development report that was previously marked as Exhibit 11.

A I have it.

Q And if you can also get out in front of you the '393 patent. And that was previously marked

as Exhibit 3 to your deposition.

A Okay. I have it.

Q Okay.

MR. POLLACK: Doctor, just give me one second.

MS. HASPER: Gonna dig for your own copies?

MR. POLLACK: Yeah.

MS. HASPER: All right.

BY MS. HASPER:

Q If you could just look at the face of the '393 patent.

I'm sorry. I'm wrong. I wanted you to get out the '117 patent. My apologies. And that was what was previously marked as Exhibit 4.

A I have it.

Q Now, are you aware, from your own history having patents, that a patent may claim priority to earlier filed applications or -- or be the utility or provisional applications?

A Yes.

MR. POLLACK: Objection to form. Lack of foundation.

BY MS. HASPER:

Q And do you see on the first page of the

'117 patent the section that's -- that's titled, "Related U.S. Application Data"?

A Yes.

Q And do you see that that lists a number of patent -- previous patents or applications of which the application which matured into the '117 patent is a divisional, or continuation -- or a continuation in part?

A Yes. I see that.

Q Do you see that the earliest date listed there is for an application No. 08-957736 filed on October 24th, 1997, now abandoned?

A Yes, I see that.

Q Okay. Can you turn in Exhibit 11 to page 25.

Now, earlier today, Mr. Pollack asked you to look at the dates of manufacture for some of the lots that were included in Appendix A of your report, including starting with lot LRX97J01 that is listed on this page. Do you see that lot?

A Yes.

Q And do you see the date of manufacture on that lot?

A October 1997.

Q Yeah. Now, earlier today, Mr. Pollack

asked you whether or not that lot or any of the lots listed to its right on this chart could have been made using the Moriarty process, based on the publication date of the Moriarty article in 2004 or its submission date in 2003. Do you recall is that?

A I do recall that.

MR. POLLACK: Objection to form. Mischaracterizes.

BY MS. HASPER:

Q Looking now at the priority information for the '117 patent and the dates listed therein under your related U.S. application data and looking at the manufacturing dates for these lots, do you believe that these lots could have been made using the Moriarty process?

MR. POLLACK: Objection. Cause of action.

THE WITNESS: Yes. So that -- I was actually very confused by that, because counsel represented to me that the development batches were made by Moriarty. And I, of course, accepted that as being correct.

And so I got confused by the -- I forgot about this earlier application. So indeed, those lots could have -- I believe, were made by the

Moriarty process.

BY MS. HASPER:

Q And I'll just follow up on one point, you know that previously -- and you can still see it here on this document above -- that the manufacturer for those is either Steroids or SynQuest and the subscript 5 notes that Steroids is a company that is now known as SynQuest. Do you see that?

A Yes.

Q And you also know that Steroids, or SynQuest, to your knowledge, was a contract manufacturer for United Therapeutics; is that correct?

MR. POLLACK: Objection. Leading.

THE WITNESS: Yes. That's my understanding.

BY MS. HASPER:

Q Okay.

A Actually, I remember that clearly now from the previous trial.

Q Do you remember anything else about Steroids, or SynQuest, and their relationship to either United Therapeutics or Dr. Moriarty?

A I don't recall the relationship off the top of my head.

Q Okay. Do you know what Dr. Moriarty's relationship to Steroids or SynQuest was?

MR. POLLACK: Objection to form. Lack of foundation.

THE WITNESS: I'm trying to remember.

Getting back to the -- I seem to remember that Dr. Moriarty was either a consultant and/or a founder of Steroids.

BY MS. HASPER:

Q So it's your belief that Dr. Moriarty was associated with Steroids, Ltd.?

MR. POLLACK: Objection. Leading and mischaracterizes.

THE WITNESS: My vague recollection tells me that that's -- that there was such a relationship, as I recall.

BY MS. HASPER:

Q Okay. Thank you. I don't want to test your memory too much. I just want to see what you did recall.

If you can look at a couple pages earlier in this same document to page 22 of Moriarty Deposition Exhibit 11.

A Page 22 numbered at the bottom?

Q Yes. The number where it says, "P. 22,"

just sort of off-center at the bottom.

A Yeah. Got it.

Q Do you see the section here that is headed, "Total Related Substances"?

A Yes.

Q And do you see where underneath that says that, "Total related substances in the drug substance is based on the sum of 1AU90, 2AU90, 970W86, 3AU90, UT15 methyl ester, UT15 ethyl ester, 750W93, 751W93, and total unidentified impurities."

Did I read that correctly?

A Yes.

Q Does that comport with your understanding of what total related substances indicates in the batch records and other documents that you have reviewed for this case?

MR. POLLACK: Objection. Leading.

THE WITNESS: Yes. And that's exactly what I said when counsel asked me about what my understanding of total related substances was. I said it was the known impurities which are listed, and the total unidentified impurities.

BY MS. HASPER:

Q Okay. Thank you. You can put away this document.

Now, if you can get out the '393 patent that's Williams Deposition Exhibit 3 and the Phares publication. That's Williams Deposition Exhibit 16.

A Okay. So the '393 and Phares?

Q Yes.

A Okay.

Q In Phares, if you will open to page -- it's 42 of the exhibit, but as we noted earlier, it's page 40 of the document. So the bottom-most numbering is page 42, but there's also a number 40 in the middle of the page.

A Yes.

Q This is a scheme that you were discussing earlier with Mr. Pollack; is that correct?

A Yes.

Q Can you open up the '393 patent to claim 9 from the second to last page of the claims at columns 19 through 20.

A I'm there.

Q Now, if you'll look at claim 9, step (a). Step (a) -- am I correct in reading, "It requires calculating a compound of formula 5 with an alkylating agent to produce a compound of formula 6"; is that correct?

MR. POLLACK: Objection. Leading.

THE WITNESS: Yes. That's correct.
BY MS. HASPER:
Q And then in column 20, it depicts the structures for both compound 5 and compound 6; is that correct?
MR. POLLACK: Objection. Leading.
THE WITNESS: Yes. That's correct.
BY MS. HASPER:
Q Now, looking at the structures in the scheme on page 42 of Phares -- that's 42 of the deposition exhibit -- you indicated earlier today -- please confirm if this is correct -- that structure 11-B, where an R is H, is the enantiomer of structure 5; is that correct?
MR. POLLACK: Objection to form. Leading.
THE WITNESS: Yes. I believe that's correct.
BY MS. HASPER:
Q And looking at step (1) below, the first step -- step (1), small (i), reacting that enantiomer of formula 5 as indicated below, how would you describe that step?
A So compound 11-B is treated with chloroacetonitrile -- that's CL, CH2, CN in step (1)

under (i) and potassium carbonate.

Q And would you characterize that as an alkylation step?

MR. POLLACK: Objection. Leading.

THE WITNESS: Yes. That's an alkylation of the phenolic oxygen atom with chloroacetonitrile to form the methyl nitrile product.

BY MS. HASPER:

Q And step (a) of the patent requires the use, specifically, of formula 5 to produce a compound of formula 6; is that correct?

MR. POLLACK: Objection. Leading.

THE WITNESS: Yes.

BY MS. HASPER:

Q Is formula 5 the same as compound 11-B?

A No.

Q How are they different?

A They're enantiomers.

Q Okay. And if you react compound 11-B as indicated in step (1)(i), do you produce compound 6?

A No.

Q What do you produce?

A The enantiomer of compound 6.

Q And so just to make sure I understand what you're saying, performing step (1) sub --

small (i) on compound 11-B differs from step (a) of claim 9 in that it involves the enantiomers of the compounds required by step (a); is that correct?

MR. POLLACK: Objection. Leading.

THE WITNESS: That's correct.

BY MS. HASPER:

Q Now, step (b) of compound -- of claim 9, I'm going to read it and just confirm that I'm reading this correctly -- "requires hydrolyzing the product of formula 6 of step (a) with a base"; is that correct?

MR. POLLACK: Objection. Leading.

THE WITNESS: That's what it says.

BY MS. HASPER:

Q And what is the relationship between the -- oh, sorry. Let me first say this: So then step (1), sub 2, of the process in Phares, how would you describe that reaction?

A That's the hydrolysis of the nitrile functional group to the potassium carboxylate.

Q And that's performed -- well, what is the starting material for that particular step?

A That would be the enantiomer of structure 6 in column 20 of claim 9.

Q So step (1), small (ii), differs from

step (b) of claim 9 of the patent in that it is using the enantiomer of formula 6, rather than formula 6; is that correct?

MR. POLLACK: Objection. Leading.

Counsel, would you like to take his chair instead or --

MS. HASPER: I don't appreciate your sass. I was -- I've listened to you ask questions all day. And I certainly don't appreciate you when you completely, inappropriately call leading objections when I'm asking him to confirm that I've read something correctly from a document that is in front of us all.

MR. POLLACK: That's not what you asked now.

MS. HASPER: No.

MR. POLLACK: And you're asking leading questions, and you are on redirect.

BY MS. HASPER:

Q Would you like to answer the question, or would you like it repeated after this interruption?

A I want to be sure I'm answering the right question. Could the question be repeated?

MS. HASPER: Would the court reporter, perhaps, read it back.

(Record read by the reporter as follows:)

"QUESTION: "So step (l), small (ii), differs from step (b) of claim 9 of the patent in that it is using the enantiomer of formula 6, rather than formula 6; is that correct?"

MR. POLLACK: And the objection is "Leading."

THE WITNESS: That's correct.

BY MS. HASPER:

Q In your opinion, does step (l) -- let me start over.

In your opinion, what is the relationship between step (l) as recited on page 42 of Exhibit 11, the Phares patent -- sorry, Exhibit 16, the Phares patent -- to steps (b) and (a) in claim 9 of the '393 patent?

A So what's happening in step (l) is (i) is the alkylation of the benzindine triol structure 5, but it's the enantiomer of structure 5 with chloroacetonitrile, which is the alkylating agent. And that produces, in the case of the Phares document, the enantiomer of structure 6, that's

depicted at column 20, line 15 or so.

And then the next step of transformation (l) under (ii) is a potassium hydroxide methanol hydrolysis of nitrile functional group to give initially the potassium carboxylate which on workup would give the enantiomer of treprostinil, which is shown as structure 2 in the Phares document.

Q So is it your understanding that steps (a) and (b) of the -- of claim 9 of the '393 patent and step (l) of the synthesis on this page of the Phares reference are the same or different?

A They're different because we're using a different optical isomer -- nonsuperimposable mirror image of what is required by claim 9.

Q And ultimately, does one get the same product or a different product if one follows steps (a) and (b) of claim 9 versus step (l) of the scheme on this page of the Phares patent?

MR. POLLACK: Objection. Leading.

THE WITNESS: One necessarily gets a different product. It's the nonsuperimposable mirror image of treprostinil. So you get a different product.

BY MS. HASPER:

Q Thank you.

A Nonbiologically active compound.

Q Thank you very much for your time today, Dr. Williams. If Mr. Pollack has any additional questions --

FURTHER EXAMINATION

BY MR. POLLACK:

Q I do. I have some recross for you.

I'd like you to pull out Deposition Exhibit 4. That's the Moriarty patent.

I think you indicated to your counsel that you had some knowledge of how the patent continuation system worked; is that right?

That's what you --

A Yes. Yes.

Q Okay. If you look where it says, "62" -- you see where I'm looking?

A On the face page, line 62 -- 62. Yeah.

Q Okay. Well, let me go a little above that. The application that led to the Moriarty patent, you see it was filed on July 1st, 2002? Do you see that?

A Yes.

Q Okay. That's long after the dates in, you know, the process development document,

Exhibit -- I think it was 11; right? 2002 is long after the 1998 and 1999 dates we were looking at; is that right?

A I don't know if I characterize it as "long after." It's a few -- couple, four years.

Q Fair enough.

And do you see the -- it says, "The early application is depending on" -- something called a "division." You see that? It's a division of another application?

Do you know what that means?

MS. HASPER: Objection. Seeks a legal conclusion.

THE WITNESS: I'm not a lawyer, so I don't know the correct technical definition of a "divisional application."

BY MR. POLLACK:

Q Okay. Do you have any understanding of what a divisional application is?

A Well, I know that you can file a patent application and then file additional versions thereof after that. And I think some of those are sometimes called "continuation in parts" or "divisionals." But, again, I don't know the technical differences between these.

Q Okay. Have you ever heard that a divisional is a kind of application which is filed for an invention which is different than the one claims in the prior application?

Did you ever hear that before, and that's why it's called a "divisional"?

A Yeah. I -- I don't know.

Q Okay. That's news to you? That a divisional is for a different invention than what's in the prior applications? You've never heard that before?

A Yeah. I'm not a patent expert.

Q Okay.

A I don't know the technical metes and bounds of what that means.

Q Sure. And if we go from that one, the next one -- that divisional, by the way, ended up in a patent. You see that? 6,441,245?

A Yes.

Q Okay. Did you look at that patent in forming your opinion?

A I do remember the '245 patent from the Sandoz litigation, but I haven't looked at it recently. But I've certainly looked at the '245 patent before.

Q Okay. What's in the '245 patent?

A I don't remember.

Q You don't remember.

Did it claim treprostinil?

A I don't remember.

Q You see after that, it says that patent is a continuation in part of a prior application that was filed in 2000. Do you see that?

A Yes.

Q Okay. Do you know what a "continuation in part" is?

MS. HASPER: Objection. Seeks a legal conclusion.

THE WITNESS: I don't know the technical legal definition of "continuation in part."

BY MR. POLLACK:

Q I understand. But do you have any understanding of what a continuation in part is?

A Well, there's a relationship to the preceding application. And I don't know, again, what is allowable, and what makes it, you know, completely separate invention. So --

Q Okay. I know you have a number of patents; right?

A Yes.

Q Did some of them involve continuations in part?

A Yes, I believe so.

Q Okay. And you were made aware of when those continuations in part were filed that what that meant was additional material was added to the specification of the patent. Did they tell you that?

A That rings a bell. But, again, I leave this all up to the tech-transfer office at the university.

Q Okay. So as you sit here now, do you know whether any of the material from the application filed in 1997 is relevant to the Moriarty process and claims that we've been discussing today?

A I believe there is relevant material.

Q Okay.

A I don't -- you know, I don't have the document in front of me.

Q Okay.

A I'd be happy to look at it.

Q Okay. But as you sit here now, or, you know, you've formed your opinion, do you know whether this 1997 document has the synthesis of the

Moriarty process in the document?

A You know, I simply just don't know.

Q Okay. And I'd like to turn back to the exhibit your counsel gave you, Exhibit 26. It's this corrected version.

A Yes.

Q Okay. We were looking at -- I'm looking at that version. I see you still list total related substances at .9545 even on this corrected version in the new Exhibit 26. Do you see that?

A Yes.

Q Okay. Having looked at the data we saw today and the averages that we saw today, showing, you know, an average total related substances for the 46 Moriarty samples of point -- approximately .3, do you still think that this Exhibit 26 doesn't need to be corrected to reflect .3 for the Moriarty samples?

A No.

Q So you still want to stand by including ten cherry-picked samples from the other exhibit that you added?

MS. HASPER: Objection. Mischaracterizes the document. Mischaracterizes testimony.

THE WITNESS: Yeah. I would not --

again, I would not characterize those ten development batches as cherry-picked because by the same token, the development batches for the '393 process patches were also included. So I stick by that the comparison was done fairly. And I'm not about to change anything, other than the numerical corrections due to the typographical error.

BY MR. POLLACK:

Q Now, the development batches you were referring to, if would you turn to -- in Exhibit 26, this exhibit that we were just looking at -- did you put it away?

A This one (indicating)?

Q Okay.

So the development batches you were referring to, that's -- those are the one, two, three, four -- five batches that came from Exhibit 2005? Is that what you were referring to?

A Yes.

Q Okay. And you're saying: Well, it's totally fair for me to add five batches to a sum of 157 samples.

MS. HASPER: Objection. Mischaracterizes the document.

BY MR. POLLACK:

Q Right? That's what you did; right?

MS. HASPER: Objection. Mischaracterizes the document and mischaracterizes the testimony.

BY MR. POLLACK:

Q How many samples in total are in Appendix B?

A I believe it's 121.

Q I'm sorry. 121.

So there were 116 samples that weren't development batches?

MS. HASPER: Objection. Beyond the scope of Cross.

THE WITNESS: That's -- that's -- the information I had, if there were more development batches available, I would have put those in. I didn't eliminate anything deliberately.

And I would just simply say that the '393 process, you're starting off with a better process. So the development batches are -- were better because you're starting with a superior process to begin with.

So I didn't eliminate development batches. If they -- had they been more of them, I would have factored them in.

BY MR. POLLACK:

Q Sure. I'm not saying you did eliminate development batches.

I'm saying you added development batches to the other appendix to bring the number down, isn't that right?

MS. HASPER: Objection. Mischaracterizes the document. Mischaracterizes testimony. Asked and answered. Beyond the scope of cross and argumentative by this point.

THE WITNESS: No.

BY MR. POLLACK:

Q No. But you're saying it's fair to add only 5 samples to 116 here, that that's a fair comparison with what you did in Appendix A?

MS. HASPER: Same objection. Beyond the scope of Cross. Argumentative. Mischaracterizes the document. Mischaracterizes the testimony.

THE WITNESS: I worked with everything that I was able to find.

BY MR. POLLACK:

Q Well, you didn't find anything; right? Counsel gave you all these -- all this information.

MS. HASPER: Objection.

BY MR. POLLACK:

Q Isn't that right?

MS. HASPER: Same objections.

THE WITNESS: Yes.

BY MR. POLLACK:

Q Okay.

A But I asked if there was any -- I asked several times: Is there anything else?

And they said: This is all we could find.

So they -- they got from UTC everything that was available, to my knowledge. So --

Q All right. You didn't do any investigation to see if that was really true, though, did you?

MS. HASPER: Same objection.

THE WITNESS: I didn't do any further investigation, no.

MR. POLLACK: No further questions.

MS. HASPER: None for me.

THE REPORTER: I have nothing.

(Laughter)

THE VIDEOGRAPHER: This ends the deposition of Robert M. Williams, Ph.D.

Total number of media used was four.

We're off the record. The time is 6:40 P.M.

(The deposition concluded at 6:40 P.M.)

* * *

DECLARATION UNDER PENALTY OF PERJURY

I, Robert M. Williams, Ph.D., do hereby certify under penalty of perjury that I have read the foregoing transcript of my deposition taken on August 26, 2016; that I have made such corrections as appear noted on the Deposition Errata Sheet, attached hereto, signed by me; that my testimony as contained herein, as corrected, is true and correct.

Dated this _____ day of _____, 20___, at _____, California.

_____

Robert M. Williams, Ph.D.

DEPOSITION ERRATA SHEET

Page No._____ Line No. _____

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Robert M. Williams, Ph.D. Dated

STATE OF CALIFORNIA)
)
COUNTY OF SAN DIEGO)

I, Harry A. Palter, a Certified Shorthand Reporter of the State of California, do hereby certify:

That prior to being examined, the witness in the foregoing proceedings was by me duly sworn to testify to the truth, the whole truth, and nothing but the truth;

That said proceedings were taken before me at the time and place therein set forth and were taken down by me in shorthand and thereafter transcribed into typewriting under my direction and supervision;

I further certify that I am neither counsel for, nor related to, any party to said proceedings, nor in any way interested in the outcome thereof.

In witness whereof, I have hereunto subscribed my name.

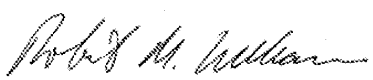
Dated: 8.30.2016

_____
HARRY ALAN PALTER
CSR No. 7708

T

Deposition Errata

PAGE	LINE	FROM	TO	REASON
11	20	type	Teva	Court reported did not hear correctly
22	6	paid	retained	Court reported did not hear correctly
40	11	lotsa	lots of	Spelling error
43	16	Cymedex	Scitemex	Spelling error
55	10	reactive	reacted	Spelling error
59	1	Cree	crude	Spelling error
62	2	transfused	trans-fused	Typographical error
92	3	38090	1AU90	Typographical error
118	10	instead	in standard	Typographical error
140	2	use San Diego	used can be	Court reported did not hear correctly
140	21	mixed	mixture	Spelling error
153	16	end of	ANDA	Court reported did not hear correctly
182	4	lotsa	lots of	Typographical error
184	14	Orrin	Oren	Spelling error
191	24	pertinence	percent	Spelling error
193	19	to	of	Spelling error
193	20	an	a	Spelling error
200	10	proteinate	protonate	Spelling error
221	9	tuna kit	tunicate	Spelling error
221	11	tuna kit	tunicate	Spelling error
243	8	in	and	Typographical error



September 15, 2016

Robert M. Williams

United Therapeutics
CORPORATION

PATENT OWNER
UNITED THERAPEUTICS CORPORATION

IPR2016-00006

U.S. Patent No. 8,497,393

November 29, 2016

UT Ex. 2061
SteadyMed v. United Therapeutics
IPR2016-00006

Petitioner Bears the Burden of Proving Invalidity

- "In an inter partes review, the burden of persuasion is on the petitioner to prove 'unpatentability by a preponderance of the evidence,' 35 U.S.C. § 316(e), and that burden never shifts to the patentee."
  - *In re Magnum Oil Tools International, Inc.* (Fed. Cir. 2016), citing *Dynamic Drinkware*, 800 F.3d at 1378; Paper No. 48.
- "[T]he petitioner continues to bear the burden of proving unpatentability after institution, and must do so by a preponderance of the evidence at trial."
  - *In re Magnum Oil Tools International, Inc.* (Fed. Cir. 2016); Paper No. 48.
- "[T]he Board has an obligation to assess the question anew after trial based on the totality of the record."
  - *Id.*

Prior Art at Issue

- The only prior art treprostinil examples in this IPR are (a) the single example in Moriarty 2004 of treprostinil acid (Ex. 1004, p. 13) and (b) the single example in Phares WO 2005/007081 of diethanolamine salt of treprostinil, form B (Ex. 1005, pp. 87-88).

- Kawakami and Ege do not disclose treprostinil or any prostacyclin derivative and do not disclose how to purify such compounds specifically.

- To the extent Petitioner's evidence shifts burden of production, Patent Owner need only present sufficient evidence to rebut that evidence relied upon by Petitioner.

Claim Construction in an IPR Analysis

- "While it is true that, as a general rule, the words of a patent claim are to be given their plain, ordinary and accustomed meaning to one of ordinary skill in the relevant art, *Toro Co. v. White Consol. Indus., Inc.*, 199 F.3d 1295, 1299 (Fed. Cir. 1999), *a court must nevertheless examine the remaining intrinsic evidence to determine whether the patentee has set forth an explicit definition of a term contrary to its ordinary meaning, has disclaimed subject matter, or has otherwise limited the scope of the claims*."
  - *Day Intern., Inc. v. Reeves Brothers, Inc.*, 260 F.3d 1343, 1349 (Fed. Cir. 2001) (emphasis added) (PO Resp. at pp. 13-14).
- The Federal Circuit in *SafeTCare Mfg* incorporated limitations into claim construction where the specification repeatedly indicated that the invention operated by "pushing (as opposed to pulling) forces," and then characterized the "pushing forces" as "an important feature of the present invention."
  - *SafeTCare Mfg., Inc. v.Tele-Made, Inc.*, 497 F.3d 1262, 1269-70 (Fed. Cir. 2007)(PO Resp. at p. 14).

Proper Claim Construction Requires Consideration of Impurities Present In The Product

Example 6

Comparison of the Former Process and a Working Example of the Process According to the Present Invention

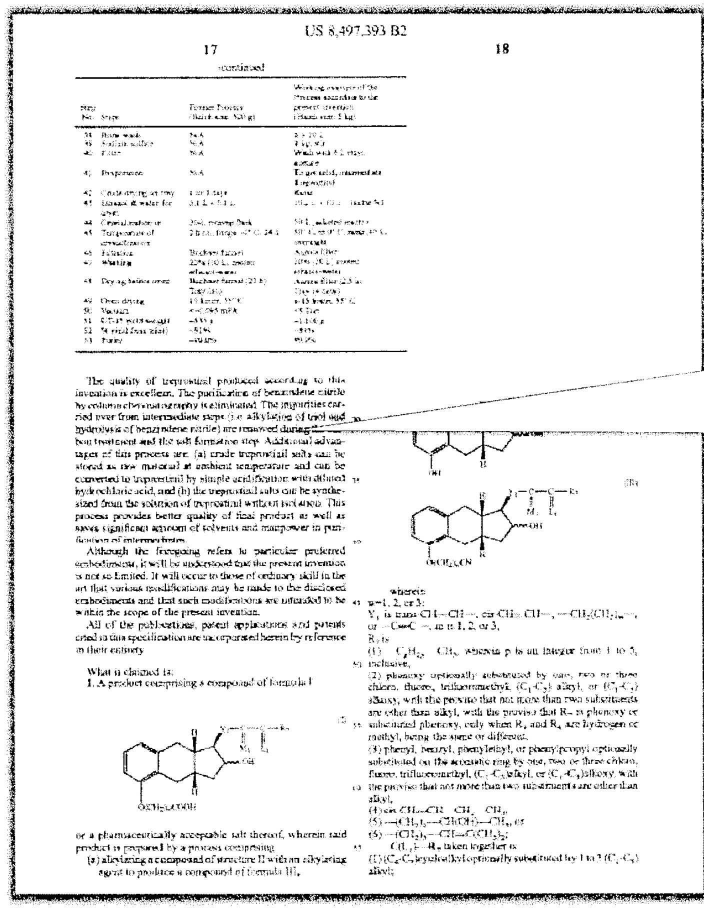
-continued

Step No.	Steps	Former Process (Batch size: 500 g)	Working example of the Process according to the present invention (Batch size: 5 kg)
38	Brine wash	N/A	
39	Sodium sulfate	N/A	
40	Filter	N/A	
41	Evaporation	N/A	
42	Crude drying on tray	1 or 3 days	
43	Ethanol & water for cryst.	5.1 L + 5.1 L	
44	Crystallization in	20-L rotavap	
45	Temperature of crystallization	2 h r.t., fridge	
46	Filtration	Buchner funnel	Auro
47	Washing	20% (10 L) cooled ethanol-water	20% ethan
48	Drying before oven	Buchner funnel (20 h) Tray (no)	Auro Tray
49	Oven drying	15 hours, 55° C.	6-15 h
50	Vacuum	<–0.095 mPA	<5 Tor
51	UT-15 yield weight	~535 g	~1,100
52	% yield from triol)	~91%	~89%
53	Purity	~99.0%	99.9%

Example 6 in the '393 Patent specification indicates the purity of a working example of the invention is 99.9% whereas purity of former Moriarty product was ~99.0%

- Ex. 1001, 17:step 53. (PO Resp. at p. 16)

Proper Claim Construction Requires Consideration of Impurities Present In The Product



- ’393 patent specification further identifies differences in impurities

“impurities carried over from intermediate steps (i.e., alkylation of triol and hydrolysis of benzindene nitrile) are removed during the carbon treatment and salt formation step”

- Ex. 1001, 17:29-32.

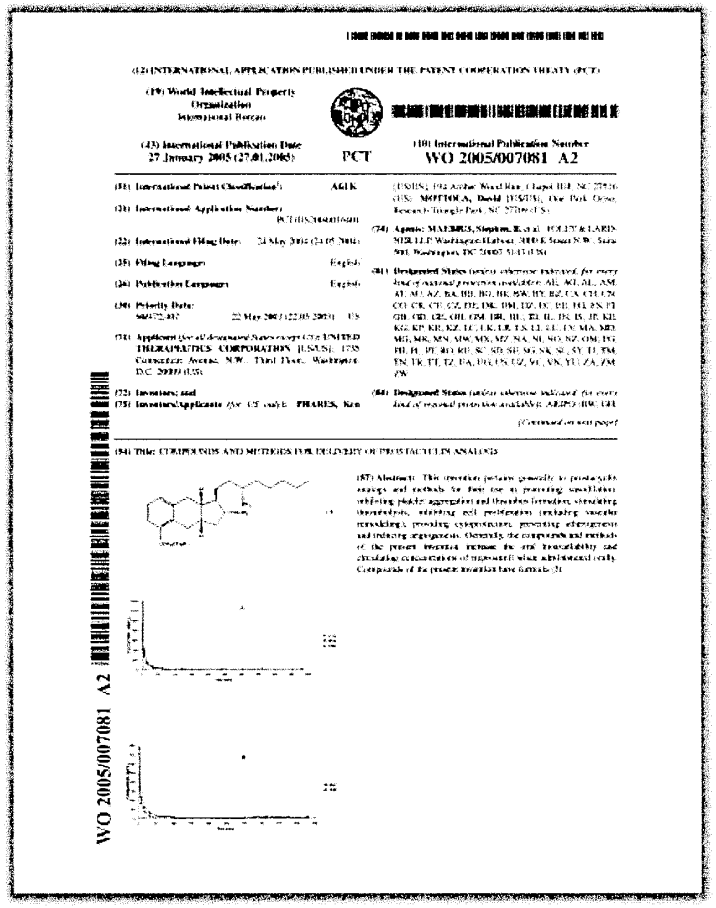
Proper Claim Construction Requires Consideration of Impurities Present In The Product

- Prosecution history clarified that impurity profiles were important to the claimed invention
  - "[e]ach of treprostinil as the free acid and treprostinil diethanolamine prepared according to the process specified in claim 1 or 10 . . . is physically different from treprostinil prepared according to the process of 'Moriarty' due to *differences in their impurity profiles*."
    - Ex. 1002 at 344. (emphasis added) (PO Resp. at p. 16)
  - UTC thereafter filed the Walsh Declaration, which demonstrated that the claimed product had a different *impurity profile and higher purity* than a representative batch of Moriarty's product.
    - Ex. 1002 at 347-349. (PO Resp. at p. 16)
  - Claims allowed within eight days of the submission of Walsh's Declaration demonstrating differences in impurities.
    - *Id.* at 354.

Proper Claim Construction Requires Consideration of Impurities Present In The Product

- The '393 patent specifically distinguishes the purification limitation [eliminating purification after step (a) as required in claims 8 & 16] over the prior art. Ex. 1001, Example 6. Moriarty expressly discloses that the compound of formula (VI) from step (a) is purified.
  - Ex. 2020 at ¶104; PO Resp. at p. 32.
- No evidence from Petitioner of the impact of eliminating column purification step from Moriarty 2004 publication; the only direct comparative evidence in the record for claims 8 and 16 is Ex. 6 in '393 patent.
  - Ex. 2020 at ¶104; PO Resp. at p. 32.

Phares Does Not Anticipate Any '393 Patent Claim



(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization International Bureau

(43) International Publication Date: 27 January 2005 (27.01.2005)

PCT

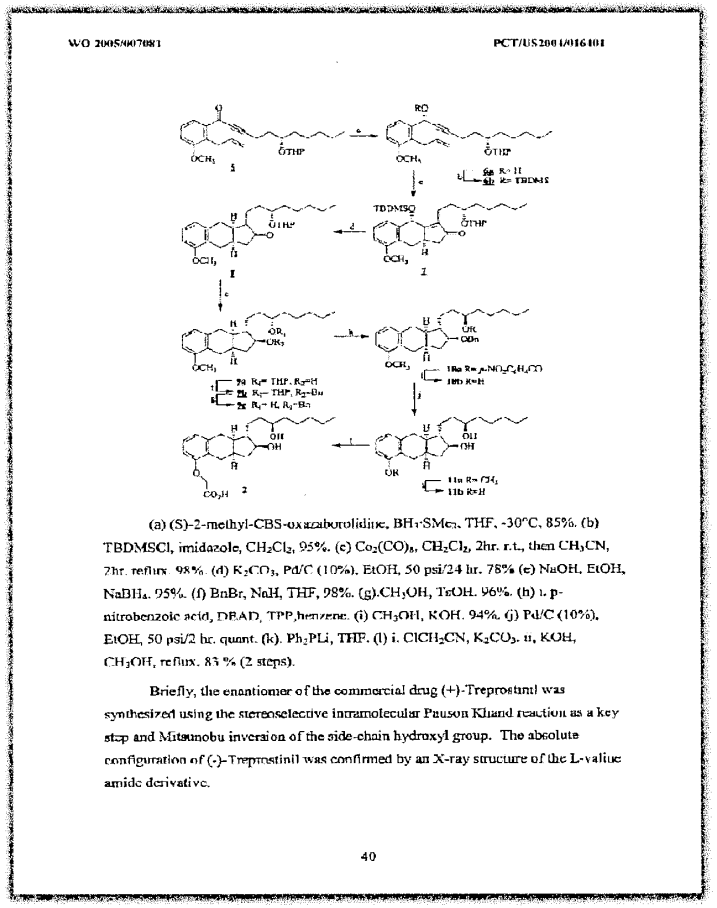
(10) International Publication Number: WO 2005/007081 A2

(54) Title: CEPROSTENOLS AND METHODS FOR DELIVERY OF PROSTACYCLIN ANALOGS

WO 2005/007081 A2

- Phares was disclosed on the face of the '393 patent
- Phares fails to disclose any detailed synthesis of treprostinil
- Phares fails to disclose any impurity or impurity profile for treprostinil or treprostinil diethanolamine
- Phares fails to disclose any purity level for treprostinil diethanolamine

Synthesis Disclosed In Phares Is Not For Treprostinil



WO 2005/007081 PCT/US2004/016101

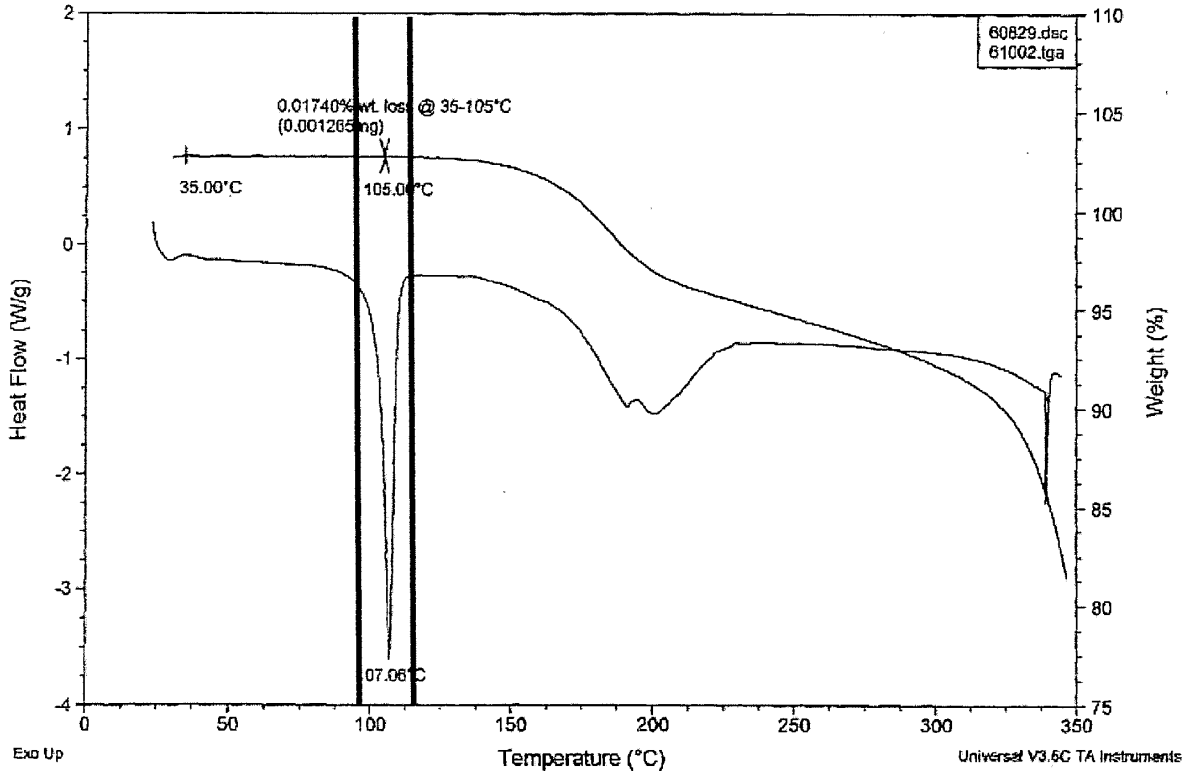
(a) (S)-2-methyl-CBS-oxazaborolidine, BH_3·SMe$_2$, THF, -30°C, 85%. (b) TBDMSCl, imidazole, CH_2Cl_2, 95%. (c) $Co_2(CO)_8$, CH_2Cl_2, 2hr. r.t., then CH_3CN, 2hr. reflux 98%. (d) K_2CO_3, Pd/C (10%), EtOH, 50 psi/24 hr. 78% (e) NaOH, EtOH, $NaBH_4$, 95%. (f) BnBr, NaH, THF, 98%. (g) CH_3OH, TsOH. 96%. (h) i. p-nitrobenzoic acid, DBAD, TPP,benzene. (i) CH_3OH, KOH. 94%. (j) Pd/C (10%), EtOH, 50 psi/2 hr. quant. (k). Ph_2PLi, THF. (l) i. $ClCH_2CN$, K_2CO_3. ii, KOH, CH_3OH, reflux. 83 % (2 steps).

Briefly, 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. The absolute configuration of (-)-Treprostinil was confirmed by an X-ray structure of the L-valine amide derivative.

40

- Dr. Williams confirmed the synthesis in Phares is for the enantiomer of treprostinil, a different product.
  - Ex. 2059, 264:13-265:18; 265:20-23; Ex. 2020 ¶79
- Phares fails to disclose the source of treprostinil used in single step example making treprostinil diethanolamine.
  - Ex. 1005, p. 24; Ex. 2020, ¶79.
- Only reference to treprostinil synthesis in Phares is to early syntheses resulting in impure substances.
  - Ex. 1005, p. 9; Ex. 2020, ¶78.

Phares Fails to Disclose Purity of Treprostinil Diethanolamine



- Dr. Williams confirmed broad approximate 10 degree melting point range from Phares indicated a less pure substance. Ex. 2020, ¶76.

Phares Form B Diethanolamine Salt Example Is Not the Same as the '393 Patent Product

Williams' Declaration	Rogers' Declaration
Melting point range is "broad" (¶ 76)	Melting Point range is "narrow" (¶ 87)
Cites to Marti reference (Ex. 2031) (¶ 76)	*NO SUPPORT*
Conclusion: Cannot determine purity from melting point range of Phares (¶ 76)	Conclusion: Phares at least as pure as '393 (¶ 88)

Phares Does Not Anticipate Any Claim of the '393 Patent

- Petitioner's expert Dr. Rogers acknowledges Phares form B has a different melting point range than the '393 patent products and "[a]ny difference in their measured melting point, Ts, is due to differing levels of impurities."
  - Ex. 1022, ¶72 and 82
- Phares form B sample made for polymorph screen by a very different process that converts to form B from form A, it is not clear where the specific batch of form B used for analysis came from, and is not a large scale batch.
  - Ex. 2020, ¶73; PO Resp., p. 25.
- Petitioner has failed to show the Phares product is the same as the products disclosed in the '393 patent.
  - PO Resp. at pp. 22-26.

Phares and Moriarty Do Not Render the '393 Claims Obvious

JOC*Article*

The Intramolecular Asymmetric Pauson–Khand Cyclization as a Novel and General Stereoselective Route to Benzindene Prostacyclins: Synthesis of UT-15 (Treprostinil)

Robert M. Moriarty,*,† Neena Rao,‡ Livia A. Enache,‡ Murugaiah S. Reed,‡ Hitesh Batra,‡ Liang Guo,‡ Raju A. Penmasta,‡ James P. Staszewski,‡ Sudersan M. Tuladhar,‡ Om Prakash,† David Crich,† Arun Hirtopeanu,§ and Richard Gilardi||

A general and novel solution to the synthesis of biologically important stable analogues of prostacyclin PGI$_2$, namely benzindene prostacyclins, has been achieved via the stereoselective intramolecular Pauson–Khand cyclization (PKC). This work illustrates for the first time the synthetic utility and reliability of the asymmetric PKC route for synthesis and subsequent manufacture of a complex drug substance on a multikilogram scale. The synthetic route surmounts issues of individual step stereoselectivity and scalability. The key step in the synthetic sequence involves efficient stereoselection effected in the PKC of a benzenetriyne under the agency of the benzyloxymethyl (BOM) group, which serves as a temporary stereodirecting group that is subsequently removed via benzylic hydrogenolysis concomitantly with the catalytic hydrogenation of the enone PKC product. Thus the benzylic chiral center dictates the subsequent stereochemistry of the stereogenic centers at three carbon atoms (C_9, C_{9a}, and C_3).

- Moriarty was disclosed on the face of the '393 patent
- Moriarty fails to disclose steps (c) or (d) from the '393 patent in the synthesis of treprostinil and does not disclose treprostinil diethanolamine
- Moriarty fails to disclose any impurity or impurity profile for treprostinil
- Purity level disclosed in Moriarty cannot be compared to '393 Patent purity

Winkler Improperly Compared Purity Levels

- "When purity is determined by comparison of a sample to a reference standard *such as assay purity, one cannot directly compare the purity values of two samples in any meaningful way unless each value was achieved by comparison to the same reference standard*. Neither the Walsh Declaration nor Moriarty identifies a specific reference standard." (emphasis supplied)
  - Ex. 2034, pp. 28-29; Ex. 2035, pp. 5-8; Ex. 2020, ¶ 88; PO Resp., pp. 2, 29

- Moriarty 2004 purity of "99.7%" cannot be compared to Walsh, '393 data or any FDA data in the record.
  - Ex. 1004, p. 13

Winkler Improperly Compared Purity Levels

- Winkler mistakenly thought that an "assay" purity in the '393 patent represented HPLC error rate rather than a *relative* purity level compared to a reference standard, which gave rise to his further misunderstanding about the Walsh Declaration, the '393 specification, & Moriarty purity measurements.
  - Ex. 1001, col. 13, l. 2; Ex. 2020 ¶¶ 89-93; PO Resp. at pp. 29-30
- Winkler later acknowledged that assay purity determinations over 100% and FDA purity measurement limits are valid; however, the Institution Decision was based on Winkler's erroneous initial purity conclusions.
  - PO Response at 3; Ex. 2051 at 64:7-9; Paper No. 12 at pp. 8, 17, 19, 48

Winkler Improperly Compared Purity Levels

- Dr. Wiliams: "the *level of detection for measuring impurities in these treprostinil samples was somewhere between 0 and 0.05%,* not something in excess of 0.4% as Dr. Winkler erroneously concludes" (emphasis supplied).
  - Ex. 2020, at ¶92; PO Resp. at p. 3
- Dr. Ruffolo: the Certificates of Analysis purity data presented in the Walsh, Ruffolo and Williams Dec.'s is the same data required by FDA in its purity specification for treprostinil *and relied upon by UT to comply with FDA's requirements* .
  - Ex. 2022 at ¶32; Ex. 2020 at ¶94; PO Resp. at pp. 3-4

Petitioner Bears the Burden of Proving Invalidity

- Institution Decision was based on Winkler's erroneous initial purity conclusions (Paper No. 12 at pp. 8, 17, 19, & 48)
- '393 comparative data, FDA data submitted in this IPR & Walsh's Declaration should all be credited over Winkler's debunked Declaration/misunderstanding of purity
- When Winkler's mistaken testimony about purity levels is removed, Petitioner has not carried its threshold burden

Significant Differences Exist Between Batches Made by the '393 Patent and Moriarty Processes

Moriarty Process Impurities (Average Percent Detected)								
1AU90	2AU90	3AU90	750W93	751W93	97W86	ethyl ester	methyl ester	Total Related Substance
0.0473	0.0407	0.2545	0.1646	0.1025	0.0405	0.0889	0.1028	0.9545

'393 Patent Process Impurities (Average Percent Detected)								
1AU90	2AU90	3AU90	750W93	751W93	97W86	ethyl ester	methyl ester	Total Related Substance
0.0004	0.0004	0.0455	0.0643	0.0488	0	0.1208	0.005	0.2944

- Dr. Williams analyzed over 170 batches of treprostinil and treprostinil diethanolamine made by either the Moriarty process or the '393 patent process to analyze impurities and total related substances
  - Ex. 2020, ¶¶94-98

Significant Differences Exist Between Batches Made by the '393 Patent and Moriarty Processes

Moriarty Process Impurities (Average Percent Detected)								
1AU90	2AU90	3AU90	750W93	751W93	97W86	ethyl ester	methyl ester	Total Related Substance
0.0473	0.0407	0.2545	0.1646	0.1025	0.0405	0.0889	0.1028	0.9545
'393 Patent Process Impurities (Average Percent Detected)								
1AU90	2AU90	3AU90	750W93	751W93	97W86	ethyl ester	methyl ester	Total Related Substance
0.0004	0.0004	0.0455	0.0643	0.0488	0	0.1208	0.005	0.2944

- Greater than 100 fold reduction in 1AU90 and 2AU90 impurities
  - Ex. 2020, ¶¶94-98

Significant Differences Exist Between Batches Made by the '393 Patent and Moriarty Processes

Moriarty Process Impurities (Average Percent Detected)								
1AU90	2AU90	3AU90	750W93	751W93	97W86	ethyl ester	methyl ester	Total Related Substance
0.0473	0.0407	0.2545	0.1646	0.1025	0.0405	0.0889	0.1028	0.9545

'393 Patent Process Impurities (Average Percent Detected)								
1AU90	2AU90	3AU90	750W93	751W93	97W86	ethyl ester	methyl ester	Total Related Substance
0.0004	0.0004	0.0455	0.0643	0.0488	0	0.1208	0.005	0.2944

- Twenty fold reduction in methyl ester impurity
  - Ex. 2020, ¶¶94-98

Significant Differences Exist Between Batches Made by the '393 Patent and Moriarty Processes

Moriarty Process Impurities (Average Percent Detected)								
1AU90	2AU90	3AU90	750W93	751W93	97W86	ethyl ester	methyl ester	Total Related Substance
0.0473	0.0407	0.2545	0.1646	0.1025	0.0405	0.0889	0.1028	0.9545

'393 Patent Process Impurities (Average Percent Detected)								
1AU90	2AU90	3AU90	750W93	751W93	97W86	ethyl ester	methyl ester	Total Related Substance
0.0004	0.0004	0.0455	0.0643	0.0488	0	0.1208	0.005	0.2944

- Significant reductions in 750W93, 751W93, and 3AU90 impurities
- 97W86 impurity eliminated in '393 patent process
  - Ex. 2020, ¶¶94-98

Significant Differences Exist Between Batches Made by the '393 Patent and Moriarty Processes

Moriarty Process Impurities (Average Percent Detected)								
1AU90	2AU90	3AU90	750W93	751W93	97W86	ethyl ester	methyl ester	Total Related Substance
0.0473	0.0407	0.2545	0.1646	0.1025	0.0405	0.0889	0.1028	0.9545

'393 Patent Process Impurities (Average Percent Detected)								
1AU90	2AU90	3AU90	750W93	751W93	97W86	ethyl ester	methyl ester	Total Related Substance
0.0004	0.0004	0.0455	0.0643	0.0488	0	0.1208	0.005	0.2944

- Overall reduction in impurities by approximately 0.7%
  - Ex. 2020, ¶¶94-98

Significant Differences Exist Between Batches Made by the '393 Patent and Moriarty Processes

Moriarty Process Impurities (Average Percent Detected)								
1AU90	2AU90	3AU90	750W93	751W93	97W86	ethyl ester	methyl ester	Total Related Substance
0.0473	0.0407	0.2545	0.1646	0.1025	0.0405	0.0889	0.1028	0.9545

'393 Patent Process Impurities (Average Percent Detected)								
1AU90	2AU90	3AU90	750W93	751W93	97W86	ethyl ester	methyl ester	Total Related Substance
0.0004	0.0004	0.0455	0.0643	0.0488	0	0.1208	0.005	0.2944

- Ethyl ester actually increased in '393 patent demonstrating another difference between the '393 and Moriarty batches
  - Ex. 2020, ¶¶94-98

'393 Product Has Higher Ethyl Ester Impurities Than Moriarty

- Dr. Williams also found that ethyl ester unexpectedly increased in the '393 product of the batches he reviewed compared to the Moriarty batches he reviewed
  - Ex. 2020, ¶¶94-98; PO Resp. at p. 10
- This point is not challenged by Petitioner
- '393 product is different regardless of claim construction due to higher impurity level of ethyl ester compared to Moriarty

Petitioner Challenges Averages But Ignores Other Evidence Supporting Williams Declaration

- "*Looking past the average data*, it is also worth noting that, out of all the batches of treprostinil product made by the '393 patent process which I reviewed, 1AU90 was only detected in a single batch (01A07001) and 2AU90 was also only detected in a single batch (01A07003), and both impurities were only detected at a level of 0.05% or less. Furthermore, batches 01A07001 and 01A07003 were both identified as 'optimization batches' (as distinguished from commercial batches)." (emphasis supplied).
  - Ex. 2020 at ¶ 97, PO Resp. at p. 4

- Dr. Williams relied on these *individual impurity values and trends*, not just calculated averages to support his conclusion that the products are different.

Petitioner Challenges Averages But Ignores Other Evidence Supporting Williams Declaration

- "the averages presented in the Process Optimization Report still show significant differences between '393 treprostinil products and the Moriarty treprostinil products. Specifically, Table 2 of the Process Optimization Report shows that on average 97W86 was detectable *in these 96 batches, and that these 96 batches contained higher average levels of 3AU90, 750W93, 751W93, and total impurities as compared to the averages for the '393 treprostinil product*. Ex. 2005 at 7; Appendix B. " (emphasis supplied) .
  - UT Ex. 2005, at 7; Ex. 2020 at footnote 1

- These 96 batches relied upon by Williams were *not used in the other average calculations criticized by Petitioner for including development batches*.

Petitioner Objects To Admissibility Of Certain Moriarty Batches But Filed No Motion To Exclude Them

- Petitioner's Reply objects to relevance of certain Moriarty batches, but yet Petitioner filed no Motion to Exclude as to this evidence.
  - Paper No. 52, p. 7.
- However, Petitioner also objected to relevance of the Moriarty batches in its evidentiary objections, in response to which Patent Owner supplemented the record with authenticating Declarations.
  - Ex. 2052; Paper No. 43, p. 11.
- Petitioner cannot maintain its position on lack of relevance after objecting and then failing to move to exclude, depriving Patent Owner of its right to rely on timely served supplemental evidence.

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Additional Comparative Data in Dr. Williams Declaration Stands Unchallenged By Petitioner and Confirms Dr. Williams Conclusions

Table 2. RELEASE TESTING DATA RANGE FOR UT-15 (TREPROSTINIL) API
SUMMARY 2000 TO 2006 FOR CHICAGO SITE
BATCH SIZE 350 GRAMS TO 1 KILOGRAM
NUMBER OF BATCHES: 96

TEST	SPECIFICATION	MINIMUM	MAXIMUM	AVERAGE
Specific Rotation	Not less than +42.0° and not more than +49.0° at 589 nm and 25 °C, volatiles-free basis	+43.3°	+47.7°	+45.8°
Residue on Ignition	Not more than 0.2%, w/w	0.0 %, w/w	0.2%, w/w	0.0%, w/w
Water (Karl Fischer)	Not more than 2.0%, w/w	0.1 %, w/w	1.8%, w/w	0.4%, w/w
Residual Solvents by Gas Chromatography				
▪ Ethyl Acetate	Not more than 0.5%, w/w	ND	<0.1 %	<0.1%
▪ Ethanol	Not more than 0.5%, w/w	0.0 %	0.2 %	0.1%
▪ Acetic Acid	Not more than 0.5%, w/w	ND	0.2 %	<0.1%
▪ Methanol	Not more than 0.1%, w/w	ND	<0.1 %	<0.1%
Melting Range	Not less than 120.0 °C and not more than 126.0 °C	120.1 °C	125.2 °C	Low:121.6 °C High:122.7 °C
Heavy Metals	Not more than 0.002%	Not more than 0.002%	Not more than 0.002%	Not more than 0.002%
Assay (HPLC)	Not less than 97.0% and not more than 101.0%, w/w, on the volatiles-free basis	98.9 % w/w	100.3 % w/w	99.5 %, w/w
Impurities				
▪ 1AU90	Not more than 0.4%	ND	0.2 %	<0.05 %
▪ 2AU90	Not more than 0.1%	ND	<0.05 %	<0.05 %
▪ 97W86	Not more than 0.2%	ND	0.07 %	<0.05 %
▪ 3AU90	Not more than 1.0%	0.09 %	0.4 %	0.2 %
▪ UT-15 methyl ester	Not more than 0.2%	ND	0.1%	<0.05 %
▪ 98W86		ND	<0.05 %	<0.05 %
▪ UT-15 ethyl ester	Not more than 0.5%	<0.05 %	0.4 %	0.1 %
▪ 750W93	Not more than 0.5%	<0.05 %	0.2 %	0.1 %
▪ 751W93	Not more than 0.3%	<0.05 %	0.3%	0.07 %
▪ Unidentified	Not more than 0.1% AUC each	ND	0.6% (Total)	0.05 %
Total Related Substances	Not more than 3.0%	0.3 %	0.8 %	0.5 %

w/w = weight/weight; ND = not detected; AUC = area under the curve.

- Ex. 2005 at 7; Ex. 2020 at FN 1.

7

UT Ex. 2005
SteadyMed v. United Therapeutics
IPR2016-00006

Additional Comparative Data in Dr. Williams Declaration Stands Unchallenged By Petitioner and Confirms Dr. Williams Conclusions

- The averages of impurities presented in the Process Optimization Report analyzing 96 Moriarty batches also show significant differences between '393 treprostinil products and the Moriarty treprostinil products.
  - Ex. 2005 at 7; Ex. 2020 at FN 1.

- These 96 batches contained higher average levels of 3AU90, 750W93, 751W93, and total impurities as compared to the averages for the '393 treprostinil product and lower overall average impurities.
  - Ex. 2005 at 7; Ex. 2020 at FN 1.

FDA Expressed a Long-Felt Need For Each Individual Known Impurity To Be Minimized

- Each of the known impurities are "sources of potential adverse toxicities to patients. Impurities, therefore, can only add to the risk assessments, which are often unknown, made by regulatory agencies in the evaluation of new drug products."
  - Ex. 2040 at 3-4 and 5-8; Ex. 2022 at ¶ 36; PO Resp. at p. 7.
- Even trace impurities can pose serious health risks.
  - Ex. 2022 at ¶ 40; PO Resp. at p. 12.
- To FDA, a product is different if it presents a reduced risk profile due to reduced amounts of individual known impurities, even if there is currently no known adverse effect in patients attributable to those impurities.
  - Ex. 2022 at ¶ 36; PO Resp. at pp. 7-8.

The '393 Patent Met the Long-Felt Need of Improved Purity

- Patent Owner requested and FDA approved a higher purity specification to reflect the treprostinil product resulting from Patent Owner's switch to the '393 patent steps.
  - Ex. 2006, 2003; PO Resp. at p. 12.

- "[W]hile FDA approval is not determinative of nonobviousness, it can be relevant in evaluating the objective indicia of nonobviousness."
  - *Knoll Pharm. Co., Inc. v. Teva Pharm. USA, Inc.,* 367 F.3d 1381, 1385 (Fed. Cir. 2004); PO Resp. at p. 48.

The '393 Patent Met the Long-Felt Need of Improved Purity

- FDA initially rejected UT's requested purity specification change, leading to resubmission with additional evidence.
  - Ex. 2006 at 1; Ex. 2022 at ¶ 66; PO Resp. at pp. 12 and 48.
- "any change in the synthesis or manufacture of the drug substance that may affect its impurity profile and/or the physical, chemical, or biological properties of a drug is considered a *major change*."
  - Ex. 2050 at 17. (emphasis added); Ex. 2022 at ¶72; PO Resp. at p. 12.
- "Because the FDA allowed the drug specification for purity to be changed to reflect the higher level of purity, from a lower level of 97% to 98%, around means of 99% to 100%, respectfully, resulting from the '393 patent process, it is clear that the FDA considered this to represent a major/significant change."
  - Ex. 2022 at ¶72; PO Resp. at p. 12.

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FDA's Drug Purity Specifications Are Rigorously Analyzed & Commercially Important

- Purity data must be prepared according to detailed FDA guidelines.
  - Ex. 2022, ¶53, citing: Ex. 2006 p. 6, Ex. 2044 pp. 34-35, and Ex. 2035 pp. 8-11
- UT's data had to meet these requirements.
  - Ex. 2022 ¶ 57
- If a Certificate of Analysis for a batch does not meet the FDA's purity specification in any aspect, it cannot be sold for use by patients.
  - Ex. 2022 ¶ 32; PO Resp. p. 12

'393 Patent Product Is Structurally Different Regardless Of Batch-To-Batch Variability In Starting Material

- Petitioner has not established that any specific batch of Moriarty treprostinil is not physically changed by performing step (c), and all the evidence suggests that it is.
  - PO Resp. at p. 12
- Petitioner presents no test data of its own.
- The FDA agreed that the evidence presented by the Patent Owner in this IPR warranted a change in purity specification.
  - PO Resp. at p. 12; Ex. 2006 at 4-6; Ex. 2022 at ¶¶66-72.

The '393 Patent Product Is Structurally Different Regardless Of Batch-To-Batch Variability In Starting Material

- "The chemical manufacturing steps have not changed during the transfer to [supplier A] and [supplier B] from the process used by UT in Chicago to prepare benzindene triol."
  - Ex. 2006 at 3.
- "There is a release specification for benzindene triol that must be achieved for each lot of benzindene triol before it is released for use by UT to prepare treprostinil. This is the same specification that was used by United Therapeutics in our Chicago facility."
  - *Id.*
- "*In all lots [of benzindene triol from suppliers A, B, C, and D], the total unidentified impurity level (%AUC) decreased from triol [step (a)] to UT-15C intermediate [step (c)].*"
  - *Id.*

Winkler Fundamentally Misunderstood Certain Purity Measurements

- The level of detection for measuring impurities in these treprostinil samples was somewhere between 0 and 0.05%, not something in excess of 0.4% as Dr. Winkler erroneously concluded.
  - Ex. 2020 at ¶92; PO Resp. at p. 3.
- The Certificates of Analysis purity data presented in the declarations of Drs. Walsh and Williams is the same data required by FDA in its purity specification for treprostinil and relied upon by UT to comply with FDA's requirements
  - Ex. 2022 at ¶32; Ex. 2020 at ¶94; PO Resp. at pp. 3-4.
- Walsh's Declaration should be credited over Winkler's debunked Declaration/misunderstanding of purity
  - Petitioner did not depose Dr. Walsh, a further reason to credit Dr. Walsh's Declaration over Dr. Winkler

Petitioner's Expert Dr. Winkler Fundamentally Misunderstood Certain Purity Measurements

- Dr. Winkler mistakenly thought that an "assay" purity in the '393 patent represented HPLC error rate rather than a *relative* purity level compared to a reference standard, which gave rise to his further misunderstanding about the Walsh Declaration, the '393 specification, & Moriarty purity measurements.
  - Ex. 2020 at ¶¶ 89-93; PO Resp. at pp. 29-30.
- Winkler later acknowledged that assay purity determinations over 100% and FDA purity measurement limits are valid, however, the Institution Decision was based on Dr. Winkler's erroneous initial purity conclusions.
  - PO Response at 3; see also Ex. 2051 at 64:7-9; Paper No. 12 at pp. 8, 17, 19, & 48.

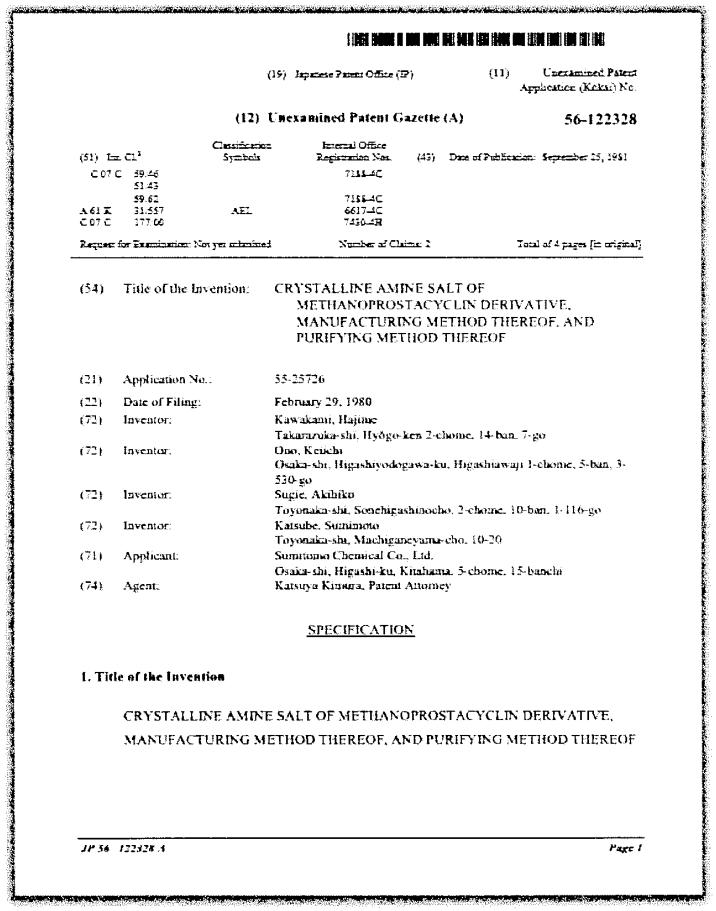
Claims 6,10, 15, 21, & 22 Are Not Obvious

- Only instituted ground for claims 6, 10, 15, 21, and 22 is obviousness based on Moriarty, Phares, Kawakami & Ege
  - Institution Decision at 37.
- "the absence of a known or obvious process for making the claimed compounds overcomes any presumption that the compounds are obvious based on close relationships between their structures and those of prior art compounds."
  - *In re Hoeksema*, 399 F.2d 269, 274 (C.C.P.A. 1968); PO Response at p. 45.
- Petitioner fails to provide any motivation or reason a POSA would look to Kawakami or Ege to purify treprostinil or any related prostacyclin.
  - PO Resp. at pp. 34-44.

No Reasonable Expectation To Further Purify Moriarty By Combining Phares, Ege, & Kawakami

- Petitioner contradicts itself by asserting that Moriarty is already as pure as the '393 product, but yet a POSA would be motivated to apply further purification efforts to Moriarty based on Phares, Ege & Kawakami.
  - Compare Petitioner Reply at 4-6 and 19-20.
- Kawakami relates to use of a *different salt* to purify a *different impurity* present in a *much larger amount* (at least 22.8%) in a *different compound*
  - PO Response at pp. 39-44.
- A POSA would have no reason to turn to Kawakami or Ege given these differences.
  - Ex. 2020 at ¶ 106, PO Response at p. 37.

A POSA Would Not Turn to Kawakami



(19) Japanese Patent Office (JP) (11) Unexamined Patent Application (Kokai) No.

(12) Unexamined Patent Gazette (A) **56-122328**

(51) Int. Cl.³	Classification Symbols	Internal Office Registration Nos.	(43) Date of Publication: September 25, 1981
C 07 C 59/46		7184-4C	
51/43			
59/62		7158-4C	
A 61 K 31/557	AEL	6617-4C	
C 07 C 177/00		7430-4H	

Request for Examination: Not yet submitted Number of Claims: 2 Total of 4 pages [in original]

(54) Title of the Invention: CRYSTALLINE AMINE SALT OF METHANOPROSTACYCLIN DERIVATIVE, MANUFACTURING METHOD THEREOF, AND PURIFYING METHOD THEREOF

(21) Application No.: 55-25726
(22) Date of Filing: February 29, 1980
(72) Inventor: Kawakami, Hajime
Takarazuka-shi, Hyōgo-ken 2-chome, 14-ban, 7-go
(72) Inventor: Ono, Keiichi
Osaka-shi, Higashiyodogawa-ku, Higashiawaji 1-chome, 5-ban, 3-530-go
(72) Inventor: Sugie, Akihiko
Toyonaka-shi, Semchigashinocho, 2-chome, 10-ban, 1-116-go
(72) Inventor: Katsube, Sunimoto
Toyonaka-shi, Machiganeyama-cho, 10-20
(71) Applicant: Sumitomo Chemical Co., Ltd.
Osaka-shi, Higashi-ku, Kitahama, 5-chome, 15-banchi
(74) Agent: Katsuya Kimura, Patent Attorney

SPECIFICATION

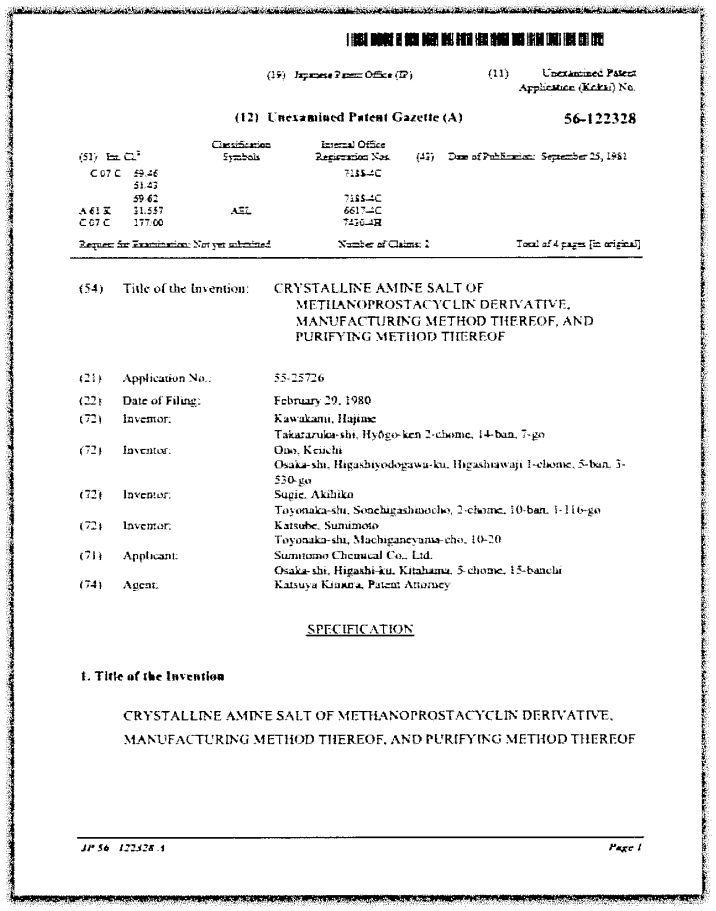
1. Title of the Invention

CRYSTALLINE AMINE SALT OF METHANOPROSTACYCLIN DERIVATIVE, MANUFACTURING METHOD THEREOF, AND PURIFYING METHOD THEREOF

JP 56-122328 A Page 1

- Kawakami uses a different salt to remove a different sort of impurity from a different structure.
- a POSA would have no reason to combine the teachings of Kawakami with Moriarty and Phares in the particular manner of the asserted grounds in the Petition, or a reasonable expectation of success of achieving a more pure treprostinil product by such a combination.
  - Ex. 2020 ¶114; PO Resp. at p. 41.

Kawakami Teaches Away From Claim 15



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(72) Inventor: Kawakami, Hajime
Takarazuka-shi, Hyôgo-ken 2-chome, 14-ban, 7-go

(72) Inventor: Ono, Kenichi
Osaka-shi, Higashiyodogawa-ku, Higashiawaji 1-chome, 5-ban, 3-520-go

(72) Inventor: Sugie, Akihiko
Toyonaka-shi, Sonehigashinocho, 2-chome, 10-ban, 1-116-go

(72) Inventor: Katsube, Sumimoto
Toyonaka-shi, Machiganeyama-cho, 10-20

(71) Applicant: Sumitomo Chemical Co., Ltd.
Osaka-shi, Higashi-ku, Kitahama, 5-chome, 15-banchi

(74) Agent: Katsuya Kimura, Patent Attorney

SPECIFICATION

1. Title of the Invention

CRYSTALLINE AMINE SALT OF METHANOPROSTACYCLIN DERIVATIVE, MANUFACTURING METHOD THEREOF, AND PURIFYING METHOD THEREOF

JP 56 122328 A Page 1

- Petition selectively uses Kawakami only for teaching regenerating the acid after salt formation, while ignoring the fact that it suggests using a different salt than what is taught by Phares for the purpose of purifying a much less pure starting material.
  - PO Resp. at p. 41.

Petitioner Mischaracterizes Dr. Williams Testimony Regarding Batch Analysis

- Petitioner alleged that Williams did not know if 10 data points in his analysis were produced under the Moriarty process.
  - Petitioner's Reply pp. 2 & 6.
- Dr. Williams clarified on redirect that they "were made by the Moriarty process."
  - Ex. 2059, 254-256.

Petitioner Mischaracterizes Dr. Williams Testimony Regarding Batch Analysis

- Petitioner also falsely alleged that the Moriarty batches were "cherry-picked" by including developmental batches with poor results.
  - Petitioner's Reply pp. 2 & 6.
- Dr. Williams clarified that he relied on Dr. Aristoff's selection of Moriarty batches from a separate case, *United Therapeutics v. Sandoz*.
  - Ex. 2059, 94:29-95:9.
- Those same batches were previously used to show how **good** the Moriarty batches were compared to a previous method.

Petitioner Mischaracterizes Dr. Williams Testimony Regarding Batch Analysis

- *In United Therapeutics v. Sandoz, Inc.*, the Court ruled that the same Moriarty batches used by Dr. Williams had fewer amounts of impurities and a lower amount of total related substances over batches made by the prior art.
  - 2014 WL 4259153, C.A. Nos. 12–CV–01617, 13–CV–316 (D.N.J. August, 29, 2014).

- Dr. Williams also clarified that developmental batches for both the Moriarty and '393 patent process were used in his analysis.
  - Ex. 2059, 101:21-102:13.

Petitioner Mischaracterizes Dr. Williams Testimony Regarding Batch Analysis

- Petitioner also alleged that Dr. Williams "had no explanation for why he included 10 development batches… for his analysis of Moriarty batches, but only 5 development batches… for his analysis of '393-Patent batches".
  - Petitioner's Reply p. 7.

- But Dr. Williams actually testified that "these were all the batches we could find records for".
  - Ex. 2059, 94:25- 95:9

Petitioner Mischaracterizes Dr. Williams Testimony Regarding Batch Analysis

- Dr. Williams' testimony stated only that *calculation* was correct, not that it was a "a fair analysis" as claimed in Petitioner's reply.
  - Ex. 2059 p. 219; Petitioner's Reply p. 2

- Petitioner also alleged that Dr. Williams testimony suggested that Steadymed's calculation of 99.7% "should be relied upon." Dr. Williams merely confirmed that calculation was correct using Steadymed's selected numbers.
  - Petitioner's Reply pp. 2-3;

Petitioner Mischaracterizes Dr. Williams Testimony Regarding Batch Analysis

- Petitioner also alleged that Dr. Williams did not perform calculations on data in Appendices A and B of his declaration, "having relied solely on counsel's work". Dr. Williams actually testified that he "checked the calculation" performed by counsel.
    - Petitioner's Reply pp. 8-9; Ex. 2059, 102:12-20

Petitioner Mischaracterizes Dr. Williams Testimony Regarding Batch Analysis

- Petitioner also alleged that the free acid is *less pure* than the diethanoleamine salt, and not more pure as UT represented to the FDA in Exhibit 2006. Dr. Williams could not provide an explanation for this discrepancy, which contradicts the Walsh Declaration. Dr. Williams stated that this wasn't something he considered in forming his opinion, and that he'd need more time to consider it; he simply wasn't able to provide an immediate explanation.
    - Petitioner's Reply p. 12; Ex. 2059, 199:6-18; Ex. 2059, 198:1-199:5, 199:19-21

Petitioner Mischaracterizes Dr. Williams Testimony Regarding Batch Analysis

- Petitioner also alleged that Dr. Williams concedes that the process in Phares for making treprostinil's (-)-enantiomer carries out the same alkylation step (a) and hydrolysis step (b) in the '393 Patent's claims, thus disclosing these steps for treprostinil. Dr. Williams stated on redirect that it was, in fact, a different step because in Phares you're using and producing the enantiomers, not the specified structures.
  - Petitioner's Reply p. 13; Ex. 2059, 264:15-265:23

Petitioner Grossly Mischaracterizes Dr. Williams Testimony Regarding Batch Analysis

- Petitioner also alleged that Dr. Williams, who is "not a polymorph expert," contends nevertheless that the melting point of two samples of the same polymorph (crystal form) cannot be compared to determine their relative purities. Dr. Williams' Declaration states that, when different solvents and crystallization conditions are used, you can't directly compare melting points to determine purities, not that melting points can't ever be compared to determine purity, and he reiterated this point at his deposition.
  - Petitioner's Reply p. 14; Ex. 2059, 158:17-18; 156:25-157:2; 159:6-160:12; Ex. 2020 ¶ 75

Petitioner Mischaracterizes Dr. Williams Testimony Regarding Batch Analysis

- Petitioner also alleged that, as admitted by Dr. Williams, melting point is one of the most common ways to identify different polymorphs; but the cited portion of Dr. Williams' transcript actually says "Q. Well, why do you think they do that? Why do you think they append a melting point to each polymorph? [Objection] THE WITNESS:· Well, certainly, that's a physical characteristic of an individual solid form."
  - Petitioner's Reply p. 14; Ex. 2059, 158:20-25

Petitioner Mischaracterizes Dr. Williams Testimony Regarding Batch Analysis

- Petitioner also alleged that Dr. Williams concedes that the same treprostinil diethanolamine salt polymorph—Form B—is presented in the Phares reference and '393 Patent; while Dr. Williams conceded they were both "called" polymorph B, he said he couldn't "be 100 percent certain" they were the same crystal form because the melting points differed.
  - Petitioner's Reply P. 15; Ex. 2059, 168:6-11, 168:12-169:2

Petitioner Mischaracterizes Dr. Williams Testimony Regarding Batch Analysis

- Petitioner also alleged that while Dr. Williams relies on his "personal experience" observing different melting points for crystals made with different solvents, he conceded that he knew of no literature to support his opinion; Dr. Williams does base it on his own experience but in the cited testimony states, regarding literature references, "I'm sure I could find it if I was asked to".
    - Petitioner's Reply p. 15; Ex. 2059, 184:22-185:2, 184-185:2

Petitioner Mischaracterizes Dr. Williams Testimony Regarding Batch Analysis

- Petitioner also alleged that Dr. Williams conceded that the one article he relied upon in his declaration, Ex. 2030, in fact describes different crystal forms having different melting points, and not the same crystal form having different melting points; but Dr. Williams' testimony was actually the opposite: "I'm not sure I can come to that conclusion. And what I did cite from this article is that the conclusion, which I quoted in my Declaration, and it's also based on my experience of crystallizing the same compound on different days from different solvents under slightly different conditions, you can get a different melting point. And it depends on the scale and lots of things."
    - Petitioner's Reply p. 15; Ex. 2059, 180:9-25, 181:17-182:13

Petitioner Mischaracterizes Dr. Williams Testimony Regarding Batch Analysis

- Petitioner also alleged that it is now confirmed that UT's Moriarty purity varies by at least 0.6%, and indeed, Dr. Williams conceded he had no reason to disagree with this 0.6% value; but directly before the cited portion, Dr. Williams said that he was "not familiar" with the standard deviation function in Excel because he doesn't use it "in [his] normal course of work."
  - Petitioner's Reply P. 16; Ex. 2059, 218:22-24, 218:15-21

Petitioner Mischaracterizes Dr. Williams Testimony Regarding Batch Analysis

- Petitioner also alleged that Dr. Williams' own example of "product" in his own writing—Ex. 2028—uses "product" to mean a product created by nature, and not by a chemical reaction, when it refers to "the natural product from marine sources." But Dr. Williams testimony actually was:

  "Q· · ·All right.· It's not a -- it's not a chemical reaction; this is a biological reaction; correct? A· · ·They're still reactions, so it's the product of, ultimately, chemical-bond formation.· So it's still understood by a person skilled in the art of a product of chemical reactions."

  - Petitioner's Reply p. 22; Ex. 2020, ¶ 63; Ex. 2059, 221:19-25

CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of Exhibit 2061 was served on November 23, 2016 via email to the counsel of record for the Petitioner at the following address: Steadymed-IPR@dlapiper.com.

Date: November 23, 2016

/Stephen B. Maebius/
Stephen B. Maebius
Registration No. 35,264
Counsel for Patent Owner

4843-5539-4874.1

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Paper No. 28
Entered: May 12, 2016

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 B2

Before LORA M. GREEN, JONI Y. CHANG, and
JACQUELINE T. HARLOW, *Administrative Patent Judges.*

HARLOW, *Administrative Patent Judge.*

DECISION
Redacted Institution of *Inter Partes* Review
37 C.F.R. § 42.108

I. INTRODUCTION

Petitioner, SteadyMed LTD ("SteadyMed"), filed a Petition requesting an *inter partes* review of claims 1–22 of U.S. Patent No. 8,497,393 B2 (Ex. 1001, "the '393 patent"). Paper 1 ("Pet."). Patent Owner, United Therapeutics Corporation ("UTC"), filed a Preliminary Response on January 14, 2016. Paper 10[1] ("Prelim. Resp."). We have jurisdiction under 35 U.S.C. § 314, which provides that an *inter partes* review may not be instituted unless the information presented in the petition "shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition."

For the reasons set forth below, we institute an *inter partes* review of claims 1–22 of the '393 patent.

A. Related Matters

The '393 patent is asserted in: *United Therapeutics Corp. v. Sandoz, Inc.*, No. 14-cv-05499 (D.N.J.); *United Therapeutics Corp. v. Teva Pharmaceuticals U.S.A., Inc.*, No. 14-cv-05498 (D.N.J.); and *United Therapeutics Corp. v. Watson Laboratories, Inc.*, No. 15-cv-05723 (D.N.J). Pet. 1. SteadyMed is not party to the above identified litigations. *Id.*

[1] Paper 10 is the Unredacted Preliminary Response. Paper 8, filed concurrently with Paper 10, is a redacted version of the Preliminary Response.

B. The '393 Patent

The '393 patent, titled "Process to Prepare Treprostinil, the Active Ingredient in Remodulin®," issued July 30, 2013, from U.S. Patent Application No. 13/548,446 ("the '446 application") (Ex. 1002), filed July 13, 2012. Ex. 1001, [54], [45], [21], [22]. The '446 application is a continuation of U.S. Patent Application No. 12/334,731 ("the '731 application") (Ex. 1002), filed on December 15, 2008, now issued as U.S. Patent No. 8,242,305 ("the '305 patent"). Ex. 1001, [63]. The '393 patent claims priority to U.S. Provisional Patent Application No. 61/014,232 (Ex. 2008), filed December 17, 2007. Ex. 1001, [60].

The '393 patent recites 22 product-by-process claims for prostacyclin derivatives, including treprostinil.[2] *Id.* at 17:51–21:16; Pet. 5; Prelim. Resp. 3. The process disclosed by the '393 patent takes advantage of carbon treatment and salt formation steps to remove impurities, eliminating the need for purification by column chromatography. *Id.* at 17:29–32; *see also id.* at 5:41–45 ("purification by column chromatography is eliminated . . . . [T]he salt formation is a much easier operation than column chromatography.").

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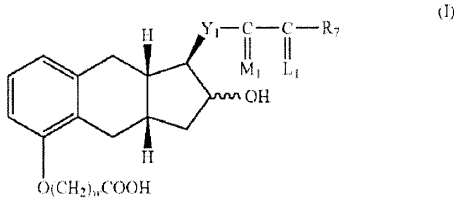
[2] The '305 patent, which issued from the parent to the application for the '393 patent, recites claims to a process for the preparation of prostacyclin derivatives comprising steps similar to those set forth in the product-by-process claims of the '393 patent. *Compare* Ex. 1001, 17:51–21:16, *with* Ex. 2007, 17:39–24:3.

The process for forming prostacyclin derivatives described in the '393 patent includes four steps: (a) alkylating a prostacyclin derivative to form an alkylated prostacyclin derivative; (b) hydrolyzing the alkylated prostacyclin derivative with a base to form a prostacyclin acid; (c) contacting the prostacyclin acid with a base to form a prostacyclin carboxylate salt; and (d) optionally reacting the prostacyclin carboxylate salt formed in (c) with an acid to form the desired compound, or pharmaceutically acceptable salt thereof. *Id.* at 1:65–3:19.

C. Illustrative Claim

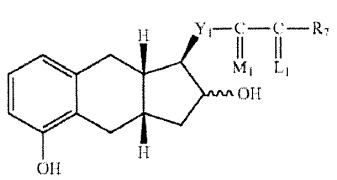
Each of the challenged claims is a product-by-process claim. Of the challenged claims, claims 1 and 9 are independent. Claim 1, reproduced below, is illustrative of the claimed subject matter.

1. A product comprising a compound of formula I

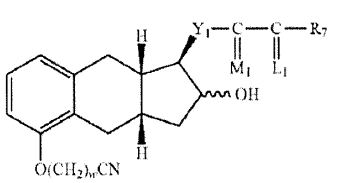


or a pharmaceutically acceptable salt thereof, wherein said product is prepared by a process comprising

a) alkylating a compound of structure II with an alkylating agent to produce a compound of formula III,



(II)

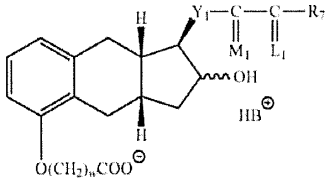


(III)

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)[3] with a base B to form a salt of formula I_s.



(I_s)

and

d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula I.

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[3] We note that the reference to "step (h)," rather than "step (b)," in claim 1 is an apparent typographical error. *See* Ex. 1001, 3:66–67 ("(c) contacting the product of step (b) with a base B to for a salt of formula IV_s"); *see also* Pet. 25; Ex. 1009 ¶ 51.

Ex. 1001, 17:51–19:29. Claim 9 is drawn to a product comprising a specific treprostinil compound within the genus set forth in claim 1, and made by the process recited in claim 1. *Id.* at 19:48–20:46.

D. Prior Art Relied Upon

SteadyMed relies upon the following prior art references (Pet. 4–6):

Phares	WO 2005/007081 A2	Jan. 27, 2005	(Ex. 1005)
Kawakami	JP 56-122328A	Sept. 25, 1981	(Ex. 1006[4])

Moriarty et al., *The Intramolecular Asymmetric Pauson-Khand Cyclization as a Novel and General Stereoselective Route to Benzindene Prostacyclins: Synthesis of UT-15 (Treprostinil)*, 69 J. Org. Chem. 1890–1902 (2004) ("Moriarty") (Ex. 1004); and

Seyhan N. Eğe, ORGANIC CHEMISTRY 543–547 (2d ed. 1989) ("Eğe") (Ex. 1008).

E. Asserted Grounds of Unpatentability

SteadyMed asserts the following grounds of unpatentability (Pet. 3–4):

Claims	Basis	Reference(s)
1–5, 7–9, 11–14, and 16–20	§ 102(b)	Phares
1–5, 7–9, 11–14, and 16–20	§ 103(a)	Moriarty and Phares or Kawakami
6, 10, 15, 21, and 22	§ 103(a)	Moriarty, Phares, Kawakami, and Eğe

[4] SteadyMed submitted a certified English translation of Kawakami as Ex. 1007. As discussed in Part II.F below, UTC argues the admissibility of this translation.

II. ANALYSIS

A. 35 U.S.C. § 325(d)

UTC urges the exercise of our discretion under 35 U.S.C. § 325(d) to deny some or all of the grounds of unpatentability presented by SteadyMed because the same, or substantially similar issues were addressed during prosecution. Prelim. Resp. 25–26. UTC states that the Patent Office considered Moriarty alone, and in combination with Phares, during prosecution of the '393 patent. *Id.* at 8–10, 26. UTC also reports that Phares was considered alone, and in combination with Moriarty, during prosecution of U.S. Patent Application No. 13/910,583 ("the '583 application") (Ex. 2010) filed June 5, 2013, which is a continuation of the '446 application. *Id.* at 11–14.

Regarding the patentability of claims 6, 15, 21, and 22, in particular, UTC asserts that Eğe "is nothing more than a first-year organic chemistry textbook," and that SteadyMed "relies on nothing more than conclusory statements in three paragraphs of the [Declaration of Jeffery D. Winkler]" to support its unpatentability arguments. *Id.* at 26. UTC therefore contends that SteadyMed "has provided no evidence of probative value that is any different than what was already before the Patent Office during prosecution." *Id.* at 26–27.

Although it is within our discretion to "reject the petition or request because, the same or substantially the same prior art or arguments previously were presented to the Office" pursuant to 35 U.S.C. § 325(d), we decline to do so here.

We note that during prosecution of the '446 application, which issued as the '393 patent, the Examiner rejected the claims as anticipated by Moriarty, but subsequently withdrew that rejection, without elaboration, in response to a declaration filed by David A. Walsh ("Walsh Declaration") (Ex. 1002, 346–350), one of the named inventors of the '393 patent, and the Executive Vice President of Chemical Research and Development at UTC. Ex. 1002, 344, 346–360. Although Phares is listed as a cited reference on the face of the '393 patent (Ex. 1001, [56]), we observe that the Examiner neither relied on, nor otherwise discussed Phares during prosecution of the '446 application (Ex. 1002, 295–296, 327–330, 359). In addition, neither Eğe nor Kawakami was considered during prosecution of the '446 application. *Id.* at 235–359. The grounds of unpatentability asserted in the instant Petition likewise differ from the rejections entered by the Examiner during prosecution of the '731 application, the parent to the '446 application. *See* Ex. 1002, 122–124.

Moreover, as discussed in detail in Part II.B below, the Declaration of Jeffrey D. Winkler ("Winkler Declaration") (Ex. 1009), submitted in support of SteadyMed's Petition, calls into question Dr. Walsh's conclusion that treprostinil prepared according to the process claimed in the '393 patent is "physically different from treprostinil prepared according to the process of 'Moriarty'" (Ex. 1002, 347 (¶ 6)). Ex. 1009 ¶¶ 63–71. In addition, as set forth in Part II.F, we disagree with UTC's characterization of Dr. Winkler's testimony as conclusory. *See, e.g.*, Ex. 1009 ¶¶ 80–90.

We, therefore, decline to exercise our discretion to deny the Petition pursuant to 35 U.S.C. § 325(d). *See Nestle USA, Inc. v. Steuben Foods, Inc.*, Case IPR2014-01235, slip op. at 7 (PTAB Dec. 22, 2014) (Paper 12) ("[W]e conclude that Petitioner's arguments regarding the unpatentability of claims 18–20, which include arguments relating to Biewendt and a combination of references previously not considered and supported by a declaration previously not considered, are persuasive. . ."); *Merial Ltd., v. Virbac*, Case IPR2014-01279, slip op. at 9 (PTAB Jan. 22, 2015) (Paper 13) (noting the different burdens of proof and evidentiary standards applicable to *ex parte* examination and *inter partes review* proceedings).

B. Claim Construction

In an *inter partes* review, claim terms in an unexpired patent are given their broadest reasonable interpretation in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b); *see also In re Cuozzo Speed Techs., LLC*, 793 F.3d 1268, 1278–79 (Fed. Cir. 2015) ("Congress implicitly approved the broadest reasonable interpretation standard in enacting the AIA," and "the standard was properly adopted by PTO regulation."), *cert. granted sub nom. Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 890 (2016) (mem.). Under this standard, we may take into account definitions or other explanations provided in the written description of the specification. *In re Morris*, 127 F.3d 1048, 1054 (Fed. Cir. 1997). Any special definition for a claim term must be set forth in the specification with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d

1475, 1480 (Fed. Cir. 1994). Only those terms that are in controversy need be construed, and only to the extent necessary to resolve the controversy. *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999).

"Product" / "A product comprising a compound [of/having] formula [I/IV] . . . or a pharmaceutically acceptable salt thereof"

Independent claims 1 and 9 recite the phrase "[a] product comprising a compound [of/having] formula [I/IV] . . . or a pharmaceutically acceptable salt thereof . . . ." Ex. 1001, 19:48–20:46. In addition, each challenged dependent claim recites the term "product." *Id.* at 17:51–21:16. Because the parties advance similar arguments pertaining to the construction of these terms, we address these terms together.

SteadyMed asserts that the phrase "[a] product comprising a compound [of/having] formula [I/IV] . . . or a pharmaceutically acceptable salt thereof" should be interpreted to mean "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." Pet. 11. SteadyMed contends that because independent claims 1 and 9 recite "[a] product comprising," the claim term "product" should be construed to include "the treprostinil compound along with other substances (including impurities)," i.e., a "chemical composition." *Id.* at 11.

UTC counters that "[a] product comprising a compound [of/having] formula [I/IV] . . . or a pharmaceutically acceptable salt thereof" should be interpreted as "a substance resulting from a chemical reaction constituted primarily of formula I/IV or a pharmaceutically acceptable salt thereof." Prelim. Resp. 21. As an initial matter, UTC notes that SteadyMed's proposed construction refers only to Formula I, and asserts that SteadyMed "inexplicably read[s] Formula IV out of the term entirely." *Id.* at 22.

UTC further argues that the claims and Specification of the '393 patent use "product" to refer to a substance resulting from a chemical reaction. *Id.* at 17. UTC also contends that the prosecution history for the '393 patent supports its proposed construction because "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." *Id.* at 18–19. UTC points to chemistry textbooks as buttressing its position that a skilled artisan would understand the claim term "product" as referring to "a substance resulting from a chemical reaction." *Id.* at 19. UTC further reasons that "the 'product' claimed in a product-by-process claim is necessarily a substance that results from the process specified in that claim" (*id.*), and that SteadyMed's proposed construction "contradicts this inherent limitation of the claims" (*id.* at 22).

On this record, and for purposes of this decision, we interpret the phrase "[a] product comprising a compound [of/having] formula [I/IV] or a

pharmaceutically acceptable salt thereof," to mean "a product including, but not limited to, a compound [of/having] formula [I/IV] or a pharmaceutically acceptable salt thereof."

The claim term "product," as it is used in the '393 patent, does not require construction because the claimed "product" is defined by the limitations recited in the challenged claims. This is evidenced by independent claims 1 and 9, which recite "[a] product comprising . . . ," and go on to define the essential elements of the claimed product. The transitional term "'comprising' is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim." *Genentech, Inc. v. Chiron Corp.*, 112 F.3d 495, 501 (Fed. Cir. 1997); *see also* Ex. 1001, 4:23–25 (defining "comprising" as "including, but not limited to"). Thus, the open-ended structure of the challenged claims forecloses limitation of the term "product" beyond that achieved by the recited claim elements.

Indeed, neither UTC nor SteadyMed identifies any disclosure in the '393 patent or its prosecution history that necessitates a contrary understanding of the term "product." For example, the portions of the Specification to which UTC points comport with an understanding of "product" as being defined only by the recited claim elements. *See* Ex. 1001, 5:45–46, 7:16–20, 17:37–40. Furthermore, far from disavowing or otherwise limiting claim scope, the portions of the prosecution history identified by UTC are consistent with an understanding that the claimed "product" is defined solely by the recited claim elements. *See* Ex. 1002,

315, 328–329, 346–350. We similarly are unpersuaded that the chemistry textbook glossaries to which UTC points (Exs. 2011, 2012, 2014) provide a basis for narrowly interpreting "product" to require that the product result from a chemical reaction.

Regarding the larger claim phrase "[a] product comprising a compound [of/having] formula [I/IV] . . . or a pharmaceutically acceptable salt thereof," as explained above, we determine that the embedded claim term "comprising" means "including, but not limited to." *See Genentech*, 112 F.3d at 501; *see also* Ex. 1001, 4:23–25. Accordingly, we reject UTC's proposal that claims 1 and 9 be read to require a product "*constituted primarily of* formula I/IV or a pharmaceutically acceptable salt thereof." Prelim. Resp. 21 (emphasis added).

"[A/the] process comprising"

SteadyMed argues that the claim phrase "[a/the] process comprising," which appears in independent claims 1 and 9, should be interpreted as "a process that includes, but is not limited to, the recited process steps, and may include, without limitation, any other non-recited steps." Pet. 12. UTC counters that this claim phrase should be construed to mean "a/the process including but not limited to." Prelim. Resp. 23–24. For the reasons set forth above, we agree with UTC that these claim phases should be interpreted to mean "a/the process including, but not limited to."

Product-by-Process Claims

Each of the challenged claims is a product-by-process claim. Ex. 1001, 17:51–21:16; Pet. 5; Prelim. Resp. 3. The general rule when determining patentability of a product-by-process claim is to "focus . . . on the product and not on the process of making it." *Amgen, Inc. v. Hoffman-La Roche Ltd.*, 580 F.3d 1340, 1369 (Fed. Cir. 2009). This general rule embodies the long-standing principle that "an old product is not patentable even if it is made by a new process." *Id.* at 1370. An exception applies when process steps recited in the claim impart "structural and functional differences" to the claimed product. *Greenliant Sys., Inc. v. Xicor LLC*, 692 F.3d 1261, 1267–1268 (Fed. Cir. 2012). If the exception applies, the structural and functional differences conveyed by the recited process steps "'are relevant as evidence of no anticipation' although they 'are not explicitly part of the claim.'" *Id.* at 1268 (citing *Amgen*, 580 F.3d at 1370).

SteadyMed contends that the challenged claims do not yield a treprostinil product having structural or functional differences as compared to treprostinil products produced by prior art methods. Pet. 19–22. Specifically, SteadyMed asserts that the Walsh Declaration, relied on by UTC during prosecution as evidencing differences in the treprostinil products of the '393 patent and Moriarty, fails to demonstrate any functional or structural differences between the instantly claimed and prior art treprostinil products. *Id.* SteadyMed relies on the Winkler Declaration (Ex. 1009) to support its position. *Id.*

UTC acknowledges that "at the time of the '393 patent, there existed at least three prior art methods" for making treprostinil. Prelim. Resp. 33. Relying on the Walsh Declaration, UTC asserts that the process steps recited in independent claims 1 and 9 are entitled to patentable weight because they yield a "physically different and improved final product with significantly reduced overall impurities and a distinct and unexpected impurity profile" as compared to treprostinil produced using prior art methods. *Id.* at 3.

The Walsh Declaration compares the impurity profile of treprostinil free acid "prepared according to the process of 'Moriarty'" to the impurity profiles of treprostinil free acid and treprostinil diethanolamine "prepared according to the process specified in claim 1 or [9]" of the '393 patent.[5] Ex. 1002, 347–348 (¶ 6). Dr. Walsh concludes that the treprostinil free acid and treprostinil diethanolamine prepared according to the process of claims 1 and 9 is physically different from the treprostinil diethanolamine prepared according to the process of Moriarty "at least because neither of [the '393 patent products] 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'." *Id.* at 349 (¶ 8). In addition, Dr. Walsh provides "data obtained from representative Certificates of Analysis" indicating that treprostinil free acid "prepared

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[5] Issued claim 9 of the '393 patent is identified as claim 10 in the Walsh Declaration, and other documents in the prosecution history in the '393 patent.

according to 'Moriarty'" is 99.4% pure, while the treprostinil free acid and treprostinil diethanolamine "prepared according to the process specified in claim 1 or [9]" are 99.8% pure and 99.9% pure, respectively. *Id.* at 347–348 (¶ 6).

SteadyMed disputes Dr. Walsh's contention that there are physical differences between the treprostinil products of the '393 patent and prior art. Pet. 19–22; *see also* Ex. 1009 ¶¶ 63–71. As an initial matter, SteadyMed points out that the 99.7% treprostinil purity reported by Moriarty (Ex. 1004, 13) is higher than the 99.5% purity recited in claims 2 and 10 of the '393 patent, the only challenged claims that recite a purity level. Pet. 20; *see also* Ex. 1009 ¶ 65. In addition, Dr. Winkler testifies that the limited sample set, consisting of "*only two specific batches* of treprostinil" (Ex. 1009 ¶ 66), and absence of any disclosure concerning the reaction conditions, reagents, and solvents used in carrying out the process of claims 1 and 9 of the '393 patent (*id.* ¶ 67), undermine the veracity of Dr. Walsh's conclusion regarding the purity of these products. *Id.* ¶¶ 66–67. SteadyMed also observes that the statement in the Specification of the '393 patent that in one embodiment the purity of treprostinil is "at least 90.0%, 95.0%, 99.0%, 99.5%" (Ex. 1001, 8:66–67), supports the conclusion that the 99.8% purity purportedly achieved by Dr. Walsh "is based on a particular set of process steps that are not claimed and which must have been found after the filing date." Pet. 20.

Dr. Winkler additionally testifies that the alleged differences in purity between the treprostinil batches described by Dr. Walsh are attributable to

experimental error. *Id.* ¶¶ 68–70. Dr. Winkler testifies that "the literature on [High Performance Liquid Chromatography's ("HPLC's")] precision indicates that the 'RSD' or 'relative standard deviation' for a typical instrument is about 1%. (Ex. 1017.)." *Id.* ¶ 70. Dr. Winkler further observes that "[i]n 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)." *Id.* Dr. Winkler, thus, concludes that "[t]his 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." *Id.* On this record, we credit Dr. Winkler's testimony, as it is consistent with the disclosures of the prior art and the disclosure of the '393 patent itself.

UTC does not challenge SteadyMed's arguments concerning the shortcomings of the Walsh Declaration. Rather, UTC points to correspondence with, and reports submitted to, the Food and Drug Administration ("FDA") relating to the acceptance of a supplemental new drug application for treprostinil. Prelim. Resp. 36–38. UTC contends that these reports show that "the purity of the treprostinil improved close to 100%" for treprostinil prepared as described in claims 1 and 9 of the '393 patent as opposed to the prior process implemented by UTC. Prelim. Resp. 38; *see also* Ex. 2006, 3–4.

On the record before us, and for purposes of this decision, we conclude that the process steps recited in the challenged claims do not impart structural or functional differences to the claimed product.

As an initial matter, we observe that the challenged product-by-process claims are drawn to "[a] product comprising a compound" of either formula I or formula IV, or a pharmaceutically acceptable salt of the recited formula. Ex. 1001, 17:51–19:29, 19:48–20:46). "'Comprising' is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim." *Genentech*, 112 F.3d at 501. Thus, a product comprising a particular compound must contain that compound, but may additionally include other substances, such as impurities. On this record, therefore, it is unclear how claims 1, 3–9, and 11–22, which claim a product comprising a particular compound, but do not recite limitations concerning the purity profile of that product, could be restricted to a product including the claimed compound, but also having a particular purity profile. In addition, although claims 2 and 10 require a purity of at least 99.5% (Ex. 1001, 19:29–30, 20:47–48), these claims similarly are drawn to a product comprising a compound, and do not specify the type of impurities that may be present in the compound or restrict the amount of any particular impurity that may be present, so long as the product remains at least 99.5% pure.

Furthermore, the evidence presently before us, including UTC's own testing results, suggests that inter-batch variability in impurity profiles,

experimental error in impurity measuring equipment, and variations in reagents, solvents, and reaction conditions, rather than the instantly recited process steps, account for any purported improvements in purity reported by UTC. We observe that UTC offers no explanation for the variation between the 99.7% purity reported by Moriarty, and the 99.4% purity Dr. Walsh obtained for treprostinil purportedly prepared according to the process described by Moriarty. Neither does UTC offer reasoning for crediting Dr. Walsh's results over those reported by Moriarty himself. Similarly, UTC neglects Dr. Winker's assessment of the experimental error present, but unaccounted for, in the impurity measurements reported in the Walsh Declaration, and fails to account for the absence of any disclosure regarding the experimental protocols followed by Dr. Walsh, such as the reaction conditions, or the solvents or reagents used, in synthesizing treprostinil according to Moriarty or the '393 patent.

Moreover, the Process Optimization Report (Ex. 2005) proffered by UTC supports the conclusion that the process steps recited in the '393 patent do not produce a treprostinil product that differs, either structurally or functionally, from that produced using prior art methods.

The Process Optimization Report discloses the impurity analyses for five batches of treprostinil identified by UTC as having been prepared using the process recited in the '393 patent. Ex. 2005, 4–6; *see also* Prelim. Resp. 36 ("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,[6] which was performed on specific batches of the diethanolamine salt intermediate produced by steps (a)-(c) [redacted].").
The Process Optimization Report states that the purity of these batches, as determined by HPLC analysis, ranged from [redacted] to [redacted].[7] Ex. 2005, 6. Additionally, the Process Optimization Report indicates that each of the following impurities were detected by HPLC analysis in one or more of the above referenced treprostinil batches: [redacted]. *Id.*

We also observe that although UTC sought, and obtained from the FDA, modification of the specification for the HPLC assay for treprostinil to require a purity range of 98%–102%, rather than 97%–101%, [redacted] Ex. 2006, 3–4, 6; Ex. 2003. Notably, UTC's specification for treprostinil produced according to the '393 patent permits

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[6] We note that UTC likely intended to reference independent claim 9 of the '393 patent, rather than dependent claim 10; however our analysis is equally applicable to claim 9 or claim 10.

[7] The reported batch purity values were [redacted] for an average purity of [redacted] Ex. 2005, 6.

each of the following impurities: [redacted]. Ex. 2006, 6. The analysis of treprostinil purportedly prepared according to the process of Moriarty, set forth in the Walsh Declaration, reveals that each of the impurities detected in Moriarty treprostinil was present in an amount [redacted] *Compare* Ex.1002, 347, *with* Ex. 2006, 6.

Accordingly, on the record before us, and for purposes of this decision, we conclude that the process steps recited in the challenged claims of '393 patent do not impart structural or functional differences to the claimed product as compared to prior art processes, and therefore, that these process steps do not patentably limit the claimed product. We note, however, that the factual dispute between the parties concerning the existence of any structural or functional differences between treprostinil products produced according to the process recited in the '393 patent and prior art processes, as well as arguments addressing our concerns regarding the relevance of the impurity profile of a product obtained by the recited process to the patentability of claims drawn to a product *comprising* a compound, are appropriate for further development at trial.

C. Principles of Law

To establish anticipation, each and every element in a claim, arranged as recited in the claim, must be found in a single prior art reference. *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369 (Fed. Cir. 2008). "A reference anticipates a claim if it discloses the claimed invention 'such that a skilled artisan could take its teachings in combination with his own knowledge of the particular art and be in possession of the invention.'" *In re Graves*, 69 F.3d 1147, 1152 (Fed. Cir. 1995) (emphasis omitted) (quoting *In re LeGrice*, 301 F.2d 929, 936 (CCPA 1962)).

A patent claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the claimed subject matter 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. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

> When a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability. For the same reason, if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the

> same way, using the technique is obvious unless its actual application is beyond his or her skill. *Sakraida* [*v. Ag Pro, Inc.*, 425 U.S. 273 (1976)] and *Anderson's–Black Rock* [*v. Pavement Salvage Co.*, 396 U.S. 57 (1969)] are illustrative—a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions.

KSR, 550 U.S. at 417.

The level of ordinary skill in the art is reflected by the prior art of record. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001); *In re GPAC Inc.*, 57 F.3d 1573, 1579 (Fed. Cir. 1995); *In re Oelrich*, 579 F.2d 86, 91 (CCPA 1978).

D. Anticipation Grounds of Unpatentability Based on Phares

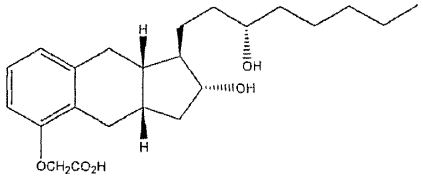
SteadyMed asserts that claims 1–5, 7–9, 11–14, and 16–20 are unpatentable under § 102(b) as anticipated by Phares. Pet. 22–37. Claims 2–5, 7, 8, and 19 depend directly from claim 1, and claims 11–14, 16–18, and 20 depend, directly or indirectly, from claim 9. In support of its assertion, SteadyMed provides detailed explanations as to how Phares discloses each claim limitation (*id.*), and relies upon the Winkler Declaration (Ex. 1009) to support its positions.

UTC counters that the treprostinil product of Phares is physically different from that produced by the process disclosed in the '393 patent, and, therefore, that the process steps disclosed in the claims of the '393 patent are limiting for purposes of the patentability determination. Prelim. Resp. 33–36. UTC also argues that SteadyMed improperly engages in picking and choosing among distinct embodiments in Phares to piece together an

anticipation argument as to the recited process steps. *Id.* at 29–31. UTC further asserts that explicit disclosure of certain claimed process steps is absent from SteadyMed's anticipation analysis, and that SteadyMed fails to show that those limitations are inherently disclosed by Phares. *Id.* at 31–36.

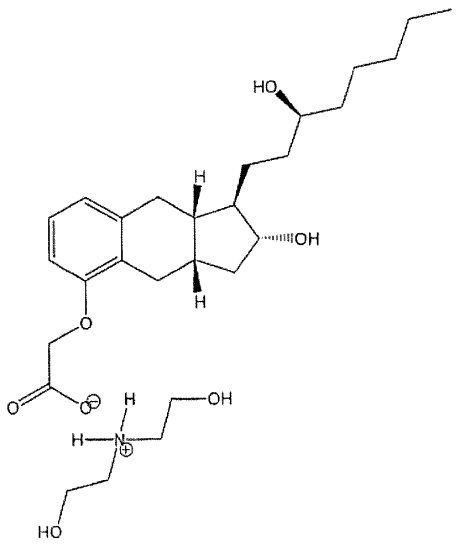
Phares

Phares describes "compounds and methods for inducing prostacyclin-like effects in a subject or patient," including treprostinil and derivatives thereof. Ex. 1005, 10. The chemical structure of treprostinil disclosed by Phares, on page 10 of Exhibit 1005, is reproduced below:



Id. Phares explains that "[t]reprostinil is a chemically stable analog of prostacyclin, and as such is a potent vasodilator and inhibitor of platelet aggregation." *Id.*

Phares further discloses that "[a] preferred embodiment of the present invention is the diethanolamine salt of treprostinil. . . . A particularly preferred embodiment of the present invention is form B of treprostinil diethanolamine." *Id.* at 11. The structure of the diethanolamine salt of treprostinil described by Phares, on page 99 of Exhibit 1005, is reproduced below:

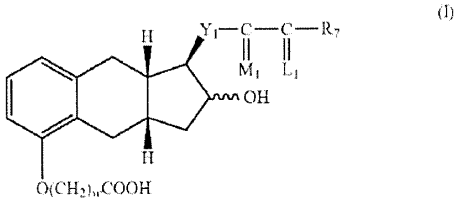


Id. at 99 (claim 49). Phares reports that form B of the diethanolamine salt of treprostinil "appears to be a crystalline material which melts at 107°C." *Id.* at 91.

Phares describes the synthesis of (-)-treprostinil, the enantiomer of treprostinil. Ex. 1005, 41–42. Phares explains that "[e]nantiomers of these compounds . . . can be synthesized using reagents and synthons of enantiomeric chirality of the above reagents." *Id.* at 41. In particular, Phares teaches that "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." *Id.* at 42. Phares discloses the following reaction procedure: "i. $ClCH_2CN$, K_2CO_3. ii, KOH, CH_3OH, reflux. 83 % (2 steps)." *Id.*

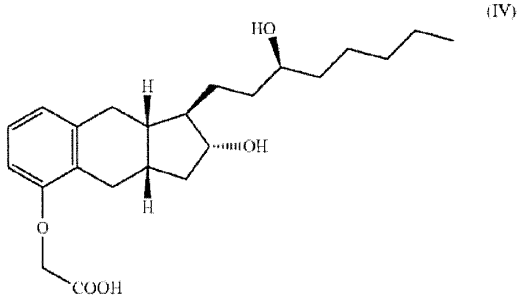
A product comprising a compound [of/having] formula [I/IV] . . . or a pharmaceutically acceptable salt thereof

Claim 1 of the '393 patent recites "[a] product comprising a compound of formula I



(I)

or a pharmaceutically acceptable salt thereof," and sets forth a series of process steps for obtaining the claimed product. Claim 9 recites "[a] product comprising a compound having formula IV



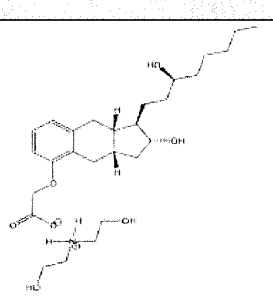
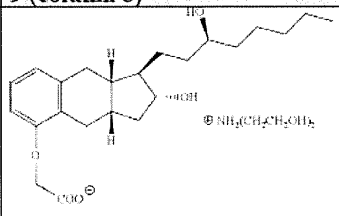
(IV)

or a pharmaceutically acceptable salt thereof," and includes the same process steps for obtaining the claimed product as recited in claim 1. 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. Accordingly, we address these claims together.

SteadyMed contends that "Phares discloses in its Claim 49 the identical, pharmaceutically acceptable treprostinil diethanolamine salt" claimed in the '393 patent. Pet. 26; *see also* Ex. 1005, 24, 85–93, 99

(claim 49); Ex. 1009 ¶¶ 50–53. In support of SteadyMed's position, Dr. Winkler testifies that "[o]ther than a change in formatting, the two structures [for treprostinil diethanolamine salt] from Phares and the '393 Patent are identical." Ex. 1009 ¶ 53.

Paragraph 52 of the Winkler Declaration depicts a side-by-side comparison of the chemical structures disclosed in claim 49 of Phares, and column 8, lines 50–63 of the '393 patent, reproduced below:

Phares (Ex. 1005), Claim 49	'393 Patent (Ex. 1001), Claims 1 & 9 (column 8)
	

Id. ¶ 52. As shown in the figure from paragraph 52 of the Winkler Declaration, the treprostinil diethanolamine salt disclosed by Phares is structurally identical to that disclosed in the '393 patent.

As set forth in Part II.B above, SteadyMed, relying on the Winkler Declaration, further asserts that the process disclosed in claims 1 and 9 of the '393 patent does not result in a treprostinil product that is physically different or unique from treprostinil produced by prior art methods. Pet. 19–22; *see also* Ex. 1009 ¶¶ 63–71. In support of this position, Dr. Winkler testifies that "[i]n both the '393 Patent and Phares (Ex. 1005), treprostinil diethanolamine salt Form B is made . . . . Phares further discloses a melting point of 107° C (Ex. 1005, p. 91 & Fig. 21) for the Form B salt."

Ex. 1009 ¶ 59; *see also* Ex. 1005, 90–93; Pet. 27. Dr. Winkler also testifies that Phares discloses the same procedure as is claimed in the '393 patent, but describes this procedure in reference to the synthesis of the enantiomer of treprostinil. Ex. 1009 ¶¶ 55–57; Ex. 1005, 41–42; Pet. 25–26. Dr. Winkler thus concludes that in "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." Ex. 1009 ¶ 62; *see also id.* ¶ 60 (citing Ex. 1018, 6); Pet. 27–28.

SteadyMed also contends that Phares anticipates the process steps recited in claim 1. Pet. 24–28; Ex. 1005, 24, 41–42, 85–93, 99 (claim 49); Ex. 1009 ¶¶ 44–71.

UTC does not dispute Phares' disclosure of a treprostinil product; rather, as previewed in relation to its claim construction arguments above, UTC contends that the treprostinil product of Phares is "physically different" from that claimed in the '393 patent, and, therefore, not anticipatory. Prelim. Resp. 33–36. UTC argues that as Phares does not disclose which treprostinil starting material is used, it "cannot inherently anticipate the final treprostinil product of the '393 patent because each method would result in a distinct impurity profile." Prelim. Resp. 34. Referring to the Walsh Declaration, UTC further asserts that "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." *Id.* UTC also asserts that SteadyMed's reliance

on the melting point of the treprostinil product of Phares as a proxy for purity is misplaced because "melting point does not disclose any specific impurity level and instead may demonstrate a different form, or polymorph, of treprostinil diethanolamine altogether." *Id.* at 35.

UTC additionally argues that Phares does not disclose the same process for generating treprostinil as recited in claims 1 and 9, and that SteadyMed improperly "cobbles together disclosure from four disparate portions of Phares covering multiple distinct embodiments" to arrive at the claimed invention. Prelim. Resp. 27. Further, UTC asserts that even if SteadyMed were permitted to pick and choose steps from various embodiments of Phares, SteadyMed nevertheless must rely on inherency to prove anticipation because "Phares lacks express disclosure of certain claim elements." *Id.* at 28.

The present record supports SteadyMed's contention that the treprostinil diethanolamine salt taught by Phares is identical in structure to the pharmaceutically acceptable treprostinil diethanolamine salt recited in claims 1 and 9. Pet. 24; *see also* Ex. 1005, 24, 99 (claim 49); Ex. 1009 ¶¶ 52–53. Dr. Winkler testifies that the process for producing treprostinil disclosed by Phares yields the same form (Form B) of treprostinil diethanolamine salt as the process of the '393 patent, and that the treprostinil diethanolamine salt of Phares is at least equal in purity to the treprostinil product of the '393 patent. Ex. 1009 ¶¶ 59–62. Dr. Winkler further testifies that Phares discloses the same process for synthesizing treprostinil as the

'393 patent. Ex. 1009 ¶¶ 55–57, 62; Ex. 1005, 41–42; Pet. 25–26. On this record, we credit Dr. Winkler's testimony.

We are not persuaded by UTC's arguments concerning the possibility that treprostinil produced according to Phares might have a different impurity profile than that produced according to the process disclosed in the '393 patent. First, for the reasons set forth in Part II.B above, it is unclear on this record how the use of the transitional phrase "comprising" excludes any impurities that may possibly be produced by the process of Phares. In addition, the present record supports a finding that the impurity profiles for treprostinil diethanolamine salt prepared as described by Phares and that prepared according to the '393 patent are the same. As explained above, Dr. Winkler's testimony regarding the form and melting point of Phares' treprostinil product, is consistent with the conclusion that the products of Phares and the '393 patent are the same.

Furthermore, we note that, as explained in Parts II.A and II.B above, the inter-batch variability in treprostinil impurity profiles, experimental error inherent in impurity measurements, and the variety and extent of impurities permitted in UTC's specification for the manufacture of treprostinil according to the process of the '393 patent, which remained unchanged when UTC migrated from a prior art process to the process of the '393 patent, support the conclusion that the process steps recited in claims 1 and 9 of the '393 patent do not impart any structural or functional differences over prior art treprostinil products.

Accordingly, given the evidence before us in this record, we conclude that SteadyMed has established adequately for purposes of this decision that Phares teaches the treprostinil diethanolamine salt product recited in claims 1 and 9. Because we determine, on the record before us, and for purposes of this decision, that the process steps recited in claims 1 and 9 do not impart structural or functional differences to the claimed treprostinil product and are therefore not limiting, we do not address the parties' contentions concerning Phares' anticipation of the recited process steps.

Conclusion

UTC has not raised any additional arguments with regard to the dependent claims other than those addressed above. We have reviewed SteadyMed's evidence, arguments, and claim charts, and conclude that SteadyMed has sufficiently demonstrated that the dependent claims are also anticipated by Phares. Thus, for the foregoing reasons, we conclude that SteadyMed has shown a reasonable likelihood of prevailing on its assertions that claims 1–5, 7–9, 11–14, and 16–20 are anticipated by Phares.

E. Obviousness Grounds of Unpatentability Based on Moriarty and Phares

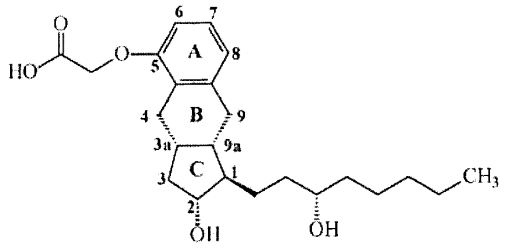
SteadyMed asserts that claims 1–5, 7–9, 11–14, and 16–20 are unpatentable under § 103(a) as obvious in view of Moriarty and Phares. Pet. 37–52. Claims 2–5, 7, 8, and 19 depend directly from claim 1, and claims 11–14, 16–18, and 20 depend, directly or indirectly, from claim 9. In support of its assertion, SteadyMed provides detailed explanations as to how

the combination of Moriarty and Phares discloses each claim limitation (*id.*), and relies upon the Winkler Declaration (Ex. 1009) to support its positions.

UTC counters that "Phares fails to disclose the synthetic route or purity of the claimed treprostinil product. Moriarty adds nothing to cure these deficiencies." Prelim. Resp. 43. UTC asserts that the process described in the '393 patent "unexpectedly reduced the impurity level in the claimed treprostinil product even more" than Moriarty, and reiterates its position that treprostinil produced according to the process of the '393 patent has "a superior purity profile compared to the prior art." *Id.* at 44.

Moriarty

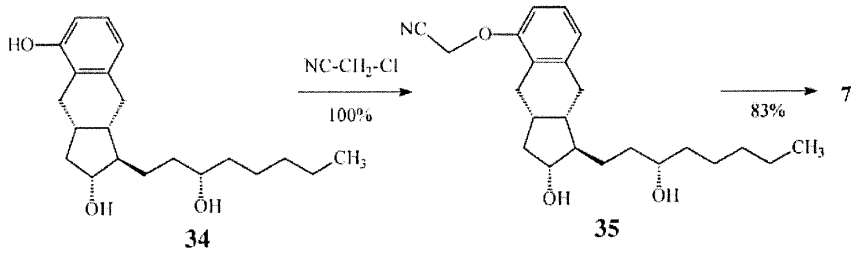
Moriarty describes the synthesis of treprostinil "via the stereoselective intramolecular Pauson-Khand cyclization." Ex. 1004, 1. Formula 7 of Moriarty is reproduced below:



7

Id. at 3. Formula 7 of Moriarty depicts the chemical structure of treprostinil. *Id.*

An excerpt of Scheme 4 of Moriarty is reproduced below:



Id. at 6. The excerpted portion of Scheme 4 of Moriarty illustrates the alkylation Formula 34 to yield Formula 35, and subsequent hydrolysis of Formula 35 with a base (followed by acidification) to yield Formula 7, treprostinil. Ex. 1004, 6, 13.

A product comprising a compound [of/having] formula [I/IV] . . . or a pharmaceutically acceptable salt thereof

SteadyMed contends that Moriarty and Phares respectively disclose treprostinil acid and treprostinil diethanolamine salt, as recited in claims 1 and 9 of the '393 patent. Pet. 22–23, 24, 33, 39, 48; *see also* Ex. 1004, 6, 13; Ex. 1005, 24, 99 (claim 49); Ex. 1009 ¶¶ 74, 76. Furthermore, Dr. Winkler testifies that the combination of Moriarty and Phares "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." Ex. 1009 ¶ 76.

SteadyMed asserts that Moriarty discloses steps (a) and (b) of claims 1 and 9, and that Phares discloses step (c) of these claims. Pet. 43; *see also* Ex. 1004, 6, 13; Ex. 1005, 24; Ex. 1009 ¶ 74. Dr. Winkler testifies

that a relevant skilled artisan would have recognized that the treprostinil acid produced in Moriarty could be purified by contacting it with a base as described by Phares. Ex. 1009 ¶ 74. In addition, as discussed in Part II.D above, Dr. Winkler testifies that Phares "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)." *Id.* ¶55. Dr. Winkler further testifies that a relevant skilled artisan would have had "more than a reasonable expectation of success that the reaction of treprostinil with diethanolamine would be successful" because "Phares (Ex. 1005, p. 24, p. 99, Claim 49) performed the same reaction and it was successful." Ex. 1009 ¶ 80.

UTC reasserts the arguments described above concerning the purity of treprostinil produced according to the process disclosed in the '393 patent. UTC acknowledges that Moriarty itself was an improvement over the prior art, but contends that "the '393 patent unexpectedly reduced the impurity level in the claimed treprostinil product even more." Prelim. Resp. 44. Specifically, UTC contends that "performing step (c) on a product that resulted from steps (a) and (b) provided a product with reduced impurities." *Id.* UTC also reiterates its arguments concerning the Walsh Declaration, and highlights the purported differences in the impurity profile of treprostinil produced according to Moriarty compared to that produced according to the '393 patent.

The present record supports SteadyMed's contention that the treprostinil diethanolamine salt disclosed by the combination of Moriarty

and Phares is identical in structure to the pharmaceutically acceptable treprostinil diethanolamine salt recited in claims 1 and 9. Pet. 41–42; *see also* Ex. 1004, 6, 13; Ex. 1005, 24, 99 (claim 49); Ex. 1009 ¶ 76.

First, as explained in Part II.B above, the present record does not support the conclusion that claims drawn to "[a] product comprising a compound . . ." can be distinguished from prior art products on the basis of differences in the impurity profiles of those products.

Moreover, as explained in detail in Parts II.A, II.B, and II.D above, we determine that the present record supports the contention that the treprostinil product of Moriarty and Phares is the same as that produced according to the steps recited in claims 1 and 9 of '393 patent.

As discussed in Part II.B, the Walsh Declaration fails to disclose the protocols followed in producing the Moriarty and '393 patent treprostinil samples analyzed, and fails to account for the experimental error in Dr. Walsh's impurity measurements. In addition, the inter-batch variability in the types and amounts of impurities observed in treprostinil prepared according to the '393 patent, and the fact that the treprostinil Dr. Walsh prepared according to Moriarty satisfies the FDA purity specification for treprostinil prepared per the '393 patent, lends further support to the conclusion that no structural or functional differences exist between treprostinil produced according to Moriarty, and that produced according to the'393 patent.

Similarly, as discussed in Part II.D, the present record supports a finding that the impurity profile of treprostinil diethanolamine salt prepared

as described by Moriarty in combination with Phares is the same as that prepared according to the '393 patent. Dr. Winkler's testimony regarding the form and melting point of Phares' treprostinil product (Ex. 1009 ¶¶ 59–60, 62), as well as his testimony regarding the disclosure by Phares of the same synthesis process as described by Moriarty (Ex. 1009 ¶¶ 55–57), is consistent with the conclusion that treprostinil diethanolamine generated by reacting Formula 7 of Moriarty with a base, as disclosed by Phares, to form a salt of Formula 7 would result in a treprostinil diethanolamine salt of at least equal purity to that disclosed in the '393 patent.

Accordingly, given the evidence before us in this record, we conclude that SteadyMed has established adequately for purposes of this decision that the combination of Moriarty and Phares renders obvious the treprostinil diethanolamine salt product recited in claims 1 and 9. Because we determine, on the record before us, and for purposes of institution, that the process steps recited in claims 1 and 9 do not impart structural or functional differences to the claimed treprostinil product and are therefore not limiting, we need not address the parties' contentions concerning the obviousness of the recited process steps.

Conclusion

UTC has not raised any additional arguments with regard to the dependent claims other than those addressed above. We have reviewed SteadyMed's evidence, arguments, and claim charts, and conclude that SteadyMed has sufficiently demonstrated that the dependent claims are also rendered obvious by the combination of Moriarty and Phares. Thus, for the

foregoing reasons, we conclude that SteadyMed has shown a reasonable likelihood of prevailing on its assertions that claims 1–5, 7–9, 11–14, and 16–20 are obvious in view of Moriarty and Phares.

F. Obviousness Grounds of Unpatentability Based on Moriarty, Phares, Kawakami, and Eğe

SteadyMed asserts that claims 6, 10, 15, 21, and 22 are unpatentable under § 103(a) as obvious in view of Moriarty, Phares or Kawakami, and Eğe. Pet. 37–52. Although SteadyMed nominally identifies this ground of unpatentability as being over "Moriarty (Ex. 1004) with Phares (Ex. 1005) or Kawakami (Exs. 1006 & 1007) and in further combination with Ege (Ex. 1008)" (Pet. 53 (emphasis omitted), as discussed below, SteadyMed explicitly relies on Kawakami in arguing unpatentability in view of Moriarty, Phares, and Eğe. Accordingly, we understand SteadyMed's stated ground of unpatentability as relying on the combination of Moriarty, Phares, Kawakami, and Eğe. Claims 6, 21, and 22 depend, directly or indirectly, from claim 1, and claims 10 and 15 depend directly from claim 9. In support of its assertion, SteadyMed provides detailed explanations as to how the combination of Moriarty, Eğe, Phares, and Kawakami discloses each claim limitation (*id.*), and relies upon the Winkler Declaration (Ex. 1009) to support its positions.

UTC contends that Kawakami should not be considered as evidence of unpatentability because the declaration certifying the accuracy of the translation is deficient. Prelim. Resp. 38–39. UTC also asserts that Eğe is merely a generic introductory chemistry text, and irrelevant to the

'393 patent. *Id.* at 47. UTC further argues that SteadyMed has not identified a rationale for, or expectation of success in, combining either Moriarty, Phares, and Eğe, or Moriarty, Kawakami, and Eğe. *Id.* In addition, UTC contends that SteadyMed improperly asserts that the cited combination would inherently result in the claimed product. *Id.* at 54.

Kawakami

Kawakami describes "a crystalline dicyclohexylamine salt of a methanoprostacyclin derivative, a manufacturing method thereof, and a purifying method thereof." Ex. 1007, 3. Kawakami discloses obtaining a dicyclohexylamine salt by "mixing a methanoprostacyclin derivative [I] . . . with dicyclohexylamine in an appropriate solvent." Ex. 1007, 5–6. Kawakami explains that "[t]he dicyclohexylamine salt of the methanoprostacyclin derivative [I] thus obtained generally has fairly high purity, and the purity can be further improved by recrystallization as needed with the use of an appropriate solvent." *Id.* at 6.

Kawakami further teaches that "[t]he 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." *Id.*

Eğe

Eğe is an organic chemistry textbook. Ex. 1008, 1. Eğe discloses:

> Carboxylic acids that have low solubility in water, such as benzoic acid, are converted to water-soluble salts by reaction

> with aqueous base. 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.

Id. at 8 (reference omitted).

Compliance with 37 C.F.R. § 42.63(b)

Kawakami is a Japanese patent application. Ex. 1006. SteadyMed submitted an English translation of Kawakami (Ex. 1007), as well as an affidavit certifying that translation (Ex. 1011) with its Petition.

UTC nevertheless contends that Kawakami should not be considered as evidence of unpatentability because the President of the translation service, rather than the individual who prepared the translation, executed the certification affidavit. Prelim. Resp. 38–39. UTC asserts that certification affidavit is objectionable because the affiant lacks personal knowledge of the relevant facts, the accuracy of the translation cannot be determined, and the translator is shielded from cross-examination. *Id.* at 39.

In view of the record before us, and for purposes of this decision, we decline UTC's invitation to disregard Kawakami. No credible prejudice to UTC has been called to our attention, and none is apparent. An English translation of Kawakami was available to UTC in time to prepare its Preliminary Response.[8] Furthermore, UTC has not identified any error in

[8] It does not appear that UTC has served objections on SteadyMed concerning the adequacy of the English translation of Kawakami or the certifying affidavit.

the translation that would call into question its authenticity. Regarding UTC's contention that the accuracy of the translation cannot be determined absent a certification affidavit from the translator himself, we note that the commission of an independent translation would confirm the veracity of the translation submitted by SteadyMed. We also observe that even if the individual personally responsible for generating the English translation of Kawakami had submitted a certification affidavit, UTC would not have had the opportunity to cross-examine him prior to the submission of its Preliminary Response.

Accordingly, on the record before us, and for purposes of this decision, we decline UTC's request that we disregard Kawakami. We observe, however, that the adequacy of the Kawakami translation and certification affidavit may be subject to further challenge during trial.[9]

Rationale to Combine Prior Art Teachings

Building on the rationale for combining Moriarty and Phares discussed in Part II.E above, SteadyMed contends that a relevant skilled

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[9] Pursuant to 37 C.F.R. § 42.64(b)(1), "[a]ny objection to evidence submitted during a preliminary proceeding must be served within ten business days of the institution of the trial. . . . The objection must identify the grounds for the objection with sufficient particularity to allow correction in the form of supplemental evidence." "The party relying on evidence to which an objection is timely served may respond to the objection by serving supplemental evidence within ten business days of service of the objection." 37 C.F.R. § 42.64(b)(2). Furthermore, "[a] motion to exclude evidence must be filed to preserve any objection. . . . The motion may be filed without prior authorization from the Board." 37 C.F.R. § 42.64(c)

artisan would add further purification steps from Kawakami and Eğe because Kawakami "discloses that the dicyclohexylamine salt of a methanoprostacyclin derivative 'can be easily reverted to the free methanoprostacyclin derivative by *conventional methods*,'" and that the "fairly high purity" of the salt obtained "can be further improved by recrystallization as needed with the use of an appropriate solvent." Pet. 53; *see also* Ex. 1007, 6; Ex. 1009 ¶ 83. Dr. Winkler testifies that, as evidenced by Eğe, a relevant skilled artisan "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." Ex. 1009 ¶ 84; *see also* Pet. 53–54.

Dr. Winkler elaborates on this rationale for combining the cited references, testifying that a relevant skilled artisan

> 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.

Ex. 1009 ¶ 88; *see also* Ex. 1008, 8; Pet. 54.

UTC does not address the combination of Moriarty, Eğe, Phares, and Kawakami. Instead, UTC addresses Moriarty, Eğe, and Phares as one combination, and Moriarty, Eğe, and Kawakami as an alternative combination. Prelim. Resp. 46–47.

As an initial matter, UTC asserts that Eğe is irrelevant to the '393 patent because it does not discuss prostacyclin derivatives or pharmaceutical synthesis. *Id.* at 47. UTC argues that Eğe in fact "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." *Id.* at 48.

Regarding the combination of Moriarty, Eğe, and Phares, UTC contends that "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." Prelim. Resp. 50. Pertaining to the combination of Moriarty, Eğe, and Kawakami, UTC asserts that SteadyMed "fails to establish that a [relevant skilled artisan] would reasonably expect the teachings of Kawakami to extend to the products in Moriarty." *Id.* at 52.

UTC also argues that Dr. Winkler's testimony regarding the reasons a relevant skilled artisan would want to form treprostinil diethanolamine salt, and treat it with a strong acid to convert it back to its free form (treprostinil) is improperly conclusory. *Id.* at 50, 52.

On the record before us, and for purposes of this decision, we agree that SteadyMed has sufficiently demonstrated that a relevant skilled artisan would have had reason to include the carboxylate salt formation and regeneration of the neutral carboxylic acid with the syntheses of Moriarty and Phares based on the teachings of Kawakami and Eğe.

We recognize, but do not find persuasive, UTC's position that Eğe is irrelevant to the synthesis of prostacyclin derivatives, and that it teaches away from the use of salt formation for purifying a mixture of compounds that includes other carboxylic-acid containing compounds as impurities. First, we observe that SteadyMed relies on Eğe not for any teachings specific to prostacyclin derivative synthesis, but rather, to support the contention that the addition of a strong acid to a carboxylate salt to regenerate the neutral carboxylic acid is a conventional purification technique in organic chemistry. Pet. 53–55; Ex. 1009 ¶¶ 86, 88. In particular, Dr. Winkler testifies that 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)" (Ex. 1009 ¶ 85), and that Eğe, an introductory organic chemistry text, "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" (*id.* ¶ 86). On this record, we credit Dr. Winkler's testimony, as it is consistent with the prior art.

Second, we note that even crediting UTC's position that the use of salt formation would not be effective for purifying treprostinil from its stereoisomers (Prelim. Resp. 47–48), the present record suggests that it would be effective for removing other impurities (Pet. 53–55; Ex. 1009 ¶¶ 86, 88). Moreover, as explained below, the present record, including Kawakami, indicates that treprostinil diethanolamine salt formation followed

by regeneration of treprostinil using a strong acid is an effective purification step. Pet. 53–55; *see also* Ex. 1007, 6; Ex. 1008, 8; Ex. 1009 ¶¶ 82–90.

Additionally, we agree with SteadyMed that a relevant skilled artisan would have had reason to combine Moriarty, Phares, Kawakami, and Eğe. Pet. 53–55; Ex. 1009 ¶¶ 82–90. For example, Dr. Winkler testifies that a relevant skilled artisan would want to include a carboxylate salt formation and regeneration of the neutral carboxylic acid as described by Eğe with the syntheses of Moriarty and Phares because Kawakami teaches 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.'" Ex. 1009 ¶ 86; *see also* Ex. 1007, 6; Pet. 53–55. Dr. Winkler additionally testifies that a skilled artisan would be motivated to form treprostinil diethanolamine salt, and treat it with a strong acid to "obtain excellent crystallinity and increased purity" of the final treprostinil product (Ex. 1009 ¶ 88), and that a skilled artisan would have a reasonable expectation of success in performing such reaction because it is "a common reaction in organic chemistry and this process is well within the skill of one of ordinary skill in the art" (*id.* ¶ 90).

On this record, we credit Dr. Winkler's testimony, as it is consistent with the prior art. Moreover, we disagree with UTC that Dr. Winkler's testimony is improperly conclusory. Rather, as illustrated by the excerpts of his testimony referenced above, Dr. Winkler supports his opinions with

reference to the cited art, as well as his experience as a chemist and chemistry professor.

Accordingly, on the record before us, we agree that SteadyMed has sufficiently demonstrated that one of ordinary skill in the art would have included the carboxylate salt formation and regeneration of the neutral carboxylic acid of Eğe with the syntheses of Moriarty and Phares based on Kawakami's disclosure that the conversion of salts of prostacyclin derivatives to their free forms by conventional methods increases purity of the final product. *See KSR*, 550 U.S. at 417 ("[I]f a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill.").

Claims 6, 15, and 21

Claims 6, 15, and 21 each recite the product of either claim 1 or claim 9, subject to additional process steps. For example, claim 6 recites "[t]he product of claim 1, wherein the acid in step (d) is HCl or H_2SO_4." Ex. 1001, 19:39–40. Claim 15 similarly recites "[t]he product of claim 9, wherein the acid in step (d) is HCl." *Id.* at 20:59–60. Claim 21 simply recites "[t]he product of claim 1, wherein step (d) is performed." *Id.* at 21:13.

The present record supports SteadyMed's contention that claims 6, 15, and 21 would have been obvious in view of Moriarty, Eğe, Phares, and

Kawakami. Pet. 53–56; Ex. 1009 ¶¶ 82–90. For example, Dr. Winkler testifies that

> the combination of Moriarty (Ex. 1004) and Phares (Ex. 1005) (or Kawakami, Exs. 1006 & 1007) and Ege (Ex. 1008) would disclose . . . 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.

Ex. 1009 ¶ 89; *see also* Pet. 54. In addition, as explained above, Dr. Winkler testifies that a skilled artisan would have made the cited combination, with an expectation of success, in order to obtain a treprostinil product of improved purity. Ex. 1009 ¶¶ 88–90; Pet. 54–55. On this record, we credit Dr. Winkler's testimony.

UTC does not offer evidence or argument to suggest that the additional process steps recited in claims 6, 15, and 21 impart structural or functional differences to the claimed product beyond that discussed above in Parts II.B, II.D, and II.E. Rather, UTC contends that SteadyMed has not asserted that the products of claims 6, 15, and 21 would have been obvious in view of the cited art. Prelim. Resp. 54. UTC frames SteadyMed's position as an argument that the recited process steps would have been obvious, and would have inherently resulted in the claimed product. *Id.*

We do not find UTC's contentions persuasive. We observe that claims 6, 15, and 21 differ from their respective independent claims only in that they require the performance of optional step (d) from claims 1 and 9, and in the case of claims 6 and 15, specify the acid to be used in carrying out that process step. Ex. 1001, 19:39–40, 20:59–60. As set forth in detail in Parts II.A, II.B, II.D, and II.E, on the record before us, and for purposes of

this decision, we conclude that the process steps recited in the challenged claims, including step (d), do not impart structural or functional differences over prior art treprostinil products.

Furthermore, we disagree with UTC's characterization of SteadyMed's obviousness argument. We note, for example, that under the general rule for the interpretation of product-by-process claims, which we determine applies here, the products of claims 1, 6, and 21 are interpreted to be the same, namely, the product of claim 1. Likewise, the same analysis applies for the products of claims 9 and 15.

Accordingly, given the evidence before us in this record, we conclude that SteadyMed has established adequately for purposes of this decision that the combination of Eğe, Phares, and Kawakami renders obvious the treprostinil products of claims 6, 15, and 21. Because we determine, on the record before us, and for purposes of institution, that the process steps recited in claims 6, 15, and 21 do not impart structural or functional differences to the claimed treprostinil product, we do not address the parties' contentions concerning the obviousness of the recited process steps.

Claim 10

Claim 10 recites "[t]he product of claim 9, wherein the purity of product of step (d) is at least 99.5%." Ex. 1001, 20:47–48. The present record supports SteadyMed's contention that claim 10 is obvious in view of Moriarty, Eğe, Phares, and Kawakami. Pet. 55–56; *see also* Ex. 1009 ¶¶ 82–90. As detailed in Parts II.B, II.D, and II.E, the present record supports SteadyMed's position that Moriarty discloses treprostinil free acid having a

purity of 99.7% (Pet. 20; *see also* Ex. 1004, 13; Ex. 1009 ¶ 65), and Phares discloses treprostinil diethanolamine salt of the same form and at least the same purity as that claimed in the '393 patent (Pet. 27–28; Ex. 1005, 88–93; Ex. 1009 ¶¶ 59–62). The present record further supports SteadyMed's contention that even if Dr. Walsh's impurity measurements are credited, the 0.1% difference between the purity of the sample prepared according to Moriarty, and claim 10 is within the expected level experimental error for impurity measurements, and the degree of inter-batch variability in impurity content is such that Dr. Walsh's results are insufficient to support a conclusion of nonobviousness. Pet. 19–22; *see also* Ex. 1009 ¶¶ 63–71.

UTC does not offer evidence or argument to suggest that the additional process step recited in claim 10 imparts structural or functional differences to the claimed product beyond that discussed above in Parts II.A, II.B, II.D, and II.E. Neither does UTC present any additional argument regarding the recited purity requirement beyond those already addressed above. UTC does reassert its position, discussed with regard to claims 6, 15, and 21, that SteadyMed has not asserted that the product of claim 10 would have been obvious in view of the cited art. Prelim. Resp. 54. For the reasons set forth above, however, we do not find this contention persuasive.

Accordingly, given the evidence before us in this record, we conclude that SteadyMed has established adequately for purposes of this decision that the combination of Eğe, Phares, and Kawakami renders obvious the treprostinil product of claim 10. Because we determine, on the record before us, and for purposes of institution, that the process steps recited in claim 10

do not impart structural or functional differences to the claimed treprostinil product, we do not address the parties' contentions concerning the obviousness of the recited process steps at this time.

Claim 22

Claim 22 recites "[t]he product of claim 21, wherein the product comprises a pharmaceutically acceptable salt formed from the product of step (d)." Ex. 1001, 21:14–16. The present record supports SteadyMed's contention that claim 22 is obvious in view of Moriarty, Eğe, Phares, and Kawakami. Pet. 56–57; *see also* Ex. 1009 ¶¶ 82–90. As discussed above in Parts II.D and II.E, the present record supports SteadyMed's position that the cited combination renders obvious a pharmaceutically acceptable treprostinil salt.

UTC does not offer evidence or argument to suggest that the additional process step recited in claim 22 imparts structural or functional differences to the claimed product beyond that discussed above in Parts II.A, II.B, II.D, and II.E. Neither does UTC present any additional argument regarding the recited purity requirement beyond those already addressed above. UTC does reassert its position, discussed with regard to claims 6, 15, and 21, that SteadyMed has not asserted that the product of claim 22 would have been obvious in view of the cited art. Prelim. Resp. 54. For the reasons set forth above, however, we do not find this contention persuasive

Accordingly, given the evidence before us in this record, we conclude that SteadyMed has established adequately for purposes of this decision that the combination of Eğe, Phares, and Kawakami renders obvious the

treprostinil products of claim 22. Because we determine, on the record before us, and for purposes of institution, that the process steps recited in claims 22 do not impart structural or functional differences to the claimed treprostinil product, we do not address the parties' contentions concerning the obviousness of the recited process steps at this time.

Conclusion

For the foregoing reasons, we conclude that SteadyMed has shown a reasonable likelihood of prevailing on its assertions that claims 6, 10, 15, 21, and 22 are obvious in view of Moriarty, Eğe, Phares, and Kawakami.

G. Secondary Considerations of Non-Obviousness

UTC contends that objective indicia of non-obviousness, such as purported evidence of long-felt but unmet need, unexpected results, commercial success, and copying support the patentability of the challenged claims of the '393 patent. Prelim. Resp. 55–58.

We conclude that the evidence of secondary considerations currently of record is not sufficient, at this point in the proceeding, to support UTC's contention. As an initial matter, we observe that "secondary considerations are better considered in the context of a trial when the ultimate determination of obviousness is made." *Crocs, Inc. v. Polliwalks, Inc.*, Case IPR2014-00424, slip op. 16 (PTAB Aug. 20, 2014) (Paper 8). In addition, we note that UTC's contentions regarding long-felt need and unexpected results are predicated on UTC's claim that treprostinil made according to the process described in the '393 patent has fewer impurities than treprostinil produced by other methods. However, as explained in Parts II.B, II.D, and

II.E above, the present record does not support that contention. We also observe that UTC does not offer evidence of a nexus between the claimed invention and its commercial success. For example, UTC does not offer evidence concerning its relative share of the market for treprostinil products, or demonstrating that its revenues or market share increased after it began manufacturing treprostinil according to the process described in the '393 patent. Finally, we note that the mere existence of litigation concerning the '393 patent alone is insufficient to establish copying. *See Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1325 (Fed. Cir. 2004) ("Not every competing product that arguably fails within the scope of a patent is evidence of copying. Otherwise every infringement suit would automatically confirm the nonobviousness of the patent.").

H. Other Asserted Grounds of Unpatentability

SteadyMed also asserts the following ground of unpatentability:

Claims	Basis	Reference(s)
1–5, 7–9, 11–14, and 16–20	§ 103(a)	Moriarty and Kawakami

In light of the grounds specifically discussed above, on the basis of which we institute review, we exercise our discretion and decline to consider these other grounds asserted in the Petition. *See* 37 C.F.R. § 42.108(a). We observe that SteadyMed presents the above ground of unpatentability and the obviousness of claims 1–5, 7–9, 11–14, and 16–20 in view of Moriarty and Phares, a ground on which we institute review, in the alternative.

III. CONCLUSION

For the foregoing reasons, we determine that the information presented in the Petition establishes that there is a reasonable likelihood that SteadyMed would prevail in challenging claims 1–22 of the '393 patent. At this juncture, we have not made a final determination with respect to the patentability of the challenged claims, nor with respect to claim construction.

IV. ORDER

For the foregoing reasons, it is

ORDERED that pursuant to 35 U.S.C. § 314(a), an *inter partes* review is hereby instituted for the following grounds of unpatentability:

Claims	Basis	Reference(s)
1–5, 7–9, 11–14, and 16–20	§ 102(b)	Phares
1–5, 7–9, 11–14, and 16–20	§ 103(a)	Moriarty and Phares
6, 10, 15, 21, and 22	§ 103(a)	Moriarty, Phares, Kawakami, and Eğe

FURTHER ORDERED that no other ground of unpatentability asserted in the Petition is authorized for this *inter partes* review; and

FURTHER ORDERED that pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial; the trial will commence on the entry date of this decision.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Hitesh Batra et al.
Assignee:	UNITED THERAPEUTICS CORPORATION
Title:	PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
Appl. Number:	14/849,981
Filed:	9/10/2015
Examiner:	Yevgeny Valenrod
Group Art Unit:	1672

THIRD PARTY SUBMISSION UNDER 37 CFR § 1.501 OF PATENT OWNER WRITTEN CLAIM SCOPE STATEMENTS

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450
ATTENTION: Director, Technology Center 1600 (1672)

Dear Commissioner:

The undersigned hereby submits six public documents (collectively, "Documents 1-6"), which are patent owner written claim scope statements and additional information of relevance to the examination of the above-identified patent application (the "Batra Application") assigned to United Therapeutics Corp. ("Patent Owner"), in accordance with 37 C.F.R. § 1.501(a)(2). This submission includes the requisite forum and proceeding in which patent owner filed each statement, the specific papers submitted in that proceeding that contain the statements, and how each statement submitted is a statement concerning the scope of any claim in the patent.

The submitted documents are written statements of the patent owner and applicant United Therapeutics Corporation in a separate proceeding before the Office—*SteadyMed Ltd. v. United Therapeutics Corp.*, IPR No. 2016-000006—in which patent owner took a position on the scope of claims in the related parent patent, U.S. Patent No. 8,497,393, or they are documents, pleadings, or evidence from IPR No. 2016-000006 that address these written statements. All documents, where necessary, are submitted in redacted form.

The undersigned submits that he and she are not individuals who have a duty to disclose information with respect to the above-identified application under 37 C.F.R.§ 1.56.

I. The forum and proceeding in which patent owner filed each statement.

All six documents being submitted are from the following proceeding: *SteadyMed Ltd. v. United Therapeutics Corp.*, IPR No. 2016-000006, instituted on April 8, 2016. These documents complete the record regarding Patent Owner's statements regarding claim construction in the parallel IPR2016-000006 regarding the '393 Parent Patent, and related to the claim construction of the pending claims in the Batra Application.

II. Patent owner written claim scope statements, and documents, pleadings, or evidence being submitted.

The list of documents being submitted and enclosed herewith includes the following Documents 1-6, in accordance with 37 C.F.R. § 1.501(a)(2):

Document 1 — Patent Owner Redacted Response in IPR2016-000006, Paper No. 35, concerning claim construction in parent patent U.S. Patent No. 8,497,393.

Document 2 — Declaration of Robert M. Williams, Ph.D. in Support of Patent Owner Response to Petition (Redacted), in IPR2016-000006, Ex. 2020, concerning claim construction in parent patent U.S. Patent No. 8,497,393.

Document 3 — Petitioner's Redacted Reply in IPR2016-000006, Paper No. 52 (September 27, 2016), concerning claim construction in parent patent U.S. Patent No. 8,497,393.

Document 4 – Redacted Deposition Transcript of Dr. Robert M. Williams, Ph.D., Exhibit 2059 in IPR2016-000006.

Document 5 – Redacted Deposition Transcript of Dr. Robert R. Ruffolo, Jr., Ph.D., Exhibit 2058 in IPR2016-000006.

Document 6 — "Spreadsheet of 46 batches from Exs. 2053 and 2036," Exhibit 1021 (Redacting 2 values from Ex. 2053 not publicly disclosed) in IPR2016-000006.

III. How each document submitted is a statement concerning the scope of any claim in the patent.

A concise explanation of the relevance of each of Documents 1-6 is provided below, in accordance with 37 C.F.R. § 1.501(b)(1).

Document 1

Document 1, the Patent Owner Redacted Response in IPR2016-000006, Paper No. 35, concerns claim construction in parent patent U.S. Patent No. 8,497,393 (the "'393 Parent Patent"). The document addresses the meaning of the claim terms "product" in product-by-process claims, and the interpretation of the scope of product-by-process claims. The claims in the Batra Application are product-by-process claims.

Document 1 also makes statements regarding how purity affects the claim construction of the claims in the '393 Parent Patent, which are relevant to the same question of the scope of the current claims in the Batra Application.

Document 2

Document 2, the Declaration of Robert M. Williams, Ph.D. in Support of Patent Owner Response to Petition (Redacted), in IPR2016-000006, Ex. 2020, concerns claim construction in the '393 Parent Patent. It agrees with and reiterates the statements regarding claim construction found in Document 1, the Patent Owner Redacted Response in IPR2016-000006, Paper No. 35, and is relevant for the same reasons.

Document 3

Document 3, the Petitioner's Redacted Reply in IPR2016-000006, Paper No. 52, makes statements opposing the claim constructions proposed by Patent Owner in the '393 Parent Patent, which are relevant to the same question of the scope of the current claims in the Batra Application. Document 3 completes the record regarding Patent Owner's statements regarding claim construction in the parallel IPR2016-000006 regarding the '393 Parent Patent.

Document 3 proves that the statements regarding purity of the prior art Moriarty and Phares treprostinil and treprostinil diethanolamine salt and the scope of the claims made in Documents 1 and 2 are false, and that data provided by the Patent Owner to support the scope of the claims and the prior art were distorted by cherry picking questionable data points and adding them to the analysis to lower the average purity value of the prior art. *See especially* Document 3 at pp. 2-3, 4-9. A corrected analysis of the data, approved by Patent Owner's own Declarant Robert M. Williams, shows that the correct purity value for the prior art is the same as for the claimed invention in the '393 Parent Patent, *see especially id.* at pp. 8-9, which is the

same scope as the claims now presented in the Batra Application, and shows that the claim construction of the terms "pharmaceutical composition" and "comprising" in the Batra Application proposed by the Applicant and Patent Owner is meaningless. *See especially* Document 3 at pp. 9-10.

Document 3 addresses and completes Patent Owner and Applicant's statements regarding the meaning of the terms "pharmaceutical composition" and "comprising" in the Batra Application that was proposed by Patent Owner. Document 3 proves that there are no fixed set of impurities associated with the product-by-process claims in the Batra Application, but that the set of impurities is a moving target that varies from batch to batch. *See especially* Document 3 at p. 11. And Document 3 shows that the scope of the terms "pharmaceutical composition" and "comprising" in the Batra Application cannot be fixed by much better than ±2%, in contradiction with Patent Owner and Applicant's claim construction arguments in the Batra Application. *See especially* Document 3 at 15-17. Thus, Patent Owner's statements regarding claim construction in the Batra Application are contradicted by Document 3.

Document 4

Document 4 is the Deposition Transcript of Dr. Robert M. Williams, Ph.D., Exhibit 2059 in IPR2016-000006. Dr. Williams is Patent Owner and Applicant's Declarant in the Batra Application, and makes statements in his Declaration regarding the construction of product-by-process claims. This deposition addresses the statements made by Dr. Williams in his Declaration, and shows that these statements were based on his being misled by Applicant's counsel into believing a calculation that he did not perform supported Applicant's claim construction. *See especially* Ex. 2059, 79:3-10, 81:2-13, 82:1-11, 103:24-104:20, 112:24-114:2. These statements addresses the claim construction of the product-by-process claims at issue in both the Batra Application and the '393 Parent Patent. It shows that the construction of product-by-process claims advocated by Patent Owner and Applicant in the Batra Application should be ignored, and that the prior art purity was the same as in the claimed invention. *See especially* Ex. 2059, 217:11-219:20.

Document 4 also shows that certain data relied upon by Patent Owner and Applicant to support its arguments for the construction of the claims in the Batra Application were cherry-picked to reduce the average purity values of treprostinil made in accordance with the Moriarty

prior art, and which define the scope of the claims and the terms "pharmaceutical composition" and "comprising" in the Batra Application. *See especially* Ex. 2059, 112:20-113:20, 270:15-271:6. Moreover, it shows that the scope of the terms "pharmaceutical composition" and "comprising" in the Batra Application cannot be fixed by much better than ±2%, in contradiction with Patent Owner and Applicant's claim construction arguments in the Batra Application. *See especially* Ex. 2059, 133:134:24-135:4.

Document 5

Document 5 is the Deposition Transcript of Dr. Robert R. Ruffolo, Jr., Ph.D., Exhibit 2058 in IPR2016-000006. Dr. Ruffolo is Patent Owner and Applicant's Declarant in the Batra Application, and makes statements in his Declaration regarding the construction of product-by-process claims. This deposition addresses the statements made by Dr. Ruffolo in his Declaration, and shows that these statements contradict Patent Owner and Applicant's assertion regarding claim construction of product-by-process claims, including whether such claims are structurally and functionally unique. *See especially* Ex. 2058, 159:20-161:7, 179:23-180:17, 217:11-218:5. These statements addresses the claim construction of the product-by-process claims at issue in both the Batra Application and the '393 Parent Patent. It shows that the construction of product-by-process claims advocated by Patent Owner and Applicant in the Batra Application should be ignored, because contrary to the Patent Owner's statement during the Batra Patent Application's prosecution, the patent's specification does not even mention or characterize what impurities are present in treprostinil, which Patent Owner maintains as a trade secret to this day. *See especially* Ex. 2058, 234:16-235:12, 93:19-94:24, 233:5-12. It also contradicts Patent Owner's claim construction arguments regarding structural and functional differences, since Dr. Ruffolo testified that there were no such functional differences. *See especially* Ex. 2058, 159:20-161:7, 257:22-258:9.

Document 5 (Ex. 2058) also contradicts Patent Owner's construction of "pharmaceutical composition" and "comprising" in the Batra Application because contrary to Patent Owner's arguments, the impurities are not uniquely associated with the claims of the Batra Application. Document 5 proves that there are no fixed set of impurities associated with the product-by-process claims in the Batra Application, but that the set of impurities is a moving target that varies with the solvents used, and whether intermediate products were purified. *See especially*

Ex. 2058, 239:8-241:14. Thus, Patent Owner's statements regarding claim construction in the Batra Application are contradicted by Document 5.

Document 6

Document 6, a "Spreadsheet of 46 batches from Exs. 2053 and 2036," Exhibit 1021 in IPR2016-000006, proves that the statements made in Documents 1 and 2 regarding claim construction and the scope of the claims were false. Document 6 compiles all batches shown to be made by the Moriarty process and demonstrates that the average purity of Moriarty products was the same as in the claimed invention. Patent Owner's own Declarant Robert M. Williams testified that the calculation in Exhibit 1021 was performed correctly.

Date: October 21, 2016

/s Stuart E. Pollack /
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Respectfully submitted,

/s Lisa A. Haile /
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CERTIFICATE OF SERVICE

The undersigned certifies that a copy of the attached THIRD PARTY SUBMISSION UNDER 37 CFR § 1.501 OF PATENT OWNER WRITTEN CLAIM SCOPE STATEMENTS was served by FIRST CLASS MAIL to the following:

Stephen B. Maebius
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Date: October 21, 2016

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PTO/SB/42 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U. S. DEPARTMENT OF COMMERCE

37 CFR 1.501 INFORMATION DISCLOSURE CITATION IN A PATENT (Sheet1 of 1)	Docket Number (Optional) 14/849.981	Patent Number
	Applicant Hitesh Batra et al.	
	Issue Date	Art Unit 1672

U.S. PATENT DOCUMENTS

EXAMINER INITIAL	DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE

FOREIGN PATENT DOCUMENTS

	DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
						☐	☐
						☐	☐
						☐	☐
						☐	☐
						☐	☐

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

		Patent Owner Redacted Response in IPR2016-000006, Paper No. 35, concerning claim construction in parent patent U.S. Patent No. 8,497,393. - Document 1 See Attached
		Declaration of Robert M. Williams, Ph.D. in Support of Patent Owner Response to Petition (Redacted), in IPR2016-000006, Ex. 2020, concerning claim construction in U.S. Patent No. 8,497,393. - Document 2 See Attached
		Petitioner's Redacted Reply in IPR2016-000006, Paper No. 52 (September 27, 2016), concerning claim construction in U.S. Patent No. 8,497,393. - Document 3 See Attached
		Redacted Deposition Transcript of Dr. Robert M. Williams, Ph.D., Exhibit 2059 in IPR2016-000006. Document 4 See Attached
		Redacted Deposition Transcript of Dr. Robert R. Ruffolo, Jr., Ph.D., Exhibit 2058 in IPR2016-000006. - Document 5 See Attached
		"Spreadsheet of 46 batches from Exs. 2053 and 2036," Exhibit 1021 (Redacting 2 values from Ex. 2053 not publicly disclosed) in IPR2016-000006. - Document 6 See Attached

EXAMINER	DATE CONSIDERED

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 Response to Petition

4814-0612-4340.3

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TABLE OF AUTHORITIES

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I. INTRODUCTION

United Therapeutics Corporation ("UTC") submits this Response in accordance with 35 U.S.C. § 316(a)(8) and 37 C.F.R. § 42.120, responding to the instituted grounds of the Petition for *Inter Partes* Review filed by SteadyMed Ltd. ("SteadyMed") challenging claims 1-22 of U.S. Patent No. 8,497,393 ("the '393 patent"). The Declaration of Dr. Williams ("Ex. 2020") and of Dr. Ruffolo ("Ex. 2022") are filed herewith in support of the Response (Ex. 2020 and Ex. 2022, respectively). The Board should conclude that SteadyMed has failed to prove by a preponderance of the evidence that the instituted claims are unpatentable, as required under 35 U.S.C. § 316(e).

II. SUMMARY OF THE ARGUMENT

SteadyMed's anticipation and obviousness arguments are flawed for two fundamental reasons. First, SteadyMed's arguments rely on Moriarty (Moriarty *et al.*, J. Org. Chem. 2004, 1890-1902; Ex. 1004) and Phares (International Publication No. WO 2005/007081; Ex. 1005), but neither reference discloses the same highly pure treprostinil or treprostinil diethanolamine product claimed by the '393 patent when properly construed, let alone the same synthesis recited in the instituted claims. In fact, the Office considered both references during prosecution of the '393 patent, and the Office construed the claims of the '393 patent in a way that distinguished the product of the '393 patent specifically from the Moriarty

product. Moreover, a person of ordinary skill in the art ("POSA") would not look to either Eğe (Seyhan N. Eğe, Organic Chemistry 543-547 (2d ed. 1989) (Ex. 1008) or Kawakami (JP 56-122328A) (Ex. 1007) as neither reference is relevant to further purification of the complex treprostinil carboxylic acid structure that is at issue in the '393 patent, and a POSA would have no reasonable expectation of success in combining these references with either Moriarty or Phares.

Second, SteadyMed's anticipation and obviousness arguments are flawed because they misunderstand, both the error associated with such measurements and the difference between "assay purity" against a standard and measurements of purity that directly measure the level of impurities. As explained in the Williams and Ruffolo Declarations, this misunderstanding resulted in Petitioner's incorrect assertion that there are inconsistencies between the purity values recited in the '393 specification, the Walsh Declaration, and the Moriarty prior art. Ex. 2020 at ¶¶88-89; Ex. 2022 at ¶¶73-74. Dr. Williams notes that the '393 patent itself expressly refers to assay purity values as "HPLC (assay)" values whenever it uses such measurements, as opposed to other purity values based on measuring amount of impurities. Ex. 2020 at ¶89. Dr. Ruffolo further explains that FDA drug approval system rests on precise measurements of individual impurities that make up a purity "specification" for a drug, which can be reliably determined within the detection limits of HPLC measurements. Ex. 2022 at ¶¶32-35 and 44-50. Dr.

Ruffolo also specifically notes that it is routine to have assay purity values above 100% because it is a relative value measurement. Ex. 2022 at ¶53.

SteadyMed's purported expert, Dr. Winkler, confirmed this misunderstanding. Dr. Winkler acknowledged at his deposition that FDA's purity specification of less than 0.1% for the impurity 2AU90 indicates that precise measurements of impurities are possible: "I would think that the error in the measurement for 2AU90 would be, should be less than 0.1 percent." Ex. 2051 at 64:7-9. Dr. Winkler further acknowledged that he did not know how the treprostinil purity specification adopted by FDA could change from 101% to 102% and stated that he viewed purity levels above 100% as errors: "I think the thing that I am able to conclude from the data that is on page 6 of this, of this letter [Ex. 2006] is that the error in the HPLC assay could be as high as 1 percent in the first column and by my analysis could be as high as 2 percent in the second column." Ex. 2051 at 86:15-21; 24-25; 87:2-9. As Dr. Williams explained, Dr. Winkler's conclusions on this point appear "to arise from Dr. Winkler's fundamental misunderstanding of how assay purity values are calculated." Ex. 2020 at ¶¶90-92; *see also* Ex. 2022 at ¶¶74. Moreover, Dr. Winkler admitted he did not know what the actual error was associated with the measurements submitted in the Walsh declaration. Ex. 2051 at 62:16-25; 63:2-14. Because Dr. Winkler does not understand the basic differences in types of purity measurements and their related

errors that are used in the '393 patent, discussed in the Walsh Declaration, and which form the basis for FDA's regulation of drug product manufacturing, his declaration should not be credited.

Moreover, the Williams Declaration establishes that there are measurable structural differences between the average impurity profiles of the Moriarty product and the claimed product based on data obtained from 175 batches. Ex. 2020 ¶¶94-99, Appendices A-B; see also Ex. 2005, Ex. 2036, Ex. 2037, Ex. 2052, Ex. 2053. The average impurity profiles show that Moriarty process and the '393 process produce two physically distinct products that contain different total and specific impurities. *Id.* Specifically, the claimed product essentially lacks certain impurities found in the Moriarty product, such as [redacted], and [redacted]. Ex.2020 at ¶¶96-97. The claimed product also contains much smaller amounts of other impurities that are found in the Moriarty product, such as [redacted], [redacted]. *Id.* at ¶96.

Furthermore, based on the same 175 batches, the average purity of the '393 product is [redacted] greater than the average purity of the Moriarty product, thereby corroborating that the Moriarty process and the '393 process produces two physically distinct products that contain measurable and significant structural differences. *Id.* at ¶98.

Finally, the initial claim construction of the preamble "a product… comprising" urged by SteadyMed and adopted by the Board would violate the canon that patent claims may not be construed to encompass material that was clearly disavowed in order to obtain allowance of claims. Even under the broadest reasonable interpretation standard, the Board has found in its own cases that the prosecution history may limit the plain meaning of a limitation in a claim, which otherwise is presumed to apply. The '393 claims were allowed after submission of the Walsh Declaration, which established the differences between the '393 products and the Moriarty product. This disavowal of the Moriarty subject matter is further reinforced by additional intrinsic evidence. The '393 patent includes a side-by-side comparison in Example 6 to show the difference between the Moriarty product and the '393 product and repeatedly references higher purity and different impurity profile compared to Moriarty. In the face of this disavowal, it is improper to construe "a product …comprising" to allow the impurities "without limitation," as such a construction would encompass the impurity profile of Moriarty.

In addition, the Williams Declaration explains why Phares cannot anticipate the claimed products because of the particular conditions used to prepare the Phares product for polymorph screening and because of the uncertain provenance of starting treprostinil used to make the diethanolamine salt.

As to instituted grounds 2 and 3, Dr. Williams also explains why the references in the instituted obviousness grounds would not have been combined in the asserted manner due to lack of motivation and the failure of the references to provide an expectation of success for achieving the purity level and impurity profile of the '393 patent in the specific case of treprostinil. Kawakami teaches away from the selection of diethanolamine, the salt specifically claimed in claims 14 and 18. Lastly, secondary considerations of long-felt need and unexpected results would rebut any case of obviousness as to grounds 2 and 3.

In view of the foregoing, SteadyMed has not met its burden of proving the unpatentability of claims 1-22 by a preponderance of the evidence, as required under 35 U.S.C. § 316(e).

III. STRUCTURAL/FUNCTIONAL DIFFERENCES OF THE CLAIMED PRODUCTS OVER THE CITED ART

The combined Declarations of Dr. Williams and Dr. Ruffolo establish that the '393 product has a different impurity profile than the Moriarty product, and in fact, that the '393 product has higher average purity. These differences matter. FDA uses both overall purity and levels of individual impurities ("purity specification") as a basis to regulate the manufacturing of pharmaceuticals. Batches that fall outside of the purity specification cannot be sold or used to treat

patients. Thus, differences in purity and impurity profile are not merely academic, but critical to the successful manufacture of a clinical product.

A. The Importance of Purity in Pharmaceuticals

As noted by the '393 patent itself, "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. 1:57-61. The invention therefore "provides for a process that is more economical, safer, faster, greener, easier to operate, and provides higher purity." *Id.*, col. 5:47-50. As the treprostinil product is a drug product subject to the rules of FDA, the reduction of impurities is of great importance in the drug. Drug purity is defined by FDA as "relative freedom from extraneous matter in the finished product, whether or not harmful to the recipient or deleterious to the product." See, Ex. 2022 at ¶33; see also 21 C.F.R. §600.3 (r) (2015). The purity of a drug is of such importance to FDA that the purity level of a drug substance must appear in the drug product specification, which is a collection of data about the drug required by FDA. *See*, Ex. 2022 at ¶¶32-34. "Regulatory agencies have also sought to increase levels of purity, and consequently decrease levels of impurities, in order to provide to the maximum extent possible, the highest level of safety to patients." *Id.* at ¶36. This is due to

the fact that even trace amounts of impurities can sometime pose serious health concerns.

For example, the drug penicillin is one of the best known and extensively studied examples of trace impurities that can cause serious, life-threatening adverse events. *Id.* at ¶62. While penicillin is safe and effective for most people, it can cause serious allergic reactions resulting in anaphylaxis and death. *Id.* Because the amount of trace impurity of penicillin needed to cause an allergic reaction is so low, FDA has mandated the production of penicillin active pharmaceutical ingredient (API) and finished product to be made in buildings entirely separate from buildings that manufacture other APIs or finished drug product. *Id.*, *see also* FDA Guidance for Industry, Non-Penicillin Beta-Lactam Drugs: A CGMP Framework for Preventing Cross-Contamination, (2013) (Ex. 2047) at 1-6. The same is true for the drug cephalosporin. Ex. 2022 at ¶63; *see also* Ex. 2047 at 1-6.

Additionally, human insulin is another example. For many years, human insulin was derived from pig pancreases, but then it became possible to produce human insulin in the bacteria *E. coli* using large bioreactors. Ex. 2022 at ¶64. Even though the human insulin derived from *E. coli* was highly pure, it contained very small trace amounts of *E. coli*, a very dangerous bacteria causing reactions (directly from the trace amounts of bacteria, and not due to infection) in some people even in trace amounts. *Id.* As a result, the product needed to be even more

highly purified to further minimize or eliminate the trace bacterial contaminants. *Id.* These examples highlight the importance of drug purity in pharmaceutical formulations and the potential risks to patients between two products that differ in their impurity profile and purity. By having a different impurity profile and overall purity, two products are structurally and functionally different.

B. The '393 Product Has A Different Impurity Profile and a Higher Purity Than Moriarty

As detailed in Dr. Williams' Declaration and supporting exhibits, comparing the average impurity profiles for the '393 product and the Moriarty product using data obtained from over 175 batches reveals measurable structural differences, as the two processes produce physically different products which contain different total and specific amounts of impurities. Ex. 2020 ¶¶94-99 and Appendices A-B; *see also* Ex. 2005, Ex. 2036, Ex. 2037, Ex. 2052, Ex. 2053. The batch reports show that the Moriarty product and the claimed product exhibit different impurity profiles and that the claimed product has a higher average purity than Moriarty's product. *Id.*

Moriarty Process Impurities (Average Percent Detected)								
1AU90	**2AU90**	**3AU90**	**750W93**	**751W93**	**97W86**	**ethyl ester**	**methyl ester**	**Total Related Substance**
0.0473	0.0407	0.2545	0.1646	0.1025	0.0405	0.0889	0.1028	**0.9545**
'393 patent Process Impurities (Average Percent Detected)								
[redacted]								

4814-0612-4340.3

						[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

In total, the '393 product has [redacted] times fewer impurities than the Moriarty product.[1] Ex. 2020 ¶¶94-95. Additionally, certain specific impurities found in the prior art Moriarty product are essentially eliminated in the '393 product, as the '393 product does not contain detectable amounts of the impurity [redacted], and none of the commercial batches of the '393 product contain detectable amounts of [redacted] or [redacted]. Ex. 2020 ¶¶94, 96-97. Other impurities, including [redacted], [redacted], [redacted], and [redacted], are also greatly [redacted] in the '393 product as compared to the Moriarty product, while the level of the [redacted] impurity is slightly [redacted] in the '393 product. Ex. 2020 ¶96. These substantial differences between the impurity profiles of the '393 product and the Moriarty product constitute structural differences between the claimed product and the prior art.

Furthermore, the average purity based on data from over 175 batches is higher for the '393 product than that of Moriarty. As shown above, the average purity of a Moriarty batch was 99.05% while the average purity of a '393 batch

[1] Moriarty Total Related Substances: 0.9545; '393 patent Process Total Related Substances: [redacted]

was [redacted]. Ex. 2020 ¶¶94-99. This is a marked improvement in overall purity. Moreover, the purity analyzed in these batches – the total related substances – is exactly the same type of analysis Dr. Walsh referred to in his declaration when referring to purity of the '393 patent process versus that of the Moriarty process. Thus, this analysis is consistent with how the inventor interpreted the purity of the '393 patent. And this analysis also persuaded the Office to allow the claims.

The Institution Decision cited to the Walsh Declaration for revealing "that each of the impurities detected in [the tested batch of] Moriarty treprostinil was present in an amount below that identified as acceptable in UTC's own specification for treprostinil produced according to the process disclosed in the '393 patent." Paper 12 at 20-21. First, the above data shows that the average amount of each impurity and the average purity is different between Moriarty treprostinil and the '393 product. Second, whether an isolated batch of Moriarty treprostinil does or does not satisfy the new FDA purity specification is not relevant to patentability. The question for patentability is whether or not a given batch of *starting* Moriarty treprostinil (steps a and b of the '393 independent claims) will be physically changed when step (c) is performed *on that batch*. The above averages show that it does change, as do the large scale synthesis examples 4-6 in the '393 patent. While Moriarty treprostinil may show inter-batch variation in overall purity and impurity profiles, the data of record establishes that

performing step (c) *on a given starting batch* of Moriarty treprostinil will lead to a higher purity and a different impurity profile in the end product. Petitioner has not established that any specific batch of Moriarty treprostinil is not physically changed by performing step (c), and all the evidence suggests that it is.

C. The Differences In Impurity Profile And Average Purity Between The '393 Product And Moriarty Are Functionally Important

The higher purity of the claimed product resulted in FDA approving a new assay purity for the treprostinil drug as noted in the January 2009 letter submitted to FDA by UTC. Ex. 2006 at 4-6; Ex. 2022 at ¶¶66-68; Ex. 2020 at ¶91. Furthermore, this change constitutes a "major" change according to the classification system for manufacturing changes used by FDA. Ex. 2022 at ¶¶70-72. FDA requires continuous testing of pharmaceutical batches to ensure that they fall within the established purity specification. Ex. 2022 at ¶¶32-40. If a given batch falls outside the established purity specification, then it will be rejected by FDA and cannot be sold for patient use. *Id.* at ¶32. FDA is so concerned about purity of pharmaceuticals that it requires companies to test for very tiny amounts of individual known impurities carried over into the final product based on the manufacturing process. *Id.* at ¶¶32-40. Thus, the change in the '393 product is commercially important and has real-world value.

IV. CLAIM CONSTRUCTION

In the Decision on Institution (Paper 28), the preliminary claim construction construes "[a] product comprising a compound [of/having] formula [I/IV] or a pharmaceutically acceptable salt thereof" and "product" in an unreasonably broad manner. The Board is not bound by that preliminary construction based on an incomplete record. *See e.g.*, *The Scotts Co., LLC v. Encap, LLC*, IPR2013-00110, Paper 79 (PTAB June 24, 2014) (overturning preliminary claim construction in final written opinion) (Ex. 2024). On the fuller record now available to it, the Board should adopt UTC's construction of the disputed terms.

A. Intrinsic Evidence Can Override The Presumption That "Comprising" Creates An "Open" Claim Construction

The claims at issue in an IPR must be given their broadest reasonable interpretation (BRI) in light of the specification, but the Board must still interpret claim terms according to established principles. The transition phrase "comprising" is only *presumed* to be an "open" phrase. *Crystal Semiconductor Corp. v. TriTech Microelectronics Int'l, Inc.*, 246 F.3d 1336, 1348 (Fed. Cir. 2001) ("In the parlance of patent law, the transition 'comprising' creates a presumption that the recited elements are only a part of the device, that the claim does not exclude additional, unrecited elements."). "While it is true that, as a general rule, the words of a patent claim are to be given their plain, ordinary and accustomed

meaning to one of ordinary skill in the relevant art, *Toro Co. v. White Consol. Indus., Inc.*, 199 F.3d 1295, 1299 (Fed. Cir. 1999), a court must nevertheless examine the remaining intrinsic evidence to determine whether the patentee has set forth an explicit definition of a term contrary to its ordinary meaning, has disclaimed subject matter, or has otherwise limited the scope of the claims." *Day Intern., Inc. v. Reeves Brothers, Inc.*, 260 F.3d 1343, 1349 (Fed. Cir. 2001).

The intrinsic record, both the specification and the prosecution history, must be reviewed to determine if there are limits to terms in the claims that would otherwise be given their presumptive plain meanings. Prosecution history "limits the interpretation of claims so as to exclude any interpretation that may have been disclaimed or disavowed during prosecution in order to obtain claim allowance." *Standard Oil Co. v. American Cyanamid Co.*, 774 F.2d 448, 452 (Fed. Cir. 1985). Similarly, the specification may contain repeated statements distinguishing the prior art that limit the claims. *SafeTCare Mfg., Inc. v.Tele-Made, Inc.*, 497 F.3d 1262, 1269-70 (Fed. Cir. 2007) (finding disclaimer where the specification repeatedly indicated that the invention operated by "pushing (as opposed to pulling) forces," and then characterized the "pushing forces" as "an important feature of the present invention").

Under the BRI standard, the Board should take into account both the specification and the prosecution history because the patent examiner and the

applicant have already worked together to determine the scope of the claimed invention. *See In re Buszard*, 504 F.3d 1364, 1366-67 (Fed. Cir. 2007) ("The patent examiner and the applicant, in the give and take of rejection and response, work toward defining the metes and bounds of the invention to be patented."); *In re Zletz*, 893 F.2d 319, 321 (Fed. Cir. 1989) ("When the applicant states the meaning that the claim terms are intended to have, the claims are examined with that meaning, in order to achieve a complete exploration of the applicant's invention and its relation to the prior art.").

The Board has followed these principles of claim construction in other IPR proceedings. *See, e.g.*, *The Scotts Co., LLC v. Encap, LLC*, IPR2013-00110, Ex. 2024 at 14-16. In *Scotts*, the Board changed its preliminary claim construction of "being in a solid state at time of coating" because the Board found that the patent owner had disavowed claim scope during prosecution in order to overcome a specific prior art reference. Ex. 2024 at 15. The Board relied on statements made in Examiner Interview Summaries which confirmed that claim amendments and arguments presented overcame the prior art. *Id.*; *see also* Prosecution History of U.S. Patent No. 6,209,259 (Ex. 2025). As another example, the Board recently construed a phrase to exclude trace amounts of a substance based on statements made during prosecution distinguishing prior art containing trace amounts of the substance. *Daicel Corp. v. Celanese Int'l Corp.*, IPR2015-00171, Paper 86 at 41

(PTAB June 23, 2016). Thus, the BRI cannot be divorced from the intrinsic evidence, including the prosecution history. Such a construction is not reasonable.

B. The Distinct Impurity Profile And Higher Purity Of the '393 Patent Product Were Clearly Considered Part of the Claimed Product During Prosecution

As explained during prosecution,"[e]ach of treprostinil as the free acid and treprostinil diethanolamine prepared according to the process specified in claim 1 or 10 . . . is physically different from treprostinil prepared according to the process of 'Moriarty' due to differences in their impurity profiles." Ex. 1002 at 344. In fact, the Examiner required UTC to provide evidence in declaration form showing that the product of claims 1 and 10 was different than Moriarty's product. *Id.* at 328. In response, UTC filed the Walsh Declaration, which demonstrated that the claimed product had a different impurity profile and higher purity than Moriarty's product. *Id.* at 347-349. It was upon these statements and evidence that Moriarty was overcome, and shortly thereafter the Examiner issued a Notice of Allowance. *Id.* at 354-360.

In addition, the '393 specification repeatedly refers to the differences of the '393 product compared to Moriarty. The entirety of Example 6 in the '393 specification is a large scale, side-by-side comparison between Moriarty and the '393 product, which shows a purity of 99.0% for Moriarty and 99.9% for the '393 product. Ex. 1001, 17:step 53. At the end of this example, the '393 specification

further states that "impurities carried over from intermediate steps (i.e., alkylation of triol and hydrolysis of benzindene nitrile) are removed during the carbon treatment and salt formation step" (Ex. 1001, 17:29-32), which are the same differences (higher purity and different impurity profile) that UTC relied upon in the Walsh Declaration during prosecution as noted above.

These statements by UTC demonstrate that the claimed "product" must have an impurity profile conferred by its process steps. *See Purdue Pharma L.P. v. Endo Pharms. Ins.*, 438 F.3d 1123, 1136 (Fed. Cir. 2006); *see also Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 997 (Fed. Cir. 2006) (statements made during prosecution history that distinguished the claimed invention from the prior art constituted a prosecution disclaimer); *see also United Therapeutics Corp. v. Sandoz, Inc.*, 2014 WL 4259153, *54-56 (D.N.J. Aug 29, 2014) (finding compounds made by different processes resulted in different impurity profiles meaning they were structurally different).

D. The Plain Meaning Of "Product" In The Context Of The '393 Product-By-Process Claims Requires The Characteristics Conferred By The Process Steps Be Present

The term "product" in the context of the '393 patent should be construed as "a substance resulting from a chemical reaction." This is consistent with the '393 patent itself (Ex. 1001 at col. 3, lines 3, 4, 65, and 66; col. 5, line 45; col. 6, lines 65 and 66; and col. 7, line 17), as well as the understanding of a POSA and the

generally accepted definition in chemistry. Ex. 2020 at ¶¶60-62. Additionally, Dr. Williams and Dr. Winkler both use the term product to refer to the result of a chemical reaction in their own work. Id. at ¶¶63-65; *see also* Ex. 2031 at 155:2-11 ("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."). To construe the term "product" as "a chemical composition" is too broad and improperly disregards a significant portion of the intrinsic record. As described above, a product is the result of a chemical reaction and has its own impurity profile depending upon how it is made. "A chemical composition" could be anything and is in no way limiting to what the term "product" actually means. Ex. 2020 at ¶¶66-68.

V. GROUND 1: PHARES FAILS TO EXPLICITLY OR INHERENTLY DISCLOSE EACH AND EVERY LIMITATION OF CLAIMS 1-5, 7-9, 11-14 OR 16-20

The Board instituted Ground 1 based on the conclusion that Phares teaches the treprostinil diethanolamine salt product recited in claims 1 and 9, and that the recited process steps of the claims do not impart structural or functional differences over Phares' treprostinil diethanolamine salt. As discussed below, SteadyMed has failed to establish anticipation based on Phares.

A. SteadyMed Cannot Pick and Choose From Unrelated Portions of Phares to Establish Anticipation

In attempting to show anticipation, SteadyMed cites four different portions of Phares, Ex. 1005, as teaching the combined elements of claims 1 and 9. However, SteadyMed 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 22-24 and 33-34.

The portions of Phares cited by SteadyMed each relate to distinct subject matter, and Phares provides no description that would lead to the combination of these separate disclosures. Ex. 2020 at ¶¶79-84. Phares' only disclosure of steps (a) and (b) is directed to the enantiomer (-)-treprostinil, which are not the same as the synthesis for treprostinil. Ex. 2020 at ¶¶79-81. In fact, the intermediate products disclosed in the enantiomer synthesis as well as several reagents are different than the synthesis of treprostinil. *Id.* at ¶81. In contrast, Phares' separate alleged disclosure of step (c) is silent as to how the starting treprostinil acid was prepared. Ex. 1005 at 85. Thus, there is no reason set forth in Phares to combine the single teaching of steps (a) and (b) directed to one enantiomer with the other teachings of step (c), which are all directed to the other enantiomer. Ex. 2020 at ¶¶79-81.

Despite the alleged disclosure in Phares' that enantiomers of the disclosed compounds can be prepared using the proper chiral reagents, Phares itself teaches that treprostinil can be prepared in other ways that do not include steps (a) and (b), including the processes disclosed in US Patent Nos. 4,306,075 (Ex. 2032) and 5,153,222 (Ex. 2033). Ex. 1005 at 11; Ex. 2020 at ¶78. Thus, a POSA would reasonably conclude that the diethanolamine salts of Phares were prepared based on other disclosed methods that do not require steps (a) and (b). Ex. 2020 at ¶78. If the diethanolamine salts of Phares were prepared differently than the recited process steps, nothing in Phares establishes that the diethanolamine salts are necessarily the claimed product.

B. The Proper Construction of a "product comprising a compound [of/having] formula [I/IV] or a pharmaceutically acceptable salt thereof" Precludes A Finding That Phares Anticipates the Present Claims

The Board's institution of Ground 1 was partly based on its preliminary finding that "comprising" does not exclude impurities that may possibly be produced by the process of Phares and that the impurity profile of Phares' diethanolamine salt is identical to that of the claimed product. *See* Paper 12 at 30. However, such a finding does not take into consideration the reasonable construction of "product comprising a compound [of/having] formula [I/IV] or a

pharmaceutically acceptable salt thereof," which is set forth in this Response and supported by the record now before the Board.

As discussed above in Section IV, both the specification and the prosecution history of the '393 patent distinguish the claimed product from prior art treprostinil products based on its higher purity and different impurity profile, which is achieved through the recited process steps. Thus, to prevail on Ground 1, SteadyMed must show that the Phares' diethanolamine salt necessarily possesses an impurity profile that is distinct from that of the Moriarty product and with higher purity.

Steadymed simply assumes that the diethanolamine salt discussed by Dr. Winkler is prepared from Moriarty treprostinil and does not acknowledge that the source of treprostinil would impact both the overall purity and impurity profile of the resulting salt. As exemplified in the '393 patent, the claimed process provides an improved treprostinil product due to its superior purity. As evidenced by the Williams Declaration and the batch record data, the claimed product has an average purity of [redacted] and a distinct impurity profile from Moriarty's product. Ex. 2020 at ¶¶94-99. Importantly, SteadyMed has failed to show that, at a minimum, the Phares' diethanolamine salt possesses an impurity profile that is distinct from that of the Moriarty product and contains fewer overall impurities than the Moriarty product. Nor has SteadyMed shown that the Phares'

diethanolamine salt has a higher purity than the Moriarty product. Indeed, SteadyMed's only argument regarding the purity of Phares' diethanolamine salt is based on the theory that the higher melting point of Phares' diethanolamine salt necessarily means that it must be at least equal in purity to that of the exemplified batches in the '393 patent. *See* Petition at 27-28. However, for the reasons noted below, that is an incorrect conclusion based on the evidence now in the record.

C. The Higher Melting Point of Phares' Diethanolamine Salt Does Not Necessarily Mean That it is of Higher Purity Than the Diethanolamine Salts of the '393 Patent

The Board relied on incorrect statements in the Winkler Declaration alleging that Phares' diethanolamine salt must be more or at least equally pure as the claimed product solely because the former has a higher melting point. Paper 12 at 28-29. However, melting point is just one factor in assessing a compound's purity and is not necessarily a reliable metric of purity. This is especially applicable to Phares because only one melting point value was obtained in a sample for a polymorph screen. A POSA would not rely upon a single melting point value, absent any other impurity information, to determine the purity of a substance made under unspecified conditions. Ex. 2020 ¶76. Indeed, the "higher" melting point of Phares' diethanolamine salt could be indicative of the inclusion of impurities or the result of the use of different solvent systems for the crystal forms. *Id.* Accordingly,

the purity of a compound cannot be assessed based solely on its melting point value.

Moreover, even if the melting point could be relied upon, the data cited by Dr. Winkler does not indicate a product of high purity. To the contrary, Fig. 21 of Phares "shows a broad melting peak with a range of close to 10 degrees which is indicative of a lower purity substance." Ex. 2020 ¶76; *see also*, Marti, E., *Purity determination by differential scanning calorimetry*, Thermochimica Acta, 5(1972) 173-220 at 214 ("The melting of diphenyl is extremely sharp because of the purity level; on the other hand, the melting region of phenacetin-benzamide is rather broad.") (Ex. 2031).

Additionally, Phares discloses several different conditions for preparing Polymorph A of the diethanolamine salt and that Polymorph A is required to make Polymorph B. Ex. 2020 at ¶73. The '393 patent does not indicate that making Polymorph A first is required. *Id.* Phares also indicates many conditions used to make Polymorph A and Polymorph B, but it is not clear what conditions were specifically used for the sample analyzed in Figure 21 that Dr. Winkler relies upon. *Id.* at ¶¶73-74. It is well known that the use of different solvent systems in forming different crystal forms can have a significant effect on the melting point of a substance, as well as other characteristics, including purity, and a higher melting point does not always mean a higher purity. *Id.* at ¶¶75-76; *see also* R. Adhiyaman,

et.al., *Crystal modification of dipyridamole using different solvents and crystallization conditions*, Int'l J. Pharm.321 (2006) 27-34 at 33 ("Adhiyaman") ("In conclusion, it can be said that the crystallization conditions and medium used have major effect on dipyridamole crystals habit modification under ambient conditions. The crystals showed significant changes in the shape, size, melting points, dissolution rate, XRD patterns and DSC curves.") (Ex. 2030).

Dr. Williams, therefore, has concluded that "[i]t is known in the art that sample size, rate of heating, the recrystallization solvent(s) used, and the conditions under which the crystalline sample was obtained can significantly affect the DSC data. Dr. Winkler's conclusion based on this single vague and incompletely described DSC data is not scientifically sound." *Id.* at ¶76.

Thus, nothing in Phares establishes that the disclosed diethanolamine salt is at least of equal purity to the diethanolamine salts of the '393 patent. With respect to claim 2 of the '393 patent specifically, nothing in Phares discloses a purity of at least 99.5%. Ex. 2020 at ¶82. For this additional reason, Phares cannot anticipate claim 2.

D. Phares Fails To Disclose the Claimed Process for Making Treprostinil or Any Purity or Impurity Profile for Treprostinil Diethanolamine

SteadyMed has failed to establish that Phares' diethanolamine salt (Form B) is the claimed product.

First, as Dr. Williams notes, the samples of treprostinil diethanolamine disclosed in Phares were "made for a polymorph screen, not large scale batches." Ex. 2020 ¶73. Accordingly, "the samples of polymorph B described in Phares are prepared in a completely different way under different conditions than those described in the '393 patent." Ex. 2020 ¶75. Specifically, Phares discloses first preparing polymorph A by any one of a variety of methods and then preparing polymorph B from some sample of polymorph A. In contrast, the '393 patent makes no mention of first forming polymorph A. Ex. 2020 ¶¶73-74. Additionally, Phares describes reaction conditions for making the polymorph samples that are not described anywhere in the '393 patent. *Id.* In particular, the reaction conditions disclosed for the sample of polymorph B characterized by Phares, heated slurries of form A in 1,4-dioxane and toluene, are not described anywhere in the '393 patent. *Id.* It is well-known that the use of different reaction conditions, including different solvents, can significantly affect the characteristics of a given crystal form. Ex. 2020 ¶75. As a result, the diethanolamine salt disclosed in Phares cannot be directly compared to the diethanolamine salt disclosed in the '393 patent.

Second, the Williams Declaration clearly establishes that the claimed product has an average purity of [redacted], thus giving it a superior purity and distinct impurity profile over that of the prior art treprostinil products. Ex. 2020 ¶¶94-99. The purity of the claimed product provides a structural difference from the prior art

treprostinil, as evidenced by the differences in the average impurity profiles for the Moriarty product and the '393 product. *Id.*, Ex. 2036, Ex. 2037. Indeed, the higher purity of the claimed product resulted in FDA approving a new purity specification for the treprostinil drug as noted in the January 2009 letter submitted to FDA by UTC. Ex. 2006 at 4-6; Ex. 2022 at ¶¶70-72; Ex. 2020 at ¶91.

The impurity profile of the *starting* treprostinil acid used to prepare the Phares diethanolamine salt is crucial to assess whether the diethanolamine salt is the same as the claimed product, *i.e.*, whether the impurity profile of the diethanolamine salt in Phares is identical to that of the claimed product. Ex. 2020 ¶¶76-78. However, nowhere does Phares disclose the process of preparing the treprostinil acid used to prepare the diethanolamine salt. As acknowledged in both Phares and the '393 patent, several different processes can produce treprostinil acid. *See, e.g.*, Ex. 1005 at 11; *see also,* Ex. 2020 ¶78. Each known process can produce a treprostinil acid with a unique impurity profile. Ex. 2020 ¶78. Because Phares does not disclose the process of preparing the starting treprostinil acid for the diethanolamine salt, the impurity profile of the diethanolamine salt cannot be established. Without knowing the impurity profile and level of purity of Phares' diethanolamine salt, SteadyMed cannot show that it is necessarily identical to the claimed product or has equal purity to the claimed product.

Consequently, SteadyMed has not carried its burden on Ground 1.

VI. GROUND 2: MORIARTY AND PHARES FAIL TO RENDER OBVIOUS CLAIMS 1-5, 7-9, 11-14, OR 16-20

Moriarty does not teach salt formation and regeneration of the free acid. SteadyMed attempts to cure this deficiency in Moriarty by citing Phares for allegedly teaching step (c). However, Moriarty teaches three distinct methods of preparing the treprostinil free acid. Nothing in Moriarty directs a POSA to select one specific process over the three disclosed for purposes of further modification by adding a salt formation step. Furthermore, SteadyMed fails to recognize that the performance of step (c) after steps (a) and (b) unexpectedly results in a product with an improved average purity over that of the prior art. Indeed, the Williams Declaration demonstrates that, out of 122 samples, the claimed product has an average purity of greater than [redacted]. Ex. 2020 at ¶¶94-95 and Appendices A-B.

As discussed above, the claimed product is structurally different from Moriarty's product because the claimed product has a distinct impurity profile, including a marked reduction in several specific impurities, and a higher average purity relative to Moriarty's product. Ex. 2020 at ¶¶94-99 and Appendices A-B. This evidence shows that, in the recited combination, performing step (c) in conjunction with steps (a) and (b) of the present claims produces a treprostinil product that is significantly improved over that of the prior art. Ex. 2020 at ¶¶48-49, 70.

Moreover, Moriarty's product cannot render obvious the claimed product because during prosecution of the '393 patent, UTC overcame a rejection based upon Moriarty by providing evidence of representative sample impurity profiles, showing the physical difference between the product of the '393 patent and the Moriarty product. Ex. 1002 at p. 347. Phares does not cure this deficiency because, as noted above, nothing in Phares establishes that the diethanolamine salt either 1) has an impurity profile similar to the claimed product or 2) has an overall purity at least equal to the claimed product.

In particular, it would not have been obvious to use the salt formation step of Phares to decrease amounts of at least [redacted] and [redacted], which are stereoisomers of treprostinil, and accordingly, are acidic rather than neutral or basic. Ex. 2020 at ¶102. Thus, when subject to salt-forming conditions, a POSA would expect that any undesired stereoisomer of treprostinil would be included in the final salt product because the stereoisomer would also be converted to the corresponding salt under such salt-forming conditions. A POSA has no reasonable expectation of success in removing any undesired treprostinil stereoisomer impurities by salt formation and subsequent regeneration of the free acid. *Id.* Instead, a POSA would expect the salt formation and subsequent regeneration to produce a final product with the same initial amount of stereoisomer impurities before the salt formation step. *Id.* Yet these impurities are each detected in only a single optimization batch

of the '393 product, and in none of the commercial batches. Even taking these optimization batches into consideration, this represents a greater than 100-fold reduction as compared to the Moriarty product. *Id.* at ¶¶94-96.

Additionally, as described above, there is no basis for comparing the "purity" in Moriarty with the purity described in the Walsh Declaration. *Id.* at ¶88. Walsh's Declaration makes clear that purity in terms of the '393 patent is assessed by looking to the total related substances of a batch. *Id.* at ¶¶88-89. The Moriarty reference, while not specifying a reference standard, does refer to a comparison to an authentic sample. *Id.* As a result, it is not clear what method was used to determine the purity in Moriarty and therefore a direct comparison of the value reported in Moriarty cannot be made to the '393 patent.

Moreover, Dr. Winkler fundamentally misunderstands the error associated with various purity measurements used in the Walsh Declaration, the '393 patent, the prior art, and FDA. Dr. Winkler states in his declaration that:

> 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.

Ex. 1009 at ¶69.

He goes on to state that "HPLC's precision indicates that the 'RSD' or 'relative standard deviation' for a typical instrument is about 1%." *Id.* at ¶70.

This is wrong for several reasons. First, during his deposition, Dr. Winkler admitted he did not know what the actual error in the measurement was for the data submitted in the Walsh Declaration during prosecution of the '393 patent. Ex. 2051 at 62:16-25; 63:2-14.[2] While he did not know the error associated with the measurements made in the data submitted with the Walsh Declaration, he did admit that "the error in the measurement for the [redacted] [treprostinil impurity] would be, should be less than .1 percent," and in general, "[t]he error should be less than the maximum number reported, that's correct, for the measurement of the materials described here." Ex. 2051 at 63:25-64:4; 64:7-16. By his own admission, the error associated with the measurement of impurities in treprostinil batch records such as those submitted in Walsh's Declaration are therefore far less than the alleged error of 1% or 0.4% he stated in his declaration.

[2] Indeed, Dr Winkler admitted he was not familiar with FDA guidelines regarding impurity profiles for a drug, did not know what is required in order to change a drug specification, and was not familiar with published guidances from FDA regarding changes to new drug applications or abbreviated new drug applications. Ex. 2051 at 19:3-24.

In contrast, FDA requires that impurity determinations must be measured at or below 0.05% for drugs such as treprostinil. *See*, Ex. 2022 at ¶47; Ex. 2020 at ¶92. As Dr. Ruffolo explains, impurities in drug substances such as treprostinil that are administered in dosages less than 2 grams per day require that impurities be reported if they are present at a level less than or equal to 0.05%. *See, e.g.*, Ex. 2022 at ¶¶44-47; *see also* ICH Impurities in New Drug Substances Q3A(R2) monograph at 5-11 (Ex. 2038). "As a result of these thresholds, by definition, the limit of detection for impurities (and therefore total related substances) must be at least as low as 0.05%." Ex. 2022 at ¶50.

Furthermore, the '393 patent is directed to an improved and more pure treprostinil product. *See, e.g.*, Ex. 1001, 17:27-40. Given that Moriarty discloses the use of column chromatography for purification, a POSA would not be motivated to create the salt form in Phares, as Phares does not disclose any benefit or increased purity as a result of using the diethanolamine salt. Ex. 2020 at ¶101. "In fact, Phares does not allege that the diethanolamine salt is superior in any way to the treprostinil product of Moriarty and instead identifies other earlier treprostinil disclosures as a means to create the treprostinil used to form the diethanolamine salt." *Id.* A POSA would not have a reasonable expectation of success by using salt formation as a purification step separate from or in addition to the column chromatography of Moriarty, as Phares does not disclose any alleged

benefit to forming the salt and a POSA would have no expectation that only certain acidic and neutral impurities would be reduced or completely eliminated while others remained. *Id.* at ¶102. Thus, the combination of Moriarty and Phares cannot render obvious claims 1-5, 7-9, 11-14, or 16-20.

Similarly, as described above, there is no basis to compare the purity disclosed in Moriarty to the measurements obtained in the '393 patent or those obtained by Dr. Walsh in his declaration, and therefore, claim 2 would also not be rendered obvious by the combination of Phares and Moriarty for this additional reason. *Id.* at ¶103.

Claims 8 and 16 also require the additional limitation that the formula (VI) compound of step (a) is not purified. In fact, the '393 patent specifically distinguishes this limitation over the prior art. Ex. 1001, Example 6. Moriarty expressly discloses that the compound of formula (VI) from step (a) is purified. Ex. 2020 at ¶104. Phares does not disclose any synthesis for treprostinil and, even in the abbreviated synthesis of the enantiomer, no details of purification are disclosed. *Id.* Thus, claims 8 and 16 are not rendered obvious by the combination of Phares and Moriarty for this additional reason. Process advantages should be considered as secondary considerations to rebut obviousness, even if the process steps or advantages are not considered in the initial determination of whether there is *prima*

facie obviousness (where the products are compared regardless of how they are made).

Consequently, SteadyMed has not carried its burden on Ground 2.

VII. GROUND 3: MORIARTY, PHARES, KAWAKAMI, AND EĞE FAIL TO RENDER OBVIOUS CLAIMS 6, 10, 15, 21, AND 22

A. The Product of Claims 6, 15, and 21 Are Different Than the Prior Art Treprostinil Products

The Board concluded that the process steps of claims 6, 15, and 21, including step (d), do not impart structural or functional differences over prior art treprostinil products. Paper 12 at 46-47.

Based on the evidentiary record now before the Board, and in view of the reasons set forth in Section III, above, the free acid substance formed by step (d) of claims 6, 10, 15, 21 and 22 is structurally different from the prior art treprostinil products in Phares and Moriarty. The evidentiary record shows that the free acid substance of claims 6, 10, 15, 21 and 22 contains a distinct impurity profile and a higher average purity over the treprostinil free acid of Moriarty, and thus is structurally different. Further, Phares' diethanolamine salt of treprostinil is structurally and functionally distinct from the free acid substance formed by step (d) of claims 6, 15 and 21.

1. The '393 Patent Product is Structurally and Functionally Distinct from Moriarty's Product

As explained in the Williams Declaration and discussed above, the free acid substances of claims 6, 10, 15, 21 and 22 are structurally distinct from Moriarty's product because the formation of the salt in step (c) leads to a product that has a distinct and improved impurity profile. *See* Sections III, VI, *supra*. Additionally, the average purity of the product of claim 21 is about [redacted] greater than that of Moriarty. Ex. 2020 ¶¶94-99 and Appendices A-B. Indeed, as evidenced by Dr. Ruffolo's Declaration, a [redacted] difference in average purity for a highly potent drug, such as treprostinil is a very significant difference. *See, e.g.*, Ex. 2022 at ¶70.

B. There Is No Motivation For A POSA To Combine Moriarty and Phares with Eğe and Kawakami

In the Institution Decision, the Board determined "on the record before us, and for purposes of institution, that the process steps recited in claims 6, 15, and 21 do not impart structural or functional differences to the claimed treprostinil product, we do not address the parties' contentions concerning the obviousness of the recited process steps." Paper 12 at 47. However, the fuller record now indicates that the claimed treprostinil product is structurally and/or functionally different from Moriarty's treprostinil free acid and Phares' treprostinil diethanolamine salt. Thus, the recited process steps must now be considered.

Similarly, the board credited Dr. Winkler's opinion regarding the combination of Kawakami and Eğe with Moriarty and Phares. Paper at 42. Dr. Winkler, however, too easily dismisses the complexity and difficulty associated with further purifying a drug substance as complex as treprostinil. Dr. Winkler attempts to portray the chemistry involved in the '393 patent as "nothing more than basic organic chemistry techniques – in my view 'organic chemistry 101'" in an effort to minimize the significant invention of the '393 patent. Ex.1009 at ¶3. Yet, Dr. Winkler contradicts himself by defining a POSA as having "a master's degree or 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." *Id.* at ¶14. Indeed, Dr. Winkler goes on to testify that to understand the science and chemistry of the patent, you would need that level of skill in the art. Ex. 2051 at 29:12-16. As a result, a POSA would not look to an undergraduate textbook like Eğe, for example, to figure out improved purification techniques for a complex drug substance such as treprostinil.

1. There Is No Motivation to Follow the Carboxylate Salt Formation With Regeneration of the Carboxylic Acid

The Board credited Dr. Winkler's opinion regarding the combination of Kawakami and Eğe with Moriarty and Phares. Paper 12 at 42. Dr. Winkler,

however, too easily dismisses the complexity and difficulty associated with further purifying a drug substance as complex as treprostinil. After first referencing "organic chemistry 101" to minimize the significance of the '393 patent (Ex. 1009 at ¶3), Dr. Winkler contradicts himself by defining a POSA as having "a master's degree or 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." *Id.* at ¶14. At his deposition, Dr. Winkler conceded that, to understand the science and chemistry of the '393 patent, you would need this higher level of skill in the art. Ex. 2051 at 29:12-16. As a result, a POSA would not look to an undergraduate textbook like Eğe, for example, to figure out improved purification techniques for a complex drug substance such as treprostinil.

As explained previously, the claimed free-acid compounds, including treprostinil, produced by the processes of claims 6, 10, 15, and 21 provide 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, UTC demonstrated that treprostinil free acid made by the claimed methods provides a compound that lacks or reduces the levels of the impurities found in the free acid treprostinil of the Moriarty process.

Neither Phares nor Eğe 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 V.E., *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). "Given that the purification techniques disclosed in Moriarty include chromatography and recrystallization after many years of research to optimize the process of making treprostinil, a POSA would not have been motivated to use a salt purification technique disclosed in an undergraduate chemistry textbook. More importantly, a POSA would not have had a reasonable expectation of success in further purifying the treprostinil product of Moriarty by using such a technique. To the extent a POSA was motivated to further purify treprostinil, a POSA would have focused on the known impurities and investigated methods of removing those." Ex. 2020 at ¶106. Indeed, stereoisomers were known impurities in treprostinil. *Id.* Eğe, however, simply discloses that "carboxylic acids that have low solubility in water, such as benzoic acid, are converted to water-soluble salts by reaction with aqueous base. 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." *Id.* at ¶107.

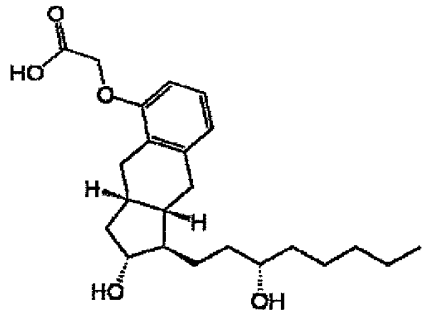
Indeed, the only example given in Eğe is of benzoic acid – a very simple aromatic acid that is quite different from the structure of treprostinil, as it has no chiral centers and therefore no stereoisomeric impurities. *Id.* at ¶108. Given that Eğe only predicts the removal of neutral and basic compounds by a salt purification step followed by acidification and only describes a simple non-chiral carboxylic acid, a POSA would have no motivation to look to Eğe for purification and no reasonable expectation of success given that many of the impurities in treprostinil are acidic stereoisomers. *Id.* at ¶¶108-109.

As discussed above, the average impurities found in samples of the Moriarty product include three different stereoisomers of treprostinil free acid. Eğe 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 would have understood Moriarty, Phares, and Eğe 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 Eğe actually teaches away from the usefulness of this step when impurities include acidic stereoisomers are present because a POSA would have to ignore Eğe's teaching that these types of impurities could not be removed by carboxylate salt formation. *See* Ex. 2020 ¶¶107-109; *see also United States v. Adams*, 383 U.S. 39, 42-43 (1966).

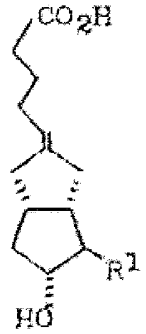
The Institution Decision cites *KSR* for the proposition that "a technique has been used to improve one device, and a POSA would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill." Paper 12 at 45. However, the simple application of this proposition regarding devices (a predictable art) should not be applied to an unpredictable field, such as the chemical arts, without truly examining whether the technique would improve *similar compounds* in the *same way*. *See, e.g., In re Fisher*, 427 F.2d 833, 839 (C.C.P.A., 1970)(contrasting "predictable factors, such as mechanical or electrical elements" from "unpredictable factors, such as most chemical reactions"); *see also, Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008).

For example, Kawakami teaches purification of a methanoprostacyclin derivative by forming the dicyclohexyl amine salt and then regenerating the free acid to achieve a "fairly high" purity. Analogizing to the language cited from *KSR*, a POSA must have recognized that the "technique" of salt formation followed by regeneration of the free acid would improve *similar compounds* in the *same way*.

However, as can be seen by the below comparison, the structures of treprostinil and the methanoprostacyclin derivative of Kawakami are structurally very different – they are not *similar compounds/devices*.



Treprostinil



methanoprostacyclin compound in Kawakami

First, the methanoprostocyclin compound in Kawakami is a-two fused-ring structure, while treprostinil is a three-fused-ring structure. Ex. 2020 at ¶112. Second, Kawakami does not actually disclose a purification method for separating diastereomers, but instead one for separating E and Z isomers. Ex. 2020 ¶¶112-113.

Indeed, Kawakami teaches that the starting material does not vary at each chiral center other than the alkene double bond. *Id.* In other words, Kawakami discloses a mixture of two compounds: (1) the E-isomer of a stereoisomerically pure compound and (2) the Z-isomer of a stereoisomerically pure compound. *Id.* at ¶113. Treprostinil contains no mixture of E and Z isomers because it does not contain a carbon-carbon double bond that is capable of forming E and Z isomers. Indeed, the use of a specific salt to isolate a specific E/Z isomer does not reasonably suggest that salt formation of a much more complex compound with

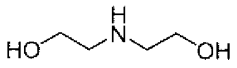
multiple chiral centers such as treprostinil could be isolated from entirely different impurities and then converted back to the free acid form. *Id.*

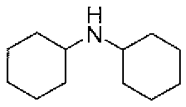
Thus, the purification of treprostinil from its stereoisomers and related impurities is quite different from the purification of the methanoprostacyclin derivative from its structural isomer – the compositions are not improved in the *same way*.

As a result of these differences, "a POSA would not have looked to Kawakami (or Eğe) if they were looking for additional purification techniques for treprostinil because neither reference discloses how to remove stereoisomeric impurities." *Id* at ¶112.

2. Kawakami Would Have Motivated One of Ordinary Skill In The Art To Select A Dicyclohexyl Amine Salt, Teaching Away From The Diethanolamine Salt of Claims 14 and 18

Not only are there structural differences between treprostinil and the "methanoprostacyclin compound" in Kawakami, but the counter-ion used to prepare the salt is structurally different. *Id.* at ¶114. Specifically, Kawakami teaches preparing the dicyclohexyl amine salt, whereas particular claims of the '393 patent require use of the diethanolamine salt.





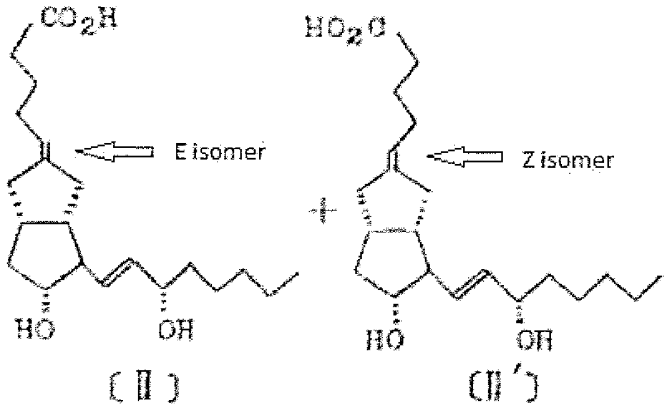
Diethanolamine **dicyclohexyl amine**

Because Kawakami uses a different salt to remove a different sort of impurity from a different structure, a POSA would have no reason to combine the teachings of Kawakami with Moriarty and Phares in the particular manner of the asserted grounds in the Petition, or a reasonable expectation of success of achieving a more pure treprostinil product by such a combination. Ex. 2020 ¶114. For this reason, claims 14 and 18 are separately patentable.

3. Kawakami Does Not Provide A Reasonable Expectation Of Success That Treprostinil Products Could Be Further Purified Because Different Impurities Are Targeted

The purification of treprostinil from its stereoisomers and related impurities is quite different from the purification of the methanoprostacyclin derivative from its structural isomer, and thus, Kawakami provides no reasonable expectation of success. Ex. 2020 ¶¶112-114

To illustrate this point further, Kawakami is directed to purifying E- and Z-isomers of methanoprostacyclin compound 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. SteadyMed 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. As explained in the Williams Declaration, the use of a specific salt to isolate a specific E/Z isomer does not reasonably suggest that salt formation of an entirely different compound, such as treprostinil, could be isolated from entirely different impurities, such as stereoisomers and related impurities. Ex. 2020 ¶¶112-114.

Furthermore, the Kawakami reference would have provided no motivation or rationale to attempt to remove the trace impurities of the Moriarty treprostinil free acid through the process of salt formation followed by conversion back to the

free acid. Indeed, Kawakami was concerned with isolating a particular isomer from a 7:2 E/Z isomeric mixture. Ex. 1007 at 4. In other words, the composition in Kawakami contained, at most, a purity of 77.8% prior to the salt formation step. Kawakami provides a crude purification of the desired E-isomer through a particular salt formation, and suggests that not all impurities were removed by formation of a salt and conversion back to the free acid. *Id.* at 5 ("purity can be further improved by recrystallization"). Nothing in the reference suggests that a substance as pure as the Moriarty treprostinil free acid (a substance with about 99.4% assay purity) – a substance that had already been "further improved" by recrystallization (*see* Ex. 1004 at 13, right column) – would be improved by formation of a salt and conversion back to the free acid. Ex. 2020 ¶¶113-114.

Thus, even if formation of a salt and conversion back to the free acid was known in the art, it would not have rendered the present claims obvious without some motivation and expectation of success in its use on the Moriarty treprostinil free acid. To put it another way, there would have been no reason to incur additional time and expense to form a salt of the valuable, relatively pure Moriarty treprostinil free acid only to then convert it back to the free acid, even though the addition would have been technologically possible. *In re Omeprazole Patent Litigation*, 536 F.3d 1361 (Fed. Cir. 2008).

4. Any "Close" Structural Similarity of the Moriarty Free Acid Does Not Render the Claims Obvious

As explained above, the claimed substance is structurally different from Moriarty's treprostinil free acid because the claimed substance has an improved and different impurity profile. Even if the Board views an improvement in impurity profile of, e.g., [redacted], as a close relationship between the substances of the present claims and of Moriarty, there is no obviousness because there was not a known or obvious process for making the claimed free acid substance. *See In re Hoeksema*, 399 F.2d 269, 274 (C.C.P.A. 1968)("the absence of a known or obvious process for making the claimed compounds overcomes any presumption that the compounds are obvious based on close relationships between their structures and those of prior art compounds"). For the reasons set forth in the previous sections, conducting a salt-formation purification step on the known treprostinil free acid of Moriarty would not have been obvious, so the mere existence of a "close relationship" in the products cannot be used to deny patentability.

5. Additional Claim Limitations Are Not Disclosed by the Cited Prior Art

In addition to the reasons above, certain dependent claims would also not have been obvious in light of the combination of Phares, Moriarty, Eğe, and Kawakami. Claim 6 requires the acid in step (d) to be either HCl or H_2SO_4 and

claim 15 requires the acid to be HCl. Similarly, claim 21 requires step (d) is performed. Phares, Moriarty, and Kawakami all do not disclose the use of either HCl or H_2SO_4 and do not disclose converting a carboxylic acid salt back to its salt form using an acid. Ex. 2020 at ¶115. "Eğe cites HCl as an example in the conversion of benzoic acid, but as described above, a POSA would not have looked to Eğe to further purify a complex carboxylic acid such as treprostinil from its stereoisomers and other impurities and would have no reasonable expectation of success by using HCl based on this disclosure." *Id.* In addition to the reasons above, claims 6, 15, and 21 would not be obvious in light of any combination of the cited prior art.

Like claim 2, claim 10 requires that the product be 99.5% pure and that step (d) be performed. The only purity limitation disclosed in any cited prior art reference is in Moriarty and, as explained above, that purity cannot be directly compared to the purity recited by the claims. Similarly, Moriarty does not perform steps (c) or (d). *Id.* at ¶116. A POSA would have no motivation to look to Phares, Kawakami or Eğe to improve the purity to at least 99.5% and, given that none of these references disclose a purity amount, would have no reasonable expectation of success in achieving that purity. *Id.* Finally, claim 22 requires an extra step of forming a pharmaceutically acceptable salt from the product of step (d). SteadyMed and Dr. Winkler cite no evidence whatsoever for this additional step.

"In fact, none of the references cited even suggest converting a carboxylic acid to a salt form, then regenerating the carboxylic acid, then forming a pharmaceutically acceptable salt from that." *Id.* at ¶117. For this additional reason, claim 22 is not obvious in light of the combination of Phares, Moriarty, Kawakami, or Eğe.

Consequently, SteadyMed has not carried its burden on Ground 3.

VIII. SECONDARY CONSIDERATIONS REBUT ANY POSSIBLE CASE OF OBVIOUSNESS

SteadyMed has not established a *prima facie* case of obviousness. Thus, UTC is not obligated to provide evidence of objective indicia of non-obviousness. Nonetheless, objective indicia of non-obviousness confirm that the claims of the '393 patent would not have been obvious and, in fact, represent 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. *See generally*, Ex. 2022 at ¶¶31, 65. 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. *Id.*; Ex. 2022 at ¶54. Specifically, the FDA as a matter of course seeks to minimize all impurities in drug substances and particularly in highly potent drug substances such as treprostinil. Ex. 2022 at ¶¶ 31, 54. The reduction and removal of several types of impurities met the long-felt need expressed by the FDA to minimize impurities as much as possible. *Id.* at ¶¶ 31, 75. Additionally, because the '393 patent product was so successful, it resulted in a change in the drug specification submitted to FDA. *Id.* at ¶¶66-67. The change indicated that the assay purity of the new drug substance made by the '393 patent process increased in purity from an assay range of [redacted] to [redacted] - a full [redacted] increase in assay purity. *Id.* at ¶ 70. The range of assay values of [redacted] as well as the amount above 100% does not indicate an error associated with the measurement, but just the acceptable value of this measurement approved by the FDA. *Id.* at ¶¶ 69-70. The fact that UTC submitted a [redacted] increase in assay purity to FDA is considered a "major" change by FDA. *Id.* at ¶ 72. *See Knoll Pharm. Co., Inc. v. Teva. Pharm. USA, Inc.*, 367 F.3d 1381, 1385 (Fed.Cir. 2004) (while FDA approval is not determinative of nonobviousness, it can be relevant in evaluating the objective indicia of nonobviousness). In fact, even a change as small as 0.1% of impurities can have an impact on a drug substance. *See, e.g., id.* at ¶¶ 32, 45. Given that FDA consistently wants drug substances to have fewer

impurities and in less amounts, the '393 patent invention met that need by further reducing and removing certain specific impurities and by increasing the overall assay purity of the drug substance.

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 certain non-acidic impurities as well. *See, supra*, Section XI.B.1; Ex. 2020 ¶¶94-97, 102, 108-109. Indeed, Eğe itself predicted that a salt formation followed by regeneration using an acid would remove only basic and neutral impurities. *Id.* at ¶107. The unpredictability of this result is supported by the fact that the salt purification step did not reduce all non-acidic impurities; in fact, the '393 product has slightly increased levels of one such impurity, [redacted]. Ex. 2020 ¶96. Thus, a person of skill in the art would not have expected the results of the '393 patent to be so successful at reducing the levels of so many impurities.

IX. Conclusion

For the foregoing reasons, the Board should hold that SteadyMed has failed to carry its burden attacking the patentability of the instituted claims because none

of the prior art cited by SteadyMed anticipates or renders obvious any claim of the '393 patent.

Respectfully submitted,

Date: July 6, 2016

/Stephen B. Maebius/
Stephen B. Maebius
Reg. No. 35,264

CERTIFICATE OF COMPLIANCE

This Paper contains 11,230 words according to the word processing program in which it was created, excluding the portions exempted by 37 C.F.R. ¶42.24(a)(1). Accordingly, this Paper complies with the requirements of 37 C.F.R. § 42.24(b)(1).

Date: July 6, 2016

Signature: /Stephen B. Maebius/
Stephen B. Maebius

CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of the foregoing Patent Owner Response and accompanying exhibits was served on counsel of record for Petitioner on July 6, 2016 by filing through the Board's PRPS system and 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: July 6, 2016

Signature: /Stephen B. Maebius/
Stephen B. Maebius

4814-0612-4340.3

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

DECLARATION OF ROBERT M. WILLIAMS, Ph.D., IN SUPPORT OF PATENT OWNER RESPONSE TO PETITION

TABLE OF CONTENTS

I have been retained by the law firm of Wilson Sonsini Goodrich & Rosati ("WSGR") as an expert consultant to United Therapeutics Corporation ("UTC") in connection with the above-identified matter to provide expert testimony concerning U.S. Patent No. 8,497,393 ("the '393 Patent", Ex. 1001) by Batra *et al.*, entitled "Process to prepare Treprostinil, the active ingredient in Remodulin," issued on July 30, 2013. At the request of Counsel for UTC, I hereby submit this expert declaration.

I. Qualifications and Background

A. Education and Experience

1. I am a tenured University Distinguished Professor of Chemistry at Colorado State University (CSU). I currently serve as the Director for the Colorado Center for Drug Discovery. I also served as co-Director (Experimental Therapeutics) for the Infectious Diseases Supercluster Initiative and also served as co-Director for the Cancer Supercluster Initiative at CSU. My *curriculum vitae* is attached hereto as Exhibit A (Ex. 2021).

2. I received a B.A. in Chemistry from Syracuse University in 1975, and did laboratory research in the field of synthetic organic chemistry under the guidance of the recent Nobel Laureate Professor Ei-ichi Negishi. In 1979, I received both a Master's degree and Ph.D. degree in Organic Chemistry from the Massachusetts Institute of Technology (MIT) under the direction of Professor William H. Rastetter. Upon graduating from MIT, I spent one year (1979-80) as a postdoctoral fellow at Harvard University in the laboratories of the Nobel Laureate, the late Professor Robert B. Woodward, whose laboratory was subsequently managed by Professor Yoshito Kishi.

3. Subsequent to my fellowship at Harvard, I served as an Assistant Professor at Colorado State University from 1980–84. I was tenured and promoted early, to the rank of

Associate Professor in 1985, and in 1988, I was promoted to the rank of Full Professor. In 2002, I was named a University Distinguished Professor, which is my current position. University Distinguished Professor is the highest academic rank at Colorado State University, and there are a maximum of twelve University Distinguished Professors at any given time out of a faculty of 1,200. This is a lifetime appointment until retirement, whereupon Emeritus status is granted. In addition to my positions at Colorado State University, I was a Visiting Professor of Chemistry at Harvard University from 1994–95, at which time I was sponsored by Professor Stuart L. Schreiber and taught a sophomore organic chemistry course for pre-medical students, Chem 17. I was also a Visiting Professor of Chemistry at the University of California at Berkeley in 1990 and worked in the laboratory of Professor Peter G. Schultz.

4. I have extensive experience in the field of synthetic organic chemistry and medicinal chemistry with an emphasis on biologically active compounds including anti-tumor agents, heterocycles, antibiotics, anti-fungal agents, anti-viral agents, immunomodulators, amino acids, peptides and alkaloids, among many other classes of biologically active organic substances. My organic chemistry research interests include the total synthesis of novel natural and synthetic products, heterocyclic chemistry, asymmetric synthesis, synthetic methodology, process chemistry, and reaction mechanisms. I have extensive experience in the synthesis, chemistry, conformational analysis, biochemical activity, and biological activity of a range of organic compounds.

5. My research laboratory at Colorado State University has worked extensively on the chemistry and biology of numerous drugs over my career, including Quinocarcin (Quinocarmycin citrate), Tetrazomine, Bioxalomycin, Ecteinascidin 743 (Yondelis® or trabectidin), Renieramycin, Cribrostatin-4, Jorumycin, the Mitomycins, FR900482, FK973,

FK317, FK228 (Romidepsin), Largazole, Stephacidins A and B, Avrainvillamide, Spirotryprostatins, TMC-95A/B, Rottlerin, and Antimycin, amongst many others.

6. I have been the Principal Investigator on numerous research grants from Federal agencies, such as the National Institutes of Health (NIH) and the National Science Foundation (NSF) as well as from various Foundations, and corporations to synthesize biologically active compounds on both small laboratory scale as well as larger industrial scales.

7. I held a funded research collaboration with the Infectious Diseases Research Institute (IDRI), in Seattle, Washington, to develop several novel adjuvants for the treatment and prevention of autoimmune diseases, infectious diseases and cancer (2010).

8. From 1991-1993, I held a research grant from Symphony Pharmaceuticals, located in Philadelphia, Pennsylvania, to prepare anti-HIV drugs based on inhibition of the HIV protease. I supervised a graduate student who prepared several very potent peptide isosteres that exhibited in vitro activity against HIV.

9. I have taught undergraduate and graduate courses in organic chemistry, organic synthesis, biosynthesis, biological chemistry, drug design, and the synthesis of natural products. I have also lectured at numerous professional conferences, universities, and in corporate R&D laboratories in those areas.

10. I am a Scientific Founder, Acting President, and Chair of the Scientific Advisory Board of Cetya Therapeutics, a company that is developing several drugs, including drugs for the treatment of various cancers, multiple myeloma, autoimmune diseases, and hemoglobinopathies. I also direct all of the process scale synthesis optimization and drug formulation studies being conducted on Cetya's HDAC inhibitors. This includes injectable formulations as well as oral formulations. Specifically, I directed and supervised post-doctoral researchers in my laboratory

(on behalf of Cetya Therapeutics) to formulate the poorly water-soluble drug Largazole, including a myriad of synthetic analogs of Largazole prepared in my laboratory, as a polysorbate-80/ethanol co-solvent excipient system. This formulation has been used in animal studies for obtaining critical dose-escalation and pharmacokinetic data. I have also specifically directed and supervised the formulation of Largazole and related analogs in various PEG-based (polyethylene glycol) excipient systems. This work is currently being conducted in collaboration with oncologist Dr. Douglas Thamm of the Colorado State University Animal Cancer Center, pharmacologist Dr. Dan Gustafson of the Colorado State University Animal Cancer Center, Dr. Kimberly Stegmaier of the Dana-Farber Cancer Institute/Harvard Medical School and Dr. James E. Bradner of the Dana-Farber Cancer Institute/Harvard Medical School. The animal studies commenced in 2010, and the drug formulation studies are being conducted in my laboratory at Colorado State University under my direction.

11. I was a Scientific Founder, Member of the Scientific Advisory Board, and Member of the Corporate Board of Directors for Xcyte Therapies, a company devoted to developing *ex vivo* T-cell therapies for treating cancer, autoimmune, and infectious diseases, including HIV. As a Scientific Founder and Member of the Board of Directors of Xcyte Therapies, I was deeply involved in writing the patents and developing formulation strategies for both topical and injectable drugs based on FK228 (Romidepsin).

12. As a Scientific Founder and Acting Vice-President of Discovery Chemistry of HemaQuest Pharmaceuticals (Seattle, Washington), I have directed the pre-clinical and clinical synthesis, scale-up and formulation studies of several of the companies' drugs. These include both water-soluble drugs and hydrophobic, poorly water-soluble drugs for therapeutic applications in both cancer and hemoglobinopathies. I directed both the medicinal chemistry

efforts as well as the pre-process optimization work for potential industrial-scale syntheses of our lead drug candidates.

13. In addition, I am a Scientific Founder and member of the Scientific Advisory Board of Sapientia Therapeutics, located in Philadelphia, Pennsylvania. I am the acting Director of the Medicinal Chemistry, Process Chemistry and Drug Formulation efforts of this company to develop novel small-molecule inhibitors of protein kinase C-delta for autoimmune diseases, cancer and scleroderma. My laboratory has synthesized the first lead compounds, which are protein kinase C-delta (PKC-Δ) inhibitors and are water-insoluble substances. Under my direction we have engaged in early scale-up and route optimization for our leading drug candidates.

14. As a chemist with expertise in structure-activity studies and synthesis of biologically active agents, I have been retained to consult for a number of pharmaceutical and biopharmaceutical companies for both drug discovery and process research applications over the past thirty years. I consulted for Ajinomoto Co., Japan from 2002-2014 in the general area of process chemistry in the manufacture of amino acids, their derivatives, pharmaceutical intermediates and peptide synthesis. I served as a consultant for Cubist Pharmaceutical Company (2000–03) in the general field of antibacterial agents. I consulted for NewBiotics, Inc. (2001–02) in the general fields of anti-infective agents and anti-cancer agents. I consulted for Hoffman-La Roche, Inc. (1989–92) in the field of cephalosporin-fluoroquinolone dual-action antibacterial agents, as well as on a project concerned with inhibitors of diaminopimelic acid (DAP) biosynthesis as potential antibacterial agents. I consulted for W.R. Grace (1985–90) in the area of specialty chemicals and pharmaceutical intermediates process manufacturing and process development. I was a Scientific Founder, Member of the Scientific Advisory Board,

Consultant and sub-contractor for Microcide Pharmaceutical Co. (Microcide) in their drug discovery and early process research efforts. Microcide was a biopharmaceutical company devoted to developing antibacterial agents against a range of drug-resistant bacterial and fungal infectious diseases. In addition, I have consulted for EPIX Medical, G. D. Searle, Nutrasweet, and Boehringer-Ingelheim, among others. The consulting work I performed for Nutrasweet (1990-1991), was concerned with large-scale manufacturing process chemistry for Aspartame.

15. I was a co-organizer of a special Symposium on process chemistry at The International Chemical Congress of Pacific Basin Societies, PacifiChem 2015 (December 15-18. Honolulu, Hawaii) entitled: *"New Horizon of Process Chemistry by Scalable Reactions and Technology."*

16. I have directed the research activities of more than sixty PhD students and eighty post-doctoral fellows; most of my former co-workers have gone on to successful careers in the pharmaceutical industry in both process research and medicinal chemistry.

17. I have delivered numerous named and plenary lectures at Universities, corporations, and scientific societies on the synthesis, chemistry, biology, and mechanism of action of numerous classes of therapeutic agents, as detailed in my *curriculum vitae* attached hereto as Exhibit A.

18. I have published more than 315 scientific research articles, authored numerous chapters in books, and have written a well-known textbook on the synthesis of optically active amino acids. I have particular expertise in the large-scale industrial synthesis of amino acids and their derivatives. I am also a named inventor on seventeen issued U.S. patents and published patent applications. My publications and patents are listed on my CV, provided in Exhibit 2021.

19. I currently serve on the Editorial board for *Chemistry & Biology*. I have served as Editor for the *Organic Chemistry Series* published by Pergamon Press and Elsevier (1997-2012), and *Mini Reviews in Organic Chemistry* (Bentham Science). I have also served as an editor for several other journals in the past, including *Tetrahedron: Asymmetry*, *Tetrahedron Publications*, *Amino Acids*, and the *Journal of the American Chemical Society*.

20. I am a member of the American Chemical Society, the Japan Antibiotics Research Association, the International Society of Heterocyclic Chemistry, and the American Association for the Advancement of Science. I am a Member of the University of Colorado Cancer Center, located in Aurora, Colorado. I have served as organizer or co-organizer of numerous scientific meetings and symposia, and served as the Vice President of the International Society of Heterocyclic Chemistry, Chairing the 2003 International Congress of Heterocyclic Chemistry.

21. I serve on the Scientific Advisory Board of Arch Therapeutics, located in Boston, Massachusetts, that is developing self-assembling peptides for wound healing and surgical closure.

22. I have also served on the Scientific Advisory Boards for a number of other companies. I currently serve on the External Advisory Committee for the Puerto Rico Alliance for the Advancement of Biomedical Research Excellence. I was a Scientific Founder, Director of Chemistry, and member of the Scientific Advisory Board for HemaQuest Pharmaceuticals. I was a Founding Scientist and Member of the Scientific Advisory Board of Microcide Pharmaceuticals from 1993 to 1998.

23. I have expertise in drug formulation for injectable, topical and oral medications. I have directed research programs, both through my academic laboratory at Colorado State University as well as through my various consulting engagements and as a research director

and/or consultant for companies developing medicines for numerous therapeutic indications. I have consulted on many aspects of pharmaceutical drug discovery, development, formulation, and manufacturing. This includes basic discovery and optimization, early process research, large-scale manufacturing, and drug formulation.

24. I have served as a consultant for a number of companies for both drug discovery and process research applications, including, for example, W.R. Grace Company (1985-1990, fine chemicals synthesis); Symphony Pharmaceuticals (1991-1993, anti-HIV drugs); G.D. Searle Co. (1988-1990, memory and learning enhancement agents based on NMDA receptor antagonists); Nutrasweet Co. (1990-1991, artificial sweeteners); EPIX Medical (1993-1997, MRI imaging and contrast agents); Hoffman-La Roche, Inc. (1989-1992, cephalosporin-fluoroquinolone dual-action antibacterial agents); Boehringer-Ingelheim Pharmaceuticals (1992-1993, antiviral agents); Cubist Pharmaceutical Company (2000-2003, macrocyclic peptide antibacterial agents); NewBiotics, Inc. (2001-2002, anti-infective agents and anti-cancer agents); Microcide Pharmaceutical Co. (1993-1998, analogs of macrocyclic anti-fungal agents related to echinocandin, cephalosporins, and quinolones); Xcyte Therapies (1996-2006, T-cell activation); Ajinomoto Co, Japan (2002-2014, amino acids, peptides, and other specialty chemicals); HemaQuest Pharmaceuticals (2006-2014, short chain fatty acids for treating hemoglobinopathies); Sapientia Therapeutics (2012-present, small-molecule inhibitors of protein kinase C-delta); Arch Therapeutics (2010-present, self-assembling peptides for wound healing); and most recently, Cetya Therapeutics (2012-present, histone deacetylase inhibitors as therapeutic agents for treating cancers, multiple myeloma, autoimmune diseases, and hemoglobinopathies).

25. Under my direction, my laboratory developed the technology for the asymmetric synthesis of amino acids in 1985 that was commercialized by Aldrich Chemical Co. in 1988. My laboratory devised several large-scale (multi-kilogram) process routes for the manufacture of the so-called "Williams Lactone" that has been sold by Sigma-Aldrich Chemical Company since 1988. Early manufacturing was conducted in China by several of my former co-workers at the Chengdu Institute of Organic Chemistry.

26. I have been awarded numerous prizes and awards including the NIH Research Career Development Award (1984-89), the Eli Lilly Young Investigator Award (1986), the Merck, Sharp & Dohme Academic Development Award (1991), an award from the Japanese Society for the Promotion of Science Fellowship (1999), the Arthur C. Cope Scholar Award sponsored by The American Chemical Society (2002), the Multiple Myeloma Research Foundation Senior Award (2010), the ACS Ernest Guenther Award in the Chemistry of Natural Products sponsored by Givoudan and The American Chemical Society (2011), an award from the Japanese Society for the Promotion of Science Long-term Fellowship (2012-2013), and the Organic Synthesis Award from the local Rocky Mountain section of the American Chemical Society (2012).

27. I have testified numerous times as an expert witness in process chemistry patent litigation in the following matters: Great Lakes Chemical *versus* Archimica SPA. Civil Action No. 99–728-JJF; Ranbaxy Laboratories *versus* Abbott Laboratories. Case No. 04 C 8078; Lundbeck *versus* Infosint. 06 Civ. 2869 (LAK); United Therapeutics Corp. *versus* Sandoz, Inc. C.A. Nos.: 12-1617 (PGS)(LHG) and 13-316 (PGS) (LHG); Gilead Sciences, Inc. and Emory University *versus* Cipla, Limited. Civil Action No.: 1:12-cv-06350-RJS; United Therapeutics

Corp. *versus* Teva Pharmaceuticals, USA, Inc. C.A. No.: 3:14-cv-05498 (PGS)(LHG); United Therapeutics Corp. *versus* Sandoz, Inc. C.A. No.: 3:14-cv-05499 (PGS)(LHG).

B. Materials Considered

28. In forming my opinions in this report, I have relied upon my professional experience and personal knowledge. I have also reviewed a number of documents in this case including all documents cited by the SteadyMed and UTC as well as the materials I have cited in this declaration. In this report, I have provided representative citations to exemplary documents that I have relied upon in reaching my opinions. If I am provided additional information or documents in this proceeding, I may offer further opinions regarding the additional information.

II. Legal Standards Provided By Counsel

29. I have been informed by Counsel that, during an *inter partes* review (IPR), a petitioner must prove invalidity by a preponderance of the evidence. Accordingly, I understand that the burden is on a petitioner to prove invalidity, rather than a patent owner to prove validity. I have been informed by Counsel that because each claim defines a separate invention, the validity of each claim in a patent is addressed independently of the validity of the other claims in that patent.

30. I have also been informed by Counsel that the claims of the '393 patent are "product-by-process" claims. I have also been informed by Counsel that when evaluating the validity of a patent claim, the "product" of product-by-process claims must include structural and/or functional differences over the prior art, even if they are not explicitly claimed.

A. The Person of Ordinary Skill in the Art

31. I have been informed by Counsel that a patent is to be interpreted from the perspective of a hypothetical person referred to as the person of ordinary skill in the art ("POSA")

to which the patent pertains. I am further informed that a determination of the level of ordinary skill is based on, among other things, the type of problems encountered in the art, prior art solutions to those problems, rapidity with which innovations are made, sophistication of the art, and the educational level of active workers in the field. I have been informed that in any particular case, every factor may not be present, and one or more factors may predominate. I understand the person of ordinary skill in the art is presumed to know all prior art that is reasonably relevant to the subject matter of the claimed invention.

32. I understand from Counsel that the validity of a patent claim must be assessed from the perspective of a POSA at the time of the invention.

33. Given the complexity of the chemistry involved in the '393 patent, it is my opinion that a POSA with respect to the patent-in-suit would have had, at the time of the claimed invention, a doctorate degree in chemistry, pharmaceutics, pharmaceutical sciences, medicine, or a related discipline. Alternatively, the POSA may have had a lesser degree in one of those fields, with correspondingly more experience. To the extent necessary, a POSA may have collaborated with others of skill in the art, such that the individual and/or team collectively would have had experience in synthesizing and analyzing complex organic compounds. It is my understanding that a patent is to be interpreted from the perspective of a person of ordinary skill in the art at the time of the patent's priority date.

34. I understand that SteadyMed's expert Dr. Winkler has opined that a POSA 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." Ex. 1009 at ¶14.

35. All of my opinions regarding validity contained in this report are expressed from the view of a POSA at the time of the priority date of the '393 patent. These opinions apply equally whether my definition of a POSA or Dr. Winkler's is applied.

B. Anticipation

36. I understand from Counsel that anticipation requires that each and every element of a claim is set forth in a single prior art reference, and that these elements are arranged or combined in that reference in the same way as recited by the claim. I further understand from Counsel that if there is any difference between the prior art reference and the claimed invention, there is no anticipation by that reference. Further, I understand that there is no anticipation if the elements disclosed in a prior art reference must be combined with the knowledge of one skilled in the art to achieve the subject matter of the claim. I understand that for a prior art reference to be anticipatory, it must enable a POSA to make or practice the invention without undue experimentation.

37. I also understand from Counsel that if the single prior art reference is missing a claimed feature, the reference may inherently anticipate if that missing feature is necessarily present in the single prior art reference.

38. I also understand from Counsel that if there are structural or functional differences in the product of the product by process claims of the invention from the product of the prior art that arise from the process in which it was made, those differences may be evidence of no anticipation even if those differences are not explicitly claimed.

C. Obviousness

39. I understand from Counsel that obviousness requires that a POSA would have been able to arrive at the claimed invention by modifying a single prior art reference or by

combining two or more prior art references. I also understand from Counsel that obviousness analysis must be conducted from the point of view of a POSA at the time of the invention, and that it is improper to employ hindsight or consider the inventors' own path to the invention as proof of obviousness.

40. Counsel has also informed me that obviousness requires that a POSA would have had a reasonable expectation of success in achieving the claimed invention.

41. I understand from Counsel that four factual issues are relevant to obviousness analysis: the scope and content of the prior art; the level of ordinary skill in the field of the art at the time of the invention; the differences between the claimed invention and the prior art; and various objective indicia of non-obviousness.

42. I understand from Counsel that, in addition to considering the prior art, certain objective indicia may also provide evidence that a claimed invention is not obvious. I am informed by Counsel that these objective indicia, which are also referred to as secondary considerations, may include factors such as commercial success, unexpected results, the resolution of long-felt but previously unmet needs, skepticism by others prior to achieving the invention, failure of others to achieve the invention, praise from others for the invention, and copying by others.

43. I understand from Counsel that, like anticipation, if there are structural or functional differences in the product of the product by process claims of the invention from the product of the prior art that arise from the process in which it was made, those differences may be evidence of non-obviousness even if those differences are not explicitly claimed.

III. Summary of Opinions

44. It is my opinion that the term "product" as it is used in the claims of the '393 patent should be construed using UTC's construction: "a substance resulting from a chemical reaction."

45. It is my opinion that the term "[a] product comprising a compound of formula I/IV or a pharmaceutically acceptable salt thereof" as it is used in the claims of the '393 patent should be construed using UTC's construction: "a substance resulting from a chemical reaction constituted primarily of formula I/IV or a pharmaceutically acceptable salt thereof."

46. It is also my opinion that none of the claims of the '393 patent are anticipated by or rendered obvious by the prior art.

47. My opinions and the bases for them are based on information that I know, that I have reviewed, and that I am currently aware exists. I reserve the right to supplement or amend my opinions in light of any additional evidence, testimony, or other information that may be provided to me after the date of this declaration. Additionally, I may use the cited materials to assist me in preparing demonstratives such as graphics and animations if I am asked to testify.

IV. The '393 Patent

48. The '393 patent is directed to an improved treprostinil product and improved process for making the product. I understand from Counsel that the priority date for the '393 patent is December 17, 2007.

49. The synthesis of treprostinil is complex as several improvements resulting in improved products are disclosed in the '393 patent itself. The structure of treprostinil has five chiral centers (stereogenic centers) resulting in 32 possible stereoisomers of treprostinil.

50. The '393 patent has two independent claims: Claims 1 and 9. Claim 1 requires "a product comprising a compound of formula I…or a pharmaceutically acceptable salt thereof," in which formula I can be several structures including treprostinil. Claim 9 requires "[a] product comprising a compound having formula IV…or a pharmaceutically acceptable salt thereof," in which is the structure of treprostinil. Both Claims 1 and 9 then specify that the product is prepared by a process comprising (a) alkylating a compound of Formula II or V [a benzindene triol structure] with an alkylating agent to produce a compound of Formula III or VI [a benzindene nitrile intermediate], (b) hydrolyzing the product of formula III or VI of step (a) with a base, (c) contacting the product of step (b) with a base B to form a salt of Formula Is or IVs [indicating a salt form of treprostinil with an HB+ counterion], and (d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula I or IV. Dependent Claim 7 further identifies the specific structure of Formula I of the product of Claim 1 as treprostinil. Because the other possible structures of Claim 1 are not at issue here, I will consider these Claims 1, 7, and 9 together in my analysis. Likewise, I will consider the following dependent claims together that have similar claim limitations.

51. Dependent Claims 2 and 10 provide a further purity limitation. Claim 2 further requires "[t]he product of claim 1 wherein the purity of compound of formula I in said product is at least 99.5%." Similarly, Claim 10 requires "[t]he product of claim 9, wherein the purity of product of step (d) is at least 99.5%." Thus, step (d) must be performed in claim 10, but both of these claims require a purity of at least 99.5%.

52. Dependent Claims 3 and 11 provide a further limitation on what alkylating agent may be used. Claim 3 requires the alkylating agent be $Cl(CH_2)_wCN$, $Br(CH_2)_wCN$, or $I(CH_2)_wCN$. Claim 11 requires the alkylating agent be $Cl(CH_2)_wCN$.

53. Dependent Claims 4 and 12 specify what base may be used in step (b). Claim 4 requires the base in step (b) to be KOH or NaOH and Claim 12 requires the base to be KOH.

54. Dependent Claims 5, 13, 14, 17 and 18 specify what the base B in step (c) may be selected from certain specific bases. Claims 5, 13, and 17 limit base B to the group consisting of ammonia, N-methylglucamine, procaine, tromethamine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine. Claims 14 and 18 specify that the base B is diethanolamine.

55. Dependent Claims 6 and 15 specify what acid is used in step (d). Claim 6 specifies the acid is HCl or H_2SO_4. Claim 15 specifies the acid is HCl.

56. Dependent Claims 8 and 16 specify that the process does not include purifying the compound of formula III or VI produced in step (a).

57. Dependent Claims 19 and 20 depend on Claims 1 and 9, respectively. Each dependent claim further specifies the base in step (b) is KOH or NaOH and the base in step (c) is selected from the same group specified in Claims 5, 13, and 17.

58. Claim 21 depends on Claim 1 and requires that step (d) is performed. Claim 22 depends on Claim 21 and further requires that the product comprises a pharmaceutically acceptable salt formed from the product of step (d).

V. Claim Construction

59. I understand from Counsel that different claim constructions for certain terms used in the claims of the '393 patent have been proposed by SteadyMed and UTC, and that the U.S. Patent and Trademark Office ("PTO") has entered a preliminary claim construction for certain terms.

60. I agree with UTC's construction of the term "product" as "a substance resulting from a chemical reaction" which is consistent with the plain and ordinary meaning of the term.

61. In the chemical context, "product" generally refers to the real world outcome or result of a reaction:

Generalized Chemical Reaction

Reactants → Products

I agree with UTC that the '393 patent itself distinguishes "product" to identify it as what comes at the end of a chemical process or chemical reaction. Prelim. Resp. at pp.17-18.

62. I also agree with the consistent definitions given by the several textbooks cited by UTC all referring to "product" as the result of a chemical reaction. *Id.* at 19.

63. In fact, I have used the term "product" consistently in my own publications to refer to the real world result of a chemical reaction. *See, e.g.*, Williams, et.al., *Asymmetric, Stereocontrolled Total Synthesis of Paraherquamide A*, J. Am. Chem. Soc. 2003, 125, 12172-178. ("However, the reaction was very slow and gave the desired cyclization product 64 in only 25% yield, accompanied by products from competing pathways.") (Ex. 2026); Williams, et.al., *Stereocontrolled Total Synthesis of (+)-Paraherquamide B*, J. Am. Chem. Soc. 1996, 118, 557-579 ("Compound 66 was refluxed in benzene with 20 equiv of sodium hydride, resulting in a very clean and high yielding cyclization reaction furnishing the desired product 68 in 93% yield.") (Ex. 2027); Williams, et.al., *Synthetic Studies on Et-743. Assembly of the Pentacyclic Core and a Formal Total Synthesis,* J. Org. Chem. 73.24 (2008): 9594-9600. ("The scarcity of the natural product from marine sources renders Et-743 an important target for synthesis.") (Ex. 2028).

64. Dr. Winkler also uses the term "product" as the result of a chemical reaction in his own publications and confirmed that understanding during his deposition. *See, e.g.*, Winkler, J., et.al., *A Pauson-Khand Approach to the Synthesis of Ingenol*, Org. Lett., 2005, 8, 1489-1491 at Abstact ("Pauson-Khand cyclization of dioxanone photoadduct 21 leads to the formation of a single product in good yield.") (Ex. 2029); *see also* Ex. 2051 at 155:12-157:3.

65. Specifically, Dr. Winkler confirmed that "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." Ex. 2051 at 155:2-11. This is consistent with UTC's definition as well as how Dr. Walsh interpreted the product in his Declaration submitted during prosecution of the '393 Patent. Ex. 1002 at 346-347 (showing the products containing certain other substances as impurities).

66. I disagree with the PTO's preliminary construction and SteadyMed's construction of "product" as "a chemical composition." I believe that this proposed definition is too broad and does not accurately describe the term as it is customarily used in the art and in the context of how it is defined in the '393 patent. In the chemical context, there can be no "product" if there is no corresponding reaction, process, or synthesis that it refers to. A "chemical composition" could be used to describe the starting materials, solvents, reagents, catalysts, and even the glassware used during a chemical reaction as there is no limitation on SteadyMed's construction of the term "product" on how it relates to the chemical reaction at issue.

67. In the '393 patent and each of the references I describe above, the word "product" is exclusively used to describe a substance resulting from a chemical reaction, and it is not used to describe any and all "chemical compositions."

68. SteadyMed's construction is therefore inconsistent with the understanding of a POSA and inconsistent with the '393 patent specification regarding the term "product" because "a chemical composition" is not an accurate and specific definition of the term.

69. For the reasons I previously described regarding the term "product", a POSA would understand the plain and ordinary meaning of the claim term "A product comprising a compound of formula I/IV or a pharmaceutically acceptable salt thereof," as UTC's construction: "a substance resulting from a chemical reaction constituted primarily of formula I/IV or a pharmaceutically acceptable salt thereof." This definition is consistent with how a POSA would understand the term and is consistent with its plain and ordinary meaning.

70. I disagree with the PTO's preliminary construction and SteadyMed's construction of "[a] product comprising a compound of formula I/IV or a pharmaceutically acceptable salt thereof" 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." I believe that this proposed definition is too broad and does not accurately describe the term. The entirety of the '393 patent is directed to an improved product with lower amounts of impurities and therefore the product includes its own impurity profile which provides a high level of purity and does not indiscriminately include other substances and impurities "without limitation as to the types of or relative amounts thereof."

VI. Phares Does Not Anticipate Claims 1-5, 7-9, 11-14, or 16-20 of the '393 Patent

71. I have reviewed Dr. Winkler's opinions alleging that Phares (Ex. 1005) inherently anticipates Claims, 1-5, 7-9, 11-14, and 16-20. I have also reviewed the Institution Decision in which the Board credited Dr. Winkler's opinion regarding this lack of physical differences

between the treprostinil products of the '393 patent and Phares. Paper 12 at 23-31. I disagree. Additionally, the Board credited Dr. Winkler's opinion that Phares discloses the same process for synthesizing treprostinil as the '393 patent. Paper 12 at 29-30. This is not true. Because no synthesis of treprostinil is disclosed in Phares, the diethanolamine salt described would have an unknown impurity profile and therefore cannot anticipate any claim of the '393 patent.

A. The Product Disclosed in Phares is Physically Different Than the Products Disclosed in the '393 Patent Claims

72. In order for Phares to anticipate any claim of the '393 patent, Phares must disclose every claim limitation of the product. Phares does not disclose the same product as claimed in the '393 patent.

73. Contrary to Dr. Winkler's opinion, the polymorph form and purity of the treprostinil diethanolamine salt is not the same as that claimed in the '393 patent. Specifically, Phares discloses samples made for a polymorph screen, not large scale batches. *See, e.g.*, Ex. 1005 at 85-86. In fact Phares notes several different conditions to form polymorph A including preparation using fast evaporation, slow evaporation, freeze drying, heating, and slow cooling in a variety of solvent systems including water and ethanol; water, toluene, and tetrahydrofuran. *Id.* Once polymorph A is prepared, Phares then further states that polymorph form B must be made from polymorph A, listing several conditions under which polymorph B is prepared. *Id.* Phares further notes that the polymorph B sample that was used for characterization was made from heated slurries of form A in 1,4-dioxane and toluene. *Id.* at 87. In fact, it is not clear which sample of polymorph form A was further used to create the characterized sample of polymorph B that Dr. Winkler discusses. Ex. 1009 at ¶¶58-61.

74. The '393 patent does not discuss that polymorph A must be formed first. *See, e.g.*, Ex. 1001 at col. 12-13 and 15. The '393 patent also does not describe the use of 1,4 dioxane or toluene and only describes forming the diethanolamine salt followed by cooling and filtering the salt with ethyl acetate and ethanol, and then drying. *Id.* Thus, the treprostinil diethanolamine salt formed in Phares required an extra step to first form polymorph A, under different reaction conditions with different solvents.

75. It is well-known that the use of different solvent systems in forming different crystal forms can have a significant effect on the melting point of a substance as well as other characteristics including purity. *See, e.g.*, R. Adhiyaman, et.al., *Crystal modification of dipyridamole using different solvents and crystallization conditions*, Int'l J. Pharm.321, 2006, 27-34 at 33 ("Adhiyaman") ("In conclusion, it can be said that the crystallization conditions and medium used have major effect on dipyridamole crystals habit modification under ambient conditions. The crystals showed significant changes in the shape, size, melting points, dissolution rate, XRD patterns and DSC curves.") (Ex. 2030). Given that the samples of polymorph B described in Phares are prepared in a completely different way under different conditions than those described in the '393 patent, their melting points and other analytical data cannot be directly compared.

76. Furthermore, the only data that Dr. Winkler relies upon to conclude that the polymorph B sample of treprostinil diethanolamine salt in Phares has a "higher purity than the '393 product" is that the recorded melting point was higher in one sample than the melting point of the diethanolamine salt sample of the '393 patent. Ex. 1009 at ¶¶ 59-60. This is incorrect for several reasons. First, as mentioned above, the different solvents and conditions used to form the salt can greatly affect the melting point – which is the only purported evidence

that Dr. Winkler cites for purity. Second, there is absolutely no actual purity data disclosed in Phares for the diethanolamine salt or treprostinil free acid and a POSA would not have concluded based on a single melting point example of polymorph B prepared under unknown conditions (e.g., recrystallization solvent and recrystallization conditions are not identified) would be of a higher purity than the known purity of the '393 patent. Third, even if the diethanolamine salt samples were prepared under the same work-up and purification conditions, a higher melting point does not mean that the substance must be of a higher purity. *See*, Ex. 2030 at Fig. 5 showing modified crystals in several different solvents had a higher melting point than the pure dipyridamole). Fourth, the DSC curve cited by Dr. Winkler in Fig. 21 of Phares (Ex. 1009 at ¶59) shows a broad melting peak with a range of close to 10 degrees which is indicative of a lower purity substance. *See*, Marti, E., *Purity determination by differential scanning calorimetry*, Thermochimica Acta, 5(1972) 173-220 at 214 ("The melting of diphenyl is extremely sharp because of the purity level; on the other hand, the melting region of phenacetin-benzamide is rather broad.") (Ex. 2031). Additionally, the DSC data provided does not describe the sample size, the rate of temperature increase as a function of time and does not compare this with an authentic standard of known purity melted under identical conditions. It is known in the art that sample size, rate of heating, the recrystallization solvent(s) used, and the conditions under which the crystalline sample was obtained can significantly affect the DSC data. Dr. Winkler's conclusion based on this single vague and incompletely described DSC data is not scientifically sound.

77. Dr. Winkler also points to the brief description of the formation of the treprostinil diethanolamine salt (Ex. 1009 at ¶¶50-54), but that description does not indicate what treprostinil free acid was used to make it. While the Board agreed with Dr. Winkler regarding the similarity

of the products of Phares and the '393 patent, the source of the treprostinil used to make treprostinil diethanolamine is very important and would greatly affect the impurity profile and other analytical characteristics, including DSC, of the sample.

78. In fact, Phares itself describes several references that could be used to make treprostinil, but does not identify which one, if any, was used to make the sample for the treprostinil diethanolamine salt. *See, e.g.*, Ex. 1005 at 9 ("Compounds of the present invention can also be provided by modifying the compounds found in U.S. Patent Nos. 4,306,075 ("the '075 patent", Ex. 2032) and 5,153,222 ("the '222 patent", Ex. 2033) in like manner."). The '075 patent, for example, discloses a very different and less pure treprostinil product than that of Moriarty (Ex. 1004). *See, e.g.*, Ex. 1004 at 1892-93. Thus, without knowing the source of the treprostinil used in Phares to make the treprostinil diethanolamine salt, the resulting product could have a very different purity and impurity profile and would necessarily have a distinct impurity profile if it were made by a different process than that disclosed in the '393 patent.

B. Phares Does Not Disclose Several Other Claim Limitations

79. Dr. Winkler alleges that Phares discloses the same synthesis to make treprostinil diethanolamine as the synthesis described in the '393 patent and the Board credited his opinion on this point. *See*, Ex. 1009 at ¶¶51-57; Paper 12 at 29-30. I disagree. First, there is no description whatsoever in Phares of how to make treprostinil free acid. Instead, Dr. Winkler points to the synthesis of the enantiomer of treprostinil ((-) treprostinil) which is a completely different synthesis for a different stereoisomer. Ex. 1009 at ¶57. Winkler alleges that because certain steps are used in forming the enantiomer, those steps are inherently disclosed for use with treprostinil. Ex. 1009 at ¶¶56-57.

80. I understand the Board decision did not address the additional limitations of independent Claims 1 and 9 nor the dependent claim limitations in its anticipation analysis because "the process steps recited in claims 1 and 9 do not impart structural or functional differences to the claimed treprostinil product." Paper 12 at 31. I disagree with this assertion. Even if Phares used the synthesis of Moriarty to make treprostinil, there are significant differences between the product of Moriarty and the product of the '393 patent. *See*, Section VII(A) below. Because the products are different, the process differences are relevant to the anticipation analysis.

81. The synthesis for the enantiomer of treprostinil disclosed in Phares, however, is different than the synthesis of treprostinil disclosed in the '393 patent. First, contrary to Dr. Winkler's claims, the earlier part of the synthesis used in Phares to make the enantiomer is not the same synthesis disclosed in Moriarty. Specifically, the Moriarty reference obviously does not describe the synthesis of the enantiomer of treprostinil, but also does not include the Mitsunobu inversion step described by Phares wherein the stereochemistry of the secondary alcohol moiety has to be chemically reversed. Ex. 1005 at 40. In fact, because (S)-2-methyl-CBS-oxazaborolidine is used on structure 5, the resulting structures 6-11 are diastereoisomers of the intermediates used in the synthesis of the '393 patent. As a result, intermediate products of formulas (II) and (III) of Claim 1 and intermediate products of formulas (V) and (VI) of Claim 9 of the '393 patent are not disclosed in Phares. Thus, because steps (a) – (c) of *every claim* of the patent requires these products, Phares cannot anticipate any claim of the '393 patent.

82. Second, Claim 2 requires a specific purity of 99.5%. As I discussed above, there are no specific purity measurements disclosed in Phares and a single broad melting point determination with a large melting point range does not provide evidence that the purity of the

treprostinil diethanolamine sample is at least 99.5%. *See*, Section VI(A) above. For this additional reason, Phares does not anticipate Claim 2. The purity of that sample was not calculated from the DSC data as no control to an authentic standard of known purity was performed or reported.

83. SteadyMed claims that because the synthesis of the enantiomer of treprostinil in Phares does not describe a purification step, that the claim limitation of Claims 8 and 16 that the process does not include purifying the compound of Formula III (or VI) produced in step (a) is satisfied. That is not correct. In fact, Phares does not disclose any specific details of those steps whatsoever. Indeed, if the same synthesis from Moriarty was used as Dr. Winkler suggests, purification at step (a) is specifically described in that reference. Ex. 1004 at 1901-1902. Regardless of what synthesis was used, however, the fact remains that compounds of Formula III and VI do not appear in Phares as described above.

84. Under my interpretation of the highly pure product described in each of the claims of the '393 patent, Phares does not anticipate Claims 1-5, 7-9, 11-14, or 16-20 because it does not disclose the highly-pure product of the '393 patent, the synthesis of treprostinil, nor compounds of structures (II) and (III) from independent Claim 1 or structures (V) and (VI) from independent Claim 9, which are required by all of the claims.

VII. None of the Claims of the '393 patent Are Rendered Obvious by the Prior Art

85. I understand that the Board cited additional grounds for unpatentability including obviousness based on the combination of Moriarty and Phares and obviousness based on the combination of Moriarty, Phares, Kawakami (Ex. 1007), and Eğe (Ex. 1008). I disagree that any claim of the '393 patent is rendered obvious by any combination of these references.

A. The Product of the '393 Patent Is Structurally Different Than the Product of the Prior Art

86. In his declaration, Dr. Winkler expresses his opinion that "the '393 patent processes do not result in a physically different or unique product than that disclosed in the prior art." Ex. 1009 at ¶71. I am aware that, in the Institution Decision, the Board credited Dr. Winkler's opinion regarding this lack of physical differences between the treprostinil products of the '393 patent and the prior art. Paper 12 at 16-17. I disagree with Dr. Winkler's opinion for at least the following reasons.

87. Dr. Winkler appears to base his opinion on a comparison between the '393 patent process batches identified in the declaration submitted by Dr. David Walsh, one of the inventors of the '393 patent, during prosecution (Walsh Declaration), and a single prior art process batch identified in a particular prior art publication by Moriarty . Ex. 1009 at ¶¶63-71. However, Dr. Winkler's comparison suffers from several critical flaws.

88. First, and most fundamentally, there is no basis for comparing the "purity" reported in Moriarty with the purity discussed in the Walsh Declaration. When purity is determined by comparison of a sample to a reference standard such as assay purity (*see, e.g.*, ICH Guidance For Industry: Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients (2001) ("Q7A") at 28-29 (Ex. 2034); see also Reviewer Guidance: Validation of Chromatographic Methods (1994) ("Reviewer Guidance") at 5-8) (Ex. 2035), one cannot directly compare the purity values of two samples in any meaningful way unless each value was achieved by comparison to the same reference standard. Neither the Walsh Declaration nor Moriarty identifies a specific reference standard. While Moriarty notes that the

treprostinil product obtained was compared to an authentic sample of UT-15, there is no mention of any such comparison in the Walsh Declaration.

89. Instead, with respect to the Walsh Declaration, purity must be understood not with respect to any reference standard, but with respect to the amount of total impurities reported as detected in each of the sample batches. The term "purity" must also be understood with respect to the amount of total impurities detected in the context of the '393 patent itself; wherever assay purity is referred to, the '393 patent specifies that the number indicated refers to "HPLC (Assay)." For each of the representative batches discussed in the Walsh Declaration, impurity data is presented in the same way, and thus the purity of these samples can properly be compared to each other; the same cannot necessarily be said of the sample data reported in Moriarty.

90. Second, Dr. Winkler concludes from Example 4 of the '393 patent that the instrumentation used to measure purity "can have variations of at least 0.4%," and thus any detected difference less than that can be attributed to experimental error. Ex. 1009 at ¶¶69-70. Dr. Winkler bases his estimate of experimental error on the statement "that Example 4's Batch 1 had an HPLC Assay of 100.4%, which is obviously greater than the 100% value theoretically achievable." Ex. 1009 at ¶70. This is unsupported and appears to arise from Dr. Winkler's fundamental misunderstanding of how assay purity values are calculated. HPLC assay values are calculated with respect to a reference standard; thus, any time that the sample you are measuring has a greater purity than the reference standard, the assay value will exceed 100%. As such, it is incorrect to conclude that an assay value of 100.4% must indicate an error of at least 0.4%. Dr. Winkler's conclusion on this point is therefore fundamentally flawed.

91. This explains why the assay value for drug specification submitted to the FDA changed from a range of [redacted] to [redacted]. *See*, Ex. 2003 at 6. This change was not due to

an increase in impurities, but because the purity of the product using the '393 patent process improved (as compared to the already-established reference standard) thus moving the acceptability range to a higher purity specification. *Id.* The letter notes that the scope of the range remained unchanged which simply indicates the acceptability criteria was increased, and does not index an error rate or limit of detection. Indeed, the change to the specification is further evidence that the product of the '393 patent is physically different than the product of Moriarty.

92. Indeed, Dr. Winkler's conclusion is contradicted by the impurity data actually measured for the treprostinil product made by both the '393 patent process and the prior art process according to Moriarty. For both processes, impurities are reported with specific numbers unless the amount detected fell below 0.05%; in cases where some amount of an impurity less than 0.05% was detected, it was reported as simply "less than 0.05%" or "< 0.05%." This means that the level of detection for measuring impurities in these treprostinil samples was somewhere between 0 and 0.05%, not something in excess of 0.4% as Dr. Winkler erroneously concludes.

93. Third, as Dr. Winkler himself points out, there is the possibility for "significant batch-to-batch variations in the impurity profile of each batch of treprostinil." Dr. Walsh stated that the data presented in his declaration came from representative samples of each synthetic process. Ex. 1002 at 346-347. However, there is no such indication that the purity data reported in Moriarty comes from a representative sample of the prior art process. Due to the possibility of batch-to-batch variations, if a small number of batches are to be used as the basis for comparison, it is critical that those batches be representative of their respective products and processes. Thus while one could reasonably rely on a comparison between the representative batches presented in

the Walsh Declaration, one could not reasonably add the batch discussed in Moriarty to that comparison. It is exactly this scientifically unsound comparison to Moriarty upon which Dr. Winkler bases his opinion.

94. Ideally, to avoid the risk of batch-to-batch variations unintentionally biasing the data, a comparison should be made between the average impurities detected in treprostinil products made by the '393 patent process and treprostinil products made by the prior art process. To this end, I have prepared a chart containing impurity data for 56 samples of treprostinil product as produced by the prior art process according to Moriarty through 2004 (the date of the publication), attached as Appendix A to this declaration[1], and another chart containing impurity data for 122 samples of treprostinil product as produced by the '393 patent processes, attached as Appendix B to this declaration. I have prepared these charts using impurity data from release testing of samples of the respective treprostinil products that were produced by or for UTC for the purposes of obtaining regulatory approval and/or commercial sale. *See* Appendix A, Appendix B; Ex. 2005; Ex. 2036; Ex. 2037; Ex. 2052; Ex. 2053. As the purpose of these charts is to calculate the average impurities – both specific and total – found in the treprostinil products of each process, I have necessarily assigned a value of zero where the level of impurities was

[1] I am aware that UTC's Process Optimization Report for treprostinil prepared according to the '393 process included Table 2, which provided average impurity data for 96 batches of treprostinil made according to the prior art process. UT Ex. 2005, at 7. However, Table 2 does not provide exact values for four of the eight impurities under consideration, [redacted] and does not identify the underlying batch data. *Id.* As such, I have prepared my own chart using data on 56 treprostinil samples made by the prior art method and have based my analysis, including my calculations of average for total and individual impurities, upon this chart. While I believe my chart allows for a more precise comparison between Moriarty treprostinil products and '393 treprostinil products, the averages presented in the Process Optimization Report still show significant differences between '393 treprostinil products and the Moriarty treprostinil products. Specifically, Table 2 of the Process Optimization Report shows that on average [redacted] was detectable in these 96 batches, and that these 96 batches contained higher average levels of [redacted], and total impurities as compared to the averages for the '393 treprostinil product. Ex. 2005 at 7; Appendix B.

reported as "ND" (Not Detected), and a value of 0.05 where the level of impurities was reported as being less than 0.05%. From these data, I have found the following average impurity levels:

Moriarty Process Impurities (Average Percent Detected)								
1AU90	**2AU90**	**3AU90**	**750W93**	**751W93**	**97W86**	**ethyl ester**	**methyl ester**	**Total Related Substance**
0.0473	0.0407	0.2545	0.1646	0.1025	0.0405	0.0889	0.1028	**0.9545**
'393 patent Process Impurities (Average Percent Detected)								
[redacted]								

95. These averages make clear that the '393 patent process does result in a treprostinil product that is physically different from the prior art treprostinil product. In terms of total volume of impurities, the Moriarty process resulted in [redacted] times the amount of impurities that is achieved with the '393 patent process.

96. The products from the two processes also differ significantly with respect to the individual impurities in each product's impurity profile. Notably, the '393 patent process produces a treprostinil product that does not contain any detectable amounts o[redacted]. Additionally, the '393 patent process produces a treprostinil product that, on average, contains only [redacted] each of [redacted] and [redacted] and only [redacted] of [redacted]; as compared to the Moriarty process, this represents greater than a [redacted] reduction in each of the [redacted] and [redacted] impurities and a [redacted] reduction in the [redacted] impurity. The '393 patent process also produces a treprostinil product that, on average, has significantly reduced amounts of several other identified impurities; as compared to the average of the Moriarty process, the '393 patent process produces a treprostinil product with less than [redacted] the amount of [redacted], approximately [redacted] the amount of [redacted], and approximately [redacted] the amount of

[redacted]. Conversely, the '393 patent process produces a treprostinil product which actually contains slightly more [redacted] impurity than was detected in the treprostinil product of the Moriarty process.

97. Looking past the average data, it is also worth noting that, out of all the batches of treprostinil product made by the '393 patent process which I reviewed, [redacted] was only detected in a single batch ([redacted]) and [redacted] was also only detected in a single batch ([redacted]), and both impurities were only detected at a level of 0.05% or less. Furthermore, batches [redacted] and [redacted] were both identified as "optimization batches" (as distinguished from commercial batches) and thus are not properly representative of treprostinil products made by the '393 patent process.

98. From these data, it is clear that the treprostinil product produced by the '393 patent process has a markedly different impurity profile than the treprostinil product of the Moriarty prior art process, and as such is physically distinct from the prior art product. Moreover, it could not have been obvious that employing the process of the '393 patent would result in a reduction of impurities as compared to the Moriarty process. Indeed, the '393 patent process actually results in an [redacted] in one detected impurity, [redacted]. Furthermore, it is also clear that the treprostinil product produced by the '393 patent process has a higher average purity than the Moriarty product. The treprostinil product of the '393 patent has an average purity of [redacted] while the Moriarty product has an average purity of 99.05%. Thus, the treprostinil product of the '393 patent has an average purity that is [redacted] higher than that of Moriarty's.

99. Therefore, it is my opinion that the treprostinil product produced by the process used in the '393 patent Claims 1 and 9 is physically different than the treprostinil product produced by Moriarty.

B. Claims 1-5, 7-9, 11-14, and 16-20 Are Not Rendered Obvious by the Combination of Moriarty and Phares

100. As described above, the product of Moriarty is physically different than the product of the '393 patent process. Even if the Moriarty synthesis was used to make treprostinil, a POSA would not have been motivated to make the diethanolamine salt identified in Phares.

101. Specifically, the '393 patent notes that the salt formation step results in an improved and more pure treprostinil product. Given that Moriarty discloses the use of column chromatography for purification, a POSA would not have been motivated to create the salt form in Phares as Phares does not disclose any benefit or increased purity as a result of using the diethanolamine salt. In fact, Phares does not allege that the diethanolamine salt is superior in any way to the treprostinil product of Moriarty and instead identifies other earlier treprostinil disclosures as a means to create the treprostinil used to form the diethanolamine salt. *See*, Section VI(A) above.

102. Additionally, a POSA would not have had a reasonable expectation of success in making the higher purity treprostinil product claimed in the '393 patent by the use of a salt formation step. As identified above, the impurities of treprostinil include [redacted] ([redacted]), [redacted] ([redacted]), the [redacted] starting material ([redacted]), and the [redacted]. As described above, the '393 patent process essentially eliminated the [redacted] impurities [redacted], and [redacted] impurity [redacted], but did not eliminate another [redacted] which likely has the same [redacted] as the other

stereoisomers. Similarly, the [redacted] impurity increased while the [redacted] impurity decreased. A POSA would have expected that all of the stereoisomers would remain as salt impurities, but that is not the case. Instead, the impurity profile of the '393 patent process yields an unexpected result by removing [redacted] while [redacted] impurity and [redacted] another. A POSA could not have predicted this outcome based on the salt formation described in Phares.

103. Regarding Claim 2, neither Moriarty nor Phares discloses treprostinil or treprostinil diethanolamine at a purity of 99.5%. As described above, Phares does not disclose any purity measurement (see Section VI above) and the purity measurement identified in Moriarty does not identify how the measurement was taken (see Section VII(A) above). Regardless of the purity identified in Moriarty, a further analysis of all batches made by the Moriarty process up to the time of the reference itself reveals an average purity of [redacted] while the average purity of the '393 patent batches is [redacted]. Given that the error rate must be below 0.05% for these measurements (see Section VII(A) above), the '393 patent process batches are significantly better in terms of overall purity. For this additional reason, Claim 2 is not rendered obvious by the combination of Moriarty and Phares.

104. Regarding Claims 8 and 16, Phares does not disclose any synthesis for treprostinil and therefore cannot disclose whether purification was needed for step (a). (*See*, Section VI(B) above). As previously described, Moriarty specifically discloses that purification is performed at step (a). See Section VII(B) above). In fact and most significantly, the '393 patent itself identifies that as a distinguishing feature over the prior art. *See, e.g.*, Ex. 1001 at Example 6. For this additional reason, Claims 8 and 16 are not rendered obvious by the combination of Moriarty and Phares.

C. Claims 6, 10, 15, 21, and 22 Are Not Rendered Obvious by the Combination of Moriarty, Phares, Kawakami, and Ege

105. Each of Claims 6, 10, 14, 21, and 22 require the additional step (d) of independent Claims 1 and 9 which is to react the salt formed in step (c) with an acid to form the compound of formula I or IV (treprostinil). Claim 22 further requires a pharmaceutically acceptable salt formed from the product of step (d). Step (d) is not disclosed in any way in Moriarty, Phares, Kawakami, or Eğe. Additionally, it is my opinion that it would not have been obvious to combine these references to arrive at the claimed inventions of Claims 6, 10, 15, 21, or 22.

106. First, there is no teaching or suggestion to perform step (d) in either Moriarty or Phares and similarly no reference to reverting back to treprostinil free acid from any treprostinil salt. Given that the purification techniques disclosed in Moriarty include chromatography and recrystallization after many years of research to optimize the process of making treprostinil, a POSA would not have been motivated to use a salt purification technique disclosed in an undergraduate chemistry textbook. More importantly, a POSA would not have had a reasonable expectation of success in further purifying the treprostinil product of Moriarty by using such a technique. To the extent a POSA was motivated to further purify treprostinil, a POSA would have focused on the known impurities and investigated methods of removing those. At the time of the invention, it was known that the formation of diastereomers occurred in the formation of treprostinil. *See*, Ex. 1004 at 1897-99. Thus, a POSA would have focused on how to remove those types of impurities.

107. Eğe simply discloses that "carboxylic acids that have low solubility in water, such as benzoic acid, are converted to water-soluble salts by reaction with aqueous base. Protonation of the carboxylate anion by a strong acid regenerates the water-insoluble acid. These properties

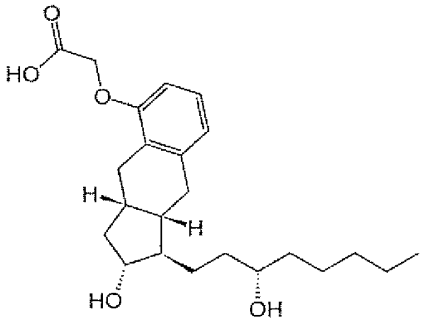
of carboxylic acids are useful in separating them from reaction mixtures containing neutral and basic compounds." Ex. 1008 at 8. This disclosure, however, would not have provided a POSA with a motivation to make the treprostinil free acid disclosed in Moriarty, convert that to the salt form of Phares, then convert the salt form back to the free acid.

108. First, Eğe does not provide any detail regarding how this reaction could be applied to more complex carboxylic acids or if it even could be applied. Specifically, the only carboxylic acid referenced in Eğe as an example is benzoic acid, a very simple aromatic acid, which is structurally very different from treprostinil acid. Indeed, benzoic acid has no chiral centers and therefore no stereoisomers and there is no suggestion in Eğe that this step could be used in purifying more complex carboxylic acids such as treprostinil which have stereoisomeric impurities. Second, Eğe specifically notes that "these properties of carboxylic acids are useful in separating them from reaction mixtures containing neutral and basic compounds," therefore Eğe would not apply to purifying carboxylic acids with stereoisomeric impurities because each stereoisomer would necessarily be an acidic impurity. As described above, the impurities that are removed from the '393 patent product include some, but not all acidic impurities and some but not all neutral impurities. *See*, Section VII(B) above. For these reasons a POSA would not have been motivated to combine Eğe with either Moriarty or Phares and would not have had a reasonable expectation of success in further purifying treprostinil using the acid reformation step described in Eğe.

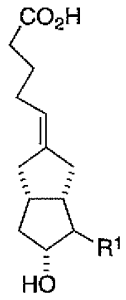
109. Indeed, given that Eğe predicts that only neutral and basic impurities would be removed, the actual average impurity profile for the '393 patent product is an unexpected result given that some but not all neutral impurities are removed as well as some but not all acidic impurities. *See*, Section VII(B) above.

110. Kawakami similarly does not provide any motivation for combining with either Phares or Moriarty and a POSA would not have had a reasonable expectation of success in preparing the products of Claims 6, 10, 15, 21, or 22 by combining these references.

111. Kawakami discloses the purification of a methanoprostacyclin derivative by forming the dicyclohexyl amine salt then regenerating the free acid to achieve a "fairly high" purity. Ex. 1007 at 6. Treprostinil and methanoprostacyclin, however, are very different structures:



Treprostinil



methanoprostacyclin compound in Kawakami

112. As shown here, the methanoprostacylin compound in Kawakami is a two-fused ring structure which is different than the three-fused ring structure of treprostinil that also includes an aromatic ring absent in the Kawakami methanoprostacyclin. These differences matter because a POSA would not have looked to Kawakami (or Eğe) if they were looking for additional purification techniques for treprostinil because neither reference discloses how to remove stereoisomeric impurities.

113. Instead, Kawakami provides a purification method for separating E and Z isomers of a starting material that is otherwise free of impurities, and not diastereomers that result from the various chiral centers that treprostinil was known to have as impurities. In fact, treprostinil

contains no mixture of E and Z isomers because it does not contain a carbon-carbon double bond that is capable of forming E and Z isomers. Indeed, the use of a specific salt to isolate a specific E/Z isomer does not reasonably suggest that salt formation of a much more complex compound with multiple chiral centers such as treprostinil could be isolated from entirely different impurities and then converted back to the free acid form. In fact, nothing in Kawakami suggests that this method could be used for a substance that was already fairly pure such as the treprostinil disclosed in Moriarty.

114. Similarly, Kawakami uses a dicyclohexylamine salt and does not use a diethanolamine salt, nor any salt counterion disclosed in the '393 patent. A POSA would have had no reason to combine the synthesis of Moriarty, use the salt only disclosed by Phares, and convert back to the free acid based on the teaching of Kawakami because Kawakami uses a different salt to separate a different structure from different types of impurities. Even if a POSA did combine these references in this way, a POSA would not have had a reasonable expectation of success in forming a more pure treprostinil product because Kawakami does not provide any information regarding the high level of purity required by the '393 patent and does not describe the separation of the types of stereoisomeric impurities known to be present in the treprostinil product. Dr. Winkler's obviousness analysis using these combinations is flawed and suffers from hindsight analysis.

115. Claim 6 requires the acid in step (d) be either HCl or H_2SO_4 and Claim 15 requires the acid to be HCl. Claim 21 requires that step (d) is performed. Phares, Moriarty, and Kawakami all do not disclose the use of either HCl or H_2SO_4 in converting a salt back to a carboxylic acid of any kind. Eğe cites HCl as an example in the conversion of benzoic acid, but as described above, a POSA would not have looked to Eğe to further purify a complex

carboxylic acid such as treprostinil from its stereoisomers and other impurities and would have no reasonable expectation of success by using HCl based on this disclosure. For this additional reason, Claims 6 and 15 would not have been rendered obvious by any combination of Phares, Moriarty, Kawakami or Eğe. Similarly, given the deficiencies described above regarding Eğe and Kawakami, Claim 21 would not have been rendered obvious by any combination of Phares, Moriarty, Eğe, or Kawakami.

116. Claim 10 requires that step (d) is performed and further requires the product to be at least 99.5% pure. The only purity limitation disclosed in any of the cited prior art references is to Moriarty in which neither step (c) or (d) is performed. There is absolutely no other disclosure of a purity of at least 99.5% in any other cited prior art reference. A POSA looking to improve the purity of treprostinil above that level would have had no reason to look to Phares, Kawakami, or Eğe and based on their disclosures, would have had no reasonable expectation of success in making a treprostinil product with that level of purity as it simply is not present in the prior art allegedly disclosing step (d).

117. Claim 22 depends on Claim 21 and further requires a pharmaceutically acceptable salt be formed from the product of step (d). Dr. Winkler cites no evidence for this additional step in the prior art. In fact, none of the references cited even suggest converting a carboxylic acid to a salt form, then regenerating the carboxylic acid, then forming a pharmaceutically acceptable salt from that. It is my opinion that there is no evidence in the prior art supporting the additional claim limitation of Claim 22 and therefore no combination of Moriarty, Phares, Kawakami, or Eğe would render this claim obvious.

I declare under penalty of perjury that the foregoing is true and correct.

Date: July 6, 2016

Robert M. Williams, Ph.D.

APPENDIX A

Impurities (Percent Detected)									Data Source
90	2AU90	3AU90	750W93	751W93	97W86	ethyl ester	methyl ester	Total Related Substances	
0.3	0.3	0.4	1.2	0.7	0.1	0	0.7	5.4	Ex. 2052, pp. 25-27
0.4	0.07	0.5	0.1	0.09	0.2	0	0.3	4.4	Ex. 2052, pp. 25-27
0.4	0.1	1	0.1	0.06	0.2	0	0.3	4.8	Ex. 2052, pp. 25-27
0.2	0.07	0.4	0.6	0.3	0	0	1.2	3.6	Ex. 2052, pp. 25-27
0.2	0.07	0.4	0.6	0.4	0.05	0	0.8	3.8	Ex. 2052, pp. 25-27
0.3	0.06	0.4	0.8	0.4	0	0	0.8	3.5	Ex. 2052, pp. 25-27
0.1	0.06	0.3	0.4	0.2	0	0	0.1	1.6	Ex. 2052, pp. 25-27
.05	0.05	0	0.2	0.1	0.05	0.1	0.05	0.4	Ex. 2052, pp. 28-30
.05	0.05	0.2	0.1	0.1	0	0	0.05	0.7	Ex. 2052, pp. 28-30
.05	0.05	1.1	0.3	0.2	0.6	0.6	0.05	2.8	Ex. 2052, pp. 28-30
.05	0.05	0	0.5	0.3	0	0.1	0.06	1.0	Ex. 2052, pp. 28-30; Ex. 2036, pp. 2-3
0	0.05	0.1	0.06	0.05	0	0	0.05	0.2	Ex. 2053, p. 19; Ex. 2036, pp. 88-89
0	0.05	0.2	0.07	0.05	0	0	0.05	0.4	Ex. 2053, p. 19; Ex. 2036, pp. 91-92
0	0.05	0.1	0.1	0.07	0	0	0.05	0.3	Ex. 2053, p. 19; Ex. 2036, pp. 94-95
0	0.05	0.2	0.2	0.09	0	0	0.05	0.6	Ex. 2053, p. 19; Ex. 2036, pp. 100-101
0	0.05	0.3	0.05	0.05	0	0.05	0.05	0.05	Ex. 2053, p. 19; Ex. 2036, pp. 33-34
0	0.05	0.2	0.1	0.06	0	0.05	0.05	0.5	Ex. 2053, p. 19; Ex. 2036, pp. 97-98

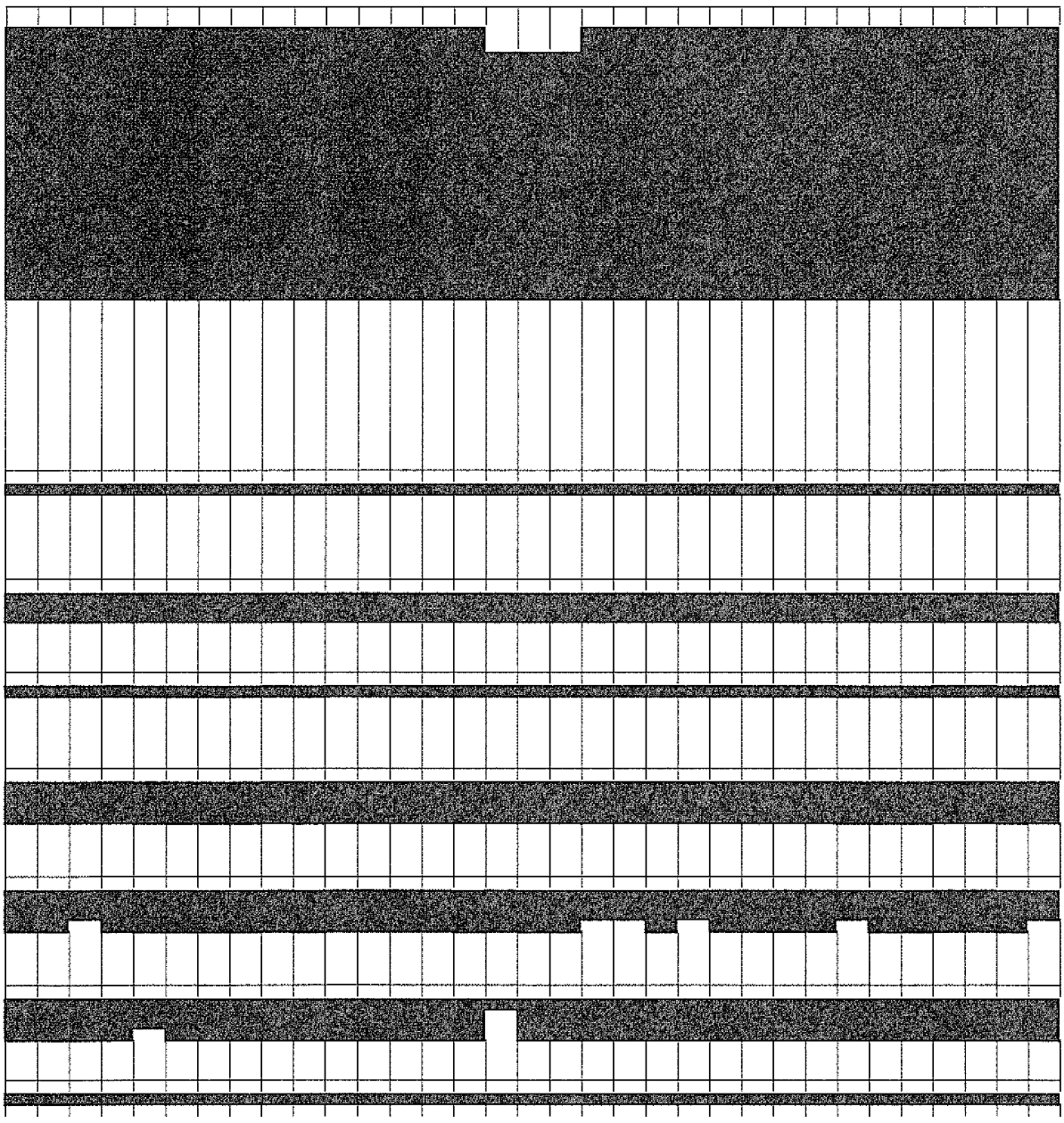
.05	0.05	0.2	0.09	0.06	0	0.05	0.05	0.4	Ex. 2053, p. 19; Ex. 2036, pp. 35-36
0	0.05	0.2	0.09	0.05	0.05	0	0	0.4	Ex. 2053, p. 19; Ex. 2036, pp. 37-38
0	0.05	0.2	0.09	0.05	0.05	0	0.05	0.4	Ex. 2053, p. 19; Ex. 2036, pp. 39-40
0.2	0.05	0.3	0.4	0.2	0.08	0.05	0.05	1.5	Ex. 2053, p. 19; Ex. 2036, pp. 41-42
0	0.05	0.3	0.09	0.05	0.05	0.05	0	0.5	Ex. 2053, p. 19; Ex. 2036, pp. 43-44
.05	0	0.2	0.05	0.05	0.05	0.08	0	0.3	Ex. 2053, p. 19; Ex. 2036, pp. 45-46
0	0	0.2	0.1	0.05	0.05	0	0	0.3	Ex. 2053, p. 19; Ex. 2036, pp. 47-48
0	0.05	0.1	0.2	0.1	0.05	0.2	0	0.6	Ex. 2053, p. 20; Ex. 2036, pp. 60-61
.05	0.05	0.2	0.05	0.05	0	0.05	0.05	0.2	Ex. 2053, p. 20; Ex. 2036, pp. 50-52
.05	0.05	0.2	0.1	0.06	0	0.07	0.05	0.4	Ex. 2053, p. 20; Ex. 2036, pp. 52-53
0	0.05	0.2	0.1	0.08	0.07	0.09	0	0.6	Ex. 2053, p. 20; Ex. 2036, pp. 54-55
0	0.05	0.2	0.05	0.05	0	0.1	0	0.4	Ex. 2053, p. 20; Ex. 2036, pp. 56-57
0	0.05	0.3	0.08	0.05	0.05	0.1	0	0.6	Ex. 2053, p. 20; Ex. 2036, pp. 58-59
0	0.05	0.2	0.05	0.05	0	0.05	0	0.4	Ex. 2053, p. 20
0	0.05	0.2	0.1	0.1	0	0.1	0	0.4	Ex. 2053, p. 20
0	0.05	0.1	0.1	0.1	0.05	0.2	0	0.6	Ex. 2053, p. 20; Ex. 2036, pp. 62-63
0	0	0.05	0.05	0.05	0	0.1	0.05	0.2	Ex. 2053, p. 20; Ex. 2036, pp. 64-65

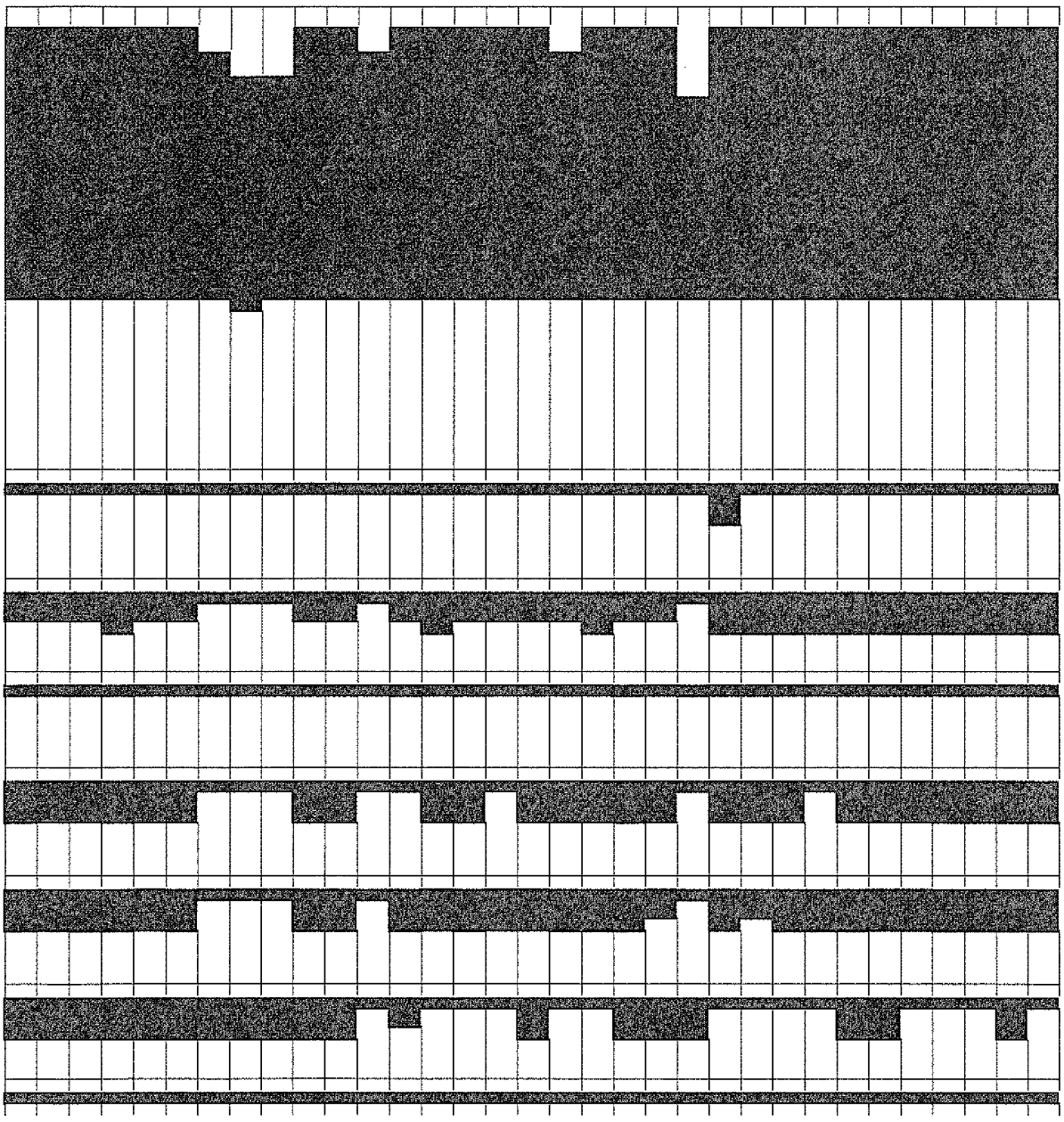
0	0.05	0.2	0.05	0.05	0	0.1	0	0.3	Ex. 2053, p. 20; Ex. 2036, pp. 66-67
0	0.05	0.2	0.06	0.05	0	0.1	0	0.4	Ex. 2053, p. 20; Ex. 2036, pp. 68-69
0	0.05	0.2	0.05	0.05	0	0.1	0	0.3	Ex. 2053, p. 20; Ex. 2036, pp. 70-71
0	0	0.4	0.1	0.08	0.05	0.1	0.05	0.8	Ex. 2053, p. 21; Ex. 2036, pp. 72-73
0	0.05	0.3	0.06	0.05	0.05	0.2	0.05	0.6	Ex. 2053, p. 21; Ex. 2036, pp. 74-76
0	0	0.4	0.05	0.05	0	0.1	0.05	0.6	Ex. 2053, p. 21; Ex. 2036, pp. 78-79
0	0	0.2	0.09	0.06	0	0.1	0	0.5	Ex. 2053, p. 21; Ex. 2036, pp. 80-82
0	0	0.1	0.2	0.1	0.07	0.1	0	0.6	Ex. 2053, p. 21; Ex. 2036, pp. 83-85
0	0	0.3	0.06	0.05	0	0.2	0.05	0.5	Ex. 2053, p. 21; Ex. 2036, pp. 31-32
0	0	0.3	0.1	0.07	0	0.1	0.05	0.6	Ex. 2036, pp. 29-30
0	0	0.3	0.1	0.06	0	0.1	0.05	0.6	Ex. 2036, pp. 27-28
0	0	0.3	0.2	0.1	0.05	0.2	0.05	0.9	Ex. 2036, pp. 25-26
.05	0.05	0.2	0.06	0.05	0.05	0.1	0.05	0.4	Ex. 2036, pp. 23-24
.05	0.05	0.2	0.05	0.05	0.05	0.09	0.05	0.3	Ex. 2036, pp. 21-22
.05	0.05	0.2	0.06	0.05	0.05	0.1	0.05	0.4	Ex. 2036, pp. 19-20
0	0	0.2	0.2	0.08	0.05	0.1	0.05	0.6	Ex. 2036, pp. 17-18
0	0	0.2	0.05	0.05	0	0.1	0	0.4	Ex. 2036, pp. 15-16
0	0	0.2	0.1	0.06	0.05	0.2	0.05	0.6	Ex. 2036, pp. 13-14
0	0	0.2	0.05	0.05	0	0.2	0	0.5	Ex. 2036, pp. 11-12
0	0	0.1	0.1	0.06	0.05	0.1	0.05	0.4	Ex. 2036, pp. 8-10
0	0	0.2	0.09	0.05	0	0.1	0.05	0.4	Ex. 2036, pp. 6-7

0	0	0.2	0.07	0.05	0	0.2	0.05	0.5	Ex. 2036, pp. 4-5
73	**0.0407**	**0.2545**	**0.1646**	**0.1025**	**0.0405**	**0.0889**	**0.1028**	**0.9545**	
90	**2AU90**	**3AU90**	**750W93**	**751W93**	**97W86**	**ethyl ester**	**methyl ester**	**Total Related Substances**	

urities reported as not detected ("ND") a value of 0 has been assigned; for impurities reported as <0.05, a value has been assigned.

APPENDIX B





reported as not detected ("ND") a value of 0 has been assigned; for impurities reported as <0.05, a value of 0.05 has

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

STEADYMED LTD.

Petitioner,

v.

UNITED THERAPEUTICS CORPORATION

Patent Owner.

Case IPR 2016-00006

Patent No. 8,497,393B2

PETITIONER'S REPLY TO PATENT OWNER'S RESPONSE TO PETITION

37 C.F.R. § 42.23

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Petitioner SteadyMed, Ltd. submits this reply pursuant to 37 C.F.R. § 42.23.

I. SUMMARY OF THE ARGUMENT

As SteadyMed explained in its Petition, purifying by crystallization is taught in undergraduate chemistry courses: it's Organic Chemistry 101. Even Patent Owner United Therapeutics' (UT) expert recognizes this fact:

> Q: How long has crystallization been around as a method of purification?
>
> A: I don't know how long it's been around.
>
> Q: Before 2007?
>
> A: Oh, yes.
>
> Q: Did you learn about it when you were in college at the university?
>
> A: Yes, I did. [...]
>
> Q: And when did you go to college?
>
> A: In 1968 I started. In 1968.
>
> ...
>
> Q: ... But how far back does doing that process you just described, how far back does that go?
>
> The Witness: Decades.

(Ex. 2058, 175:19-176:22, 179:11-17).

Even though the purification process claimed in the '393 Patent is so trivial an undergraduate student in the late 1960s would know how to do it, UT maintains that a product made by the '393 Patent process is "materially and functionally" distinct from products of the prior art Moriarty (Ex. 1004) and Phares (Ex. 1005) references. UT relies on 175 measurements showing the average purity of products

made by one process included in the '393 Patent's claims is [redacted]. (Resp., 34; Ex. 2020, ¶¶ 94-99.) And it relies on measurements alleged to show that one version of the Moriarty process produced an average purity of 99.0%. (Ex. 2020, ¶ 98.) Except that the 99.0% value is a distortion of this data, that required UT, and its attorneys who actually performed this calculation (Ex. 2059, 79:3-10, 81:2-13, 104:14-20), to select 10 data points from another source to lower the purity results (*id.*, 112:22-113:20).

As confirmed by Dr. Williams (*id.*, 218:3-219:16), a fair analysis of the data without the 10 data points shows that the value of [redacted], reported in [redacted] itself, is consistent with UT's purity measurements for batches made according to the Moriarty process (Ex. 2059, 219:17-20). Data purporting to show a lower purity, including UT's Walsh Declaration, mischaracterizes the Moriarty process' purity.

UT's expert Dr. Williams initially believed UT's counsel's calculations. But Dr. Williams conceded that: (1) he performed no calculations on this data himself; (2) he only "spot-checked" the data that was selected by counsel; and (3) he "did not know" whether the 10 data points were produced under the Moriarty process. (Ex. 2059, 81:2-13; 82:1-11; 103:24-104:20; 112:24-114:2). Accordingly, no weight should be afforded to his declaration, or UT's reliance on his declaration. Dr. Williams agreed that SteadyMed's calculation of [redacted] purity was correctly

performed, and should be relied upon (*id.*, 217:11-219:20). This corrected calculation supported what SteadyMed stated in its Petition: that the [redacted] showed that treprostinil made by Moriarty was of similar purity, and similarly, the particular example of treprostinil diethanolamine salt made by Phares was as pure as the examples in the '393 Patent. This calculation confirms that the '393 Patent claims merit cancellation.

UT relies on these now-discredited differences in purity values to argue there was a "long-felt unmet need" for more pure treprostinil. (Resp., 12, 47-48; Ex. 2022, ¶¶ 70-72). But UT's long-felt-need expert Dr. Ruffolo concedes that the claims are not limited to treprostinil, nor treprostinil salt, but include hundreds of thousands of other compounds, for which UT provides no evidence regarding long-felt need or impurities. (Ex. 2059, 71:17-72:17; Ex. 2058, 234:16-235:17.) Except for those claims that are limited to treprostinil alone (only claims 10 and 15), or treprostinil diethanolamine salt (claims 14 and 17), Dr. Ruffolo is not offering an opinion that there is a long-felt need for any other claims. (Ex. 2058, 109:18-121:23.) And even for the products in claims 10, 14, 15, and 17, Dr. Ruffolo concedes that: (1) the FDA requires only a [redacted] purity level, which is *much lower* than any levels produced by the prior art, (Ex. 2058, 159:20-161:7); and, (2) the FDA would allow treprostinil batches produced by the Moriarty process to be sold, (Ex. 2058, 179:23-180:17), since Moriarty products are "highly, highly pure,"(*id.*

217:11-218:5). *See also* (Ex. 2059, 151:2-25).

UT devotes much of its Response to argue that the common patent claim terms "product" and "comprising" were improperly construed by the Board, and should not have their usual legally defined meaning. (Resp., 5, 13-15). UT contends these terms should have special meaning in the '393 Patent, although UT's expert concedes that a plain and ordinary meaning should apply, and that the patent and prosecution history contain no language that redefine these terms. (Ex. 2059, 248:24-249:13.) UT cannot show "clear and unambiguous disclaimer" of the plain meaning of these terms.

II. UT MISCHARACTERIZES ITS OWN DATA.

A. UT's Moriarty Batches Have an Average Purity of [redacted].

In its Response and supporting Williams Declaration (Ex. 2020), UT uses Dr. Williams to present the average purity of treprostinil made by the Moriarty prior-art method, in order to contrast it to the '393 Patent product. Specifically, Dr. Williams relied on 56 batch Certificates of Analysis of treprostinil that were allegedly produced under the Moriarty method (*see* Ex. 2020, Appx. A), and contended that the treprostinil product produced by the '393 Patent process had a higher average purity than the Moriarty product ([redacted]% v. 99.05%), and thus "the treprostinil product of the '393 patent has an average purity that is [redacted] higher than that of Moriarty's." (Ex. 2020, ¶ 98; Resp., 4, 34, and 45). But UT's counsel

selected batches to include in its calculation, and cherry-picked 10 batches to drive down the average purity value of the Moriarty product from [redacted] to 99.05%. These 10 "development" batches, as UT calls them, come from a separate source, and may not have been produced by the Moriarty method. When instead, the 46 "production" batches made by the Moriarty method, and under the same analytical methods, are examined, the correct conclusion is that the Moriarty method produces the *same product as the product of the '393 Patent*: a product with [redacted] purity, just as Moriarty himself reported in his JOC article (Ex. 1004).

Because Dr. Williams and Dr. Ruffolo relied on UT's counsel's incorrect calculation, UT's experts' opinions on differences between the Moriarty product and the '393 Patent product should be disregarded.

1. UT's Data Sources.

UT attaches three exhibits that contain purity information for treprostinil made under the Moriarty method: Exhibits 2036, 2052, and 2053. (Ex. 2020, Appx. A.) Exhibit 2036 is the main source of this data, and contains 44 Certificates of Analysis from either Magellan Laboratories or Cardinal Health for commercial lots of treprostinil. Exhibit 2053 is UT's NDA Annual Report from 2003, which summarizes Certificates of Analysis and purity information from 32 commercial lots, including 30 lots that were already included in Exhibit 2036, plus two additional lots not included in Exhibit 2036. Thus, Exhibits 2036 and 2053 contain

purity data for 46 lots of treprostinil.

Exhibit 2052 is an undated but older document entitled "UT-15 Injection Drug Substance Volume 1.2 Chemistry, Manufacturing and Controls, NDA 21-272," and appears to be a portion of UT's original New Drug Application to sell treprostinil. It contains a summary of purity analyses for 13 lots of treprostinil made by third party companies called "[redacted]" "[redacted]," and "[redacted]" (Ex. 2052, 25-30.) The two [redacted] lots, made in 1986, were not included in UT's Appendix A. "These lots were manufactured by [redacted] using a slightly different route of synthesis." (*id.*, at 25 n.4.) [redacted] was also not included in UT's Appendix A. [redacted], "which was deliberately spiked for use in toxicology studies," (*id.*, at 29 n.2) was included by UT, as were "[redacted], and [redacted] [which] were tested and released using different analytical procedures previously submitted," and for which "the listed specifications do not apply ...," (*id.*, at 25 n.3). The 10 samples selected from the 13 samples in Ex. 2052 were manufactured several years before Moriarty's 2004 Journal of Organic Chemistry article (Ex. 1004). As Dr. Williams confirmed, there is no information provided on what method was used to make these lots, other than the fact that the methods used for many of them were similar to methods [redacted] used in 1986. These 10 data points have purity values far below the values reported in Exhibits 2036 and 2053.

2. Are the 10 Batches Even Moriarty Samples?

The dates of manufacture and footnotes recorded in Exhibit 2052 associated with UT's 10 cherry-picked samples make it unlikely that they were representative of treprostinil made by the Moriarty process:

> Q You don't know the details of how all these lots were made?
>
> A No. I haven't seen the detailed batch records of what went into those lots.
>
> Q Okay. So you don't know whether or not these lots were made by the '393 process, the Moriarty process, the older Aristoff process; is that right?
>
> THE WITNESS: Um, you know, I -- I'd have to investigate further. I don't know.
>
> Q Right. You -- you don't know if any of these are from the Moriarty process? At least not the ones on page 25?
>
> A So the Moriarty paper came out in 2003.
>
> ...
>
> A So I don't think it's possible that any of these could have been made by Moriarty process just based on the dates.

(Ex. 2059, 112:20-113:20). While Dr. Williams contends that these 10 samples represent "development" batches included for "fairness" (*id.*, at 81:23-82:7), he had no explanation for why he included 10 development batches out of 56 samples for his analysis of Moriarty batches, but only 5 development batches out of 157 samples for his analysis of '393-Patent batches. (*Id.*, at 270:15-271:6).

3. 46 Known Moriarty Samples Average to [redacted].

Once the cherry-picked data points are eliminated, the average purity of the 46 remaining samples increases from 99.05% to [redacted]: *the same purity as the product produced by the '393 Patent process*. SteadyMed prepared an Excel spreadsheet containing these 46 data points (Ex. 1021), and had Dr. Williams review every data point and calculation at his deposition to confirm that the [redacted] number is correct, and consistent with the number reported in Ex. 1004:

> Q: Okay. So now that we've – now that you've checked every single data point and looked at the calculations, you agree with me that this calculation of the purity is fair and accurate?
>
> A: The overall purity. But this does not reflect impurity profile.
>
> Q: Yeah I understand. I'm just talking about the overall – the level of purity.
>
> A: Yes.
>
> [...]
>
> Q: Okay. And so it is correct that for the samples from Exhibits 2036 and 20[5]3, the 46 samples, the average level of purity was [redacted] percent for the samples made under the Moriarty process?
>
> A: Yes.
>
> Q: Okay. That [redacted] value, that is consistent with the value that [redacted]?
>
> A: They're the same numbers.

(Ex. 2059, 218:25-219:20). By contrast with Dr. Williams' careful review of SteadyMed's calculation, Dr. Williams did not perform any calculations on UT's

data in Appendices A and B, having relied solely on counsel's work. (*id.*, 81:2-13; 82:1-11; 103:24-104:20; 112:24-114:2).

When the science is done properly, UT's data proves that Dr. Moriarty's [redacted] reported value in Ex. 1004 is correct.

4. Any Difference in "Impurity Profiles" is Meaningless.

UT still argues that the exact identity of the impurities generated by each process in the tiny [redacted] set of impurities matters. UT ignores that the '393 Patent claims contain at least hundreds of thousands of compounds (Ex. 2059, 71:17-22), for which none of the impurities have ever been characterized, (*id.*, 72:12-17). And the '393 Patent does not even characterize the impurities of treprostinil (Ex. 2058, 234:16-235:12), which UT maintains as a trade secret requiring a protective order, (Ex. 2058, 93:19-94:24, 233:5-12). As UT's expert Dr. Ruffolo conceded, "I see primarily purities of the parent compound, which is what I believe the invention is related to" and "so I see comparisons between the old process and new process with purities, but – but I don't see, unless I've missed it, I don't see the impurities." (Ex. 2058, 235:6-12.) Secret impurities not identified in the '393 patent for treprostinil, or for hundreds of thousands of other compounds, cannot make the claims patentable.

In any event, neither Dr. Williams nor Dr. Ruffolo opined that the impurity profile of treprostinil mattered:

Q: Do ... any of these particular impurities have deleterious biological consequences? [...]

A: I'm not a clinician, so I don't know.

Q: You don't know?

A: I don't know.

(Ex. 2059, 47:4-13; *see also* Ex. 2058, 257:22-258:9.)

Dr. Ruffolo agrees that both the prior-art and '393 Patent treprostinil are "highly, highly pure." (Ex. 2058, 217:24-218:5.) The FDA only requires [redacted] purity for treprostinil, so achieving higher purity is immaterial to the product, (Ex. 2058, 159:20-161:7), and Moriarty-process treprostinil was, and can still be, sold to the public, (Ex. 2058, 179:23-180:17). Where Moriarty and '393-Patent treprostinil have the same purity, as proven by the [redacted]-purity level, there are no functional differences between them, as Dr. Williams conceded. (Ex. 2059, 67:2-15.)

B. The Walsh Declaration Is Questionable.

During prosecution of the '393 Patent, UT relied on the Walsh Declaration, and differentiated the '393 Patent product from Moriarty's product by showing a "representative sample" of Moriarty product containing 0.6% impurities, which was contrasted with '393 Patent treprostinil diethanolamine salt and treprostinil having 0.1% and 0.2% impurities, respectively. (Ex. 1002 at 343-350.). As noted by UT, the '393 Patent claims were allowed after submission of the Walsh Declaration. (Resp., 5).

The 46 samples contained in Exhibits 2036 and 2053, and a new exhibit submitted by UT—Exhibit 2006—contradict the Walsh Declaration. As Dr. Winkler observed, the data in the Walsh Declaration was derived from a single sample, and significant batch-to-batch variations in the impurity profile of each batch of treprostinil could affect the results. (Ex. 1009, ¶ 66).

Dr. Winkler's concern is confirmed by UT's results from the 46 batches. For example, Moriarty Batch No. [redacted], dated January 25, 2004, and having a purity of [redacted] which is the [redacted] for these batches, had only [redacted]: [redacted]. (Ex. 2036, 5.) According to Dr. Walsh's June 4, 2013 Declaration, "treprostinil as the free acid prepared according to the process specified in claim 1 or 10 of the present application has only three impurities ...." (Ex. 1002, 348-49.) Moreover, "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." (Ex. 1002, 349.) Yet Moriarty Batch No. [redacted] did not contain detectable amounts of any of these impurities either, proving that

Dr. Walsh could not make his conclusion.

UT told the FDA that treprostinil diethanolamine salt made in accordance with the '393 Patent "[redacted]." (Ex. 2006, 3-6.) Yet these impurities, supposedly removed by carrying out step (d) in the '393 Patent's claims, are not described in the Walsh Declaration, which instead presents "Impurities ... [Total Related Substances]" as 0.2% for the free acid, and 0.1% for the salt, (Ex. 1002, 348), meaning that the free acid is *less pure* than the diethanolamine salt, and not more pure as UT represented to the FDA in Exhibit 2006. Dr. Williams could not provide an explanation for this discrepancy (Ex. 2059, 199:6-18), which contradicts the Walsh Declaration.

III. DR. WILLIAMS' TESTIMONY CONFIRMS THAT PHARES ANTICIPATES CERTAIN '393 PATENT CLAIMS.

Phares (Ex.1005) makes the same treprostinil diethanolamine salt claimed in every claim of the '393 Patent where optional step (d) is not completed, as explained in SteadyMed's Petition and Dr. Winkler's Declaration (Ex. 1009, ¶¶ 44-71.) UT responds by rejecting the Board's claim construction, discussed later in this Reply, and with three factual arguments: (1) that SteadyMed cannot show that Phares used the Moriarty process, claimed in steps (a) and (b) of the '393 Patent's claims; (2) that SteadyMed cannot show that Phares' treprostinil diethanolamine

Form B salt has the same purity level as the '393 Patent's Form B salt; and (3) that HPLC Assay Analysis can measure purity better than 0.4%, even though Dr. Winkler pointed out that the error in UT's own equipment is at least 0.4%, (Ex. 1009, ¶ 70).

But Dr. Williams concedes that the process in Phares for making treprostinil's (-)-enantiomer carries out the same alkylation step (a) and hydrolysis step (b) in the '393 Patent's claims, thus disclosing these steps for treprostinil. And the attached Declaration of Robin D. Rogers (Ex. 1022), SteadyMed's polymorph expert, explains why the melting point of treprostinil diethanolamine salt Form B can be compared between the '393 Patent and Phares reference, and that the particular sample in Phares had at least the same purity as the '393 Patent's examples. Finally, UT's own data showed that the average purity of Moriarty samples was [redacted], proving that batch variation is at least [redacted] and UT's representation to the FDA stated that treprostinil purity will be maintained between [redacted], (Ex. 2006), proving a [redacted] variability applies to purity measurements.

A. Phares discloses steps(a) and (b) of the '393 Patent.

"Q. Okay. So what we see here is there's an alkylating step (a) and a hydrolyzing step (b) on page 42 of the Phares reference. A. Yes." (Ex. 2059, 190:16-19). On Phares page 42 (Ex. 1005), as Dr. Williams concedes in this testimony, steps (a) and (b) are carried out on the mirror image version of the

compounds described in the '393 Patent claims, and as Dr. Winkler explains, the Phares patent at page 42 states that the enantiomer procedure is the same procedure used to make "the commercial drug (+)-Treprostinil." (Ex. 1009 ¶ 56; Ex. 1005, 42.) Thus, in describing that the process for making both enantiomers uses steps (a) and (b), and explaining that the process for the (-)-enantiomer is merely a variation on the already known (+)-enantiomer process, Phares inherently discloses steps (a) and (b) to create the (+)-enantiomer.

B. Phares' Higher Melting Point Means It is at Least Equally Pure.

Dr. Winkler explained that since the Phares treprostinil diethanolamine salt Form B melted at 107°C, but the same Form B in the '393 Patent melted at around 106.6 °C, the Phares sample was necessarily as pure as the '393 Patent's samples. Dr. Williams, who is "not a polymorph expert," (Ex. 2059, 158:17-18; 156:25-157:2), contends nevertheless that the melting point of two samples of the same polymorph (crystal form) cannot be compared to determine their relative purities. (Ex. 2020 ¶ 75.) According to UT and Dr. Williams, how a polymorph is made, including what solvents are used, can affect its melting point, even if the polymorphs are identical. (Resp., 22-24; Ex. 2020 ¶ 75.)

As set forth in Dr. Rogers' Declaration (Ex. 1022, ¶¶ 49-52) and admitted by Dr. Williams, melting point is one of the most common ways to identify different polymorphs. (Ex. 2059, 158:20-25); *see also* Exs. 1024-1026. Dr. Williams

concedes that in the '393 Patent, treprostinil diethanolamine salt is identified as being Form B based solely on its melting point. (Ex. 2059, 170:24-171:3.) And Dr. Williams concedes that the same treprostinil diethanolamine salt polymorph—Form B—is presented in the Phares reference and '393 Patent. (*Id.*, 168:6-11).

While Dr. Williams relies on his "personal experience" observing different melting points for crystals made with different solvents, he conceded that he knew of no literature to support his opinion. (*Id.*, 184:22-185:2.) Dr. Williams conceded that the one article he relied upon in his declaration, Ex. 2030, in fact describes different crystal forms having different melting points, and not the same crystal form having different melting points. (*Id.*, 180:9-25.)

By contrast, Dr. Rogers' Declaration cites several literature sources explaining that melting point uniquely identifies a polymorph. (Ex. 1022, ¶¶ 49-52). Thus, for the same polymorph, if the melting point differs, it is due to impurities contained in the sample having a lower melting point. (*Id.*, ¶ 64.) Dr. Rogers concludes that Phares' higher melting point is necessarily due to higher or at least identical purity. (*Id.*, ¶ 74.) Moreover, the width of the DSC peak in the Phares reference is very narrow, consistent with a very pure material. (*Id.*, ¶ 84.)

C. HPLC Analysis Has Error Bars Too Large to Distinguish the Tiny Differences in Purity Levels UT Relies Upon.

As Dr. Winkler explained, it is not possible to measure treprostinil purity levels better than 0.4%, as shown by UT's own data. (Ex. 1009, ¶ 70.) Now that UT has

provided multiple certificates of analysis for treprostinil, it is now confirmed that UT's Moriarty purity varies by at least [redacted], and indeed, Dr. Williams conceded he had no reason to disagree with this [redacted] value. (Ex. 2059, 218:22-24.)

UT's own exhibits confirm that HPLC assay analysis has a wide error range: "[redacted]." (Ex. 2006, 3.) UT's expert Dr. Williams agrees with this statement and that "[redacted]" refers to the HPLC assay for purity. (Ex. 2059, 133:17-25, 134:24-135:4.)

UT discounts that HPLC assay analysis has a wide error range by suggesting that purity should instead be measured by totaling up "total related substances," which are measurements of particular impurities identified in the HPLC analysis. (Resp., 2-3, 29-30.) But as acknowledged by Dr. Williams, some impurities will not be detected in a total-related-substance analysis (Ex. 2059, 140:5-9.). UT's expert Dr. Ruffolo confirmed that in the '393 Patent, all of the analyses are HPLC analyses of the total treprostinil against a reference standard, and not measurements of total related substances. (Ex. 2058, 153:16-154:7.) And both UT experts acknowledged that the FDA uses HPLC assay analysis to evaluate the overall purity of treprostinil, and to decide whether that treprostinil meets a [redacted] purity requirement that would allow it to be sold. (Ex. 2058, 159:20-161:7; Ex.

2059, 150:23-151:25.)

UT criticizes Dr. Winkler, falsely stating that Dr. Winkler does not understand HPLC analysis, and does not know anything about the error in UT's HPLC equipment. (Resp., 3, 30.) Dr. Winkler instead testified that there is no information regarding the error in the amount of "[redacted]," an impurity present in UT's treprostinil at about [redacted]. (Ex. 2051, 63:3-14.) The error in the [redacted] measurement is irrelevant to the error in treprostinil purity, especially where treprostinil purity is a number near [redacted] ([redacted]), 1000 times larger than the amount of [redacted]. Regarding error in HPLC Analysis of treprostinil purity, Dr. Winkler was unequivocal at his deposition:

> 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 1 percent in the first column and by my analysis could be as high as 2 percent in the second column.

(Ex. 2051, 88:12-18.)

IV. UT'S EXPERTS CONFIRM THE CLAIMS' OBVIOUSNESS.

A. Moriarty Was Recognized as the Best Method to Make Treprostinil Before the Phares Reference was Published.

UT contends that Phares does not anticipate because it does not disclose the first two steps, steps (a) and (b), which were used in the Moriarty process. As explained above, this contention is wrong. But even if it were true, UT's expert Dr. Williams provided testimony confirming that there was a strong reason to combine

Moriarty with Phares: Moriarty was well-known to be the best way to make treprostinil, and would have been the way Dr. Williams' own graduate students would have made the treprostinil in Phares before turning it into its salt.

First, Dr. Williams confirmed that steps (a) and (b) in the '393 Patent claims were disclosed by the Moriarty patent, Ex. 1003. (Ex. 2059, 53:19-54:7). Second, Dr. Williams confirmed that "a person of ordinary skill in the art in 2005 reading the Phares reference, that person would know that the best way to make treprostinil is the Moriarty method ...." (*id.*, 240:2-7). And third, he confirmed that "a typical person of ordinary skill in the art, typical graduate student, they would have found the Moriarty paper and used that technique to make treprostinil in 2005." (*Id.*, 244:10-21.) While UT's expert Dr. Ruffolo disagrees with Dr. Winkler regarding the appropriate level of skill, it is Dr. Ruffolo's opinion that the skill level should be higher than Dr. Winkler's, and that a person of ordinary skill should at least have a Ph.D. (Ex. 2058, 52:2-17.) If a graduate student would use Moriarty, then certainly a Ph.D. would do so. Thus, UT's experts essentially confirm that a person of ordinary skill in the art would combine Moriarty with Phares when making Phares' treprostinil salt.

B. UT's Experts Confirm That Crystallization Through A Salt To Purify Is Organic Chemistry 101.

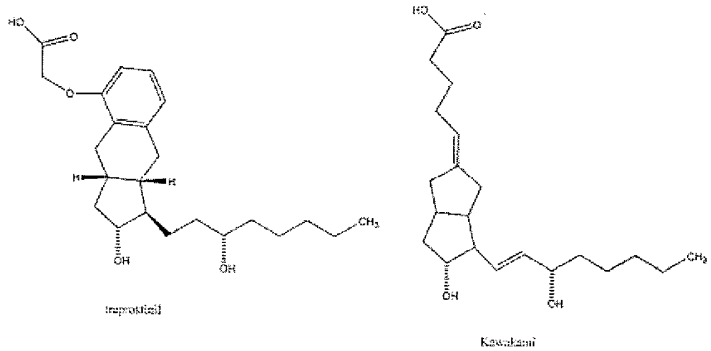
As shown by UT expert Dr. Ruffolo's testimony, *supra*, the process steps (c) and (d), which crystallize a compound as its salt and then convert the salt back to

the acid, have been around for "decades," at least as far back as the late 1960s. (Ex. 2058, 175:19-176:22, 179:11-17.) "[I]f a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 417 (2007). UT cannot claim that using this elementary chemistry technique is nonobvious merely because UT applied it to treprostinil.

UT also argues that the particular impurities found in treprostinil, which are said to be stereoisomers, would not have been removed using crystallization. First, there is no teaching in the '393 Patent or the prior art of record regarding what kinds of impurities are present in treprostinil, or, as conceded by UT's experts, of the hundreds of thousands of other compounds included in the claims. (Ex. 2059, 74:18-25; Ex. 2058, 234:16-235:17.) UT maintains the identity of these impurities as a trade secret, necessitating a Protective Order to cover these proceedings so that information on these impurities is not revealed. UT's secret information regarding these impurities' identity cannot be the basis for why a person of ordinary skill in the art would not use crystallization here.

Second, the Kawakami reference, Ex. 1007, used crystallization to separate stereoisomers, as confirmed by Dr. Winkler under UT's counsel's cross-examination. (Ex. 2051, 203:4-204:20.) UT distinguishes Kawakami on grounds

that it concerns a different prostacyclin, not treprostinil, and offers chemical drawings making Kawakami's prostacyclin look different from treprostinil. (Resp., 40.) But SteadyMed has generated more fair drawings of these two structures, and Dr. Williams confirmed that these drawings accurately depict the structures. (Ex. 2059, 245:23-247:1). These new drawings are submitted as Ex. 1028:



When properly depicted, treprostinil and Kawakami are similar compounds.

Finally, treprostinil can be made in any purity desired, as Dr. Williams admitted, by prior-art purification processes like chromatography, since "you could repurify and purify anything you want by chromatography to 99.99999 percent if you wanted to." (Ex. 2059, 94:8-12). While Dr. Williams contends that would be an impractical approach in large-scale manufacturing, he concedes that the '393 Patent's claims are not limited to large-scale manufacturing. (*Id.*, 187:18-188:3.) Thus, there was no barrier to making treprostinil of any purity, and while doing so by using crystallization is obvious, a product having any desired purity can be made by any method, so purer treprostinil is obvious.

V. THE BOARD CONSTRUED THE CLAIMS CORRECTLY.

UT challenges the Board's construction of the legal terms "comprising" and "product," which is surprising since that the Board generally accepted UT's constructions from UT's Preliminary Response. UT had argued that "comprising" should mean "included but not limited to." (Paper 10, at 23). And the Board agreed. (Paper 12, at 13). Now UT contends that "comprising" should not be given its usual open-ended construction. (Resp., 13.) UT points to the prosecution history as effecting a disclaimer of the usual meaning of "comprising," but "[a] statement in the prosecution history can only amount to disclaimer if the applicant clearly and unambiguously' disavowed claim scope." *Toshiba Corp. v. Imation Corp.*, 681 F. 3d 1358, 1370 (Fed. Cir. 2012). UT points to no statements in the prosecution history regarding the meaning of "comprising," but, argues that since the examiner allowed the claims, he must have construed "comprising" according to UT's non-open construction. (Resp., 16.) If that were a clear and unambiguous disavowal, every Patent Owner could argue that its claims should be construed narrowly enough to make them valid, since the initial examiner allowed them.

UT also objects to the Board's plain and ordinary meaning for the term "product," and contends that "product" should be narrowly construed. But this narrow construction is not supportable, and even UT's expert Dr. Williams conceded that "product" is broadly used in the art, assuming that it is even a term

of art and not a legal term. First, Dr. Williams acknowledged that "chemists use the word 'product' in two different contexts, routinely." (Ex. 2059, 248:4-5.) "Product" can mean in chemistry a product and its impurities, or the molecular structure alone. (*Id.*, 248:13-23.) Second, Dr. Williams conceded that the '393 Patent and prosecution history do not provide definitions for "product." (*Id.*, 248:24-249:13.) Third, Dr. Williams' Declaration recognizes that "product" is a term in patent law relating to "product-by-process" claims, (Ex. 2020, ¶ 30), but does not explain why this legal definition should not apply here. Fourth, Dr. Williams' own example of "product" in his own writing—Ex. 2028—uses "product" to mean a product created by nature, and not by a chemical reaction, when it refers to "the natural product from marine sources." (Ex. 2020, ¶ 63.) And fifth, while Dr. Winkler testified that "product" includes the product of a chemical reaction, he testified that "product" was a broad term that encompassed more. (Ex. 2051, 152:21-154:21.)

It is unclear how UT's claim constructions matter. UT seeks a construction limiting the claims by impurity profile, (Resp., 18), but UT cannot articulate how its proposed constructions for "comprising" and "product" effect this result. There is no record evidence showing that the claimed processes and their products have unique impurity profiles, and the '393 Patent lacks information regarding the impurity profiles of treprostinil or its many salts, or for the thousands of compounds in its claims. (Ex. 2059, 71:17-72:17, 74:18-25; Ex. 2058, 234:16-

235:17.) The impurity profiles are not unique to each claim, but depend on unclaimed elements like what solvents were used, (Ex. 2058, 239:22-241:14), whether the intermediate products were purified, (Ex. 2058, 239:8-20, Ex. 2059, 69:17-71:9), and what bases, acids, or other reactants that the claims allow were used. Product-by-process claims would have no definite scope under UT's analysis.

VI. NO LONG-FELT NEED FOR THESE CLAIMS' PRODUCTS.

While UT suggests there was a long-felt need for these claims' products, its long-felt-need expert Dr. Ruffolo testified otherwise: "there's nothing I can tell you about the long-felt need for those other compounds [of claim 1]," (Ex. 2058, 65:4-13); or of claim 9 (Ex. 2058, 69:20-70:11); or of claims 12, 13, 16, 17, 21, or 22 (Ex. 2058, 110:17-111:9, 114:16-117:3, 118:2-5; 118:23-119:23, 121:5-23); or of any claim that was not limited to treprostinil and treprostinil diethanolamine salt, (Ex. 2058, 68:14-25). Only claims 10, 14, 15, and 17 are limited to treprostinil or its salt.

Regarding treprostinil or its diethanolamine salt, Dr. Ruffolo conceded that he had no idea if FDA had asked for a change in purity, (*id.*, 45:15-22), nor could he identify anyone who expressed a particular desire for greater purity, (*id.*, 130:16-25.) He also recognized that one could usually purify a drug further by running purification procedures repeatedly, (*id.*, 46:9-18), which Dr. Williams confirmed was true for treprostinil, (Ex. 2059, 94:8-12), and proves that there was no need for

the "invention." Dr. Ruffolo also conceded, contrary to UT's arguments, that a change in purity specifications is not a major amendment, (Ex. 2058, 310:5-13), but that the other changes UT applied for—changing starting materials and manufacturing facilities, were major amendments (*id.*, 310:13-18).

Regarding claims 10, 14, 15, and 17, Dr. Ruffolo concedes that: (1) the FDA requires only a [redacted] purity level, which is *much lower* than any levels produced by the prior art, (*id.*,159:20-161:7); (2) the FDA would allow batches of treprostinil produced by the Moriarty process to be sold, (*id.*,179:23-180:17), since Moriarty products are "highly, highly pure," (*id.*, 217:11-218:5); and (3) there is no clinical difference between the prior-art Moriarty product and the '393 Patent product (*id.* 315:15-23). Thus, the FDA expressed no need for a purer product. Moreover, Dr. Ruffolo does not know if UT's products that he relies upon are covered by these claims. (*Id.*, 292:25-293:2.)

Dr. Ruffolo's opinion relies on Dr. Williams' incorrect calculation showing 99.0% purity, but Dr. Ruffolo concedes he did not review that calculation, nor speak to Dr. Williams, and depends entirely on Dr. Williams. (*Id.*, 262:4-263:5.) Since Dr. Williams now concedes that the correctly performed calculation shows a [redacted] purity, (Ex. 2059, 218:3-8), Dr. Ruffolo's opinions should be disregarded.

Date: September 27, 2016

Respectfully submitted,

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CERTIFICATE OF WORD COUNT

Pursuant to 37 C.F.R. § 42.24, the undersigned attorney for Petitioner certifies that the document contains 5,599 words in 14-point Times New Roman font, excluding the parts of the document that are exempted by 37 C.F.R. § 42.24(a)(1), according to the word count tool in Microsoft Word.

Date: September 27, 2016

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The undersigned certifies that a copy of the attached Petitioner's Reply was served via electronic mail to the following:

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

STEADYMED LTD.,

Petitioner,

vs.

UNITED THERAPEUTICS CORPORATION,

Patent Owner.

Case IPR2016-000006 (Patent 8,497,393)

VIDEOTAPED DEPOSITION OF ROBERT M. WILLIAMS, PH.D.

Friday, August 26, 2016

9:30 a.m.

12235 El Camino Real

San Diego, California

Reported by:

Harry Alan Palter

CSR No. 7708, Certified LiveNote Reporter

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ROBERT M. WILLIAMS, PH.D.

SteadyMed Ltd. vs. United Therapeutics Corporation

Friday, August 26, 2016

Harry Alan Palter, CSR No. 7708

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San Diego, California

Friday, August 26, 2016; 9:30 a.m.

THE VIDEOGRAPHER: Good morning. We are on the record. This is the videotaped deposition of Robert M. Williams, Ph.D., in the matter of SteadyMed, Ltd., vs. United Therapeutics Corporation.

This deposition is taking place at 12235 El Camino Real, Suite 200, San Diego, California 92130, on August 26, 2016, at 9:30 A.M.

My name is Kory Ross. I'm the videographer with U.S. Legal Support. Video and audio recording will be taking place unless all counsel agree to go off the record.

Would all present please identify themselves, beginning with the witness.

THE WITNESS: Robert M. Williams.

MR. POLLACK: Stuart E. Pollack, DLA Piper, LLP U.S., on behalf of SteadyMed, Ltd., the petitioner. I'm joined with Maya Choksi from the same law firm.

MS. HASPER: Katherine Hasper of Wilson, Sonsini, Goodrich & Rosati, on behalf of United

Therapeutics and the witness.

MR. MAEBIUS: And Steve Maebius from Foley & Lardner on behalf of patent owner.

THE VIDEOGRAPHER: Thank you, Counsel.

The certified court reporter is Harry Palter.

Will you please swear in the witness.

ROBERT M. WILLIAMS, PH.D.,

having been duly administered an oath in accordance with the California Code of Civil Procedure Section 2094, was examined and testified as follows:

EXAMINATION

BY MR. POLLACK:

Q Good morning, Dr. Williams.

A Good morning, Counselor.

Q Just as a formality to start today, could you state your name for the record and your current position.

A Robert M. Williams, university distinguished professor at Colorado State University.

Q Okay. Now, I know you've been deposed before; correct?

A Yes.

Q How many times have you been deposed?

A I don't know the exact number. It's somewhere around 17, 15 -- 16, 17, somewhere in there. I lost count, actually.

Q Okay. Were all of those patent cases?

A Yes.

Q And how many of those cases were for United Therapeutics?

A Let me see. Three. I think this would be my third deposition with United Therapeutics. But I'd have to -- I can check -- check. It may be three or four. I don't remember. I think it's for sure three.

Q Okay. But you understand all the rules of depositions at this point?

A Yes.

Q Okay. And there's no reason today that you can't give your best testimony?

A No.

Q All right.

MR. POLLACK: I'm going to mark as Williams Deposition Exhibit 1 the Petitioner's

Notice of Deposition.

(Exhibit 1 marked)

BY MR. POLLACK:

Q And Dr. Williams, are you here today in response to Petitioner's Notice of Deposition of Robert M. Williams, Ph.D.?

A Yes, that's my understanding.

Q So you've done two other depositions for United Therapeutics. Did both of those cases also involve treprostinil?

A Yes.

Q And those were two cases in New Jersey involving generic challenges to United Therapeutics Remodulin product?

A Yes.

Q Do you remember the names of the two defendants in those cases?

A Sandoz in the first case, which went to trial, and then Teva.

Q Okay. And the type of case is still ongoing?

A I believe so.

Q Have you submitted an expert report or Declaration in the Teva case?

A Yes.

Q And have you -- and you've been deposed already in that Teva case?
A Yes.
Q Did your expert Declaration or deposition concern the '393 patent at all?
A Yes.
Q Okay. Did you opine on the validity or invalidity of the '393 patent in that case?
A No.
Q Okay. What did you opine on?
A Claim construction.
Q Okay. And what were the issues regarding claim construction in that case?
MS. HASPER: Objection. Relevance.
THE WITNESS: I don't -- I don't recall off the top of my head.
BY MR. POLLACK:
Q Okay. Were they similar to the claim construction issues in the current IPR?
A I believe there was some overlap, yes.
Q Which ones were an overlap?
A Again, I'd have to go back and look at my Declaration.
Q You don't recall --
A It's -- I don't recall exactly.

Q Okay.

A I don't want to give an inaccurate answer.

Q Absolutely.

Do you recall if there was any discussion of the meaning of the term "product" in the '393 case with either -- with Teva?

MS. HASPER: Objection. Relevance.

You may answer to the extent it doesn't reveal privilege.

THE WITNESS: Again, my -- I haven't looked at that material for awhile, so I'm hesitant to give an answer right now.

BY MR. POLLACK:

Q You're not sure?

A I'm not 100 percent sure.

Q Okay. What about the word "comprising"? Was there any issue about the meaning of the word "comprising" in the '393 case?

MS. HASPER: Same objection.

THE WITNESS: I'd have to give the same answer. I don't exactly recall.

BY MR. POLLACK:

Q Well, do you know did you -- whether there was an issue or not, did you make any comments

or provide any opinions regarding the meaning of the word "comprising" in the Teva case?

MS. HASPER: Same objection.

THE WITNESS: I didn't hear you, Katherine?

MS. HASPER: Same objection.

THE WITNESS: And your question again was? Did I give --

BY MR. POLLACK:

Q Did you give any opinion of any form regarding the meaning of the term "comprising" in the Teva case regardless of what the -- ultimate issue was?

A I'd need to refresh my recollection by looking at the Declaration I submitted.

Q You don't recall as you sit here?

A I don't recall.

Q And do you know whether the Declaration you submitted, whether it was -- whether it was stamped "confidential"?

A I believe so.

MR. POLLACK: Counsel, to the extent it's available, we'd like to get a copy of his Declaration from the Teva case.

MS. HASPER: I'll look into it for you.

BY MR. POLLACK:

Q And are you also involved in certain other generic challenges to the Remodulin product, also pending the District of New Jersey?

A I know that there's a case now that I've been retained for involving Watson Laboratories.

Q Any others?

MS. HASPER: Objection. Privilege.

To the extent that you can answer without revealing attorney-client communications or confidential information, you may do so.

THE WITNESS: Not that I'm aware of.

BY MR. POLLACK:

Q Not that you're aware of? Okay.

And in the Watson case, have you submitted any opinions or formed any opinions in that case?

A Not yet.

Q Not yet? Do you know what the issues are in the Watson case?

MS. HASPER: Again, objection. Privilege.

I caution the witness not to answer to the extent that doing so would reveal privileged information.

THE WITNESS: That's at a very early stage, so I haven't done any --

BY MR. POLLACK:

Q You haven't done anything?

A No.

Q Okay. About how many hours in total have you worked on cases for United Therapeutics at this point?

MS. HASPER: Objection.

Mr. Pollack, this is -- you're asking about how much time he's spent either on his own with counsel working on --

MR. POLLACK: Okay. Stop the speaking objections now; all right?

MS. HASPER: I'm trying to explain that you're asking a line of questions which assumes --

MR. POLLACK: Okay. Just -- just say your objection.

(Indiscernible crosstalk)

THE WITNESS: Excuse me, Counselor?

BY MR. POLLACK:

Q Yes. How many hours have you worked on cases for United Therapeutics?

MS. HASPER: Objection. I instruct the witness not to answer to the extent doing so will

reveal privileged information.

THE WITNESS: I have no idea.

BY MR. POLLACK:

Q Well, more than a hundred?

MS. HASPER: Objection. Privileged.

THE WITNESS: I don't know.

MR. POLLACK: Are you instructing him not to answer?

MS. HASPER: The objection -- so I'm going to give you a standing instruction to this entire line of questioning, that to the extent Mr. Pollack asks you about privileged information, including your communications with counsel for United Therapeutics, that we request you not answer.

MR. POLLACK: I'm not asking about his communications.

BY MR. POLLACK:

Q About how much income have you received so far from United Therapeutics working on their cases?

MS. HASPER: Objection. Relevance. Prejudicial.

THE WITNESS: I don't recall.

BY MR. POLLACK:

Q Over $100,000?

MS. HASPER: Objection. Relevance. Prejudicial.

THE WITNESS: I'd have to go look at my invoices.

BY MR. POLLACK:

Q Over $50,000?

MS. HASPER: Objection. Relevance. Prejudicial.

THE WITNESS: Likely.

BY MR. POLLACK:

Q Likely over 50 -- between 50 and 100? Is that fair?

MS. HASPER: Objection. Relevance. Prejudicial.

THE WITNESS: I don't know.

BY MR. POLLACK:

Q It could be over hundred?

MS. HASPER: Objection. Relevance. Prejudicial. Asked and answered.

BY MR. POLLACK:

Q It could be over a hundred thousand dollars?

A I'm thinking I'd have to go look.

MS. HASPER: Objection. Relevance, privilege, asked and answered.

THE WITNESS: I'd have to look.

BY MR. POLLACK:

Q You'd have to look.

I'm asking if it's possible whether it was over a hundred thousand dollars?

MS. HASPER: Objection. Relevance. Privileged. Asked and answered.

THE WITNESS: I just remember I've been working on a lot of different cases at the same time.

BY MR. POLLACK:

Q Sure.

A I don't remember.

Q Sure.

What's your hourly rate?

A $650 an hour.

Q Okay. Have you worked over a hundred hours on United Therapeutics cases?

MS. HASPER: Same objection.

THE WITNESS: I'd have to give the same answer. I'd have to go back and look at my invoices. I don't -- I don't recall off the top of my head.

BY MR. POLLACK:

Q Okay. What about in this IPR? About how

many hours have you worked in this IPR?

MS. HASPER: Same objection.

THE WITNESS: I don't know.

BY MR. POLLACK:

Q No idea?

A No.

Q "No." More than 40 hours?

MS. HASPER: Same objection.

THE WITNESS: Again, I don't want to give an inaccurate answer, so I would need to look at my invoices.

BY MR. POLLACK:

Q I understand. But I'm asking just for an approximate answer. Is it more than 40 hours?

MS. HASPER: Same objection.

THE WITNESS: I don't know.

BY MR. POLLACK:

Q About how much have you invoiced for in this matter?

MS. HASPER: Same objection.

THE WITNESS: Between two and three invoices, so I'm not really sure.

BY MR. POLLACK:

Q Okay. About how much was this at each invoice?

A I do not recall.

MS. HASPER: Same objection.

BY MR. POLLACK:

Q Was each invoice larger than $50,000?

A No.

MS. HASPER: Same objection.

BY MR. POLLACK:

Q Were some of the invoices larger than $50,000?

A No, I don't think so.

Q You think all of them were below $50,000?

A Yes.

Q Okay. And there were about three invoices?

MS. HASPER: Same objection.

THE WITNESS: Again, I can't exactly recall.

BY MR. POLLACK:

Q Okay. Can you give --

A Because I'm working on other matters. Completely different matters, not for United Therapeutics. So --

Q Sure.

A I have a very accurate record on my computer, but I don't remember.

Q How many matters are you working on now?

MS. HASPER: Objection. Relevance.

THE WITNESS: Around nine right now.

BY MR. POLLACK:

Q Okay.

A I'm paid for about nine different matters.

Q All right. About how much do you earn a year doing matters?

MS. HASPER: Objection. Relevance.

THE WITNESS: Which -- what do you mean "a year"? It varies from year to year.

BY MR. POLLACK:

Q How about this year? How much in --

MS. HASPER: Same objection.

BY MR. POLLACK:

Q -- 2016 so far?

A I haven't tabulated that yet from my accountant. He's been buggin' me to give him numbers to him before September 15th. So I'll be doing that soon. I don't know.

Q Okay. Approximately how much?

A I don't know.

Q How about 2015? How much?

MS. HASPER: Same objection.

BY MR. POLLACK:

Q How much have you earned in 2015 on patent matters?

A It was somewhere around $800,000.

Q And what about 2014? A similar amount?

MS. HASPER: Same objection.

THE WITNESS: I don't recall.

BY MR. POLLACK:

Q Of that $800,000 last year, about how much of that was from United Therapeutics?

A I have no idea.

MS. HASPER: Same objection.

BY MR. POLLACK:

Q Would you say half of your time --

(Indiscernible crosstalk)

THE WITNESS: I have no idea.

BY MR. POLLACK:

Q No idea at all?

A No.

Q Okay.

MS. HASPER: I'll just repeat what got lost in the crosstalk was me saying, "Same objection." Also, "privilege."

BY MR. POLLACK:

Q Have you done work in other -- you

understand this is a proceeding called an "inter partes review"?

A Yes.

Q Have you done work in other inter partes reviews?

A Not yet, no.

Q This is your first one?

A Yes.

Q Okay. And how many cases have you testified at trial in?

A Four times.

Q Four times?

A Four different cases.

Q Okay. One of those was the Sandoz case?

A Yes.

Q That case didn't involve the '393 patent; is that right?

A No.

Q Okay. Are you involved also -- I think there's another Sandoz case involving the '393 patent? Are you involved in that one?

MS. HASPER: Objection. Foundation.

THE WITNESS: Not that I'm aware of.

BY MR. POLLACK:

Q No?

Okay. The Declaration?

MR. POLLACK: I'm going to mark as Williams Deposition Exhibit 2 the Declaration of Robert M. Williams, Ph.D., in support of patent owner response to petition.

(Exhibit 2 marked)

BY MR. POLLACK:

Q If you could just verify me that that's a fair and accurate copy of your Declaration?

A (Examining document) So this is -- yes. This is a copy of my Declaration as submitted.

Q Okay. Were there any mistakes in your Declaration that you discovered?

A Yes.

Q Okay. What are those mistakes?

A There is two minor mistakes. At paragraph 88, there's a typographical error. One, two, three, four -- fifth line down, middle, Exhibit 2034 should be Exhibit 2044.

Q Okay.

A And the second error is there is a small change to Exhibit B, entry --

Q I'm sorry, where are you?

A Exhibit B.

Q Okay.

A Page 50, the entry [redacted] was inadvertently a duplicate. So that -- that one entry needs to be crossed out.

Q Okay. Could you tell me what page we're looking at?

A 50.

Q And which entry is it?

A It's the -- I believe it's the [redacted] was inadvertently a duplicate of another -- another entry.

Q And that is the 17th one down?

A Yes. I think that's correct.

Q Okay. Other than those two corrections, are there any other corrections you want to make?

A Not that I have found.

Q Okay. Are all of your opinions in this matter -- are they all contained in your Declaration?

A Yes.

Q Okay. Who did the first draft of your expert Declaration?

A I actually made the draft of -- sort of the template of the first draft and, Counsel, Bobby Delafield, and I also worked with Katherine here. We went back-and-forth by e-mail assembling

different drafts as we went along, and discussed issues and --

Q What's Katherine's last name?

A Hasper.

Q All right. Anyone else you worked with at counsel?

MS. HASPER: You can answer to the extent it doesn't reveal privileged information.

THE WITNESS: I primarily worked with Bobby and Katherine, as I recall.

BY MR. POLLACK:

Q Who assembled the appendices "A" and "B"?

A Counsel did.

Q Did you have any questions about how counsel assembled Exhibits A and B -- or appendices "A" and "B"?

A What do you mean?

Q Did you ask them: How were these assembled?

A Yes. I worked with them, and there was underlying batch data that I was provided with, and I was able to cross-check that the entries were all accurate.

Q Okay. Who selected the particular batches that were chosen to the analyzed?

A These were -- I think these were requested by counsel from United Therapeutics.

Q Okay. You had nothing to do with the selection?

A Other than asking for as much batch data as was available.

Q Okay. Did you get all batch data that was available?

A I believe so.

Q Okay. Was there any batch data that you saw that's not included in appendices "A" and "B"?

A No.

Q Did you ask whether there was any other batch data that you could include?

A I did ask.

Q Okay. And what was the answer?

A That this was all they were able to find.

Q Okay. If we can go in your Declaration to paragraph 27.

Here in paragraph 27, you list some patent litigation matters that you were working on?

A Yes.

Q Is that right? Okay.

Are there -- it says here, "Process chemistry patent litigation." Are there other kinds

of litigation matters that you were working on that aren't in this list?

A Yes.

Q Okay. About how many other matters?

A So this lists, I believe, seven. And I've worked on somewhere around 27. So 20 other matters that -- that were not dealing with process chemistry issues.

Q Just briefly what were those other matters concerning?

A I would need to look at my list of -- of cases. I don't have a memory of all of 'em.

Q Sure. Do you have a recollection of some of them?

A I did a couple of cases on behalf of Apotex in Canada early on.

Q Apotex is a generic pharmaceutical company?

A Yes.

Let me see. I did a formulation case where I testified at trial on behalf of Hospira and Apotex against Sanofi-Aventis. That wasn't process chemistry. That was formulations. I've done a bunch of formulation cases.

Q I see on this list there are some cases

that name United Therapeutics.

A Hmm-hmm.

Q Okay. The first one lists United Therapeutics is United Therapeutics Corp. versus Sandoz. And there are two cases listed. Do you see that?

A Yes.

Q Is the first case the case that went to trial already?

A Yes.

Q Okay. And --

A I believe so.

Q And that case didn't involve the '393 patent?

A No.

Q Okay. And then there's a second case. Do you see that? 13-316?

A 13 --

Q It's in the same -- sorry. It's in the same phrase on page 11.

A That was -- I think that was a consolidated thing where there were two different -- there was a formulation patent and a process patent that were litigated at the trial --

Q Okay.

A -- as I recall.

Q And neither of them involved the '393 patent? Neither of those cases?

A No, I don't think so. No.

Q At the very bottom of the page, we see the words United Therapeutics starting?

A Yes.

Q And then it says, "versus Teva." That's the matter you're working on now?

A I believe that matter is over. I believe the parties settled.

Q Okay. Okay.

The matter in which you've given an expert on claim construction, that's a new Teva matter that's not listed here?

A Boy, I -- you know, just looking at the case numbers, I don't remember. I'd have to look at my -- at my records.

Q Okay. Looking here, you see this is a matter filed -- this Teva matter was filed in 2014. Is the matter you're working on now the one that was more recent?

A Well, as far as I -- as far as I can recall, the only two matters for UTC I'm working on right now is this one.

Q Right.
A The IPR matter.
Q Okay.
A And then the upcoming Watson case.
Q Okay. Okay. And you see it also lists here yet another matter for Sandoz?
A Oh, I'm sorry, the Sandoz one is the one I believe that settled. The Teva one might still be ongoing. I just don't recall. Nothing's happened in a while, so I don't remember.
Q Okay. Okay. And in addition to these, there's this Watson matter?
A Yes.
Q Are you working on any matters for United Therapeutics involving their -- the oral form of treprostinil?
MS. HASPER: Objection. Privilege.
THE WITNESS: Not that I can think of.
BY MR. POLLACK:
Q Okay. Nothing comes to mind?
A No.
Q Okay. When did you first get hired to work on this matter?
A I don't recall the exact date of -- when I signed my Retainer Agreement. I believe it was

either late -- late last year or early this year. I'm not exactly sure of the timing.

Q And when -- when do you actually start working substantively on the matter?

MS. HASPER: Objection. Privilege.

I instruct the witness not to answer to the extent doing so will reveal privileged communications with counsel.

THE WITNESS: I just don't recall.

BY MR. POLLACK:

Q Well, was it in the Spring? You start working on it in the Spring.

MS. HASPER: Same objection.

THE WITNESS: I don't remember.

BY MR. POLLACK:

Q Don't recall at all?

A No.

Q How about as late as Summer?

MS. HASPER: Same objection.

THE WITNESS: I was certainly working on it by the Summer, but I don't remember how early in the year or if there was anything late in 2015. I just don't remember.

BY MR. POLLACK:

Q Okay. Well, you recall -- you can look

at your Declaration. You filed that on or around July 6th. Do you recall that?

A This (Indicating)?

Q Yes.

A Yes. Okay.

Q Okay. So using that date, about how many months earlier did you start working on the IPR?

MS. HASPER: Objection. Privileged.

THE WITNESS: I just don't remember the timing.

BY MR. POLLACK:

Q Three months before?

MS. HASPER: Objection. Privileged.

THE WITNESS: Counsel, I said, "I don't remember."

BY MR. POLLACK:

Q Okay. But I'm trying to -- you know, could it have been six months before?

MS. HASPER: Objection. Privileged. Asked and answered.

THE WITNESS: I just don't recall the timing. I could easily look at my invoices.

MR. POLLACK: I'd like to request Dr. Williams's invoices in this matter.

MS. HASPER: I hear your request.

BY MR. POLLACK:

Q Okay. Do you think you started working on it substantively in late 2015?

MS. HASPER: Objection. Privileged. Asked and answered.

THE WITNESS: I -- I don't recall.

BY MR. POLLACK:

Q Nothing at all, whether --

A I just don't recall.

Q No idea?

How soon after you were retained did you start working on that?

MS. HASPER: Objection. Privileged. Asked and answered.

I instruct the witness --

MR. POLLACK: None of this is privileged. And your speaking objections are going so far. If this continues, I'm going to ask for a second deposition of him. Understood?

Go ahead.

THE WITNESS: I don't recall.

BY MR. POLLACK:

Q Okay. Other than your hourly rate, is there any other compensation you expect for working on this IPR?

A No. Other than the opportunity to play golf in Southern California tomorrow.

(Laughter)

BY MR. POLLACK:

Q Could you tell me about why you're playing golf in Southern California tomorrow?

A Because there's a great golf course near here that I like.

Q Oh, Okay.

A But United Therapeutics is not paying for it. I am.

Q How many -- how many matters have you worked with the law firm of Wilson Sonsini on?

MS. HASPER: Objection. Privileged.

This also refers -- it sounds like you're asking about case others than this case.

THE WITNESS: So give me your question one more time, please.

BY MR. POLLACK:

Q Sure. How many matters have you worked on with the Wilson Sonsini law firm?

A By "matters," do you mean litigation matters, because -- --

Q Any kind of matter.

A -- I was a cofounder of a biotechnology

company that used Wilson Sonsini's patent counsel.

Q Okay.

A That was microcide pharmaceuticals, and we use the Wilson Sonsini. So I have -- and that was their Palo Alto office.

Q Did they take -- in exchange for that legal work, did they take any kind of equity or any kind of compensation of that type?

A That, I don't remember. It was a long time ago.

Q Okay.

A It was the early '90s. I just don't remember. But I know Wilson Sonsini was patent counsel to Microcide.

Q Okay. How many other matters?

A Um, let me see.

MS. HASPER: Objection. I instruct the witness not to answer to the extent doing so would reveal any privileged information.

THE WITNESS: I have a current spinoff company that I founded and am president of in Fort Collins. And we have patent counsel from Wilson Sonsini who volunteered to work for free.

BY MR. POLLACK:

Q Really?

A Yeah.

Q Why did they do that?

A It's active-retirement-sort-of situation. So retired attorney who actually still is associated with Wilson Sonsini but wants to do something interesting instead of just playing golf, and skiing or something like that.

Q Okay.

A We were very lucky to get a very qualified attorney who's interested in our company and our technology.

Q Okay. All right. Anything else?

A I was retained to work on one other case that never materialized. So there was no -- no expert reports or anything. So I was retained, no invoices that I can recall, and the matter settled before anything happened.

Q Okay. Anything else?

A Not that I can think of.

Q Okay. I mean, other -- there's also a bunch of matters with United Therapeutics. Those were all the Wilson Sonsini firm?

A Yes.

Q Okay. And same set of questions for the Foley & Lardner firm. How often have you worked

with that firm?

A Who?

Q Do you know Mr. Maebius?

A Oh, I just met him for the first time yesterday.

Q Oh, okay. Okay.

Have you met anyone else from Mr. Maebius's firm?

A I don't think so.

Q Okay. And did you meet with Mr. Maebius yesterday to prepare for today's deposition?

A He came to the preparation that I was doing with Counselor Hasper.

Q Okay. Who else was at that preparation?

A One other attorney from UTC. Shaun -- I can't remember his last name.

Q Okay. Anyone else?

A No.

Q And other than yesterday, were there other meetings in -- that you had with counsel in preparation for today's deposition?

A No.

Q About how long did you meet with counsel yesterday?

A About nine hours.

Q And prior to yesterday's meeting with counsel, did you have telephone -- you know, meetings by telephone or other means of communication -- with counsel?

A A few with Counselor Delafield.

Q Okay. Other than Counselor Delafield, anyone else?

A No.

Q What else did you do to prepare for today's deposition?

A I reread lots of documents, patents, prior art, my own Declaration.

Q Did you search for prior art?

A Did I search for prior art?

I don't -- I don't recall.

Q You don't know, one way or the other?

A No, I don't know, one way or the other.

Q Okay. Did you search for any papers, articles, or documents that were relied upon in your Declaration?

A Well, I already had a vast amount of literature from the other cases. So I was already fairly familiar with a massive volume of literature and information relative to treprostinil. So --

Q Did any of the articles that were

attached to your Declaration -- let me rephrase.

Were all of the articles attached to your Declaration provided by counsel?

A I guess I'd need to look at my list of exhibits. I don't remember. I'd have to look --

Q Okay. If you look at paragraph 28 of your Declaration, there's a description of what you considered.

A Well, this isn't a list.

Q Well, that's the only list you provided, sir.

A Okay.

Q Let me ask you: It says there, "I have also reviewed a number of documents in this case, including all documents cited by SteadyMed and UTC, as well as the materials I have cited in the Declaration."

Other than those documents, were there any other documents not described in that sentence that you reviewed?

A No.

Q Okay. You say in the last sentence, "If I am provided additional information or documents in this proceeding, I may offer further opinions regarding the additional information."

Were you provided any additional information or documents?

A No.

Q Okay. And, therefore, you will not be, I assume, offering further opinions regarding any additional information?

A Not at this time.

Q Okay. Was there anything that you asked for from counsel that you wanted to review?

A I actually -- can I go back to a previous question you asked me?

Q Absolutely.

A You asked me if I -- if I did my own -- any literature searching?

Q Yes, yes.

A So I actually did pull up every single one of Dr. Winkler's publications.

Q Okay.

A I did that myself. And I provided all of those papers to counsel and looked through all of his papers.

Q Okay.

A So that was -- so I would consider that a literature search. It was actually a lot of work.

Q Okay. He's written a lot of papers;

right?

A That's all relative. Relative to me, no.

Q Okay.

A I've published maybe three or four times the number of papers of Dr. Winkler.

Q Okay.

A So it was actually, from my point of view, a modest amount. But it was still over a hundred papers, I think it was.

Q Yeah. You know Dr. Winkler; right?

A Yes, I do.

Q In fact, you're together in a network of experts; is that right?

A I wouldn't characterize it that way. Dr. Winkler has a -- an expert witness head-hunting firm called Cymedex, and he's contacted me at least a half a dozen times as a potential candidate to work on cases that came to his company. And none of them materialized in a retained engagement, but we've certainly talked on the phone. He's had my CV. He obviously thinks I'm a very good expert, so he's been trying to find, you know, an engagement for his company that uses me.

Q Okay. The two of you know each other; right?

A Oh, yes.
Q Yeah.
A Yeah. Organic chemistry is a small community.
Q Yeah. Would you say Dr. Winkler's a distinguished organic chemist?
A I think he's a very solid organic chemist.
Q How does "solid" differ from "distinguished"?
A So I would reserve the characterization "distinguished" to be with more accolades, national awards, and things like that, and I don't think he's quite hit that bar.
Q Okay. What about you? Have you hit that bar?
A Very fortunately, yes, I would say so. I got a major -- two major national ACS awards recently. I'm university distinguished professor, Colorado State University, which is a lifetime appointment, and there's only 12 in a campus of more than 1,200 faculty.
Q Okay.
A I don't mean to disparage Dr. Winkler. He's a very nice man, and he's a very good chemist.

Q Other than searching for Dr. Winkler's articles, do you recall any other documents that were provided solely by you for use in this proceeding?

A I provided counsel with some of my own papers.

Q And what did those papers concern? Why did you provide those?

A So I cited those in my Declaration that had to do with how I have used the word "product" in my own publications. And I also -- some of the papers from -- that I found from Dr. Winkler, how he also very, very -- in the very same way uses the word "product" in his own publications.

Q Okay.

A So we use the word the same way.

Q Other than those papers which were attached from you regarding the meaning of the word "product," was there anything else that you provided for use in this proceeding?

A Not that I can think, off the top of my head.

Q When counsel provided you with the data for appendices "A" and "B," who did the calculations based on those appendices?

A Counselor Hasper did.

Q You didn't do the calculations?

A No. But I checked them.

Q Okay. As I understand it, one of your main opinions here is that the product of the '393 patent has an average purity of [redacted] percent, while the product of the Moriarty patent has an average purity of 99.0 percent, approximately. Is that -- is that fair?

A There's more to it than that. Just the overall purity. There's also impurity -- significant impurity profile differences between the product of the two patented processes.

Q How are those different profiles significant?

A In what context?

Q Well, are any of those impurities known to be particularly harmful?

A Well, by "harmful," what do you mean "harmful"? In what context?

Q In any context.

A Well, I mean, in process chemistry, the goal is to try to get as pure an API as possible that is free of any type of extraneous impurities. And so sometimes, depending on the API material,

impurities may have deleterious biological consequences; sometimes they don't. Um --

BY MR. POLLACK:

Q Do any of the -- as far as you know, any of these particular impurities have deleterious biological consequences?

MS. HASPER: Objection. Beyond the scope of his expert Declaration.

THE WITNESS: I'm not a clinician, so I don't know.

BY MR. POLLACK:

Q You don't know?

A I don't know.

Q Okay. So other than the percentage of the impurities, if there's no knowledge about the biological deleterious effects of any of these impurities, what difference does it make which ones they are?

A So I think the stereoisomer impurities would be the ones that a process chemist would be particularly wary of. The dimer impurity and the [redacted] and [redacted] ester impurities are hydrolyzable back to treprostinil to API.

So those are both -- I guess, operationally, you can recover, actually,

treprostinil from those impurities if you needed to. And, you know, in vivo, they can be hydrolyzed in treprostinil. So they're not going to have a deleterious effect, presumably.

Q But no one knows that?

A Not for -- not that I've seen.

MS. HASPER: Same objection.

BY MR. POLLACK:

Q Let me ask you this: If -- let's say the difference in impurities between the '393 patent and the Moriarty prior art patent was [redacted] for the '393 -- same number you're relying on -- and 99.5 for the Moriarty patent, how would that change your -- your opinion?

MS. HASPER: Objection. Foundation.

THE WITNESS: Well, there's a lot more to it than just the -- and you're talking about average --

BY MR. POLLACK:

Q Average. Yeah.

A -- over --

Q Yeah. I'll give you average.

A 50, 100 batches or something like this?

Q Sure.

A Again, it's not just a simple matter of

that one of the significant advantages of the '393 process is the elimination of chromatography, which from a process chemist point of view is exceedingly important because chromatography is expensive, it's time-consuming, it adds cost of goods, there's safety issues, waste issues. And eliminating that is a -- is always a very, very desirable goal.

So the '393 process allows for the elimination of chromatography in the preparation of the final drug substance. So that's very important.

Q I don't see that opinion expressed in your Declaration, though, sir.

A Hmmm?

Q That opinion is not expressed in your Declaration, is it?

A About the elimination of chromatography?

Q Yeah.

A I -- I think it's in there, and it's certainly in the patent. The patent talks about the advantages of the elimination of chromatography.

Q Okay. But in your opinion, you talk about the difference in the impurities; correct?

A Yes. I certainly spend quite a bit of time on the impurity profiles.

Q Right. Okay.

A The differences.

Q If the difference in the quantity of impurities was only [redacted] versus 99.5, how would that affect your opinion?

MS. HASPER: Objection.

THE WITNESS: I'd have to look at actual data and impurity profiles. You're asking me a hypothetical --

BY MR. POLLACK:

Q Yes.

A -- that I'm reticent to just give an opinion on without actually seeing what you're talking about.

Q Well, you gave an opinion on the difference between 99.0 and [redacted]. I'm trying to understand how your opinion changes when it's [redacted] versus 99.5.

A Again, I would need to see data and the way in which the two processes operate that rendered the material of those relative impurities.

Q So the 99.5 is the Moriarty process. Got it? And the [redacted] is the '393 process. How would your opinion change if those were the average results?

MS. HASPER: Objection. Asked and

answered.

THE WITNESS: So I would need to see the distribution of actual impurities, and I would also need to understand the process that resulted in those materials.

BY MR. POLLACK:

Q What would you need to understand about the process?

A Well, like the '393 process I just mentioned eliminates chromatography. So crystallization gets an incredibly pure salt.

Q Let me ask you this: The claims of the '393 patent, you're allowed to do chromatography and practice those claims; right?

A Yes.

Q Okay.

A But the patent enables you to eliminate that step.

Q Okay. But the claims would include that step; right?

A They can --

Q Yeah.

A -- but again, the process -- very important part of the process is that it enables you to eliminate that step.

Q The --

A We've been going almost an hour, and my 63-year-old bladder is not as robust as it used to be. So could we take a quick break?

MR. POLLACK: Absolutely. Absolutely.

THE VIDEOGRAPHER: We are off the record. The time is 10:18 A.M.

(Off the record)

THE VIDEOGRAPHER: We are back on the record. The time is 10:25 A.M.

BY MR. POLLACK:

Q Welcome back, Dr. Williams. I have -- we've already marked as Williams Deposition Exhibit 3 a patent -- U.S. Patent No. 8,497,393, the patent at issue in this proceeding.

(Exhibit 3 marked)

BY MR. POLLACK:

Q And I've marked as Williams Deposition Exhibit 4, U.S. Patent 6,765,117, the Moriarty patent, also known as Exhibit 1003 in the proceeding.

(Exhibit 4 marked)

BY MR. POLLACK:

Q If we could start with Deposition Exhibit 4.

This is the Moriarty patent; correct?

A Yes.

Q Okay. And you've -- you've reviewed that thoroughly for your opinion in this proceeding?

A Yes.

Q If you could turn to column -- columns 9 and 10. Do you see there's a compound toward the bottom -- a compound 14? Do you see that?

A Yes.

Q Okay. And there's a step where it's being turned into compound 15? Do you see that?

A Yes.

Q Okay. I wanted to compare that to the claims in Exhibit 3, the '393 patent. And what I want to know is whether or not that change from 14 to 15 -- is that what the '393 patent refers to as "step (a)"?

A Okay. Which page of the '393 patent?

Q The claims are -- they start at column 17 --

A Oh, I'm sorry.

Q -- and then they go through to column 21.

A (Examining document) Okay. So your question was, is the conversion of 14 to 15 step (a)? Is that your question?

Q That's correct. Yes.
A Yes.
Q Okay. And my next question is: The conversion from 15 to 16 in Exhibit 4, the '117 Moriarty patent, is that what is known as "step (b)" in the claims of the '393 patent?
A Yes.
Q And looking at Exhibit 4, the '117 patent, this is showing a scheme for making compounds of the type claimed in the '393 patent but by the Moriarty method. Is that -- is that fair?
A Yes.
Q Okay. On pages 9 and 10, compound 16, is that the final compound of the process? The Moriarty process.
A Structure 16?
Q Yes.
A So that would be true where R1 is H. M in brackets on both sides is 1. All three Ms are 1. That would be treprostinil.
Q Treprostinil. But the '393 patent has a lot of other compounds to the final products; right?
A Yes.
Q Okay. Would that be a structure of final products -- let me start again.

Would structure 16 in the Moriarty patent, Exhibit -- Deposition Exhibit 4 -- would structure 16 be a structure of final compounds made in, for example, claim 1 of the '393 patent?

A No, because there's an additional step in the '393 step (c).

Q The purification step?

A The contact and the product in step (b) with a base to form a salt, which is then optionally reactive with an acid to form the carboxylic acid 16.

Q Okay. Okay. So if you did step (1) all the way through step (d) -- where step (d) is optional, though, you would get a compound of 16?

A You said, step (1) through D? What do you mean?

Q Sorry. I may have misspoken, then.

If you performed claim 1 through step (d), you would get a compound of structure 16?

MS. HASPER: Objection. Mischaracterizes the document.

THE WITNESS: So --

BY MR. POLLACK:

Q I was just trying to understand your last answer, but --

A Okay. So --

Q -- we can move on.

A Structure 16, where I specify what the variables were, R1 and M, where R1 is H, and M is the number 1, that structure would then be treprostinil acid. And included in the Markush or the more generic formula shown in claim 1, you would get treprostinil after step (d).

Q Okay. So structure 16 would be included in the products would you get in claim 1 after step (d)?

MS. HASPER: Objection. Mischaracterizes the document.

THE WITNESS: So included in the formula 1S -- I think that's what you're referring to; right? In --

BY MR. POLLACK:

Q Yes. 1 --

A So in formula 1 -- 1S where the stereochemistry of the secondary hydroxyl group, there's a wavy line that has to be defined as down -- would be a dashed line. And then these other variables, Y1, W, M1, L1, R7 -- and I believe that -- I'm certain, actually, that the definitions they call out when you plug them in correctly reads

on the structure of treprostinil.

Q Okay. Okay. I didn't want to confuse you. And I may have confused you. I was actually referring to structure 1, which is -- just turn to the very beginning of the claim, claim 1; right? The structure -- structure Ss with the base; right?

A Wait. So you've lost me now.

Q Right.

A We're at column 17.

Q Yes.

A On the '393.

Q Yeah.

A And you're asking me to look at structure 1; right?

Q You can look at anything you want to. You referred to, just now, to structure 1S, and that shows the salt -- the base salt; right?

A Yes.

Q Okay.

A That's the salt.

Q Okay.

A And after D, you get to formula 1, the treprostinil acid.

Q Right.

A Acid.

Q And 16 would be included in formula 1?

MS. HASPER: Objection. Mischaracterizes the document.

BY MR. POLLACK:

Q The '117 patent?

A Well, the molecular structure of 16 reads onto formula 1 where the variables are defined appropriately --

Q Okay.

A -- which the claim calls out.

Q Okay. Looking at the -- looking at columns 9 and 10, which show how to make treprostinil in similar structures, do you see a chromatography step?

A Well, I can see a chromatography step in every step.

Q One could do it optionally?

A Yeah. And the way organic chemistry works is that when you're going through a synthesis of this complexity the first time, every intermediate product is typically isolated by chromatography to get an analytical sample and characterize it to get it as pure as possible for analytical purposes. And then as you go from small scale to large scale, one hopes to eliminate

chromatography steps, and you take Cree material on it or crystallize intermediates if they're crystalline.

Q Okay. But here on pages 9 and -- column 9 and 10, the '117 patent, it doesn't say anything about chromatography?

A Well, a person skilled in the art looking at this would understand that this is just a reaction scheme structure with no details. One would need to look at the actual experimental -- detailed experimental procedures for each step and see if any of these steps require chromatography.

Q Okay. But as Moriarty lays out the reaction here, chromatography may be optional, but he doesn't -- here on pages 9 and 10 -- columns 9 and 10 require chromatography; is that fair?

A Well, that's --

MS. HASPER: Objection. Asked and answered. Mischaracterizes the document.

THE WITNESS: There's not enough information here. Again, I just said this is a reaction scheme. One would need to look at the actual published procedures, the experimental -- the recipe, the detailed how to do each step.

///

BY MR. POLLACK:

Q Let me ask you this: The claims for the '117 patent -- the claims, which is in the back at columns 21 to 24 --

A Okay.

Q -- do the claims of the Moriarty patent require a chromatography step?

A No, I did not see the word "chromatography" in the claims. But I know that the reality of doing synthesis like this, it does entail chromatographic separation.

Q Okay. Could we go back to your Declaration? That's Exhibit 2. I'd like to turn to paragraph 98 of your Declaration. It's on page 33.

In the last two sentences, those appear to be the conclusion sentence of your paragraph. And it says there, "The treprostinil product of the '393 patent has an average purity of [redacted] percent, while the Moriarty product has an average purity of 99.05 percent. Thus, the treprostinil product of the '393 patent has an average purity that is [redacted] percent higher than that of Moriarty's."

Do you see -- did I read that correctly?

A Yes.

Q Why is that difference important to you?

A Well, that's -- that's one important difference. This is the overall average purity. And then inside those numbers are the actual characteristic impurity profiles that come along as a signature of the synthesis. And the '393 patent process allows for elimination or significant reduction of a significant number of those impurities. And that's important.

Q Well, what if the reduction in each of those impurities was only .02 percent? Why is that important?

MS. HASPER: Objection. Foundation.

THE WITNESS: So you're -- I'm trying to understand. This is a hypothetical question?

BY MR. POLLACK:

Q Hypothetical question.

A Okay. And so you're asking me if the difference between -- just re --

Q Just pick one impurity. Let's pick [redacted]. That's one of the impurities?

A Yes.

Q What is [redacted]?

A That's one of the stereoisomers.

Q Which one?

A There's 32 stereoisomers. I don't have

the structure memorized, but I recall that it's a [redacted] stereoisomer. I think --

Q Okay.

A -- but I'd have to check.

Q All right. Anything particularly significant about that stereoisomer?

A Well, it's a carboxylic acid like treprostinil. And so in terms of separating it from the desired molecule, treprostinil, that's a challenging impurity to remove, because it has very similar PKA. They're both carboxylic acids. They have the same molecular skeleton. They're just different in stereochemistry.

Q But biologically, is there any difference between [redacted] and treprostinil?

MS. HASPER: Objection. Beyond the scope.

THE WITNESS: I don't know, but certainly treprostinil is the biologically active principal. And I'm not aware of any biological data on [redacted]. But there may be some, but I'm not a biologist.

BY MR. POLLACK:

Q That's not something you looked into?

A No.

Q You didn't speak to anyone else working on this case who looked into that?
A No.
Q Did you speak to any -- other than the attorneys, did you speak to anyone else in working on this case?
A No.
Q And are you familiar with a Dr. Ruffolo who submitted a Declaration in this case?
A I don't know him.
Q Okay. You never spoke to him?
A No.
Q Did you read his Declaration?
A Briefly and very recently.
Q Was that only in preparation for your deposition?
A No. So that was part of the big -- sort of master file that I saw, and I -- I briefly scanned through his -- his Declaration.
Q Let me ask you: Did you read his Declaration before you signed and completed your Declaration on July 6th?
A No.
Q Okay. So it was only after --
A Only after.

THE REPORTER: Try to pause a little bit, please.

THE WITNESS: I'm sorry.

BY MR. POLLACK:

Q We both have that habit.

THE REPORTER: Yes, do you.

THE WITNESS: I will try and speak much slower. Is that what you want?

THE REPORTER: Like that will happen.

BY MR. POLLACK:

Q Are you originally from New York?

A How did you guess?

Q I'm a New Yorker, also. So we're both fast-talkers.

A Huntington.

Q I'm Brooklyn, lucky you.

A But I hate the Yankees. Red Sox fan.

Q Oh, Mayor Bloomberg was; right?

Let me ask you -- you make this point about the [redacted] versus the 99.05. I'm really trying to understand, how far can the 99.05 number increase before that point is no longer that significant to your opinion?

A You know, I didn't -- I didn't do that analysis or consider -- consider that.

Q Understand. I'm asking you to just consider that now.

A I'd need to look at data -- impurity profiles and data.

Q Let's say the impurity profiles were all the same as we're seeing now, just the number has changed. So if the number is changed, and they change in such a way that we go from 99.05 to 99.5, how would that change your opinion?

MS. HASPER: Objection. Incomplete hypothetical. Beyond the scope.

THE WITNESS: Okay. So you're asking me, again, sort of a make-believe Moriarty series of batches that I've never seen. I haven't seen any such material. And Dr. Winkler didn't produce any Moriarty material batches, or he didn't do his own experiments to show that he would get that. But, again, I -- you know, I -- I'd -- I'd have to look at the data.

BY MR. POLLACK:

Q Let me ask you: What if -- what if the Moriarty batches -- the average value for the Moriarty batches was [redacted] -- the very same as your number there --

MS. HASPER: Same objection.

BY MR. POLLACK:

Q -- how would that change your opinion?

MS. HASPER: Same objection.

BY MR. POLLACK:

Q So no difference in the purity level.

MS. HASPER: Same objection.

THE WITNESS: Okay. So, again, I think your question's about overall impurity -- overall purity, [redacted] percent, which is total related substances, which is known, plus unknown impurities -- so it's just not a simple matter of overall purity. You also have to look at the impurity profiles, because that is the significant difference in the product between the '393 and the Moriarty process.

BY MR. POLLACK:

Q So you're saying even if the overall purity is the same, the distribution of those impurities -- which we don't know anything about in regard to their biological property -- but that really matters? That's your opinion?

A That's my understanding, that in product-by-process patents, the -- the new product by the new process has to have structural, functional differences. And impurity profiles are

structural differences.

Q Are there any functional differences, though, between a material -- a new material which has a impurity level -- or purity level of [redacted] and another material which has a purity level of, say, [redacted]?

MS. HASPER: Objection. Beyond the scope. Incomplete hypothetical.

THE WITNESS: I don't know. And, again, the -- you know, the -- really, the significant thing about the '393 process is the elimination of the chromatography. The way I view it, that's a functional difference. It reduces cost of goods, and solvent safety. So it's -- it's not a insignificant matter.

BY MR. POLLACK:

Q Let me ask you something: In the -- if you go to the '393 patent -- pick up Exhibit 3, again -- there's a claim 16. Do you see that claim?

A Yes.

Q It's in column 20.

A Yes.

Q Now, do you have any patents?

A Yes.

Q Okay. You understand how patent claims

work; correct?

A Generally.

Q Okay.

A I'm not a patent expert, but --

Q You know -- do you know what an independent and a dependent claim is?

A Yes.

Q Okay. What's your understanding of what a dependent claim is?

MS. HASPER: Objection to this, that it seeks a legal conclusion.

THE WITNESS: Well, generally, a dependent claim is -- follows an independent claim and typically narrows down the scope of the independent claim to a more -- some type of parameter.

BY MR. POLLACK:

Q It adds something the independent claim doesn't require; is that fair?

A Again, I'm not a lawyer. I don't know if that's ubiquitously true, but that sounds reasonable.

Q Is claim 16 -- is that a dependent claim?

A Yes. It's dependent from claim 9.

Q Okay. What is claim 16 adding?

MS. HASPER: Same objection.

THE WITNESS: So claim 16 says, "The product is claim" --

THE REPORTER: Speak up, please.

BY MR. POLLACK:

Q If you could read more slowly. He's got to type it all.

A "The product of claim 9 wherein the process does not include purifying the compound of formula VI produced in step (a), which is the nitrile."

Q What does that mean?

A So this is -- this claim is saying that you do -- you perform step (a) and then carry the nitrile through to the next step without doing a purification step, like a chromatography.

Q Okay. In your understanding, though, does that mean that claim 9 could be carried through with the chromatography?

A It could, but importantly, this patent and the process that's being used eliminates that.

Q Right. But claim 9 doesn't; right? Claim 9, you can do the chromatography.

A You could if you wanted to. It seems like a nonsensical thing to do when we know it works

really great without.

Q But claim 9 does include with the chromatography?

A It's agnostic as to chromatography; right? Doesn't say, one way or the other.

Q Sure. But claim 16 is very specific. That's done without the chromatography; right?

A Yes.

Q So that means claim 9 includes both with or without the chromatography; is that fair?

A Again, I'm not -- I'm not a patent lawyer, so I'm not sure that that is necessarily the way that's read.

Q What's your understanding?

A Yeah. It's -- I mean, it's silent on that issue. So --

Q And based on that, what do you conclude about whether chromatography is included in claim 9?

MS. HASPER: Objection to the extent it seeks legal conclusion.

THE WITNESS: So, you know, I think a person skilled in the art looking at this, again, would be informed by the specification and column 15, a real-world 5-kilogram example, says no column for that step. Whereas in the prior art process,

there's a purification column chromatography step.
So --
BY MR. POLLACK:
Q Let's take a look at claim 1.
Now, you'll agree with me that claim 1 also would include the chromatography; is that fair?
A I don't know if I would read in the requirement for chromatography. It doesn't say anything about it. It's also silent on that issue.
Q But it couldn't -- since it's silent and there's a claim that says, "Don't use chromatography," we could probably conclude that it does include chromatography, just on basic logic?
A Yeah. I suppose it could, but we -- again, the patent talks in several places about the advantage of elimination of the chromatography step.
Q Let me ask you: About how many compounds do you think there are in claim 1?
A Oh, lots. I don't know the -- I don't know the exact number.
Q Hundreds of thousands? At least?
A Very likely. But I'm not sure.
Q Okay. So for all of those hundreds of thousands of compounds, is there any information in the '393 patent about whether those hundreds of

thousands of compounds will be pure without chromatography?

A Well, the specification only deals with treprostinil itself so that's the -- I guess the important enabling example that's in the specification of the patent. But the patent teaches that if you applied this salt formation, crystallization, that -- in this structural family, one would have a reasonable expectation that you'd also be able to crystallize and purify just as was done for treprostinil.

Q Okay. You don't see any data in this patent, though, about the purity of any of these other thousands of compounds, do you?

A No. There's no data for the other compounds, but there is really great data for treprostinil.

Q Now, do you understand that claim 9 also includes treprostinil diethanolamine salt as a product?

A Yes.

Q Okay. And, in fact, if I don't carry out step (d), the optional step, and I use diethanolamine as my salt, I'm going to get treprostinil diethanolamine salts; correct?

A Yes.

Q If I don't carry out step (d), does the claim include chromatography?

A So your question is, if I do not carry out --

Q Let me rephrase my question.

If I don't carry out step (d), would it be necessary to use chromatography?

A If I -- so your question is, if you do not carry out step (d) --

Q Right.

A -- would it be necessary to use chromatography?

Q Correct.

A So I would say that you're forming a salt. And it's -- salts are perhaps the most obnoxious compounds to purify by chromatography. And it's very, very rare to, in fact, purify salts by chromatography. So the whole reason a person skilled in the art would form a salt in the first place is by trying to avoid chromatography, 'cause you can crystallize salt. Salts -- and particularly salts like this that are water soluble, that's the whole purpose of forming the salt.

Q Okay. However, if I carry out steps (a)

through (c), the claim 9 allows me to do chromatography if I so wish; correct?

A Chromatography at which step? A? I don't know where you're talking about.

Q At any of the steps.

A Well, could you, but the whole purpose of this invention is to eliminate the chromatography step.

Q Okay. By the way, you don't see in the claims where it says the invention is carried out without the chromatography step, other than the one claim, claim 16?

A No. But the spec also prominently talks about the elimination of chromatography.

Q Okay.

A And a process chemist really would zero in on that important advantage.

Q What can you tell me about the impurity profile of the thousands of compounds in claim 1?

MS. HASPER: Objection. Beyond the scope.

THE WITNESS: I could tell you about the impurity profile of one of the thousands of compounds in claim 1, treprostinil, because I have data on that.

BY MR. POLLACK:

Q Does any person of ordinary skill in the art or any person of any skill in the art know anything about the purity [sic] profile of the thousands of compounds in claim 1, other than treprostinil?

MS. HASPER: Objection. Beyond the scope.

THE WITNESS: Well, because all the structures that are called out under claim 1 have the same molecular framework as treprostinil, one would expect that the impurity profiles would very likely be similar in that you'd have to stereoisomeric impurities, and dimers, and esters, and the triol and so on.

It's very similar types of species would very likely be present, if you change the variables, like added a carbon atom to the side chain, or what have you.

BY MR. POLLACK:

Q But some of the species would be different; correct?

A What do you mean by "different"?

Q Some of the impurities would be ones not seen in treprostinil; correct?

MS. HASPER: Objection. Foundation.

THE WITNESS: Well, they would necessarily be different because you've already changed the structure. So -- so if you change even by one carbon atom, now longer -- you can't get the same exact impurities from treprostinil because you've already changed the molecular structure to a different molecule.

BY MR. POLLACK:

Q So all of those molecules would have different impurity profiles from treprostinil; is that fair?

MS. HASPER: Objection.

THE WITNESS: So -- I think -- I'm trying to give a good answer here, that you would have similar -- I guess you call them "homologous series of impurities," stereoisomeric impurities, that would almost certainly be similar. So they'd be the -- like [redacted] could be [redacted] prime for another compound, but it would be a similar stereoisomeric impurity, because they're made by the same kind of chemical steps.

BY MR. POLLACK:

Q You referred to [redacted]. Is that a name used in the literature?

A No. I think that's a UTC code number for -- for that.

Q It's a secret code number; right?

A I don't know if it's secret or not. I know that in Moriarty's GOC paper, he used UT-15 or something, which is the United Therapeutics code number. So that one wasn't secret. So I don't know if they're secret or not.

Q Right. UT-15 is the published name for treprostinil; correct?

A Yes.

Q Okay. But [redacted], you've never seen that in the literature; correct?

A Not that I can recall.

Q Okay. None of the -- have you seen in the literature where any of these impurities are characterized?

A I don't recall.

Q What about in the '393 patent? Do you see any mention in Exhibit 3 of what impurities are present in any of the compounds in the '393 patent?

A No. I don't believe they're specifically called out.

MR. POLLACK: To make things a little easier for us, I'm going to mark as separate

exhibits your appendices to your Declaration. I'm going to mark Appendix A as Williams Deposition Exhibit 5.

(Exhibit 5 marked)

MR. POLLACK: And I'll mark Appendix B as Williams Deposition Exhibit 6.

(Exhibit 6 marked)

BY MR. POLLACK:

Q If you could just verify for me that Deposition Exhibits 5 and 6 are true and accurate copies of your appendices A and B, respectively?

A (Examining documents).

(Brief pause)

Okay. Appendix A is identical. And Appendix B is identical to the one submitted but does not have the one correction that we made at the beginning of the deposition.

Q Could you do me a favor? Could you take Exhibit 6 and make the correction on there by pen?

A Okay. I don't have a pen. Can I borrow yours?

And I think it was -- oh. I think it's this one. 11 -- wait. I think it's this one. Okay. So I've just crossed out that [redacted].

Q Okay. I'd like to turn to Exhibit 5.

That's Appendix A.

A Okay.

Q Okay. And I want to look at your Data Source column. Do you see you have a column that says, "Data Source"?

A Yes.

Q Okay. This is a column that counsel created for you -- right? -- and then you checked this?

A Yes.

Q Okay. So the first -- well, let's count 'em -- one, two, three, four, five, six, seven, eight, nine, ten -- the first ten entries are all solely from an exhibit called "Exhibit 2052." Do you see that?

A Yes.

Q Okay. And then after that, all of the entries are included in an exhibit called "2036" that you attached to your Declaration. Do you recall that?

A Well, no. I think it's 2053, page 19. And then Exhibit 2036. So there's two --

Q But those were identical; right?

A Okay.

Q The 2053 and 2036, did you check that,

that they were identical?

A I don't recall right now.

Q Okay. Let me say, I also misspoke as well.

If you look on page 44, there are two samples, UT-15-011001 and UT-15-020101, about four and five rows up from the bottom? Do you see where I'm reading?

A Hmm-hmm.

Q Okay. Those two were listed as -- wait. Did I -- I think I did -- as just being from 2053; is that correct?

A That's what it says, yeah.

Q Okay. But all of the other ones are in both 2053 and 2036; is that fair?

A Yes.

MR. POLLACK: Okay. If we can mark as Deposition Exhibit 7 what was formerly called "Exhibit 2036."

(Exhibit 7 marked)

BY MR. POLLACK:

Q Did you review in detail all of the Certificates of Analysis in Exhibit 2036?

A I laid my eyes on every page, and I cross-checked some of them in detail. I didn't look

at every number on every batch record.

Q Okay. You didn't compare each one to make sure it was correct on your table?

A I said I spot-checked them, and they all seemed fine.

Q Okay. By spot-checking, though, you didn't do every single one, you --

A I didn't do every single one. I just randomly picked and found no errors.

Q Okay. Did you calculate what the average purity was of the samples in Exhibit 2036?

A Well, counsel did the calculation. And that's the summary at the bottom.

Q That's all of the samples; right? That's 2036 and 2052 and 2053; correct?

A Yes.

Q Okay. Did you calculate just what it would sum up to in 2036?

A So, in other words, eliminating the 2052, the development batches is what you're asking?

Q Yes.

A No.

Q Why -- do you have an understanding why 2052 was added -- why the samples from 2052 were added to the samples from 2036?

A Yes, because we also added development batches for the '393 process. And we -- and I thought that the fairest comparison was to look at the development batches that were used in UTC's development of the Moriarty process and the development batches from the '393 as well. I thought that was the fairest comparison.

Q That was your idea or counsel's idea?

A We discussed it. I -- I don't remember if who -- who came up with the first idea, but we agreed this was a reasonable thing to do.

Q Okay. Guess what? Ms. Choksi did the calculation for us, so I'm going to provide that to you.

So I'm going to mark as Williams Deposition Exhibit 8 a chart of all of the purities and total related impurities from the Appendix A, Deposition Exhibit 5.

(Exhibit 8 marked)

BY MR. POLLACK:

Q And I'm also going to mark -- just so you can see how we created this -- I'm going to mark as Deposition Exhibit 9 a chart containing all samples, including the ones from 2052.

(Exhibit 9 marked)

BY MR. POLLACK:

Q What we've done here is, we've just marked in highlighting which ones are from 2052. And so what we've done here is, we've used all of the samples that you did, and we also used the HPLC analysis. Do you know what I mean by that?

A Why don't you explain.

Q Yeah. If you look at, for example, 2036, Deposition Exhibit 7 -- let's go to the third page of the document, the one that says, "Page 3 of 3." And on the bottom, it says -- well, it says, "Page 3" at the bottom center. Do you see where I'm looking?

A Hmm-hmm.

Q Okay. Now, do you see there's a -- it says, "Test," and there's a number, "Assay HPLC." Do you see that?

A Yes.

Q And do you see it says, "98.4"?

A Yes.

Q Okay. So what we've done on this chart is, we've put in all of those values as well. Do you see where it says, "Assay Purity"?

A Okay. Which --

Q You can pick either 8 or 9. The only

difference is, we highlighted the ones from 2052 on 9.

A Okay.

Q Okay. So do you understand what I mean by the HPLC assay?

A So this one corresponds to --

Q Let's see. This one here that we're looking at is lot UT15-99H001. Do you see that on Exhibit 2036?

A Yes. So that's entry 11; right?

Q That's correct.

A Okay.

Q Okay. Is that number recorded fairly?

A It appears to be.

Q Okay. And what we've done at the end is, we've taken -- we'll let you go through, electronically, these spreadsheets -- we've taken all the data you used, and we did an average, as did you, and we got 99.0 by both methods, whether you use the HPLC assay, or what I'm calling "implied purity" where you subtract the total related substances.

A Wait. What --

Q On the very last page of either document.

A Oh.

Q Do you see that?
A Yes.
Q Okay. That's the same number you got; correct? Appendix A.
A Yes. Basically the same.
Q Okay. Now what I'm going to mark as Deposition Exhibit 10 is the same document, except with the first ten samples, the ones that came from Exhibit 2052 removed.
(Exhibit 10 marked)
BY MR. POLLACK:
Q If you would verify for me that Exhibit 10 is the same as 8 or 9 except with the highlighted exhibit -- lots removed.
A Okay. That appears to be the case.
Q Okay. And then what we did is, we -- we did the same thing you did. We took the average, but we did it two ways. We did it with the HPLC assay --
A Hmm-hmm.
Q -- so taking each of those numbers from 2036. You understand what I'm referring to?
A Yes.
Q And we also did it the way you did it, subtracting the total related substances from 100.

A Yes.

Q Okay. If you look on page 5, there's the result of our average. Do you see that?

A Yes.

Q And do you see that the HPLC assay -- the average was [redacted]?

A I see that.

Q Okay. Instead of 99.0. Do you see that?

A Hmm-hmm.

Q And doing it your way, the way you prefer, the result was 99.5. Do you see that?

A What do you mean --

Q Subtracting the total related substances from 100, the average was 99.5.

A Okay.

Q Do you see that?

A I'm not sure what this implied impurity is. I don't -- I don't -- what's implied impurity?

Q So that's the language I'm using. If you want to call it "purity," that's fine. It is the 100 minus the total related substances.

A Okay.

Q How did you calculate the purity of each sample?

A Okay. So the total related substances is

the -- the sum of the known impurities plus the unknown impurities.

Q Is it?

A That's my understanding.

Q Well, let's take -- let's take, for example -- let's go to the top of page 44; all right? So there's all of the impurities, and that sum is .4. Do you see that in the right?

A Yes.

Q Okay. Now, do you get .4 when you add all those numbers up?

A I have to do the calculation. Can I use my phone --

Q Absolutely.

A -- here? (Using phone).

MS. HASPER: Counsel, while Dr. Williams does the math, may I ask a question to clarify something, perhaps to avoid an extraneous objection?

You introduced Exhibit 10 and said that the highlighted rows had been removed. I noticed highlighting on two rows. Is that merely a printing error, or is that --

MR. POLLACK: Those are just simply -- I'll point that out to him. Those are simply the highlighted two rows from Exhibit 2053. Different

exhibit.

MS. HASPER: They're not also in 2036?

MR. POLLACK: -36. Correct.

MS. HASPER: All right. Thank you.

THE WITNESS: So that line -- we're talking about the top line on the top of page 44?

BY MR. POLLACK:

Q Correct.

A Let me check this again. First time I got .55.

Q That's what I get. But please feel free to do it again.

A Okay. So it's -- I get .55, the addition of those.

Q Yes.

A Known -- and those are all known impurities, I believe.

Q Right. And then the total related substances is .4?

A So I believe the reason that the -- that the numbers don't add up is that the -- the -- where the amount of impurity was less than .05, a number of .05 was put. So it's -- it's estimated conservatively high. But the actual total, which comes from, I believe, these batch documents, is

what's in this column.4.

Q Right. But, in fact, what's in that column is not the sum of the known impurities listed in your prior columns; correct?

A Again, I just explained what -- is there any confusion to what I just said?

Q Yes.

A Hmmm?

Q Yes, there is. The -- you said earlier that the sum of total related substances was the sum of each of the known impurities; correct?

A And unknown impurities.

Q And unknown impurities.

A Yes.

Q Okay.

(Mr. Snader entered the deposition at 11:24 A.M.)

BY MR. POLLACK:

Q And here we see that summing those up, they don't equal the same number; correct?

A So maybe the place to go is the source document here. This is 20 -- so the source document at page 36 shows total related substances as .4 percent.

Q I see that.

A So that's -- that's -- where these numbers came from. They weren't from the linear addition here (Indicating).

Q Right.

A Yeah.

Q Okay. We're both agreed on that; right?

A Yeah.

Q Okay. And, actually, your way of putting in what the total related substances are for compounds that are not detected or ones which are less than .05, that's sort of arbitrary, isn't it?

A No. Arbitrary?

Q Well, you could have done instead of .05, you could have made it zero for example; right?

A Yeah. So I was conservative and estimated on the high side. So less than .05 could be .000001; okay?

Q And, actually, putting it on the high side, that makes the purity lower, doesn't it? It makes it seem like it's less pure than it actually is, doesn't it?

A Yes. And I did the same thing for the '393 process batches. So they -- so the same -- to be fair, that same conservative method was used to compare both.

Q Okay. Here's what I want to know: So when -- the batches 2036 all done by Magellan, even the ones from 2053, are included to make an average, the average value is either [redacted] percent pure for HPLC analysis or a total of .5 percent impurities by total related substances. What I want to know is, who, then, decided to go out and find ten other pieces of data to try to drag that number lower to 99?

A I sort of don't like the way you just characterized that, 'cause it sounds like this was done deliberately to make the Moriarty process look worse than it is. That's not really fair.

Q Really?

A So what we did was, we looked at development batches from the '393, and we also looked at development batches from Moriarty. And, you know, either way -- I mean, if you put them in or drop them out, the impurity profiles between the two processes are different; okay? So you can't just look at the overall total related substances purity; you have to look at the actual distribution of the impurities. Because the '393 process unexpectedly -- okay? -- because of the crystallization of the salt, removes stereoisomeric

impurities -- two of them completely -- and leaving only the very small amount of the enantiomer, which is [redacted].

Q Okay.

A So just doing these -- these overall impurity comparisons and percentages, I don't think is -- is valid.

Q But you actually submitted this to the Patent and Trademark Office and told them that that was one of the significant differences between Moriarty and the '393 process, that the purity was 99.0 versus [redacted], isn't that true?

A I didn't submit anything to the Patent and Trademark Office.

Q You understand this is your Declaration that you signed.

A Yes.

Q That was submitted to the Patent and Trademark Office. You understand that?

A I thought you were talking about the -- the batch records.

Q Well, those are submitted as well.

A Yeah.

Q You understand that --

///

(Indiscernible crosstalk)

THE WITNESS: I'm sorry. I don't understand where you're --

BY MR. POLLACK:

Q You understand your Declaration?

A Yeah.

Q That it was used as evidence at the Patent and Trademark Office in this proceeding. You understand that; right?

A Yes.

Q Okay. And in that Declaration, you represented to the Patent and Trademark Office that the difference between Moriarty -- one of the differences between Moriarty and the '393 patent was that Moriarty produced an average of only 99.0, while the '393 patent produced an average of [redacted]. You recall saying that; right?

A Yes.

Q Okay. And now what we're seeing is, if we take only the data, the two data sets, created by Magellan, one for the '393 and one for the Moriarty process, in fact, the numbers are [redacted] and [redacted].

A But, again, you're talking about the overall purity. You're not talking about impurity profile.

Q Sure. I understand. I'm not disagreeing with you on that. I'm just saying, you told the Patent Office that these two differed. And one of the ways they differed was one was 99.0 and the other was [redacted]. Now we see that both are [redacted]. How does that jive with acceptable scientific conduct?

A Well, the -- again, the '393 batches were produced without chromatography. So you could repurify and purify anything you want --

Q Of course.

A -- by chromatography to [redacted] percent if you wanted to --

Q Right.

A -- okay? -- but, you know, in large-scale manufacturing, that's not practical. It's not economical. It's not safe. It's not environmentally appropriate; okay? So -- but, again, I think the -- what I was focused on was looking at -- the -- the -- the structural differences between the impurities between the two processes is different. And that is not reflected in the overall purity, no matter however you want to eliminate batches, and cherry-pick batches or however you want to do that.

Q You'd agree with me somebody here

cherry-picked some batches, didn't they?

A No, I don't think so.

Q You don't think somebody added 10 batches to take the number down from [redacted] to 99.0?

A No. We -- my understanding is, we asked for -- these were all the batches we could find records for. And these were the same -- I think these are the same 56 batches that were used by Dr. Aristoff in the -- the Sandoz litigation.

THE VIDEOGRAPHER: Sorry to interrupt, we have five minutes of video left.

MR. POLLACK: Why don't we take a short break.

THE WITNESS: Sure.

MR. POLLACK: Whatever you want.

THE WITNESS: Yeah. 15 minutes? I need a bathroom break, anyway.

THE VIDEOGRAPHER: This ends Media No. 1 in the deposition of Robert M. Williams, Ph.D. The time is 11:32 A.M.

(Off the record)

THE VIDEOGRAPHER: This begins Media No. 2 in the deposition of Robert M. Williams, Ph.D. We are back on the record. The time is 11:53 A.M.

MR. SNADER: And this is Shaun Snader,

United Therapeutics Corporation, Washington, D.C., counsel for patent owner.

BY MR. POLLACK:

Q Welcome back, Dr. Williams.

A Hmm-hmm.

Q During the break, did you speak to counsel about this case, the deposition, or any -- any matter having to do with treprostinil?

A No. We talked about golf, hotels, and restaurants.

Q Okay. If you can go back to your Exhibit 2 -- that's your Declaration.

A Okay.

Q If you turn to paragraph 98, you see there, it says, "The treprostinil product of the '393 patent has an average purity of [redacted] percent, while the Moriarty product has an average purity of 99.05." Do you see that statement?

A I see that statement.

Q And then you say, "Thus, the treprostinil product of the '393 patent has an average purity that is [redacted] percent higher than that of Moriarty's." Do you see that statement?

A Yes, I do.

Q And you understand that those statements

were given to the Patent and Trademark Office -- right? -- in this proceeding?

A Yes.

Q Are those statements not important to your opinion?

A They're important. But if we also read above, I say, "It is clear the treprostinil product produced by the '393 patent process has a markedly different impurity profile than the treprostinil product of the Moriarty prior-art process and as such is physically distinct from the prior-art product."

So my opinion in total is important in paragraph 98, not just that one little aspect.

Q Okay. Although, I know that one little aspect is the -- what's called a "conclusory sentence"?

A I don't know if I would label that as the final conclusion.

Q Even though it follows the word, "Thus"? Begins with the word, "Thus"?

A Well, I sort of begin the paragraph, ". . . from these data." That's also -- I'm making a conclusion about the impurity profile. So I'm actually making two different important conclusions

in this paragraph. So the overall purity, and I think very significantly, the impurity profile, which is different. That's the structural difference.

Q But it seems like you made the impurity profile point in paragraph 97, isn't that right?

A Let me just read that.

Well, I talked about the differences in impurity -- I talked about salient features of the impurity profile for the '393 patent process in paragraph 97.

Q Now, you said that the statement about the [redacted] versus the 99.5 was also important. Why was it important to your opinion?

A Well, it shows that in addition -- in addition to the differences in impurity profile, the structural differences is also an overall purity difference.

Q And why didn't you think that was important?

A Well, because you're looking at various aspects of the product. The overall purity, as well as the detailed components of the impurities.

Q Yeah. So why was the overall purity important for distinguishing -- if it was -- for

distinguishing the '393 product from the Moriarty product?

A Well, the Moriarty product, again, involves a very time-consuming, expensive chromatography. And if that step weren't conducted, you'd get an even worse product. So you have to perform that step, which is very, very deleterious in so many ways, as we discussed earlier. And so you still want to have a high overall purity. But it's also important to recognize that there is a difference in the individual impurities between the two processes. And the data shows that so incredibly clearly.

Q Let me ask you -- you have a paragraph 103, if you go a couple pages later. And you see there, again, you talk about the difference in purity between Moriarty or Phares and the '393 patent. Do you see that?

A So this is with regard to the treprostinil diethanolamine salt?

Q Yes. The first sentence is, but further down, you say, "Regardless of the purity identified in Moriarty, a further analysis of all batches made by the Moriarty process up to the time of the reference itself, reveals an average purity of

99.05 percent, while the average purity of the '393 patent batches is [redacted]." Do you see that sentence?

A I see that.

Q Okay. And that's referring to the treprostinil free acid; correct?

A Um, so the -- the [redacted] percent, this is the 121 batches in the table that I have. And that includes some batches of just salt, but most of them are acid.

Q So you actually looked at both salt and acid in your analysis?

A Yes. And the salt is amazing. The salt is just stunningly pure.

Q Salt, in fact, is somehow purer than the free acid, isn't it?

A That's correct.

Q Even though the last acidification step hasn't been performed?

A On the salt.

MS. HASPER: Objection.

BY MR. POLLACK:

Q On the salt.

A Sorry.

Q Yes.

MS. HASPER: Objection. Mischaracterizes

the document.

THE WITNESS: Yeah. So at the salt stage, the step (d) has not been performed.

BY MR. POLLACK:

Q Right.

Why did you think it was important in this one paragraph -- 103 that's about the salt to point out the differences in the purity of 99.05 versus [redacted] in the prior art versus the patent?

A So you've already asked me this question and I've already given you have the answer. So you're asking me the same question over and over.

Q So what's the answer?

MS. HASPER: Objection. Asked and answered.

THE WITNESS: I told you that the overall purity is important, but I also looked at the individual components of the impurities. And they're different.

BY MR. POLLACK:

Q Okay. Since it is an important point that the overall purity is important, isn't it a problem for your opinion if data points were cherry-picked to try to bring the actual purity down from [redacted] to 99.0?

MS. HASPER: Objection. Mischaracterizes his testimony and the document.

THE WITNESS: No. So I -- I -- I don't like your question, because it's -- it's accusatory and mischaracterizes the analysis that I did that I thought was very fair. I included development batches for both the Moriarty process, and I also included development batches for the '393 process. So the development batches for the '393 are also poorer than the later commercial batches. And so by the same token, those numbers bring down the average purity of the '393 process. So I thought I was being very fair.

BY MR. POLLACK:

Q Oh, really? To bring it down when it's [redacted], even with those batches?

What did it bring it down from?

A Well, I didn't -- I didn't do the calculation to eliminate those. I included both. But if you did eliminate the development batches, it would certainly improve the overall purity of the '393 batches.

MR. POLLACK: I'm going to mark as Williams Deposition Exhibit 11 a document known as "Exhibit 2052" in the case, the UT-15 injection

drug-substance chemistry manufacturing and controls submission for an NDA No. 21-272.

(Exhibit 11 marked)

MS. HASPER: And just to let you know, my realtime has not been working since we came back from the break.

THE REPORTER: Off the record.

THE VIDEOGRAPHER: Off the record. The time is 12:03 P.M.

(Off the record)

THE VIDEOGRAPHER: We are back on the record. The time is 12:05 P.M.

BY MR. POLLACK:

Q All right, Dr. Williams, I've put in front of you the Exhibit 2052, which is the source of the ten additional data points you added to your analysis. Is this 2052 the document that you relied upon?

A (Examining document) Yes.

Q Okay. Now, if you would turn to what's called at the bottom of the document in the center, "Page 25"?

A Okay.

Q Are these the lots that you added to the analysis of the average purity of the Moriarty

process?

MS. HASPER: Objection. Mischaracterizes his testimony and the documents.

THE WITNESS: So I don't think I would agree with the way you phrased your question -- that I added these. I was given all of the data together.

BY MR. POLLACK:

Q By counsel?

A Yes.

Q Hmm-hmm.

A So there was no importing separately these batches to try and obfuscate the data.

Q Right. 'Cause counsel had already calculated the average value so that you just checked that calculation; correct?

A Yes. I checked the calculation, and we did the same thing for the '393 batches. We added -- the development batches were there to do a fair comparison.

Q When you did the check of the calculation, you didn't say: Hey, why are we adding that other exhibit? Let me see how these numbers come out if I just use the set that was presented as existent 2036.

MS. HASPER: Objection.

BY MR. POLLACK:

Q You didn't do that; right?

MS. HASPER: Objection. Mischaracterizes the document and the testimony.

THE WITNESS: So I didn't do a separate calculation. I certainly looked at the charts, the exhibits. And either way you slice it, if you want to include the development batches, or you want to exclude them, my opinion does not change; okay? Because with the -- with the -- the Moriarty process, you're starting with an inferior process.

So the development batches were not as nice as the development batches that you started with the '393, 'cause it's a better, distinct, process; okay? But even if you wanted to eliminate both of them either way, the impurity profiles are different. And the '393, no matter how you slice it, gives you a superior product, a different product.

BY MR. POLLACK:

Q Okay. But one part of your opinion -- and you definitely stated this a number of places in your Declaration -- was that the Moriarty process gave you 99.0 while the '393 process gave you [redacted];

right? That was one opinion that you stated?

A That's one aspect of my opinion.

Q It's one opinion that you stated?

A One aspect of my opinion.

Q Looking now and seeing that certain of the data points were added from these older development batches and that brought down the purity from [redacted] to 99.0, do you want to now remove just that one aspect of your opinion?

MS. HASPER: Objection. Mischaracterizes his testimony and the documents.

THE WITNESS: No, because, you know, the development batches are compared fairly to development batches between two processes; okay? So, again, we're looking at an average of many, many batches over time. And so what I did not do is, I did not cherry-pick a single batch from the '393 and compared it to a single batch of the Moriarty process. So I thought it was much more significant to look at the overall picture. And I think my report very fairly and accurately provides the overall picture with the exception of that one duplicate entry, which doesn't change the number very much.

///

BY MR. POLLACK:

Q Let's think about it this way: So 46 batches show an average value for the purity of [redacted]. And 10 batches bring that number down to 99.0.

Is it not true that, fairly, one should take the 46 rather than throwing in 10 outliers? Isn't that how science is done?

MS. HASPER: Objection. Mischaracterizes the documents.

THE WITNESS: No. I don't -- I don't agree.

BY MR. POLLACK:

Q Let's take a look at this page 25 that I asked you to look at in Exhibit 11. The dates of manufacture of these lots -- do you see them? There's a line that says, "Date of Manufacture."

A Okay.

Q The first two lots are dated in 19 -- they're both in 1986. My eyes are a little weak, but I think one's July 1986, and the other one is August 1986? Do you see that?

A Okay.

Q And then the next batches are all dated in -- their date of manufacture is either 1997 or

1998; correct?

A Yes.

MR. POLLACK: I'm going to mark as Williams Deposition Exhibit 12 a document known in this case as "Exhibit 1004," which is the Moriarty Journal of Organic Chemistry Article.

(Exhibit 12 marked)

BY MR. POLLACK:

Q And can you verify for me that Exhibit 12 is the Moriarty article that's prior art that we've been referring to in this deposition?

A Yes.

Q What's the date on the Moriarty article?

A 2004.

Q Okay. What date was it received by the journal?

A June 5th, 2003.

Q Okay. How many years after was this article published compared to when these lots were manufactured in -- sorry. Let me ask my question again.

How many years are there between the lots described in Exhibit 2052 and the Moriarty article?

MS. HASPER: Objection. Vague. Relevance.

THE WITNESS: So the earliest -- the earliest date is July of '86 to 2003. Is that -- is that the year-spread that you're asking me about?

BY MR. POLLACK:

Q Year-spread. Right. Okay.

Many of the lots are from 1998 and 1999?

A So there's the date of manufacture and date of testing.

Q I'm asking the date of manufacture.

A Yes.

Q Isn't that what's relevant here, date of manufacture?

A Relevant -- relevant to what?

Q Relevant to -- I'll withdraw that question.

Okay. So, for example, one of the lots you included -- and you're free to look at your chart -- is lot No. LRX97J01, made in October 1997. Do you see that?

A I see that.

Q Okay. That is seven years before the Moriarty article was published?

A Yes.

Q Okay. Let me ask you: There's two lots you didn't include in your analysis. They're the

two that are made by -- you see there's also a line that says "Manufacturer"; correct? On the top?

A Yes.

Q Okay. And -- by the way, none of these lots that are on page 25 were manufactured by United Therapeutics; correct?

A So I believe that Steroids and SynQuest are contract manufacturers that were making the drug for United Therapeutics.

Q Right. It wasn't made by United Therapeutics itself?

A I'm not really privy to the detailed relationship between United Therapeutics and its suppliers. But if a supplier is making the drug for UTC, I believe that UTC would be the -- you know, ultimately be the manufacturer.

Q Okay. Do you know who makes treprostinil now for United Therapeutics?

A I know that there's suppliers that -- different suppliers that make different -- do different parts of the synthesis, but I'm actually not sure of the whole picture of how -- who's contributing what pieces, what companies.

Q Okay. Now, you understand the first two lots were made by Upjohn back in the '80s; correct?

A Yes.

Q Okay. And you'll agree with me that it can't be the case that way back in the '80s, Upjohn was using the Moriarty process; correct?

A No. It's not possible.

Q Okay. Now, do you notice that there's a footnote -- it's a little hard to read the typeface is small -- it's footnote 4. Do you see that footnote 4?

A Yes.

Q Can you read footnote 4 for us into the record?

A "These lots were manufactured by Pharmacia and Upjohn using a slightly different route of synthesis."

Q In reading that, is it your understanding that what they mean by that is all the other lots here were made in a way that's only slightly different from the way Upjohn made treprostinil?

MS. HASPER: Objection. Calls for speculation.

THE WITNESS: Yeah. I don't know.

BY MR. POLLACK:

Q What's your understanding of what that says?

A What? Footnote 4?

Q Yeah. Footnote 4.

A So --

MS. HASPER: Objection. Relevance.

THE WITNESS: That these -- these two 1986 lots were made by Pharmacia and Upjohn using a different -- a slightly different route of synthesis.

BY MR. POLLACK:

Q Okay.

A That's what it says.

Q Sure. Okay. And is it your understanding that the other lots, then, were not made exactly the way Upjohn made them but a fairly similar process was used?

MS. HASPER: Objection.

THE WITNESS: You know, I don't know the details.

BY MR. POLLACK:

Q You don't know the details of how all these lots were made?

A No. I haven't seen the detailed batch records of what went into those lots.

Q Okay. So you don't know whether or not these lots were made by the '393 process, the

Moriarty process, the older Aristoff process; is that right?

MS. HASPER: Objection. Mischaracterizes testimony and the documents.

THE WITNESS: Um, you know, I -- I'd have to investigate further. I don't know.

BY MR. POLLACK:

Q Right. You -- you don't know if any of these are from the Moriarty process?

A Um --

Q At least not the ones on page 25?

A So the Moriarty paper came out in 2003.

Q 2004 it came out.

A Well, yes. Yeah. The paper was published in 2004, but the technology had been put together as easily as early as 2003.

Q Okay.

A So I don't think it's possible that any of these could have been made by Moriarty process just based on the dates.

Q And yet these are the ten additional samples that you added to your analysis that brought the value down from [redacted] to 99.0; correct?

MS. HASPER: Objection. The testimony -- mischaracterizes testimony and the documents.

THE WITNESS: So I -- I guess I don't know.

BY MR. POLLACK:

Q Well, do you want to compare the lot numbers here to the lot numbers on -- if you take the exhibit that has the yellow highlighting -- that's our Exhibit 9 -- this one here (Indicating). Or you can compare it to your appendix. Either one.

A (Examining documents) So it begins with 9 -- 97J01.

Q Right. That's the third -- third column?

A Yes.

Q And that's on your -- that is on one of the ones you analyzed on your -- on your chart?

A Yes.

Q Okay. And LRX99801, you analyzed that one, too?

A Yes. That's the second entry. And then BO-1. And then they go to -- the next one is UT, but it's -- oh, that's -- yeah. So they're just in sequential order.

Q Okay. And each of these lots were just -- we were just reviewing, you're not sure what method was used to make any of these. You haven't seen the batch sheets?

A I haven't seen the batch sheets.

Q Does that -- looking at this data now, are you prepared to change your opinion about whether or not the Moriarty method, in fact, gives a [redacted] percent purity just like the '393 patent?

A No.

And you keep asking me the same question 30 different ways, and I already told you: If you wanted to throw out all the development batches from both processes and both analyses, fine --

Q Okay.

A -- that doesn't change the differences in impurity profile. And it also is not going to change the overall fact that the '393 process gives an overall higher purity than Moriarty.

So, you know, fine. Scratch out those 10 entries if you want to. It doesn't change my opinion.

Q Okay. You understand if we scratch out those 10 entries, we're going to get [redacted] for impurity --

A We're still never going to change the impurity profile.

Q I understand. I'm just talking about the one -- you said twice, at least -- I think much more

than twice -- in your opinion that the purity profile between Moriarty and the '39 -- I'm sorry -- that the purity level between the '393 patent and Moriarty were different -- let me start my question again.

You've said -- now seeing, at least twice -- and I think there were some more times -- in your Declaration that the -- an important point is that the purity level between Moriarty and the '393 patent is different, and it's different by 99.0 versus [redacted]. I just want to focus on that one opinion, nothing else.

A Okay.

Q Do you want to retract that opinion now, having seen this information at this deposition?

MS. HASPER: Objection. Asked and answered.

THE WITNESS: No.

BY MR. POLLACK:

Q No? Why not?

A Because, you know, even if the -- you eliminate these development batches, the overall purity for both processes goes up, but Moriarty's never going to catch the '393 purity.

Q Okay.

A So no matter how you want to add or eliminate data, the -- the important -- the really important thing that these spreadsheets show of these -- from these batch records is that the Moriarty process does not provide, on average, a purer material than the '393, and the impurity profiles are distinctly different. And it was unexpected that you would be able to eliminate, for example, two to three stereoisomeric impurities entirely.

Q Okay. You said it doesn't provide -- the Moriarty process doesn't provide on average a higher purity than the '393. But let me ask you another direction. Does the '393 process significantly provide a higher purity than the Moriarty process?

MS. HASPER: Objection. Asked and answered.

THE WITNESS: Yes, on average, that is definitely the case. That's what the data shows.

BY MR. POLLACK:

Q Did you include standard deviation -- you know what standard deviation is; right?

A Yes.

Q And I notice you didn't calculate any standard deviations for your average, isn't that

true?

A That is true. I did not. That's not the sort of thing anyone would do.

Q Isn't that the standard scientific method?

A It may be for some sciences, but organic chemistry and even process chemistry, you know, it's very rarely, in my experience, done.

And, you know, if you wanted to put instead deviations, I didn't calculate that. You know, I don't think it's going to change the picture. The impurity profiles are different, and the '393 process produces a superior product.

Q I'm going to -- and we'll provide this spreadsheet electronically to counsel -- but for you for now --

MS. HASPER: Is there a way I can see the spreadsheet?

MR. POLLACK: You can go look over his shoulder. That's perfectly fine.

BY MR. POLLACK:

Q We have calculated the averages and the standard deviations for all of the samples, excluding 2052. And I've given you the spreadsheet there.

You know how to use Excel; right?

A Yes.

Q Okay. So I've given you the Excel spreadsheet there. You're free to play with it and verify we did everything correctly. You'll see the standard deviations are recorded there; right?

A I see them.

Q Okay. And those were calculated using the standard Excel method. And you see that for the HPLC assay, I believe it's .6 is the standard deviation? Do you see that?

A I see that.

Q And .24, the total impurities.

A I see that.

Q Okay. Let's start with the .6.

If the standard deviation -- if it's [redacted], plus or minus .6, is there any value that the '393 patent purity could have that would be statistically different from [redacted], plus or minus .6?

MS. HASPER: Objection. Beyond the scope.

THE WITNESS: So, Counsel, I know that your focus is on this overall average purity, but my opinion is not on this average overall purity in isolation; it's the overall purity in combination

with the impurity profile. And I can't separate those two, because they're inseparable from the reality of how this drug is made and what the characteristics of the product are.

BY MR. POLLACK:

Q Okay. Yeah. I'm not trying to attack the whole of your opinion. You can keep the impurity profile part. I'm trying to understand the other prong -- the total impurities level. Is that -- you've said it's important to your opinion. So I'm now exploring why it's important to your opinion. And now seeing that that value really doesn't change much, how does removing that one leg change your opinion?

A It doesn't.

Q Okay. And should we -- since your opinion is fine without that one leg -- without the purity comparison, should we just eliminate the purity comparison from your opinion and just rely on the difference in impurity profile?

MS. HASPER: Objection. Mischaracterizes his testimony.

THE WITNESS: No.

BY MR. POLLACK:

Q Why not?

A Because, even if you eliminate these development batches, the -- the overall purity of the '393 product that is being manufactured on a commercial scale is still better than what UTC was getting with the Moriarty process. And significantly, we've eliminated chromatography, and the impurity profiles themselves are distinct.

Q You understand that the two purity-level values hardly change. You understand that -- right? -- between the Moriarty process and the '393 process?

A I don't agree.

Q Why not?

A Well, again, if -- even if we're going to chop off the tops of both of those Exhibit A and B charts, the overall -- the overall purities are still different.

Q Let me ask you something: Did you notice that the HPLC assay analysis of the -- all of the samples, excluding those ten that were made by method -- you're not even sure what method was used -- just including those, did you notice that the value was [redacted] and that that's the same value reported in the Moriarty prior art? Did you notice that?

A For the single batch made in the Moriarty paper?

Q Yes. Yes.

A Yeah. So that's not in my opinion representative.

Q Well, having now seen 56 batches that average [redacted], doesn't that show that, in fact, the [redacted] number is quite representative is? Isn't that so?

MS. HASPER: Objection. Objection. Mischaracterizes the documents.

THE WITNESS: Ask me your question one more time, please?

BY MR. POLLACK:

Q Sure. Having seen 56 samples now which came to an average of [redacted] for the purity level -- and comparing that to the [redacted] number that Moriarty reported, doesn't that show that Moriarty's value, in fact, was representative?

MS. HASPER: Objection. Same objection.

THE WITNESS: No. So 56 batches give 99.1 percent.

BY MR. POLLACK:

Q I'm sorry. 46 batches -- I apologize.

Having seen now that 46 batches give a

value of [redacted], isn't that consistent with the [redacted] value reported by Moriarty in the prior art?

A So those -- they're the same number.

MS. HASPER: Objection.

THE WITNESS: Sorry.

MS. HASPER: Objection. Mischaracterizes the document.

THE WITNESS: So, you know, I'm not really sure -- so you're referring to in here --

BY MR. POLLACK:

Q Yes.

A -- [redacted] percent of, apparently, recrystallized treprostinil in the JOC paper; right?

Q Yes.

A That's the number you're referring to; right?

Q Yes. That's the number that Moriarty reports; correct?

A Right.

Q That is on, for the record, if we look at -- let's call it page 13 of the exhibit -- page 1902 of the original article. The right-hand column, and it's just above where it says, "Acknowledgement"; right?

A Yes.

Q Is that where we're looking?

And there, it refers to a purity of [redacted] percent, and that is for the compound treprostinil, which was also known as UT-15; correct?

A Yes.

Q Okay. And that number, [redacted], is consistent with the [redacted] we see for the average of 46 samples; correct?

MS. HASPER: Objection. Mischaracterizes the document.

THE WITNESS: So -- okay. So, you know, even if those numbers are the same, if you eliminate development batches from the '393, that number goes up. And I -- again, the data in the '393 chart is very conservative because less than [redacted] was put in as [redacted] -- as [redacted]. So it's actually much purer.

BY MR. POLLACK:

Q What's much purer?

A The '393 product.

Q Well, the same is true for the Moriarty product.

A No. So you've -- you might max out if you do your own type of cherry-picking of eliminating these early development batches, but the

'393 data, again -- all of those -- all of those percentages are going to be improved if you eliminate those -- whatever it was -- number of development batches that were also -- that I also included for the '393.

Q Oh, what if I represent to you that actually that's not the case that they won't be improved?

A Okay. But, again, you can look at the impurity profiles, and there is -- [redacted] appears in only one batch and [redacted] only appears in one batch and the rest of them have zero. You cannot say the same for any -- any -- for the Moriarty on average. So the -- there's only two batches: [redacted] and [redacted]. Those are the only two batches where the stereoisomeric impurities appear. And then if you scan down the column 0000000 -- all the way down.

So that crystallization step completely obliterates those two stereoisomeric impurities. And a person skilled in the art couldn't have predicted that. And the triol, t-r-i-o-l, also was completely obliterated.

Q And did you look at -- if you look at Appendix A -- and Appendix A, that's the Moriarty

method; right?

A I'll give you your computer back.

MS. HASPER: Could I just ask counsel -- since you've been showing him an electronic document, can we get that in electronic form immediately?

MR. POLLACK: We will provide it after the --

MS. HASPER: Perhaps before lunch?

No, I'd like it before the deposition is over, please.

MR. POLLACK: I don't know if we'll be able to do that.

MS. HASPER: Well, I'm going to insist on it.

MR. POLLACK: I heard what you said.

BY MR. POLLACK:

Q Sir, take a look at Appendix A.

A Okay.

Q And if you look at [redacted] starting below the ten lots -- the first ten lots on your chart, you notice they're all zeros.

A Okay. Which entry?

Q Let's start on page 43.

A Okay.

Q Okay. And let's start below where -- below the 2052s that you used; okay? So look at Data Source and get to the line that's below the 2052s.

A Okay.

Q Okay? Do you see a bunch of zeros for [redacted]?

A Yes. And I see [redacted] for [redacted].

Q Right. But those are [redacted] you put in because it said less than [redacted]; right? That's why they're all [redacted]?

A Some of them may be actually [redacted]. [redacted] or --

Q Or less?

A Or less.

Q Okay.

A But they're detectable.

Q Okay. But, similarly, though, even under Moriarty [redacted], barely detectable, in most cases?

A Okay. But the profiles are still different, on average.

Q I'm going to mark --

A So I'm -- I need a nature break, and maybe this is a good time for lunch, perhaps?

MR. POLLACK: It's up to you.

THE WITNESS: Yeah. And it's gotten warmer in here.

MS. HASPER: Yes, it has.

THE WITNESS: Maybe we can adjust the thermostat again?

MS. HASPER: Why don't we go ahead and go off the record, and maybe we can adjust the environmentals.

THE VIDEOGRAPHER: We are off the record. The time is 12:38 P.M.

(Luncheon recess taken at 12:38 P.M.)

* * *

A F T E R N O O N S E S S I O N

Commenced at 1:34 P.M.

THE VIDEOGRAPHER: We are back on the record. The time is 1:34 P.M.

EXAMINATION (Resumed)

BY MR. POLLACK:

Q Welcome back from lunch, Dr. Williams.

A Thank you.

Q Over lunch, did you have a chance to review the spreadsheet of the 46 data points in Excel form?

A No.

Q Okay. You didn't look at that at all?

A No. I ate lunch.

Q Okay. That was it. Okay.

I'm going to mark as -- let me just do one more, sort of, housekeeping thing. I think what we'll do is, we'll mark the spreadsheet in electronic form which we've now sent to United Therapeutics' counsel, and we've now e-mailed it to the court reporter as well.

MR. POLLACK: We'll mark that as Williams Deposition Exhibit 13 so it exists on the record.

(Exhibit 13 marked)

MR. POLLACK: Now, I'm going to mark as Williams Deposition Exhibit 14 a document currently called on the record "Exhibit 2006."

(Exhibit 14 marked)

BY MR. POLLACK:

Q Exhibit 2006, also known as "Williams Deposition Exhibit 14," appears to be a letter from United Therapeutics to the FDA, dated January 2nd, 2009.

Dr. Williams; is that correct? Is that what this is?

MS. HASPER: Objection. Beyond the scope.

THE WITNESS: Wait. What are you asking me?

BY MR. POLLACK:

Q I'm asking you if Williams Deposition Exhibit 14 is a letter from United Therapeutics to the FDA, dated January 2nd, 2009.

A That's the date, and it's on United Therapeutics letterhead, and it's addressed to the Division of Cardiovascular and Renal Products -- FDA, yes.

Q Is my answer -- is the answer "yes"?

A Yes.

Q Okay. And this is one of the documents you relied upon in forming your opinion?

A I looked at a lot of documents. I believe I've seen this before.

Q If you turn to page 3 of the document -- no, let me step back.

Let me ask you: Do you know what this letter is about?

A I have to refresh my memory. I don't remember --

Q Okay.

A -- just by looking at the face page.

Q Let me ask you -- if you don't remember, you can just tell me.

If we go to page 3, you see there's a paragraph that begins, "In conclusion . . ."

A I'd like to read the letter --

Q Absolutely.

A -- to just familiarize myself with the content if you don't mind.

Q I don't mind.

A (Examining document) Okay. I've had a chance to review the document.

Q Okay. Was this a documented you used in

forming your opinion?

A Yes. I -- I remember looking to this. This is the change in the spec for the API.

Q Okay. So if we turn to page 3, Exhibit 14, you see there's a paragraph that says, "In conclusion . . .," just above the bolding? Do you see that?

A Yes.

Q And the conclusion says, "In conclusion, the lots of treprostinil API" -- that means "active pharmaceutical ingredient"; is that right?

A Yes.

Q "In conclusion, the lots of treprostinil active pharmaceutical ingredient produced by the new process in Silver Spring are of the same high-quality impurity as the commercial lots of API produced by the existing process at the Chicago facility."

Did I read that correctly?

A That's what it says.

Q Okay. Do you have any reason to disagree with that statement?

A No.

Q Okay. And when it says here, "the new process in Silver Spring," that's a process that now

includes the '393 process, is that your understanding?

A That's correct. Yes.

Q And the -- in that process, the quality and purity are being compared to the existing process at the Chicago facility. Do you see that?

A Yes.

Q Okay. And the existing processes at the Chicago facility, that was done using the Moriarty process; is that correct?

A I believe that's correct. That's what I've been told.

Q Okay. Go down just a couple paragraphs. There's a paragraph that begins with the word, "During." Do you see that?

A Yes.

Q And it says, "During the initial analytical method validation for the treprostinil assay, the results indicated that there is about 2 percent variability in the assay." Did I read that correctly?

A That's what it says.

Q Okay. Do you have any reason to disagree with that statement?

A No.

Q Okay. When referring to the treprostinil assay, that's the HPLC assay of how pure the treprostinil is?

A I don't know for certain. It doesn't say, "HPLC assay."

Q What's your understanding?

A That sounds reasonable, but I can't be certain.

Q Well, did you review this document in forming your opinion; correct?

A Yeah.

Q Okay. And when you read that, did you wonder what it was referring to?

A Not in that context, no.

Q Maybe I can help you. Let's go to page 6. And do you see there, it says, "Assay HPLC"? Do you see that row?

A Yes.

Q Okay. And do you see it refers to certain numbers --

A Yes.

Q -- in the next two rows -- columns? Yes?

A Yes.

Q Okay. Looking at page 6 and then looking back at page 3, reading those sections, can you now

conclude for me that the 2 percent variability in the assay refers to the HPLC assay?

A Yeah. I believe that's what they're talking about.

Q And so what this sentence on page 3 says is that the HPLC assay analysis for treprostinil has a plus or minus 2 percent variability; is that fair?

A So variability -- but -- I don't think that's accuracy -- variability.

Q Am I correct that what that means is that the HPLC assay analysis can only be controlled such that the outcome falls somewhere between plus or minus 2 percent of the desired amount?

A Yeah, I'm not sure about that. I mean, HPLC is an extremely sensitive technique, and you can detect levels of impurities at much, much lower than 2 percent.

Q Let me ask you: Are you an expert at analytical chemistry?

A I have a lot of expertise in analytical chemistry, yes.

Q What's your expertise in analytical chemistry?

A I have extensive experience with NMR -- nuclear magnetic resonance spectroscopy -- infrared

spectroscopy, HPLC, thin-layer chromatography, mass spectrometry, ultraviolet spectroscopy, X ray crystallography.

Q Okay. And you've used all those techniques?

A Yes.

Q Okay. But your research area is not analytical chemistry; is that fair?

A I wouldn't say it that way. My research area relies, on a daily basis, on analytical technologies and instrumentation.

Q Sure.

A So I can't -- my laboratory can't function without daily routine access to all the techniques I just enumerated.

Q Sure. But your specialty is not the design, development, construction of analytical instruments; is that fair?

A I have not designed analytical instruments. But for my entire career as a chemist, I have been using extensively all these analytical instruments, including with my own hands.

Q Let me ask you: Did you take analytical chemistry in graduate school?

A I actually didn't take any courses in

graduate school.

Q Okay. Even for the master's?

A Hmmm?

Q Even for the master's portion of your graduate school?

A So my master's degree, the way it works at MIT when you get a Ph.D. degree, you automatically get a master's degree. It wasn't like a separate thesis. I sat in on a lot of courses, but I didn't actually take any courses in graduate school.

Q Did you sit in on analytical chemistry?

A No.

Q Did you take analytical chemistry in college?

A Yes.

And I also taught graduate level spectroscopy courses when I started my independent career at Colorado State University. So I have also taught mass spec and NMR and HPLC to graduate students.

Q Okay. That course didn't include HPLC?

A The course I taught was mostly centered on spectroscopy. We did talk a little bit about HPLC, but I also teach my own graduate students

about HPLC.

Q Okay. And as part of your teaching of HPLC, do you discuss error analysis of the HPLC instrument?

A Yes, because sometimes we have to report very accurate data based on HPLC. So, yes, HPLC is much, much more sensitive than NMR.

Q I think one of the things you say in your Declaration, though is that -- let me ask you this: Is there in your view any preference for using HPLC assay analysis where you measure the peak of the substance of interest versus measuring the total related impurities?

A I didn't quite follow your question.

Q Yeah. In determining the purity of a substance, which technique is better? Using the HPLC peak of the substance of interest or using a sum of the peaks of the impurities?

A I really am sorry. I'm not following your question. It doesn't make sense to me.

Q Let me break it down, then.

The HPLC assay analysis described here -- that's an analysis in which the area under the curve for -- in this case, treprostinil, but for any other substance as well -- is compared to a reference

standard; is that fair?

A Yes.

Q Okay. And that's one technique of determining the purity of a substance; right?

A Yes.

Q Now, something else that you did in your Declaration, I believe, is you looked at a table of total related substances; correct?

A Yes.

Q And you subtracted those from 100 to get the purity analysis; right?

A Yes.

Q Okay. Which of those two techniques is preferable?

A Well, I think you need to do both. In fact, in my own research, I don't rely exclusively on HPLC. I always ask my students to corroborate through NMR as well, because some compounds are invisible by HPLC if they don't have a chromophore, if you're using a UV detector.

Q Right.

A So it's -- but for industrial process validation, you know, the assumption is that the analytical group who has established the protocols and methods is already thoroughly vetted and

confirmed and verified that the analytical technique that's going to be use San Diego reliable and sensitive within a given set of parameters for a given type of compound and impurities.

Q Right. But there could be some compounds -- some impurities in there that don't have a chromophore and wouldn't be seen in a particular HPLC analysis?

A That's possible, yes.

Q Okay. And you said you would do both. Is there any preference for one or the other, or they're both equal?

A Well, HPLC is typically faster, particularly if you have it set up in a -- you know, a robotic auto-sampler type of thing.

So NMR takes more time. You gotta prepare the samples, you have to get the spectrometer, and you have to look at everything in the spectrum. But in my own research, I insist that my students use every technique available to figure out what's in that product mixed or purified product.

Q Now, let me also ask you, though -- so I can do HPLC and just look at the peak for the substance of interest, say, treprostinil or

something else.

A Hmm-hmm.

Q Or I could look at the total related substances. And I think you said it's probably best to do both. Is there a preference, though, for total related substances or for the looking at the larger peak?

MS. HASPER: Objection. Asked and answered.

THE WITNESS: Okay. I'm not sure about this preference issue. I mean, it's important to understand -- like for batches -- you know, commercial batches of treprostinil with what the individual impurities are and how pure the main component is, and so there's impurities that are known, we know exactly what -- like the enantiomer where that --

BY MR. POLLACK:

Q Right.

A -- peak is and that type of thing, as well as unidentified impurities -- these other things that are there that you're not sure exactly what that is.

Q Okay.

A May be a mixture of things.

Q Okay. Now, in your Declaration -- and you may have misunderstood -- I thought there was some criticism of the use of reference standards. Did I misinterpret?

A You want to point me to where you think I've got a criticism?

Q Let me just ask you first: Do you have any criticism of reference standards?

A In general or specifically with respect to this matter?

Q Both.

A Well, it's important -- I mean, the reference standard itself has to be a highly purified material, and there's no such thing anywhere on this planet of something that's 100.0 percent pure.

So no matter how many times you recrystallize or do chromatography over and over again, you can approach 100 percent, but you can never get there.

So the goal is to try and have as pure a reference standard as possible, and then you measure against that, if you can ascertain what the purity of the reference standard is.

Q And that's an initial that's inherent in

all HPLC measurements; is that right?

A Yes.

Q And that's true, even if you're measuring the total related substances, you need to use a reference standard, isn't that correct?

A Well, I think -- the reference standard is the same reference standard, and they're just measuring area under the curves of other peaks. And that's added to the known ones.

Q Okay. They're not using reference standards for each impurity?

A I don't believe so, no. I mean, they know what each -- they use reference standards because they've identified for example where [redacted] -- what the retention time is that so they know where that comes.

Q Right.

A For the known ones.

Q They would use a reference standard for the known ones?

A Well, they know where that is. I don't know -- I do not believe that they separately calibrate the small peak for, like, [redacted] against the reference standard for [redacted]. It's a single reference standard for treprostinil.

Q Okay.

A Otherwise, it would just take too long.

Counselor, I apologize. The coffee here after lunch just came --

MR. POLLACK: No problem.

THE VIDEOGRAPHER: Going off the record, the time is 2:00 P.M.

(Off the record)

THE VIDEOGRAPHER: We are back on the record. The time is 2:03 P.M.

MS. HASPER: Mr. Pollack, just before you begin, I'd like to interject a posthumous objection to the introduction of the electronic document that was introduced as Exhibit 13. It's just irregular to introduce an electronic copy of something, rather than a printed copy.

MR. POLLACK: I believe we did provide a printed copy as well, which was --

MS. HASPER: Are you saying that what you introduced as Exhibit 13 was identical to what you printed out and provided as a printed copy?

MR. POLLACK: Yes. The information is identical.

MS. HASPER: Could you show me which of the other exhibits is the same as --

MR. POLLACK: We can do that off the record at some other time.

MS. HASPER: Okay. Until I have that, then I will let the objection stand. I may retract it later.

BY MR. POLLACK:

Q If you could go to -- back to an exhibit we had looked at before -- it's Exhibit 11. It's this giant book here that is also known as "Exhibit 2052."

If you could turn to -- there's a lot of numbers, I know, on these pages, but there's a P.43 at the bottom of the page.

A Okay.

Q Okay. Do you see on that page it has an explanation of total related substance equals some of all reported peaks except UT-15? Do you see that?

A Yes.

Q Okay. And what I was trying to understand here is, when it says, "reported peaks," those are peaks of the known and identified substances; is that right?

A My understanding was that total related substances includes known plus unknown.

Q Where did you get your understanding?

A I don't remember what document. I know that we -- I discussed this several times with -- with counsel, and we referred to documents. I can't remember off the top of my head which one confirmed that, but that was my understanding, anyway.

Q And that was your understanding from counsel?

A Yes.

Q Okay. Looking here, can you tell whether -- from this definition whether unidentified substances are included?

A So reported peaks is not, to me, synonymous with known species. So there could be a peak that's reported, but -- it has a certain height and area under the curve. And --

Q Okay.

A So I'm not really sure what you're asking me.

Q Yeah. I was asking you whether this indicated that it was only those peaks which were identified with a code number or other kind of name.

A No. So I believe at the -- the batch records themselves show separately the known impurities, and then unknown impurities, and then

total related substances. They're broken out separately.

Q Right. Right. Right. Earlier, though, remember we went through those numbers, and we weren't able to sum them to the number which was the total related substances? Do you recall that?

A Yes.

Q Okay.

A But I -- I explained that that's because they come from two different types of -- and that the .05 was less than .05 and the actual total related substances gives the net amount of other things besides UT-15.

Q Okay. Do you know how the less than .05s were handled?

A Well, the less than .05s were given a value in my chart of .05. So rounded up, essentially.

Q Right. I'm asking you how -- United Therapeutics, or whoever else, was compiling that data, how did they handle it?

A Well, they're reported just like that. It's less than .05. So it was detectable, but then the sum of those end up -- my understanding is, the sum of those all end up in the total related

substances value. So known plus unknown.

Q But if one's not detected or .05, how is that handled by UT or whoever was reporting the values?

MS. HASPER: Objection. Asked and answered.

THE WITNESS: You're -- I think I just explained exactly the answer to your question.

BY MR. POLLACK:

Q What was the answer? Maybe I didn't follow it.

MS. HASPER: Same objection.

THE WITNESS: I said, so if you look in the batch records themselves, they split out the individual known impurities and the unknown impurities; okay? And so the ones that are -- record a value of less than .05 percent in the summary that I gave were given a value of .05.

So that's erring on the high side -- okay? -- 'cause it could be .00001 percent, but the total related substances value, then, would have built in, you know, say one peak was .0003 -- okay? -- so it wouldn't be added in as .05. It comes just through the standard protocols that they have for -- for measuring this.

BY MR. POLLACK:

Q So you're saying even though they don't report a value, they have some value for these very, very small peaks in your view?

A Yeah. Of course, there's a value. They're visible in the chromatogram. And the computer, you know, measures the area under the curve, and you get a -- you know, this total related substances number.

Q Okay. And that -- even for peaks that are so small that there's a signal to noise problem? Those are included?

A I can't speak to signal to noise. I don't -- you know -- you know, I'm sure this has all been vetted in their validation procedures for that.

Q Okay. I mean, did you speak to anyone or --

A No.

Q -- look into --

A No.

Q Let me ask my question again: Did you speak to anyone or look into how United Therapeutics determined those values?

A No.

Q Okay.

A No. I took these -- this data -- I mean, these are all things that are produced to the FDA, and they have to be validated, and confirmed and -- so I didn't question the veracity or authenticity, accuracy, because these are, you know, important documents.

Q Let me ask you -- if you go back to Exhibit 2006, also known now as "Williams Deposition Exhibit 14" --

A Okay.

Q -- if you could turn to page 6. You see it says, "Assay HPLC"; right?

A Yes.

Q Okay. And in the right-hand column, they've set a standard for that; right? It says, "not less than [redacted] percent and not more than [redacted] percent"?

A Yes.

Q Okay. So if I have a batch and I run an HPLC assay on the batch, and the purity comes out as [redacted] percent -- by the way, that's done by -- let me make sure I understand.

These assay HPLCs, those are done by taking the area under the curve for the treprostinil and comparing that to the standard?

A I believe so, yes.

Q Okay. So if I have -- if I make a batch of treprostinil, and I measure its HPLC assay, and I get [redacted] percent, that batch passes the FDA specification; right?

A Yes.

Q I can sell that batch to the public?

A That's my understanding, yes.

Q Okay. In fact, as far as the FDA is concerned, any batch that has a purity better than [redacted] percent -- so long as it meets these other specifications -- that batch can be sold to the public; right?

MS. HASPER: Objection. Beyond the scope.

THE WITNESS: Well, I'm not an FDA expert, but my understanding is, it has to be between [redacted] percent and [redacted] percent.

BY MR. POLLACK:

Q Fair enough.

But if it's between those numbers, then it can be sold to the public?

MS. HASPER: Same objection.

THE WITNESS: As far as I know, but I'm not an FDA expert.

BY MR. POLLACK:

Q You've done a lot of ANDA litigation? Do you know what I mean by, "ANDA litigation"?

A Yes. "Abbreviated New Drug Application." The Hatch-Waxman Act.

Q And that's where a generic company tries to sell a copy of something very similar?

A Yes.

Q And the ANDA litigation you've been involved in, including some for treprostinil; right?

A Yes.

Q The ANDA filer, they report a purity as well -- right? -- for their API?

A I believe so.

MS. HASPER: Objection. Beyond the scope.

THE WITNESS: I believe so. That's what I've seen previously.

BY MR. POLLACK:

Q Okay. Have you seen that in your other litigations?

A I have.

Q Yeah. Okay.

And they need to meet the same purity specifications for their active pharmaceutical

ingredient that the brand name does; right?

MS. HASPER: Same objection.

BY MR. POLLACK:

Q Is that your understanding?

A So, again, I'm not an FDA expert, but I know that the generic also has to meet some target specification. I don't know if it's the same as the branded drug or not in every case.

Q Okay. In your experience, when you've done your ANDA cases, have you seen that the generic company meets the same purity specification as the brand name?

MS. HASPER: Same objection.

THE WITNESS: You know, I just don't -- I just don't recall, because in the ANDA cases that I have worked on, this is all prelaunch, end of product, so they have a proposed product and a proposed spec. So I don't know what happens at -- you know, after, when they're actually selling, if they, you know, start to sell their product.

BY MR. POLLACK:

Q Although, they've created a -- a batch which they provide to the FDA. You've seen that; right?

A Yes.

Q Okay. And they've made purity measurements of their batches in order to try to gain approval of their ANDA?

MS. HASPER: Same objection.

THE WITNESS: I think that's generally how it works, yeah.

BY MR. POLLACK:

Q Okay. And they've done an HPLC assay purity analysis of their active pharmaceutical ingredient. You've seen that; right?

MS. HASPER: Objection. Scope. Relevance.

THE WITNESS: Perhaps, if that's the assay that's used for that particular drug. I would assume they would be doing the same thing. But I suppose there could be other types of assays.

BY MR. POLLACK:

Q Okay. What about for treprostinil? Did companies like Sandoz, or Watson or Teva, did they submit an HPLC assay analysis for their active pharmaceutical ingredient?

MS. HASPER: Objection. Scope. Relevance.

I advise the witness not to answer if it would reveal privileged or confidential information.

THE WITNESS: I actually don't recall.
BY MR. POLLACK:
Q Okay. Let me ask you this: When a generic company is measuring the purity of their active pharmaceutical ingredient by HPLC assay analysis, they, too, need to use a reference standard; right?
MS. HASPER: Same objection.
THE WITNESS: I presume they also have to do that as well to validate their Assay Purity to the FDA.
BY MR. POLLACK:
Q And when they're doing that with their reference standard, they don't have access to the brand-name company's reference standard; right? They have to create their own?
MS. HASPER: Same objection.
THE WITNESS: I actually don't know.
BY MR. POLLACK:
Q Okay. No idea?
A I have no idea.
Q Okay.
MR. POLLACK: I'm going to mark as Williams Deposition Exhibit 15, an article by Terence L. Threlfall titled, "Analysis of Organic

Polymorphs," a review that appeared in "The Analyst," October 1995.

(Exhibit 15 marked)

BY MR. POLLACK:

Q Let me ask you: Are you familiar with Terry Threlfall?

A I don't recall. I think I've seen this before.

Q Okay.

A Are you going to tell me that I cited it in my Declaration?

Q No, I'm not. I'll tell you that you have not.

A I actually don't recognize this.

Q Okay. Do you know Dr. Threlfall?

A No.

Q Okay. I want to turn to -- if you look on the first page, 2435 and going over to 2436, there's a discussion there about how to name polymorphs.

What are polymorphs, if you could --

A Actually, polymorphs are different crystalline forms of solid compounds. They adopt different crystal-lattice configurations.

Q Do you consider yourself an expert on

crystal forms of organic molecules?

A No.

Q But you're -- you've heard of this phenomenon before?

A Yes, yes.

Q So, Dr. Threlfall discusses here, there's no clear choice on how to designate polymorphs. And one of the suggestions he has is numbering, based on order of discovery. Were you familiar with that system for naming polymorphs?

MS. HASPER: Objection. Beyond the scope.

THE WITNESS: No.

BY MR. POLLACK:

Q No? Okay.

You've never seen polymorphs named "Form 1," "Form 2," "Form 3"?

A I have.

Q Are you aware that's usually based on the order of discovery?

A I have no idea.

MS. HASPER: Same objection.

BY MR. POLLACK:

Q Okay. Now, further down, he has some other suggestions. If we go on to 2436, top of the

page, he says -- the second sentence, "The addition of a melting or upper transition point to a Roman numeral is possibly the best compromise, although care must be taken to distinguish the melting point of the polymorph and that of the transformed product."

Do you see where I'm reading?

A Yes.

Q Okay. Did I read that correctly?

A That's what it says.

Q Am I correct that one of the ways of naming polymorphs that's been proposed is to name them by assigning their -- the melting point in addition to a Roman numeral?

MS. HASPER: Objection. Scope. Relevance.

THE WITNESS: Yeah. So I'm not a polymorph expert. So --

BY MR. POLLACK:

Q Well, why do you think they do that?

Why do you think they append a melting point to each polymorph?

MS. HASPER: Same objection.

THE WITNESS: Well, certainly, that's a physical characteristic of an individual solid form.

BY MR. POLLACK:

Q The melting point is something that's unique to that particular solid form?

MS. HASPER: Same objection. Also speculation.

THE WITNESS: Yes. But I know enough about crystallization that melting points are highly dependent upon the solvent that was used, the conditions that the crystals were grown under, time, scale. There's lots of variability in that. And I've run into this many, many times over the years in my own research.

BY MR. POLLACK:

Q Okay. But those conditions create different polymorphs, isn't that the issue?

A No. It could be the same --

MS. HASPER: Same objection.

THE WITNESS: It could be the same polymorph, but depending on how the crystal was grown, there's lots of -- you know, I've consulted on this issue. Inclusion of solvent can sometimes affect melting ranges and things like this.

BY MR. POLLACK:

Q Well, if there's solvent in it, then it's known as a "solvate"; right?

A Not necessarily.

Q Why not?

A Solvates are different. Solvates are actually -- for example, hydrates are solvates where there's a certain number of water molecules that will be noncovalently associated with a molecule in the crystal lattice. And sometimes these can be highly well-defined numbers like a trihydrate. So every molecule -- say a treprostinil trihydrate, each one would have three molecules of water associated with it. And sometimes there is a range that, you know, it's not exactly 3; it's 3.6. Okay.

Q You know, we're talking about -- in this proceeding, we're talking about treprostinil diethanolamine salt Form B. You'll agree with me that they've verified that that salt is neither a hydrate nor a solvate in the Phares reference; right?

MS. HASPER: Objection.

THE WITNESS: I don't recall. I'd have to look at --

BY MR. POLLACK:

Q Do you want to look at it?

A Sure.

Q You could have "Exhibit 1005" as it was

called.

MR. POLLACK: I'm going to mark as Williams Deposition Exhibit 16 a document currently known in the case as "Exhibit 1005," also known as the "Phares," P-h-a-r-e-s, "reference."

(Exhibit 16 marked)

BY MR. POLLACK:

Q In order to make this a little bit easier for you, the discussion of the characterization of treprostinil diethanolamine salts starts on what's called "Page 90" in the bottom right-hand corner of the document. It's page 87 in the original pagination.

A (Examining document) Okay. I've looked at the paragraph on that page 90, or 87.

Q Okay. If you could move on to the section on Form B, which starts at the bottom of --

A I'm sorry.

Q -- 87 and goes onto 88. I particularly wanted to focus on moisture sorption/desorption data and thermal data, but feel free to read all of it.

A (Examining document) Okay. I've read that.

Q Okay. Based on what you've read here, can you tell whether or not the Form B described

here is a hydrate solvate or is otherwise wet with solvent?

A Well, in contrast to Form A, where it specifically says -- indicated the material is not solvated, they don't make such an affirmative statement with Form B. But I'm not a polymorph expert, so -- you know, I'm -- I wouldn't be certain.

Q Okay. So you don't understand what it says there about the minimum weight loss. That's not an indication to you that there's -- no water was contained in the crystal?

A Well, it's certainly hydroscopic. Absorbs water.

Q Hmm-hmm. Okay. But this information here, can you tell from that -- the fact that water is not desorbing? Does that indicate to you -- and I recognize you're not a crystal-form expert, but does it indicate to you that it's not a solvate, or is this outside of your area?

A It's really outside of my area.

Q Okay. And what about -- you see there it says -- do you know what a "TG" is? It says, "A TG shows minimum weight loss up to 100 degrees C."

A I've seen that acronym before. I don't

remember off the top of my head exactly what it means.

Q Have you ever seen the acronym "TGA" as it's sometimes referred to?

A Is that "thermographic metric analysis"? Yeah.

Q Yes. Are you familiar with how that technique is used with polymorphs?

A Not intimately, no.

Q Okay. You're not aware that technique is sometimes used to show that there's a solvent or solvate in a -- in a polymorph?

MS. HASPER: Objection. Asked and answered. Scope.

THE WITNESS: Yeah. I mean, I'm not very familiar with the technique, so --

BY MR. POLLACK:

Q Okay. Fair enough.

If we could go back just quickly in the Threlfall article.

You know, never mind.

A Okay.

MR. POLLACK: I'm going to mark as Exhibit Williams Deposition Exhibit 17 an excerpt from the book "Solid-State Chemistry of Drugs," by

Steven R. Byrn, Ralph R. Pfeiffer and Joseph G. Stowell.

(Exhibit 17 marked)

BY MR. POLLACK:

Q And, no, this wasn't attached to your report.

Have you either seen or read this book, ever, before?

A No.

Q Okay. Do you know any of the authors?

A No.

Q Okay. Are there any textbooks on the solid-state form of drugs that you have read?

A Not that I can think off the top of my head, no.

Q Okay. Turn to the first page of this document. This is Chapter 10 on polymorphs. Let me just ask you about the second sentence which says that, "Compounds that crystallize as polymorphs can show a wide range of different physical and chemical properties, including different melting points and spectral properties."

I just want to know if you agree with that sentence or have any reason to disagree with it?

MS. HASPER: Objection. Scope.

THE WITNESS: I don't have any reason to disagree.

BY MR. POLLACK:

Q Okay. Do you agree with it?

A I have no reason to disagree.

Q Okay. One of the things that characterizes a polymorph is its melting point. It's one of the things that uniquely identifies a polymorph; is that right?

MS. HASPER: Objection. Scope. Asked and answered.

THE WITNESS: Again, based on my limited understanding that this can be quite dependent on conditions, the solvent that was used, the scale.

BY MR. POLLACK:

Q If you look a little further down on page 143, there's a second paragraph. This, again, talks about how polymorphs are made. Do you see -- or named. Do you see that?

A Yes.

Q Okay. And they point out there's no standard numbering systems for polymorphs; right?

A That's what it says.

Q Okay. And if you go down about three,

four, five sentences, there's a sentence beginning with the word, "It." Do you see that sentence?

It says, "It has been suggested . . ."?

A Yes.

Q Okay. And I'll read it into the record.

"It has been suggested that polymorphs be numbered consecutively in the order of their stability at room temperature or by their melting point."

Did I read that correctly?

A That's what it says.

Q Okay. And so what he's proposing here is that a polymorph would be identified by its melting point. Do you see any place where he says: And it needs to be further identified by what solvent was used?

MS. HASPER: Objection. Relevance.

THE WITNESS: No, but I guess I'd have to read a lot more on -- on this -- in this article. It may be discussed later.

BY MR. POLLACK:

Q Okay. Well, this is a -- I'll represent to you, it's not discussed later. But this is the second time we've seen a proposal that polymorphs be named by their melting point; right? You saw that

in the Threlfall article as well?

A Okay. Yes. That's what it says.

Q And Threlfall also, he doesn't suggest: Oh, it needs to be named also by what solvent was used -- right?

A I didn't see that mentioned, no.

Q While we're getting that out, could you go back to the patent for me.

A The patent? Which patent?

Q The patent. The '393 patent, Exhibit 1001, now known as "Williams Deposition Exhibit 3."

A Okay.

Q And I'd like to turn to what's called "Page 8" in this exhibit. It's column 12 of the patent. And if you look in that column in the paragraph starting -- two paragraphs starting around line 35, you see it refers to, "Polymorph B of the treprostinil diethanolamine salt"; right?

A What line?

Q I'm sorry. Line 40 -- it starts around line 42 and continues down the page.

A Okay.

Q Okay. Now, that polymorph B, that's the same polymorph B that's referred to in Exhibit 1005,

the Williams Deposition Exhibit 16, the Phares reference?

A I can't be certain they're the same, 'cause Phares doesn't tell us where the treprostinil comes from.

Q It's the same polymorph, though; is that fair?

A Well, that's what it's called, "polymorph B."

Q Okay. They're both polymorph Bs; right?

A That's what they're called.

Q Do you have any reason to believe that they're different?

A Well, I certainly know where polymorph B in the patent comes from. In Phares, they do not identify the source of the treprostinil.

Q Yeah. I'm not asking about how it was made or other differences. I'm just asking in regards to what crystal form it is.

Are both of these the same crystal form, the crystal form of treprostinil diethanolamine salt in the '393 patent and the crystal form in the Phares prior art reference, which are both called Form B? Are they the same crystal form?

A I can't be 100 percent certain. This