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

(1); 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 [redacted] to [redacted].

And three more columns over, the [redacted] ester changed from [redacted] to [redacted]. And then the total related substances changed from [redacted] to [redacted].

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 [redacted], [redacted], [redacted], [redacted], UT15 [redacted] ester, UT15 [redacted] ester, [redacted], [redacted], 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 (l) below, the first step -- step (l), 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 (l)

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

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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

D

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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

Robert M. Williams September 15, 2016

Robert M. Williams

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

Boston, MA 02110-1447

BY: MAYA PRAKASH CHOKSI, ESQ.

For Patent Owner and the Witness:

WILSON SONSINI GOODRICH & ROSATI

900 South Capital of Texas Highway

Las Cimas IV, Fifth Floor

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

RUFFOLO	DESCRIPTION	PAGE
Exhibit 8	Guidance for Industry, Non-Penicillin Beta-Lactam Drugs: A CGMP Framework for Preventing Cross-Contamination HHS/FDA/CDER April 2013, UT Ex. 2047	241
Exhibit 9	Diabetes Care, Clinical Pharmacology of Human Insulin, UT Ex. 2048	242
Exhibit 10	FDA/HSS Letter Stamped Mar 10, 2014 to Dean Bunce of United Therapeutics Re Remodulin	282
Exhibit 11	Patent Owner Response to Petition	310

(Exhibits attached to transcript.)

P R O C E E D I N G S

- - -

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 benzindene triol 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 [redacted]? 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 [redacted] from .9545?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: No.

BY MR. POLLACK:

Q. Well, what did you do?

A. I divided [redacted] 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 [redacted]?

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 [redacted] 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 [redacted]?

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 [redacted] 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 [redacted] 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 [redacted] 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 [redacted] percent.

Is that -- is that what you recall?

MR. DELAFIELD: Objection.

BY MR. POLLACK:

Q. Approximately [redacted] 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 [redacted] 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 [redacted] percent; right?

A. Correct. The lower limit now is [redacted] 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 [redacted] 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 [redacted].

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 [redacted] 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 [redacted] 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 [redacted]% 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 [redacted]% 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 [redacted] 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 [redacted] 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 [redacted] percent to a mean of [redacted] percent, resulting in a higher quality product.

BY MR. POLLACK:

Q. Actually, didn't they change the specification from [redacted] percent to [redacted]?

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 [redacted] percent that they move up to [redacted], that's a higher quality product. If you take the lower level of [redacted] percent and move it up to [redacted] 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]; 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 [redacted] 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 [redacted] 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 [redacted] 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 [redacted] to [redacted] percent and a lower level from [redacted] to [redacted] 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 [redacted] to [redacted] 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 [redacted] to [redacted] 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 [redacted] to [redacted] percent is considered a major amendment?

A. They wouldn't have listed something

as a change in purity from [redacted] to [redacted] 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 [redacted] 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 [redacted] 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 [redacted] 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 [redacted] less impurity than the Moriarty process.

Q. Okay. Let me ask you.

If instead of [redacted] 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 [redacted] 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 opinion 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 [redacted] 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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ERRATA SHEET

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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"

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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Signed on the 1st day of September, 2016.

ROBERT R. RUFFOLO, JR., PHD

NO.	LOT NUMBER	ASSAY PURITY	TOTAL RELATED SUBSTANCES	RESULTS	SOURCE	IMPLIED IMPURITY FROM INDIVIDUAL IMPURITIES
11	UT15-99H001	98.4	Total Related Substances =	1.0	Ex. 2052, pp. 28-30	
			Implied Purity	99.0	Ex. 2036, pp. 2-3	99.0
12	UT15-000701	100.0	Total Related Substances =	0.2	Ex. 2053, p. 19	
			Implied Purity	99.8	Ex. 2036, pp. 88-89	99.8
13	UT15-000801	100.0	Total Related Substances =	0.4	Ex. 2053, p. 19	
			Implied Purity	99.6	Ex. 2036, pp. 91-92	99.6
14	UT15-000802	99.9	Total Related Substances =	0.3	Ex. 2053, p. 19	
			Implied Purity	99.7	Ex. 2036, pp. 94-95	99.7
15	UT15-000803	99.7	Total Related Substances =	0.6	Ex. 2053, p. 19	
			Implied Purity	99.4	Ex. 2036, pp. 100-101	99.4
16	UT15-000901	99.8	Total Related Substances =	0.5	Ex. 2053, p. 19	
			Implied Purity	99.5	Ex. 2036, pp. 33-34	99.5
17	UT15-000902	99.8	Total Related Substances =	0.5	Ex. 2053, p. 19	
			Implied Purity	99.5	Ex. 2036, pp.97-98	99.5
18	UT15-001001	99.8	Total Related Substances =	0.4	Ex. 2053, p. 19	
			Implied Purity	99.6	Ex. 2036, pp.35-36	99.6
19	UT15-010201	99.3	Total Related Substances =	0.4	Ex. 2053, p. 19	
			Implied Purity	99.6	Ex. 2036, pp.37-38	99.6
20	UT15-010202	99.8	Total Related Substances =	0.4	Ex. 2053, p. 19	
			Implied Purity	99.6	Ex. 2036, pp.39-40	99.6
21	UT15-010203	98.1	Total Related Substances =	1.5	Ex. 2053, p. 19	
			Implied Purity	98.5	Ex. 2036, pp.41-42	98.5

NO.	LOT NUMBER	ASSAY PURITY	TOTAL RELATED SUBSTANCES	RESULTS	SOURCE	IMPLIED IMPURITY FROM INDIVIDUAL IMPURITIES
22	UT15-010301	99.1	Total Related Substances =	0.5	Ex. 2053, p. 19	
			Implied Purity	99.5	Ex. 2036, pp.43-44	99.5
23	UT15-010302	99.6	Total Related Substances =	0.3	Ex. 2053, p. 19	
			Implied Purity	99.7	Ex. 2036, pp.45-46	99.7
24	UT15-010303	100.0	Total Related Substances =	0.3	Ex. 2053, p. 19	
			Implied Purity	99.7	Ex. 2036, pp.47-48	99.7
25	UT15-010801-RP	98.8	Total Related Substances =	0.6	Ex. 2053, p. 20	
			Implied Purity	99.4	Ex. 2036, pp.60-61	99.4
26	UT15-010802	99.7	Total Related Substances =	0.2	Ex. 2053, p. 20	
			Implied Purity	99.8	Ex. 2036, pp.50-52	99.8
27	UT15-010803	99.7	Total Related Substances =	0.4	Ex. 2053, p. 20	
			Implied Purity	99.6	Ex. 2036, pp.52-53	99.6
28	UT15-010901	99.1	Total Related Substances =	0.6	Ex. 2053, p. 20	
			Implied Purity	99.4	Ex. 2036, pp.54-55	99.4
29	UT15-010902	99.5	Total Related Substances =	0.4	Ex. 2053, p. 20	
			Implied Purity	99.6	Ex. 2036, pp.56-57	99.6
30	UT15-011001	99.4	Total Related Substances =	0.6	Ex. 2053, p. 20	
			Implied Purity	99.4	Ex. 2036, pp.58-59	99.4
31	[redacted]	[redacted]	Total Related Substances =	[redacted]	Ex. 2053, p. 20	
			Implied Purity	[redacted]		[redacted]
32	[redacted]	[redacted]	Total Related Substances =	[redacted]	Ex. 2053, p. 20	

NO.	LOT NUMBER	ASSAY PURITY	TOTAL RELATED SUBSTANCES	RESULTS	SOURCE	IMPLIED IMPURITY FROM INDIVIDUAL IMPURITIES
			Implied Purity	[redacted]		[redacted]
33	UT15-020202	98.8	Total Related Substances =	0.2	Ex. 2053, p. 20	
			Implied Purity	99.8	Ex. 2036, pp.62-63	99.8
34	UT15-020203	98.9	Total Related Substances =	0.2	Ex. 2053, p. 20	
			Implied Purity	99.8	Ex. 2036, pp.64-65	99.8
35	UT15-020301	99.7	Total Related Substances =	0.3	Ex. 2053, p. 20	
			Implied Purity	99.7	Ex. 2036, pp.66-67	99.7
36	UT15-020302	99.6	Total Related Substances =	0.4	Ex. 2053, p. 20	
			Implied Purity	99.6	Ex. 2036, pp.66-67	99.6
37	UT15-020303	98.9	Total Related Substances =	0.3	Ex. 2053, p. 20	
			Implied Purity	99.7	Ex. 2036, pp.70-71	99.7
38	UT15-021001	99.3	Total Related Substances =	0.8	Ex. 2053, p. 21	
			Implied Purity	99.2	Ex. 2036, pp.72-73	99.2
39	UT15-021002	100.0	Total Related Substances =	0.6	Ex. 2053, p. 21	
			Implied Purity	99.4	Ex. 2036, pp.74-76	99.4
40	UT15-021003	100.8	Total Related Substances =	0.6	Ex. 2053, p. 21	
			Implied Purity	99.4	Ex. 2036, pp.78-79	99.4
41	UT15-021101	99.6	Total Related Substances =	0.5	Ex. 2053, p. 21	
			Implied Purity	99.5	Ex. 2036, pp.80-82	99.5
42	UT15-021102	99.2	Total Related Substances =	0.6	Ex. 2053, p. 21	
			Implied Purity	99.4	Ex. 2036, pp.83-85	99.4

NO.	LOT NUMBER	ASSAY PURITY	TOTAL RELATED SUBSTANCES	RESULTS	SOURCE	IMPLIED IMPURITY FROM INDIVIDUAL IMPURITIES
43	UT15-030401	100.1	Total Related Substances =	0.6	Ex. 2053, p. 21	
			Implied Purity	99.4	Ex. 2036, pp.31-32	99.4
44	UT15-030501	99.9	Total Related Substances =	0.6	Ex. 2036, pp. 29-30	
			Implied Purity	99.4		99.4
45	UT15-030502	99.5	Total Related Substances =	0.6	Ex. 2036, pp. 27-28	
			Implied Purity	99.4		99.4
46	UT15-030503	99.9	Total Related Substances =	0.9	Ex. 2036, pp. 25-26	
			Implied Purity	99.1		99.1
47	UT15-030504	100.0	Total Related Substances =	0.4	Ex. 2036, pp. 23-24	
			Implied Purity	99.6		99.6
48	UT15-030601	100.1	Total Related Substances =	0.3	Ex. 2036, pp. 21-22	
			Implied Purity	99.7		99.7
49	UT15-030602	100.1	Total Related Substances =	0.4	Ex. 2036, pp. 19-20	
			Implied Purity	99.6		99.6
50	UT15-031001	100.4	Total Related Substances =	0.6	Ex. 2036, pp. 17-18	
			Implied Purity	99.4		99.4
51	UT15-031002	100.5	Total Related Substances =	0.4	Ex. 2036, pp. 15-16	
			Implied Purity	99.6		99.6
52	UT15-031003	100.4	Total Related Substances =	0.6	Ex. 2036, pp. 13-14	
			Implied Purity	99.4		99.4
53	UT15-031101	100.0	Total Related Substances =	0.5	Ex. 2036, pp. 11-12	
			Implied Purity	99.5		99.5

NO.	LOT NUMBER	ASSAY PURITY	TOTAL RELATED SUBSTANCES	RESULTS	SOURCE	IMPLIED IMPURITY FROM INDIVIDUAL IMPURITIES
54	UT15-031102	100.3	Total Related Substances =	0.4	Ex. 2036, pp. 8-10	
			Implied Purity	99.6		99.6
55	UT15-031201	100.5	Total Related Substances =	0.4	Ex. 2036, pp. 6-7	
			Implied Purity	99.6		99.6
56	UT15-031202	99.7	Total Related Substances =	0.5	Ex. 2036, pp. 4-5	
			Implied Purity	99.5		99.5

Results from HPLC Assay	Results from HPLC Assay
Average =	99.7
Standard Deviation =	0.5

Results from Implied Purity	Results from Implied Purity
Average =	99.5
Standard Deviation =	0.2

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Attorneys for Defendant Sandoz Inc.

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

UNITED THERAPEUTICS CORPORATION, Plaintiff, v. SANDOZ INC. Defendant.	)	Civil Action No. 3:14-cv-5499 (PGS)(LHG) **HIGHLY CONFIDENTIAL— SUBJECT TO THE PROTECTIVE ORDER**

DEFENDANT SANDOZ INC.'S INVALIDITY CONTENTIONS

Table of Contents

Pursuant to Local Patent Rule 3.3, Defendant-Counterclaim Plaintiff Sandoz Inc. ("Sandoz") hereby submits its Invalidity Contentions with respect to claims 1, 2, 4, 8, 9 and 16 ("the Asserted Claims") of U.S. Patent No. 8,497,393 ("the '393 patent"). Sandoz asserts that claims 1, 2, 4, 8, 9 and 16 of the '393 patent are invalid under the patent statutes for the reasons that follow.[1]

I. LEGAL STANDARDS FOR INVALIDITY

A. Legal Standards for Anticipation

Anticipation is a question of fact that is shown and reviewed under a clearly erroneous standard. *E.g., Rapoport v. Dement*, 254 F.3d 1053, 1057-58 (Fed. Cir. 2001). A patent claim is invalid for anticipation where each and every element of the claimed invention is disclosed in a single prior art reference. 35 U.S.C. § 102; *In re Paulsen*, 30 F.3d 1475, 1478-79 (Fed. Cir. 1994). "[W]hen a patent claims a chemical composition in terms of ranges of elements, any single prior art reference that falls within each of the ranges anticipates the claim." *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1346 (Fed. Cir. 1999).

To find anticipation, the four corners of a single prior art document must describe each and every element of the claimed invention, either expressly or inherently, such that a person of ordinary skill in the art could practice the invention without undue experimentation. *Advanced Display Sys. v. Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000). Thus, a prior art reference without express reference to a claim limitation may nonetheless anticipate by inherency. *Perricone v. Medicis Pharmaceutical Corp.*, 432 F.3d 1368, 1375-76 (Fed. Cir. 2005). "Under the principles of inherency, if the prior art necessarily functions in accordance

[1] Additional information regarding the validity of the Asserted Claims can be found in Sandoz's Notice Letter with respect to the '393 patent, which is herein incorporated by reference.

with, or includes, the claim limitations, it anticipates." *Id.*; *Continental Can Co. U.S.A., Inc. v. Monsanto Co.*, 948 F.2d 1264, 1268 (Fed. Cir. 1991) (Under the theory of inherent anticipation, if an element is not expressly disclosed in the prior art reference, the reference still will be deemed to anticipate the subsequent claim if the missing element "is necessarily present in the thing described in the reference").

"[I]nherency is not necessarily coterminous with the knowledge of those skilled in the art. Artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art." *Perricone*, 432 F.3d at 1376; *see also Schering Corp. v. Geneva Pharms., Inc.*, 339 F.3d 1373, 1378 (Fed. Cir. 2003) (concluding that inherent anticipation does not require that a skilled artisan recognize the inherent characteristic in the prior art that anticipates the claimed invention). A previously unrecognized benefit of a known process or method may be viewed as a "newly discovered result[] of [a] known process[] directed to the same purpose," and is thus anticipated. *Bristol-Myers Squibb Co. v. Ben Venue Labs. Inc.*, 246 F.3d 1368, 1376-77 (Fed. Cir. 2001) citing *In the case of Application of May*, 574 F.2d 1082 (C.C.P.A. 1978); *Perricone*, 432 F.3d at 1377-78; *King Pharmaceuticals, Inc. v. Elan Pharmaceuticals, Inc.*, 616 F.3d 1267, 1275-76 (Fed. Cir. 2010). "A court may resolve factual questions about the references in the prior art by examining the reference through the eyes of a person of ordinary skill in the art, among other sources of evidence about the meaning of the prior art." *Schering*, 339 F.3d at 1377-78. In other words, although past recognition of the inherent feature is not necessary, the court may still evaluate the opinions of those skilled in the art to determine the scope of the prior art reference. *Id.* at 1378.

B. Anticipation And Obviousness Of Product-By-Process Claims

It has long been the case that an old product is not patentable even if it is made by a new process. *Amgen Inc. v. F. Hoffmann-La Roche, Ltd.*, 580 F.3d 1340, 1366 (Fed. Cir. 2009). *See also Gen. Elec. Co. v. Wabash Appliance Corp.*, 304 U.S. 364, 373, 58 S. Ct. 899, 82 L. Ed. 1402, 1938 Dec. Comm'r Pat. 813 (1938) ("[A] patentee who does not distinguish his product from what is old except by reference, express or constructive, to the process by which he produced it, cannot secure a monopoly on the product by whatever means produced."); *Cochrane v. Badische Anilin & Soda Fabrik*, 111 U.S. 293, 311, 4 S. Ct. 455, 28 L. Ed. 433, 1884 Dec. Comm'r Pat. 230 (1884) ("While a new process for producing [the product] was patentable, the product itself could not be patented even though it was a product made [by an artificial process] for the first time.").

Product-by-process claims "enable an applicant to claim an otherwise patentable product that resists definition by other than the process by which it is made." *In re Thorpe*, 777 F.2d 695, 697 (Fed. Cir. 1985). "For this reason, even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself." *Id.*

Disclosure of a product in the prior art will anticipate a product-by-process claim covering the same product. *Smithkline Beecham Corp. v. Apotex Corp.*, 439 F.3d 1312, 1317 (Fed. Cir. 2006) ("It has long been established that one cannot avoid anticipation by an earlier product disclosure by claiming the same product more narrowly, that is, by claiming the product as produced by a particular process."). In order to anticipate, the prior art product must be the same as the claimed product that is made in a different way. *Amgen Inc. v. Hoffmann-La Roche Ltd.*, 580 F.3d 1340, 1370 (Fed. Cir. 2009). "The patentability of a product does not depend on its method of production," so "[i]f the product in a product-by-process claim is the same as or

obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d at 697.

However, "if the process by which the product is made imparts structural and functional differences distinguishing the claimed product from the prior art, then those differences are relevant as evidence of no anticipation although they are not explicitly part of the claim." *Greenliant Systems, Inc. v. Xicor LLC*, 692 F.3d 1261, 1268 (Fed. Cir. 2012). Accordingly, in determining patentability, it is necessary to consider the process in which the product is formed only if that process imparts distinctive structural or functional characteristics to the claimed product. *Id.*

C. Legal Standards For On-Sale Bar Under 35 U.S.C. § 102(b)

"The on-sale bar applies when the invention is the subject of a commercial offer for sale, and is ready for patenting before the critical date." *Netscape Communications Corp. v. Konrad*, 295 F.3d 1315, 1323 (Fed. Cir. 2002)(citing *Pfaff v. Wells*, 525 U.S. 55, 67 (1998)). "A single sale or offer to sell suffices to bar patentability." *Atlantic Thermoplastics Co., Inc. v. Faytex Corp.*, 970 F.2d 834, 836 (Fed. Cir. 1992). The on-sale bar "is not limited to sales by the inventor or one under his control, but may result from activities of a third party." *J. A. Laporte, Inc. v. Norfolk Dredging Co.*, 787 F.2d 1577, 1581 (Fed. Cir. 1986); *In re Epstein*, 32 F.3d 1559, 1564 (Fed. Cir. 1994); *Abbott Labs. v. Geneva Pharms., Inc.*, 182 F.3d 1315, 1318 (Fed. Cir. 1999)("Furthermore, the statutory on-sale bar is not subject to exceptions for sales made by third parties…[t]he fact that these sales were not made by Abbott is therefore irrelevant.").

A sale from a manufacturer to a company that will process, package and then sell the claimed invention to end users can constitute a "commercial sale" of the claimed invention under 35 U.S.C. §102(b). *Brasseler, U.S.C. I, L.P. v. Stryker Sales Corp.*, 182 F.3d 888, 891 (Fed. Cir.

1999)(rejecting the patentee's argument that the sale at issue was "not in the public and thus was not a § 102(b) sale). In *Brassler*, the Federal Circuit explained that "the public for purposes of § 102(b) is not limited to ultimate users of the product," and that "sales activity kept secret from the trade" can trigger an on-sale bar. *Id.* (internal citations and quotations omitted).

"The ready for patenting condition may be satisfied in at least two ways: by proof of reduction to practice before the critical date; or by proof that prior to the critical date the inventor had prepared drawings or other descriptions of the invention that were sufficiently specific to enable a person skilled in the art to practice the invention." *Netscape*, 295 F.3d at 1323 (internal quotations omitted). "A process is reduced to practice when it is successfully performed. A machine is reduced to practice when it is assembled adjusted and used. A manufacture is reduced to practice when it is completely manufactured." *Pfaff*, 525 U.S. at 57 n.2 (quoting *Corona Cord Tire Co. v. Dovan Chemical Corp.*, 276 U.S. 358, 383 (1928)).

"To invoke the on-sale bar, a defendant must prove that the complete claimed invention is embodied in or obvious in view of the thing sold or offered for sale before the critical date." *Atlantic Thermoplastics*, 787 F.2d at 836. In determining whether an on-sale bar invalidates a patent claim, "the court should determine whether the subject of the barring activity met each of the limitations of the claim, and thus was an embodiment of the claimed invention." *Netscape*, 295 F.3d at 1323.

In an on-sale bar analysis, the critical "question is not whether the sale, even a third party sale, 'discloses' the invention at the time of the sale, but whether the sale relates to a device that *embodies* the invention." *J. A. Laporte*, 787 F.2d at 1583 (emphasis in original). "Beyond this 'in public use or on sale' finding, there is no requirement for an enablement-type inquiry." *In re Epstein*, 32 F.3d at 1568; *see also Zenith Electronics Corp. v. PDI Communication Systems, Inc.*,

522 F.3d 1348, 1356 (Fed. Cir. 2008)("Contrary to Zenith's arguments, however, we note that the public use itself need not be enabling…Rather, we must simply determine whether the public use related to a device that embodied the invention.")(internal citations omitted). There "is no requirement that a sales offer specifically identify all the characteristics of an invention offered for sale or that the parties recognize the significance of all these characteristics at the time of the offer." *Abbott*, 182 F.3d at 1319.

D. Legal Standards for Obviousness.

A patent is invalid for obviousness if "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103 (a). The following inquiries are pertinent to resolving this issue: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; and (3) the difference between the prior art and the claims at issue. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). Against this background, the obviousness or nonobviousness of the subject matter is determined. *Id.* Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, *etc.*, might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented. *Id.* Obviousness is not determined in hindsight in view of the invention in question. Instead, prior art is considered by the hypothetical artisan at a time just before the invention was made. *Al-Site Corp. v. VSI Int'l*, 174 F.3d 1308, 132 (Fed. Cir. 1999).

A reference must be considered for all that is taught – disclosures that diverge and teach away from the invention as well as disclosures that point toward and teach the invention. *See In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988). A reference teaches away if it would

have led a person skilled in the art in a direction different from that taken by the inventor. *Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 885 (Fed. Cir. 1998). "The degree of teaching away will of course depend on the particular facts; in general, a reference will teach away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by" the inventor. *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994). It is impermissible to select only those portions of a reference that support a given position and exclude other parts necessary to the full appreciation of what the reference fairly teaches. *Bausch & Lomb, Inc. v. Barnes-Hind*, 796 F.2d 443, 448 (Fed. Cir. 1986).

The United States Supreme Court has clarified certain aspects of the obviousness analysis, particularly with respect to the Federal Circuit's requirement that there be a "teaching suggestion, or motivation" to combine the teachings of two or more separate references. In *KSR Int'l Co. v. Teleflex, Inc.*, 127 S.Ct. 1727 (2007), the Court expressly rejected a rigid requirement for a motivation to combine, stating:

> [t]he obviousness analysis cannot be confined by a formalistic conception of the words teaching, suggestion, and motivation, or by overemphasis on the importance of published articles and the explicit content of issued patents. The diversity of inventive pursuits and of modern technology counsels against limiting the analysis in this way.

KSR, 127 S.Ct. at 1741. The Court further stated:

> [i]n determining whether the subject matter of a patent claim is obvious, neither the particular motivation nor the avowed purpose of the patentee controls. What matters is the objective reach of the claim. If the claim extends to what is obvious, it is invalid under § 103. One of the ways in which a patent's subject matter can be proved obvious is by noting that there existed at the time of invention a known problem for which there was an obvious solution encompassed by the patent's claims.

KSR, 127 S.Ct. at 1741-1742. Instructing that the obviousness analysis should not be limited by

looking only at the problem that the patentee was trying to solve, the Court stated:

> [t]he question is not whether the combination was obvious to the patentee but whether the combination was obvious to a person with ordinary skill in the art. Under the correct analysis, any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed.

KSR, 127 S.Ct. at 1742. The Court noted that in some instances, the fact that it may have been "obvious to try" to make a claimed invention may be dispositive:

> [w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.

Id.

When examining the obviousness of a compound and/or a method of using that compound, structural similarity alone may be sufficient to give rise to an expectation that two compounds with similar structures will have similar properties. *In re Merck*, 800 F.2d 1091 (Fed. Cir. 1986), *citing In re Payne*, 606 F.2d 303, 313 (C.C.P.A. 1979). Structural similarity between a claimed compound and prior art compounds creates a *prima facie* case of obviousness. *In re Dillon*, 919 F.2d 688 (Fed. Cir. 1990). The burden then falls on an applicant to rebut that *prima facie* case. *Id.* at 693. A rebuttal or counter-argument can consist of test data showing that the claimed compounds possess unexpectedly improved properties from the prior art compounds. All evidence of the properties of the claimed and prior art compounds must be considered in determining the ultimate question of patentability.

The "discovery," however, that the claimed compound possesses a property not disclosed in the prior art does not by itself defeat a *prima facie* case of obviousness. *In re Dillon*, 919 F.2d

at 693. *See also In re Merck*, 800 F.2d at 1099, where the Federal Circuit stated:

> [t]he core of it is that, while there are some differences in degree between the properties of amitriptyline and imipramine, the compounds expectedly have the same type of biological activity. In the absence of evidence to show that the properties of the compounds differed in such an appreciable degree that the difference was really unexpected, we do not think that the Board erred in its determination that appellant's evidence was insufficient to rebut the *prima facie* case.

Evidence of secondary considerations, if present, must be considered in determining obviousness, but there must be a nexus between such evidence and the merits of the claimed invention. *Graham*, 383 U.S. at 17. The existence of such evidence, however, does not control the obviousness determination. *Richardson-Vicks v. Upjohn Co.*, 122 F.3d 1476, 1483 (Fed. Cir. 1997). Examples of secondary considerations are commercial success, copying, prior failure of others, licenses under the patent, a long-standing need for the invention, unexpected results, skepticism by others in the art, and contemporaneous development by others. *Graham*, 383 U.S. at 17-18; *DMI, Inc.*, 802 F.2d at 425. Commercial success is not a relevant factor in determining obviousness where others were legally barred from practicing the invention. *Merck & Co., Inc. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1376-77 (Fed. Cir. 2005).

E. Legal Standards For Obviousness-Type Double-Patenting

An "obviousness-type double patenting analysis entails two steps. First, as a matter of law, a court construes the claim in the earlier patent and the claim in the later patent and determines the differences. Second, the court determines whether the differences in subject matter between the two claims render the claims patentably distinct." *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 968 (Fed. Cir. 2001) (internal citations omitted). "A later claim that is not patentably distinct from an earlier claim in a commonly owned patent is invalid for obviousness-type double patenting." *Id.* (*citing In re Berg*, 140 F.3d 1428, 1431 (Fed. Cir.

1998)). "A later patent claim is not patentably distinct from an earlier patent claim if the later claim is obvious over, or anticipated by, the earlier claim." *Id.*

II. BACKGROUND

A. Disclosure And Claims Of The '393 Patent

The '393 patent is entitled "Process to Prepare Treprostinil, the Active Ingredient in Remodulin" and issued on July 30, 2013. The '393 patent issued from U.S. Patent Application No. 13/548,446 ("the '446 Application"), which was filed July 13, 2012. The '446 Application was a continuation of U.S. Patent Application No. 12/334,731 ("the '731 Application), which itself ultimately issued as U.S. Patent No. 8,242,305, and which was filed on December 15, 2008. The '446 Application ultimately claims priority back to Provisional Application No. 61/014,232, which was filed on December 17, 2007. The patent on its face is assigned to United Therapeutics Corporation, and the named inventors are Hitesh Batra, Raju Penmasta, Sundersan Tuladhar and David Walsh.

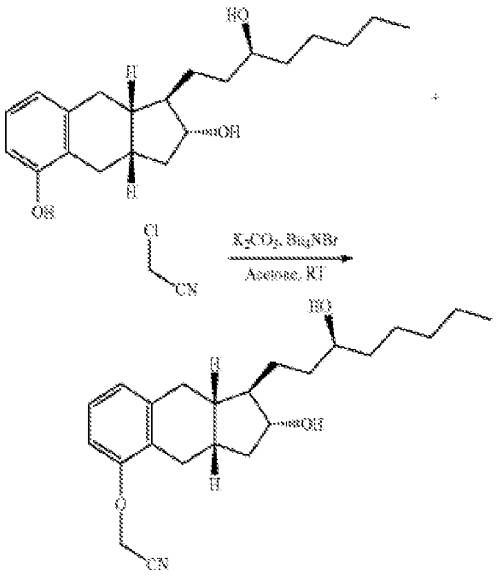
The '393 patent is directed to "an improved process to convert benzindene triol to treprostinil via salts of treprostinil and to purify treprostinil." ('393 patent, Abstract). The '393 patent discloses that "[t]reprostinil, the active ingredient in Remodulin®, was first described in U.S. Patent No. 4,306,075." ('393 patent at Col. 1:22-23). Further, "[t]reprostinil, and other prostacyclin derivatives have been prepared as described by Moriarty *et al.* in *J. Org. Chem.* 2004, 69, 1890-1902; *Drug of the Future*, 2001, 26(4), 364-374; and U.S. Pat. Nos. 6,441,245, 6,528,688, 6,765,117 and 6,809,223. Their teachings are incorporated by reference to show how to practice the embodiments of the present invention." ('393 patent at Col. 1:23-29).

The '393 Patent includes six examples, of which the first five illustrate the conversion of the benzindene triol intermediate into treprostinil free acid by way of treprostinil diethanolamine

salt through a five step process. ('393 patent at Col. 9:25-Col.17:26). The process disclosed in Examples 1-5 is set forth below:

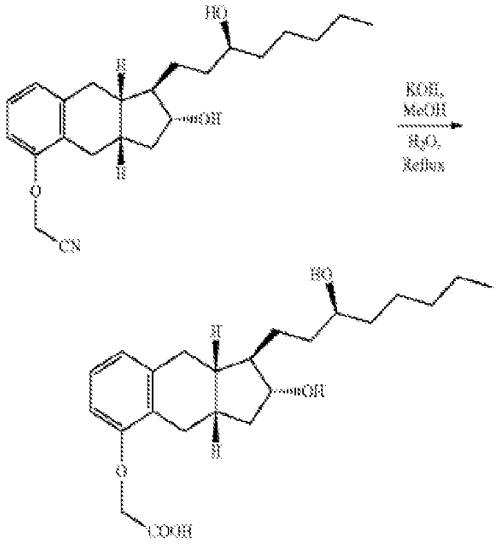
Example 1

Alkylation of Benzindene Triol



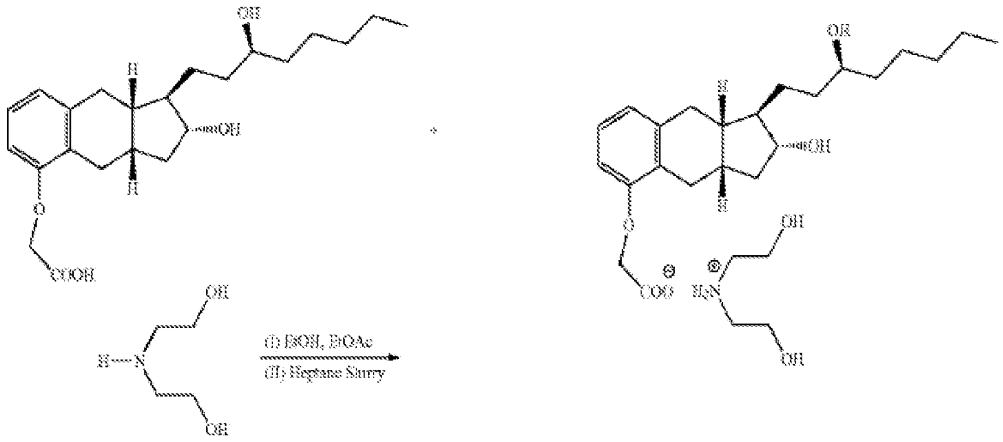
Example 2

Hydrolysis of Benzindene Nitrile



Example 3

Conversion of Treprostinil to Treprostinil Diethanolamine Salt (1:1)



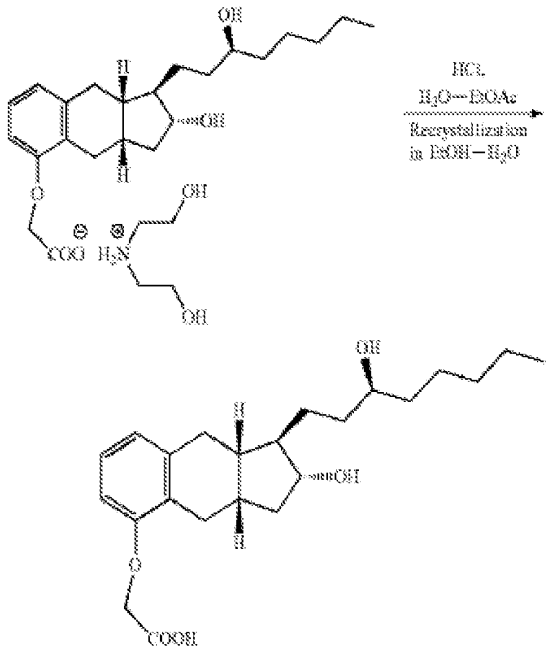
Example 4

Heptane Slurry of Treprostinil Diethanolamine Salt (1:1)

Name	Batch No.	Amount	Ratio
Treprostinil Diethanolamine Salt	1	3168 g	1
Heptane	----	37.5 L	12
Treprostinil Diethanolamine Salt	2	3071 g	1
Heptane	----	36.0 L	12

Example 5

Conversion of Treprostinil Diethanolamine Salt (1:1) to Treprostinil



('393 patent at Col. 1:9-Col. 14:65). The specification further explains the benefits of the disclosed synthetic process as follows:

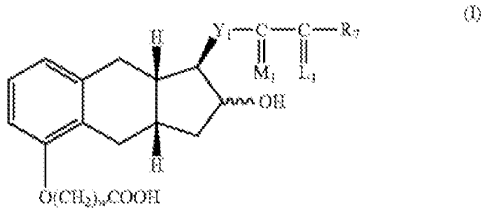
> The quality of treprostinil produced according to this invention is excellent. The purification of benzindene nitrile by column chromatography is eliminated. The impurities carried over from intermediate steps (i.e. alkylation of triol and hydrolysis of benzindene nitrile) are removed during the carbon treatment and the salt formation step. Additional advantages of this process are: (a) crude treprostinil salts can be stored as raw material at ambient temperature and can be converted to treprostinil by simple acidification with diluted hydrochloric acid, and (b) the treprostinil salts can be synthesized from the solution of treprostinil without isolation. This process provides better quality of final product as well as saves significant amount of solvents and manpower in purification of intermediates.

('393 patent at Col. 17:27-40).

There are twenty-two claims in the '393 patent, but only six claims are asserted in the present litigation: claims 1, 2, 4, 8, 9 and 16. Claims 1 and 9 are independent claims. Claims 2, 4, and 8 are dependent claims that depend from claim 1, and claim 16 is a dependent claim that depends from claim 9.

Specifically, the Asserted Claims read as follows:

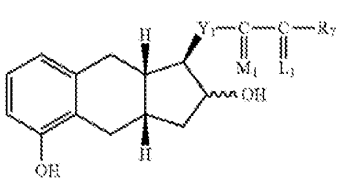
1. A product comprising a compound of formula I:



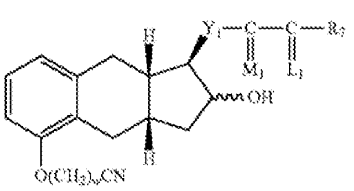
(I)

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 w=1, 2, or 3;

Y_1 is trans-CH═CH–, cis-CH═CH–, $–CH_2(CH_2)_m–$, or –C≡C–; m is 1, 2, or 3;

R_7 is

(1) $–C_pH_{2p}–CH_3$, wherein p is an integer from 1 to 5, inclusive,

(2) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3) alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl, with the proviso that R_7 is phenoxy or substituted phenoxy, only when R_3 and R_4 are hydrogen or methyl, being the same or different,

(3) phenyl, benzyl, phenylethyl, or phenylpropyl optionally substituted on the aromatic ring by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3)alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl,

(4) cis-CH═CH–CH_2–CH_3,

(5) – $(CH_2)_2$–CH(OH) –CH_3, or

(6) $–(CH_2)_3–CH═C(CH_3)_2$;

$–C(L_1)–R_7$ taken together is

(1) (C_4-C_7)cycloalkyl optionally substituted by 1 to 3 (C_1-C_5)alkyl;

(2) 2-(2-furyl)ethyl,

(3) 2-(3-thienyl)ethoxy, or

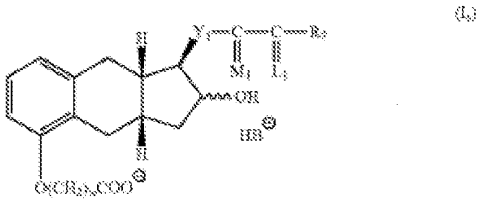
(4) 3-thienyloxymethyl;

M_1 is α-OH:β-R_5 or α-R_5β-OH or α-OR_1: β-R_5 or α-R_5:β-OR_2, wherein R_5 is hydrogen or methyl, R_2 is an alcohol protecting group, and

L_1 is α-R_3:β-R_4, α-R_4:β-R_3, or a mixture of α-R_3:β-R_4 and α-R_4:β-R_3, wherein R_3 and R_4 are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R_3 and R_4 is fluoro only when the other is hydrogen or fluoro,

(b) hydrolyzing the product of formula III of step (a) with a base,

(c) contacting the product of step (h) with a base B to form a salt of formula Is.



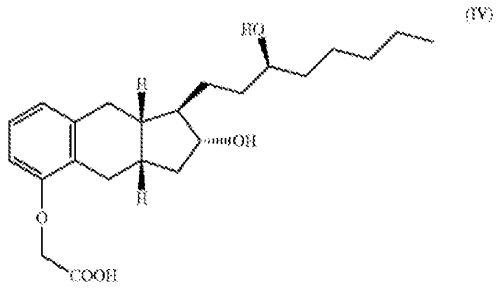
and (d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula I.

2. The product of claim 1, wherein the purity of compound of formula I in said product is at least 99.5%.

4. The product of claim 1, wherein the base in step (b) is KOH or NaOH.

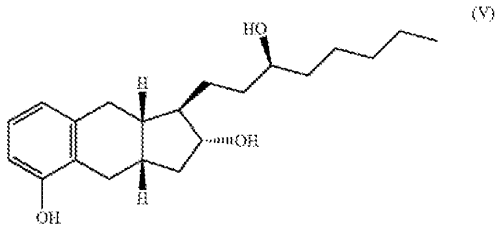
8. The product of claim 1, wherein the process does not include purifying the compound of formula (III) produced in step (a).

9. A product comprising a compound having formula IV

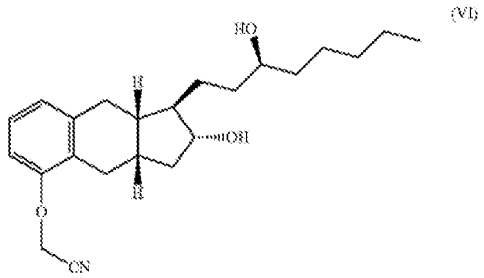


or a pharmaceutically acceptable salt thereof, wherein the product is prepared by the process comprising

(a) alkylating a compound of formula V with an alkylating agent to produce a compound of formula VI,



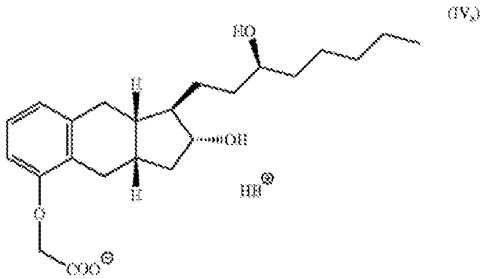
(V)



(VI)

(b) hydrolyzing the product of formula VI of step (a) with a base,

(c) contacting the product of step (h) with a base B to form a salt of formula IVs, and



(IVs)

(d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula IV.

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

Accordingly, the claimed process is directed to a "product" comprising treprostinil free acid or a pharmaceutically acceptable salt of treprostinil made through a process that comprises (1) alkylating the benzindene triol intermediate to obtain the nitrile intermediate, (2) hydrolyzing

the nitrile with a base, (3) contacting the product of step (b) with a base B to form a salt, wherein the salt includes an HB^+ cation, and (4) optionally reacting the salt with an acid to form treprostinil free acid.[2]

The term "product" as used in the Asserted Claims of the '393 patent means a product of a process for making treprostinil or other claimed prostacyclin derivatives or their salts and is not limited to products suitable for commercial use. In addition, for the purposes of an invalidity analysis, the product of the Asserted Claims is a product comprising the treprostinil compound, or a salt thereof, without additional limitations as to the composition or level of impurities. More exactly, for independent claim 1 and dependent claims 2, 4 and 8, the claimed product is a product comprising a compound of a genus that includes the treprostinil compound, or a pharmaceutically acceptable salt thereof, while for independent claim 9 and dependent claim 16, the product is a product comprising the specific treprostinil compound, or a pharmaceutically acceptable salt thereof.

All but one of the Asserted Claims do not recite any limitations as to the specific composition or other characteristics of the final product except that it comprises the treprostinil compound or a salt thereof. It is elementary that "comprising" means "including but not limited to." *CIAS, Inc. v. Alliance Gaming Corp.*, 504 F.3d 1356, 1360 (Fed. Cir. 2007). Thus, the claimed product includes embodiments in which treprostinil may constitute any proportion of the product and in which there may be any types or amounts of impurities, e.g. compounds other than treprostinil. The only exception is claim 2, which recites that the purity of the treprostinil compound or its salt must be at least 99.5%. Thus, the product of claim 2 is a product

[2] Although step (c) in both claims 1 and 9 references the "product of step (h)", Sandoz understands this to be a typographical error that should read "the product of step (b)."

comprising at least 99.5% treprostinil, without limitation as to the composition of the impurities. For the other Asserted Claims, the product is a product that includes the treprostinil compound or its salt in any purity along with any other types or amounts of other compounds.

B. Prosecution Of The '393 Patent

The '446 application, which issued as the '393 patent, was filed on July 13, 2012. The '446 application as filed included 21 claims, of which claims 1 and 10 were independent. Claim 1 was directed to a product comprising a compound of formula I, which is a genus that includes treprostinil free acid, made by a process that includes (a) alkylating a triol intermediate to obtain a nitrile intermediate, (b) hydrolyzing the nitrile with a base, (c) contacting the product of step (b) with a base B to form a salt, wherein the salt includes an HB^+ cation, and (d) reacting the salt formed in step (c) with an acid to form the compound of formula I. ('446 application at pp. 22-23). Claim 10 was directed to a product comprising the treprostinil free acid compound made by a process that includes (a) alkylating a triol intermediate to obtain a nitrile intermediate, (b) hydrolyzing the nitrile with a base, (c) contacting the product of step (b) with a base B to form a salt, wherein the salt includes an HB^+ cation, and (d) reacting the salt formed in step (c) with an acid to form treprostinil free acid. ('446 application at pp. 24-25).

In an office action dated January 3, 2013, the Examiner rejected claims 1-21 as anticipated by Moriarty *et al*. in *J. Org. Chem.* 2004, 69, 1890-1902 ("Moriarty JOC Article"). The Examiner stated that on page 1892, column 1, the Moriarty JOC Article "discloses compound 7 which has the same structure as the instantly claimed product." (1/3/2013 Office Action at p. 2). Further, "Moriarty disclose[s] a method of preparing compound 7", and "99.7% pure compound 7 is disclosed thereby meeting the purity limitations of claims 2 and 11." (*Id.*). The Examiner argued that the "instant claims are product by process" and "[s]ince the product

disclosed in the art is the same as the instantly claimed product, the patentability of the product [] does not depend on the method of production." (*Id.*).

UTC filed a response to the office action on February 8, 2013, in which it amended claims 1 and 10 such that the product comprised treprostinil free acid or pharmaceutically acceptable salts thereof, and such that step (d) was optional. (2/8/2013 Response at pp. 2-5). In addressing the anticipation rejection based on the Moriarty JOC article, UTC argued as follows:

> The product of Moriarty 2004 is physically different from the product of claims 1 and 10, in which a base addition salt is formed *in situ* with treprostinil that has not been previously isolated. Specifically, when a batch of treprostinil acid made by the type of process disclosed in Moriarty 2004 was analyzed by the applicants, it was found to contain small amounts of 4 different impurities (benzindene triol, treprostinil methyl ester, and 2 different stereoisomers of treprostinil). By contrast, not one of these four impurities was detectable in either a batch of treprostinil salt or a batch of treprostinil acid produced according to claims 1 and 10. This physical difference in the product results directly from the steps recited in claims 1 and 10, in which a salt is formed *in situ* without previously isolating treprostinil. Since Moriarty does not teach a product of present claims 1 and 10, withdrawal of the rejection is requested.

(2/8/2013 Response at pp. 9-10) (emphasis in the original).

In response, the Examiner issued a final office action on May 15, 2013 in which the Examiner maintained the anticipation rejection over the Moriarty JOC article. The Examiner acknowledged UTC's argument that "treprostinil prepared by the process of Moriarty contains 4 different impurities (benzindene triol, treprostinil methyl ester and 2 different stereoisomers of treprostinil), while the process in the instant claims results in a product where such impurities are not present." (5/15/2013 Office Action at p. 3). However, the Examiner was "unable to locate the description of the above mentioned impurities" in the Moriarty JOC article, and also found "no comparative data demonstrating the difference between the two products…upon review of the specification." (*Id.*). Accordingly, the Examiner concluded that "the evidence presented by

the application cannot be considered unless it is presented in a form of a declaration." (*Id.* at pp. 3-4).

UTC filed a response to the final office action on June 5, 2013 that included a Declaration by Dr. David Walsh ("Walsh Declaration"). In the June 5th response, UTC summarized the argument made in its February 8th response as follows:

> In the response filed February 8, 2013, Applicants submitted that the product of Moriarty 2004 is physically different from the product of claims 1 and 10, in which a base addition salt is formed *in situ* with treprostinil that has not been previously isolated. Specifically, Applicants noted that when a batch of treprostinil acid made by the type of process disclosed in Moriarty 2004 was analyzed by the applicants, it was found to contain small amounts of 4 different impurities (benzindene triol, treprostinil methyl ester, and 2 different stereoisomers of treprostinil). By contrast, not one of these four impurities was detectable in either a batch of treprostinil salt or a batch of treprostinil acid produced according to claims 1 and 10. In their February 8th response, Applicants explained that this physical difference in the product resulted directly from the steps recited in claims 1 and 10, in which a salt is formed *in situ* without previously isolating treprostinil.

(5/5/2013 Response at p. 7) (emphasis in the original).

UTC then reiterated the argument that prior art product and the claimed product were "physically different" as a result of different impurity profiles and cited to the Walsh Declaration for support, as shown below.

> To address the issue raised by the PTO, Applicants submit with the present response a declaration under 37 C.F.R. § 1.132 by Dr. David Walsh. In section 7 of his declaration, Dr. Walsh provides data from representative Certificates of Analysis with impurity profiles for treprostinil prepared according to the process corresponding to 'Moriarty', treprostinil diethanolamine prepared according to the process specified in claim 1 or 10 of the present application, and treprostinil as the free acid prepared according to the process specified in claim 1 or 10 of the present application. Based on the results provided, Dr. Walsh concludes 'that each of treprostinil as the free acid and treprostinil diethanolamine prepared according to the process specified in claims 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.'

(5/5/2013 Response at p. 8) (emphasis in the original). UTC then concluded that "[s]ince Dr. Walsh's declaration provides evidence that the product of present claims is physically difference [*sic*] than treprostinil produced according to the process of Moriarty, Moriarty cannot anticipate the present claims." (*Id.*).

The Walsh Declaration was executed on June 4, 2013 and provides purity data for three batches of treprostinil: one batch of free acid made through the Moriarty JOC article process, one batch of free acid made through the claimed process, and one batch of treprostinil diethanolamine salt made through the claimed process. (5/5/2013 Response, Walsh Declaration, at ¶ 6). The data are provided below:

Treprostinil free acid prepared according to "Moriarty"

Chromatographic Purity (HPLC) NB 1, PDR 16	1AU90:	Not more than 0.4%	ND
	2AU90:	Not more than 0.1%	< 0.05%
	97W80 (Benzindene Triol):	Not more than 0.2%	0.07%
	3AU90:	Not more than 1.0%	0.5%
	Treprostinil Methyl Ester:	Not more than 0.2%	< 0.05%
	Treprostinil Ethyl Ester:	Not more than 0.5%	0.1%
	7509P93:	Not more than 0.5%	0.1%
	7519P93:	Not more than 0.3%	0.07%
	Unidentified at:	Not more than 0.1% AUC each	ND
Total Related Substances NB 1, PDR 16	Not more than 3.0%		0.6%

Treprostinil diethanolamine prepared according to claims 1 or 10

	Compound	Specifications	
Impurities (HPLC) (Known Impurities) (UTW-11-0327)	1AU90	Not more than 0.4 %	ND
	2AU90	Not more than 0.1 %	ND
	970B6	Not more than 0.2 %	ND
	3AU90	Not more than 0.5 %	< 0.05 % w/w
	Treprostinil Methyl Ester	Not more than 0.2 %	ND
	Treprostinil Ethyl Ester	Not more than 0.5 %	ND
	750W93	Not more than 0.5 %	ND
	751W93	Not more than 0.3 %	ND
Impurities (HPLC) (Unidentified Impurities) (UTW-11-0327)	Not more than 0.2 % AUC each		0.07 % AUC (RRT 0.26)
Impurities (HPLC) (Total Related Substances) (UTW-11-0327)	Not more than 1.5 %		0.1 % w/w

Treprostinil as the free acid prepared according to claims 1 or 10

	Compound	Specifications	
Impurities (HPLC)	1AU90	Not more than 0.40%	ND
	2AU90	Not more than 0.10%	ND
	3AU90	Not more than 1.00%	ND
	750W93	Not more than 0.50%	0.05 % w/w
	751W93	Not more than 0.30%	< 0.05 % w/w
	970B6 (Benzisoxime Triol)	Not more than 0.20%	ND
	Treprostinil Ethyl Ester	Not more than 0.50%	0.13 %w/w
	Treprostinil Methyl Ester	Not more than 0.20%	ND
Impurities (HPLC) (Unidentified Impurities)	Not more than 0.10% AUC each		ND
Impurities (HPLC) (Total Related Substances)	Not more than 2.00%		0.2 %

(*Id.*). The Walsh Declaration then analyzes the above data as follow:

> The impurity profiles shown above examine the following eight impurities: 1AU90, 2AU90 and 3AU90, each of which is a stereoisomer of treprostinil; triol; methyl ester of treprostinil and ethyl ester of treprostinil; 750W93 and 751W93, each of which is a dimer of treprostinil, in which the acid group of one treprostinil molecule esterifies with an alcohol group on another treprostinil molecule. According to the first profile above, treprostinil produced according to the process of 'Moriarty' has 7 out of 8 impurities in detectable amounts. According to the second profile above, treprostinil diethanolamine prepared according to the process specified in claim 1 or 10 of the present application has only one impurity, treprostinil stereoisomer 3A90, in a detectable amount. According to the third profile above, treprostinil as the free acid prepared according to the process specified in claim 1 or 10 of the present application has only three impurities, treprostinil ethyl ester, treprostinil dimers 750W93 and 751W93.

(*Id.* at ¶ 7). Finally, the Walsh Declaration concludes as follows:

> Based on the results shown above, I conclude that each of treprostinil as the free acid and treprostinil diethanolamine prepared according to the process specified in claim 1 or 10 of the present application is physically different from treprostinil prepared according to the process of 'Moriarty' at least because neither of them contains a detectable amount of any of benzindene triol, treprostinil methyl ester, 1AU90 treprostinil stereoisomer and 2AU90 treprostinil stereoisomer, each of which were present in detectable amounts in treprostinil produced according to the process of 'Moriarty'.

(*Id.* at ¶ 8).

The Examiner concluded that the arguments made in the June 5th response were sufficient to overcome the rejection over the Moriarty JOC article, and issued a Notice of Allowance on June 12, 2013. The '393 patent issued on June 30, 2013.

UTC filed a request for a certificate of correction on January 8, 2014 to correct a misspelling in five claims: "tromethanine" in claims 5, 13, 17 19 and 20 should have been spelled "tromethamine." A certificate of correction issued on May 27, 2014 that corrected this error. UTC filed a second request for a certificate of correction on January 6, 2015 which would amend the specification and claim 1 such that the language "αOR_1:β-R_5" would read "α-OR_2:β-R_5."

III. THE ASSERTED CLAIMS OF THE '393 PATENT ARE INVALID

A. Introduction

The '393 patent contains product-by-process claims that recite an improved process for making treprostinil, the active ingredient in Remodulin®. The priority date for the '393 patent is December 17, 2007.

Treprostinil is an old compound, first patented more than 35 years ago in U.S. Pat. No. 4,306,075 (issued Dec. 15, 1981) and described in numerous subsequent prior art publications.

Remodulin®, the first commercial product to contain treprostinil, was approved by the U.S. Food and Drug Administration for the treatment of pulmonary hypertension in 2002.

Each of the 22 claims of the '393 patent is written in product-by-process form. The claims are directed to products comprising the treprostinil compound (or compounds of a genus that includes treprostinil), made by a process that includes certain process steps. Because the claims are directed to a product that comprises treprostinil, UTC listed the '393 patent in the FDA's Approved Drug Products with Therapeutic Equivalence (commonly known as the "Orange Book") as covering its Remodulin® product.

The '393 patent thus claims an old product (products comprising treprostinil) made by a new process. This fact is underscored by the Orange Book listing for the '393 patent for Remodulin®, which, as of the 2007 priority date for the '393 patent, was an old product that had been commercially available for five years.

For more than a century, however, the law has been that an old product is not patentable even if it is made by a new process. Product-by-process claims are anticipated by the disclosure of the same product in the prior art. In this case, the claimed product is a product that contains the treprostinil compound or a pharmaceutically acceptable salt thereof in any amount or concentration (with the exception of claim 2). Thus, the Asserted Claims of the '393 patent (except for claim 2) are anticipated by the disclosure of products that include the treprostinil compound, or pharmaceutically acceptable salts thereof, in any amount. Prior art disclosure of products that contain treprostinil include the Remodulin product, the Remodulin package insert, and the numerous other prior art references.

Notwithstanding this rule of law, UTC obtained the '393 patent by arguing that the claimed process results in a different product than the product disclosed in the prior art,

specifically as disclosed in the Moriarty JOC Article. While not explicitly addressed during prosecution, the Federal Circuit has held that a new process can support patentability if the process imparts "structural and functional differences" distinguishing the claimed product from the prior art. UTC told the Patent Office that the product disclosed in the Moriarty JOC Article was "physically different" from the product of the '393 patent because a batch of treprostinil produced by the Moriarty JOC Article process contained detectable amounts of four different impurities (benzindene triol, treprostinil methyl ester, and two different stereoisomers of treprostinil), that were avoided in batches of treprostinil salt or treprostinil acid made by the '393 patent process. The '393 patent issued after receipt of a declaration from the applicant containing this information, without a statement of reasons for allowance by the Examiner.

However, the treprostinil compound produced by the Moriarty process is identical to the treprostinil compound produced by the '393 process. There is no "structural" difference between the two products. Any difference in impurities produced while making treprostinil by the new '393 patent process is not a "structural" difference as described in the relevant Federal Circuit case law and cannot overcome the general rule that an old product is not patentable even if it is made by a new process. Instead, a "structural" difference relevant to patentability would be a difference in the chemical structure of the molecule produced through the claimed process. (*See Amgen*, 580 F.3d at 1367). There is no dispute that the treprostinil molecule produced through the '393 patent process is the exact same molecule as that disclosed in the prior art. Accordingly, any differences in impurity profiles cannot provide evidence of structural differences.

Moreover, UTC did not and cannot allege there is a *functional* difference resulting from the alleged difference in detectible amounts of the four individual impurities, as required by the

Federal Circuit. UTC used the Moriarty 2004 process to manufacture its Remodulin product at least until 2006, and the '393 patent process starting in 2008. Remodulin® was functionally the same both before and after the change in manufacturing process. For example, there is no evidence or indication that the Remodulin® product now produces a different clinical effect because of the change in manufacturing process.

And in any event, UTC cherry-picked the three individual batches of treprostinil it used to argue to the Patent Office that the '393 process resulted in the avoidance of the four impurities produced by the Moriarty JOC Article process. UTC's documents produced in Civil Action No. 12-cv-01617 reveal that other batches of treprostinil made by UTC contained different impurity profiles than the three batches UTC selected to disclose to the Patent Office. This is true both for batches made by the Moriarty JOC Article process and for batches made by the '393 patent process. Some batches made by the '393 patent process *had* detectible amounts of three of the four impurities UTC represented to the Patent Office were avoided by the '393 process, while some batches made by the Moriarty JOC Article process did *not* have detectible amounts of the fourth impurity UTC had said was avoided by the '393 process. The data reflect normal batch-to-batch variations in detectible impurities produced by both processes, and there is no consistent pattern of specific impurities that are present in batches made by the Moriarty JOC Article process that are avoided by the '393 process. So even if a difference in detectible amounts of specific impurities were sufficient to impart patentability to the '393 patent claims, which it is not, the facts do not support the proposition that the '393 patent process avoids impurities produced by the Moriarty JOC Article process.

B. Scope And Content Of The Prior Art

As is described in detail below, the prior art discloses both the treprostinil salt claimed in the Asserted Claims of the '393 patent as well as the claimed process steps. The pertinent disclosure of each prior art reference is summarized briefly below.

1. The '075 Patent

U.S. Patent No. 4,306,075 ("the '075 patent") issued on December 15, 1981, is entitled "Composition and Processes" and is generally directed to the disclosure of prostacyclin analogs. The '075 patent discloses that the benzindene class of analogs and their salts exhibit prostacyclin-like pharmacological properties, such as platelet aggregation inhibition, gastric secretion reduction and bronchodilation. ('075 patent, Col. 12:27-14:60). Among the specific benzindene analogs the '075 patent discloses is the compound 9-Deoxy-2',9α-methano-3-oxa-4,5,6-trinor-3,7-(1',3'-interphenylene)-13,14-dihydro-PGF_1, which is treprostinil. ('075 patent, Example 33, Col. 62:3-39).

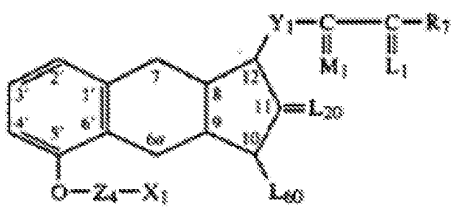
The '075 patent describes a method of making treprostinil in Example 33, and also claims the treprostinil compound. ('075 patent at Col. 56:15-Col. 59:15, Col. 62:4-39, Col. 97:46-47; *see also* Civil Action No. 12-1617 Trial Tr. at 1850:10-21). Example 33 discloses 0.096 g of treprostinil final product. ('075 patent at Col. 62:34-35). The '075 patent also discloses pharmacologically acceptable salts of the compounds disclosed therein. ('075 patent at Col. 14:56-Col. 15:42, Col. 30:41-62).

2. The '814 Patent

U.S. Patent No. 4,668,814 ("the '814 patent") is entitled "Interphenylene Carbacyclin Derivatives," was filed on January 11, 1985 and issued on May 26, 1987 to the Upjohn Company. The '814 patent specification states that the "present invention relates to novel

pharmaceutically useful compounds which are carbacyclin analogs having a tricyclic nucleus." (Civil Action No. 12-1617, D.I. 218, Ex. 1, Stipulated Fact No. 36).

The '814 patent discloses a class of compounds having the structure of Formula I, and a "new procedure for preparing compounds of Formula I(a)" (both shown below):



Formula I and Formula I(a)

(Civil Action No. 12-1617, D.I. 218, Ex. 1, Stipulated Fact No. 37). The class of compounds having the structure of Formula I(a) includes treprostinil. (*Id.* at Stipulated Fact No. 38). The '814 patent specification discloses and teaches pharmacologically acceptable salts of Formula I and I(a) at Cols. 2:13, 4:42, 8:47, 13:55-58; 13:67-14:11; 14:60-66. (*Id.* at Stipulated Fact No. 39).

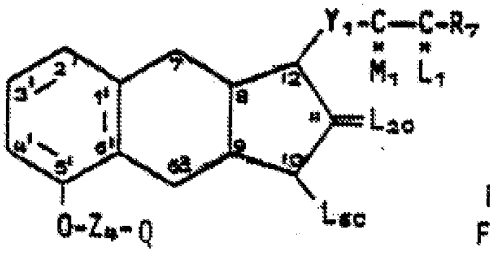
The first lines of Example 3 of the '814 patent refer to treprostinil by the chemical name "9-Deoxy-13,14-dihydro-2',9α-methano-3-oxa-4,5,6-trinor-3,7-(1',3-interphenylene)-PGF1." (Civil Action No. 12-1617, D.I. 218, Ex. 1, Stipulated Fact No. 41). The chemical name 9-Deoxy-13,14-dihydro-2',9α-methano-3-oxa-4,5,6-trinor-3,7-(1',3-interphenylene)-PGF1 disclosed in Example 3 of the '814 patent contains an obvious typographical error. In particular, there should be a prime symbol after the "3" in the phrase "(1',3-interphenylene)". (*Id.* at Stipulated Fact No. 42). The chemical name used for treprostinil in Example 3 of the '814 patent ("9-Deoxy-13,14-dihydro-2',9α-methano-3-oxa-4,5,6-trinor-3,7-(1',3'-interphenylene)-PGF1") is not verbatim the same as the chemical name disclosed in Example 1 of the '117 patent ("9-

Deoxy-2',9α-methano-3-oxa-4,5,6-trinor-3,7-(1',3'-interphenylene)-13,14-dihydro-PGF1)." The "13,14 dihydro" phrase appears at the beginning of the chemical name used in the '814 patent, but towards the end of the chemical name used in Example 1 of the '117 patent. (*Id.* at Stipulated Fact No. 43). The '814 patent discloses pharmacologically acceptable salts of treprostinil. (*Id.* at Stipulated Fact No. 44).

The '814 patent discloses an improved process of making treprostinil. (Civil Action No. 12-1617, Trial Tr. at 1850:22-1851:6). The product obtained at the end of Example 3 of the '814 patent is 1.2 grams of the treprostinil compound. (*Id.* at 1856:12-15). The 1.2 grams of treprostinil obtained is about 95% pure. (*Id.* at 1856:16-22).

3. EP '784

European Patent Publication No. 0159784A1 ("EP '784") is entitled "Carbacyclin analogues," and was filed on March 6, 1985 and published on October 30, 1985. The EP '784 specification states that "[t]he present invention relates to novel, pharmaceutically-useful compounds which are carbacyclin analogues having a tricyclic nucleus." (EP '784 at 1:2-4). In particular, the publication is directed to compounds of Formula I (shown below), pharmaceutically acceptable salts thereof, intermediates useful in preparing this compound, and the process of making those intermediates.



Formula I and Formula I(a)

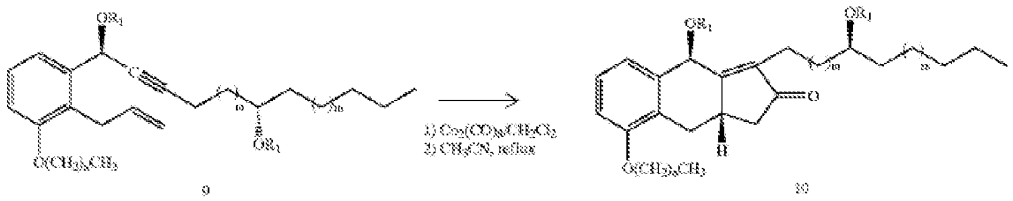
Example 9 of EP '784 discloses the chemical formula 9-Deoxy-13,14-dihydro-2',9α-methano-3-oxa-4,5,6-trinor-3,7-(1',3'-interphenylene)-PGF_1 (EP '784 at 66:23-71:29). The compound represented by chemical formula 9-Deoxy-13,14-dihydro-2',9α-methano-3-oxa-4,5,6-trinor-3,7-(1',3'-interphenylene)-PGF_1 is the treprostinil compound. EP '784 teaches that the compounds of Formula 1 or 1(a), wherein Q is $COOR_1$ (which includes treprostinil), may be used in the free acid form or in pharmacologically acceptable salt form. (EP '784 at 20:21-23). The method for making treprostinil disclosed in EP '784 is identical to the method disclosed in the '814 patent. (Civil Action No. 12-1617, D.I. 218, Ex. 1, Stipulated Fact No. 45).

4. The '117 Patent

U.S. Patent No. 6,765,117 ("the '117 patent") is entitled "Process for stereoselective synthesis of prostacyclin derivatives." (Civil Action No. 12-1617, D.I. 218, Ex. 1, Stipulated Fact No. 22). The '117 patent was issued by the PTO on July 20, 2004 and is assigned on its face to United Therapeutics Corporation. (*Id.* at Stipulated Fact No. 23; '117 patent cover page). The named inventors on the '117 patent are Robert M. Moriarty, Raju Penmasta, Liang Guo, Munagala S. Rao, and James P. Staszewski. (*Id.* at Stipulated Fact No. 25). The application that matured into the '117 patent was a division of application no. 09/541,521, filed on April 3, 2000, now U.S. Patent No. 6,441,245, which is a continuation-in-part of application no. 09/481,390, filed on January 12, 2000, which is a continuation of application no. 08/957,736, filed on October 24, 1997. (*Id.* at Stipulated Fact No. 26).

The '117 patent specification states that the "present application relates to a process for producing prostacyclin derivatives and novel intermediate compounds useful in the process." ('117 patent, Col. 1:13-16). The '117 patent explains that the invention differs from the prior art in that the "invention relates to a process for preparing 9-deoxy-PGF_1-type compounds by a

process that is stereoselective and requires fewer steps than the prior art." ('117 patent, Col. 4:23-26). The specification of the '117 patent discloses a method of synthesizing treprostinil that involves the intramolecular cyclization step, shown below:



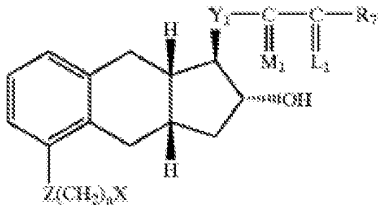
The '117 patent includes only one example, which describes a 15 step method of synthesizing treprostinil. ('117 patent at Col. 11:55-21:12). The final step of Example 1 describes a process of obtaining crude treprostinil and then purifying the crude product by silica gel chromatography using a dichloromethane solution containing 3% methanol and 0.1% acetic acid as eluent to yield 0.076 g of product (95%). ('117 patent at Col. 21:8-11).

The '117 patent is listed in the Orange Book in connection with NDA No. 21-272 for Remodulin. (Civil Action No. 12-1617, D.I. 218, Ex. 1, Stipulated Fact No. 11). The '117 patent is also listed in the Orange Book for UTC's Orenitram product, which is an oral dosage form with treprostinil diethanolamine as the API. (Orenitram Orange Book Listing). The '117 patent is designated as covering the drug substance of both Remodulin and Orenitram in the Orange Book. In listing the '117 patent in the Orange Book as covering Remodulin and Orenitram, UTC represented to the FDA that the '117 patent is a patent "with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product" and that the '117

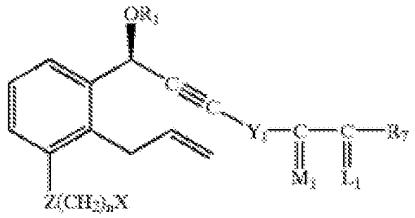
patent either "claim[s] the drug substance that is the subject of the pending or approved application or that claim[s] a drug substance that is the same as the active ingredient that is the subject of the approved or pending application." 21 C.F.R. 314.53(b)(1).

The '117 patent claims are product-by-process claims directed to treprostinil produced through a process that includes the Pauson-Khand cyclization step. ('117 patent, claims 1-4). Claim 1 reads, in pertinent part, as follows:

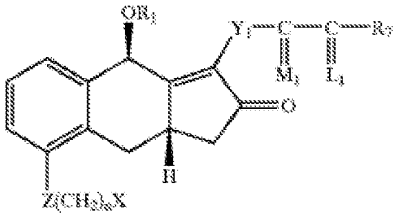
1. A stereoselectively produced isomeric compound according to the following formula:



that is produced by a process for making 9-deoxy-PGF_1-type compounds, the process comprising cyclizing a starting compound of the formula:



into a compound of the following formula:



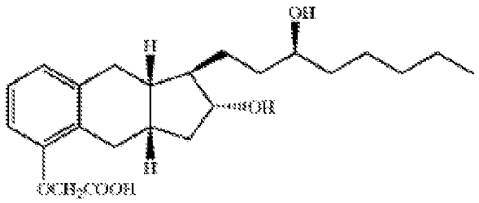
by intramolecular cyclization of the enyne,

('117 patent at Col. 21:23-59).

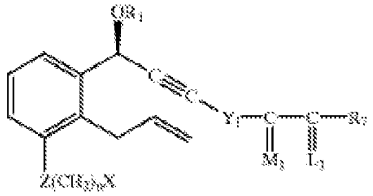
Claim 3 of the '117 patent reads, in pertinent part, as follows:

('117 patent at Col. 21:23-59).

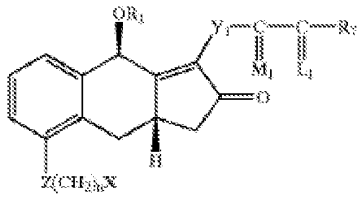
3. A stereoselectively produced isomeric compound according to the following formula:



that is produced by a process for making 9-deoxy-PFG$_2$-type compounds, the process comprising cyclizing a starting compound of the formula:



into a compound of the following formula:

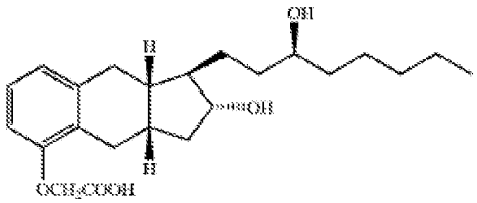


by intramolecular cyclization of the enyne,

('117 patent at Col. 22:42-Col. 23:12).

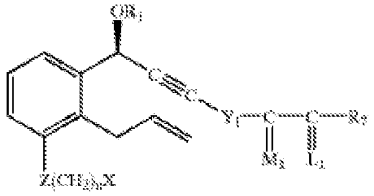
Claim 4 of the '117 patent reads in pertinent part as follows:

4. A stereoselectively produced isomeric compound in pharmacologically acceptable salt form according to the following formula:

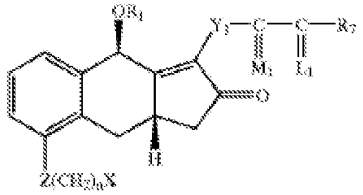


that is produced by process for making 9-deoxy-PGF_1-type compounds, the process comprising cyclizing a

starting compound of the formula:



into a compound of the following formula:



by intramolecular cyclization of the enyne,

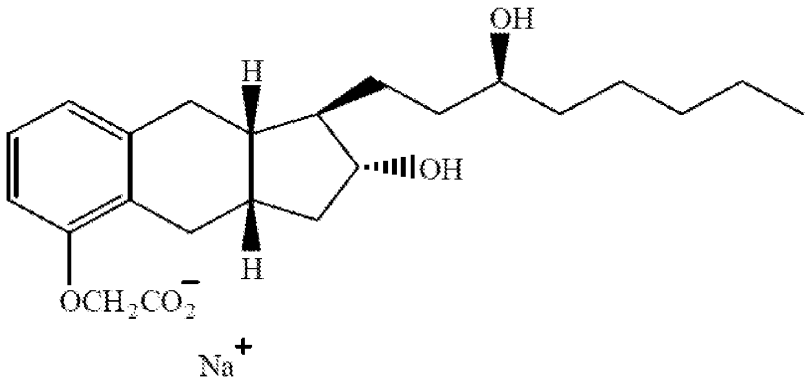
('117 patent at Col. 23:53-Col. 24:23).

5. The 2006 Remodulin® Package Insert

The 2006 Remodulin Package Insert ("Package Insert") discloses UTC's commercial treprostinil product and was approved by the FDA in March, 2006. (2006 Package Insert at 1, 15). The Package Insert states as follows:

> Remodulin® (treprostinil sodium) Injection is a sterile sodium salt formulated for subcutaneous or intravenous administration. Remodulin is supplied in 20 mL multi-use vials in four strengths, containing 1 mg/mL, 2.5 mg/mL, 5 mg/mL or 10 mg/mL of treprostinil. Each mL also contains 5.3 mg sodium chloride (except for the 10 mg/mL strength which contains 4.0 mg sodium chloride), 3.0 mg metacresol, 6.3 mg sodium citrate, and water for injection. Sodium hydroxide and hydrochloric acid may be added to adjust pH between 6.0 and 7.2.

(Package Insert at 1). The Package Insert also provides the chemical name for treprostinil sodium as "(1R,2R,3aS,9aS)-[[2,3,3a,4,9,9a-Hexahydro-2-hydroxy-1-[(3S)-3-hydroxyoctyl]-1Hbenz[f]inden-5-yl]oxy]acetic acid monosodium salt" and discloses that "[t]reprostinil sodium has a molecular weight of 412.49 and a molecular formula of $C_{23}H_{33}NaO_5$." (*Id.*). Further, the Package Insert discloses that the "structural formula of treprostinil sodium" is as follows:



(*Id.*).

6. The Remodulin Product

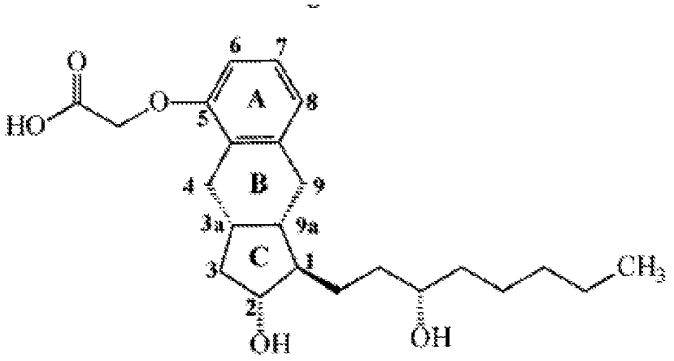
The Remodulin® product is the subject of UTC's NDA No. 21-272, and has treprostinil sodium as its active ingredient. (Civil Action No. 12-1617, D.I. 218, Ex. 1, Stipulated Fact No. 3; Package Insert). Remodulin was first approved in the United States in May 2002, and is indicated for the treatment of pulmonary arterial hypertension ("PAH"). (*Id.* at Stipulated Fact No. 4). Remodulin is an injectable product approved for sale in concentrations including 1 mg/mL, 2.5 mg/mL, 5 mg/mL, and 10 mg/mL. (*Id.* at Stipulated Fact No. 5). In November 2004, the Food and Drug Administration ("FDA") approved Remodulin for intravenous use. (*Id.* at Stipulated Fact No. 6). UTC has listed the '393 patent in the Orange Book as covering the Remodulin Product. (Remodulin Orange Book Listing).

7. Moriarty JOC Article

Moriarty, et al in *J. Org. Chem.* 2004, 69, 1890-1902 (2004) ("Moriarty JOC Article") was received for publication on June 5, 2003 and published on February 19, 2004. The Moriarty JOC Article discloses that "[t]o meet the demands of producing multikilogram quantities of UT-15 ([compound] 7) needed in the course of drug development, an efficient and economical synthesis [of treprostinil] had to be devised." (Moriarty JOC Article at 1892). The Moriarty JOC Article explains that while researchers had previously employed three methods of synthesizing the molecule (Schemes 1-3), these prior schemes resulted in "low level of control of stereochemistry," and were "deemed inadequate to the task of producing kilogram quantities of UT-15." (*Id.* at 1892-1893). Moriarty explained that "[t]he principal requirement envisioned was production of an enantiopure intermediate early in the synthesis, ideally at the tricyclic stage", and that "the intramolecular asymmetric Pauson-Khand cyclization of enynes to cyclopentenones could fulfill both requirements." (*Id.* at 1893). The Moriarty JOC Paper

concludes that "[t]the strategy of employing the highly diastereoselective 1,2-asymmetric induction in the PKC using a temporary and readily removable stereodirecting group results in an asymmetric synthesis that is superior to other methods used to date." (*Id.* at 1898).

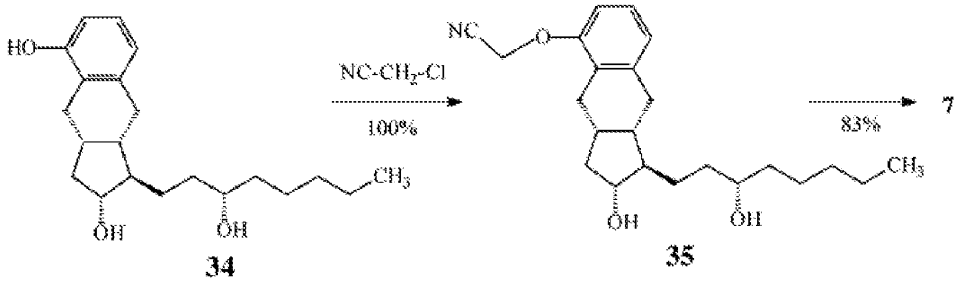
The Moriarty synthesis is depicted in Scheme 4, which results in the production of treprostinil free acid, which is depicted as compound 7.



7

(Moriarty JOC article at 1892, 1895).

The process disclosed in the Moriarty JOC article includes the steps of alkylating the benzindene triol (compound 34) to make the nitrile intermediate (compound 35) and hydrolyzing the nitrile with a base to form treprostinil free acid:



34 35

(*Id.* at 1895). The above process steps are described in the Moriarty JOC article as follows: "[t]riol **34** was alkylated at the phenolic hydroxyl group with use of chloroacetonitrile in refluxing acetone with potassium carbonate (**34** → **35**) and nitrile **35** was hydrolyzed with ethanolic potassium hydroxide to yield UT-15 (**7**) in 9% overall yield." (*Id.* at 1897). The Moriarty JOC article also includes an experimental section which describes in detail the synthesis of 441 grams of treprostinil acid having a purity of 99.7%. (*Id.* at 1902).

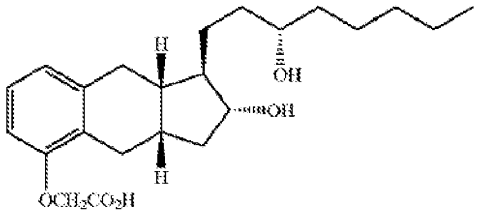
In the experimental section, the Moriarty JOC article further discloses that the hydrolysis step involved adding a solution of potassium hydroxide to a solution of nitrile in methanol and then refluxing the mixture for three hours, after which point the reaction mixture was cooled to 0°C. (Moriarty JOC Article at p. 1902). Then, hydrochloric acid was added to adjust the pH to 10-12, and the solvent was removed in vacuo, at which point the solution was extracted with ethyl acetate. (*Id.*). The aqueous layer was retained and acidified to pH 2-3 by addition of hydrochloric acid. (*Id.*).

8. The Phares Publication

U.S. Patent Application Publication No. 2005/0085540A1 ("The Phares Publication") was published on April 21, 2005. The Phares Publication is entitled "Compounds and Methods for Delivery of Prostacyclin Analogs" and is generally directed to "prostacyclin analogs and methods for their use" in various medical treatments. (Phares at 1, ¶ 0002). The Phares Publication discloses that "treprostinil sodium (Remodulin®) is approved by the Food and Drug Administration (FDA) for subcutaneous administration" and that "treprostinil as the free acid has an absolute oral bioavailability of less than 10%." (*Id.* at ¶ 0004). The purpose of the invention was to serve the "clinical interest in providing treprostinil orally," and "increasing systemic availability of treprostinil via administration of treprostinil or treprostinil analogs." (Id. at ¶

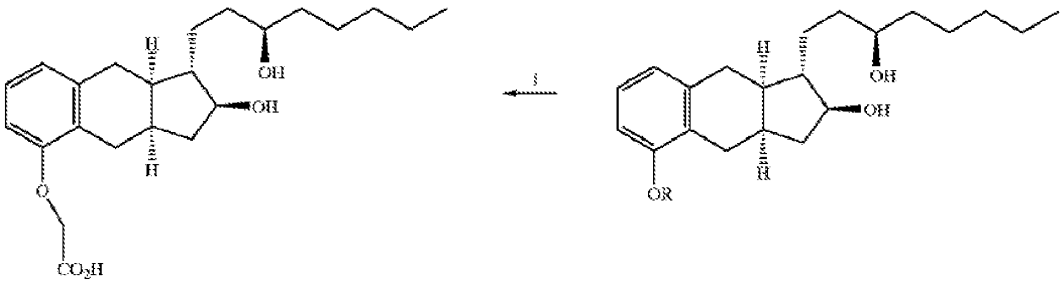
0004-0005). The Phares Publication further provides that "[a] preferred embodiment of the present invention is the diethanolamine salt of treprostinil." (*Id.* at ¶ 0051).

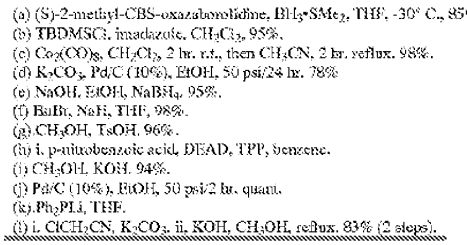
The Phares publication discloses a method of making treprostinil involving alkylating benzindene triol to form the nitrile, then hydrolyzing the nitrile with a base (KOH) to obtain the free acid. (Phares publication at ¶¶ 0143-0145). Phares teaches that chemical derivatives of (+)-treprostinil are included within the scope of the invention:



(+)-treprostinil

(*Id.* at ¶ 0050). Phares teaches the preparation of (-)-treprostinil but notes that (+)-treprostinil can be prepared in the same manner. (*Id.* at ¶¶ 0143-0145). According to Phares, (-)-treprostinil can be prepared by alkylating the benzindene triol compound shown below (note R= H) with chloroacetonitrile to form a benzindene nitrile compound which can then be hydrolyzed to the free acid of treprostinil using KOH:





(*Id.* at ¶ 0144).

The Phares publication then discloses converting treprostinil free acid into treprostinil diethanolamine salt as follows:

> Treprostinil acid acid [*sic*] is dissolved in a 1:1 molar ratio mixture of ethanol:water and diethanolamine is added and dissolved. The solution is heated and acetone is added as an antisolvent during cooling.

(Phares publication at ¶ 0105).

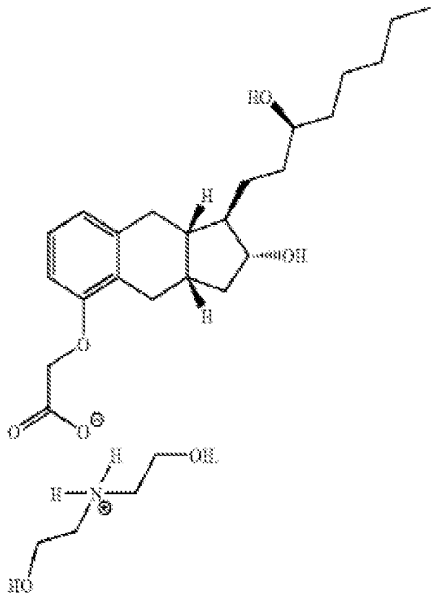
The Phares Publication also teaches that treprostinil diethanolamine can be recrystallized to yield two crystalline polymorphs, including the metastable polymorph A, and the thermodynamically more stable polymorph B. (*Id.* at ¶ 327). According to Phares, the resulting polymorphs have melting points at 103° C (Form A) and 107° C (Form B), respectively. (*Id.* at ¶¶ 0332, 0337). Phares also teaches that the recrystallized treprostinil diethanolamine can be combined with dextrose to yield a final dosing solution. (*Id.* at 214).

Finally, Phares discloses animal testing involving administration of treprostinil diethanolamine to rats in Example 1 and clinical trials using treprostinil diethanolamine salt formulations in Example 5. (Phares Publication at ¶¶ 0203-0237, 0311-0326). Pharmacokinetic testing of an oral formulation of treprostinil diethanolamine in human patients showed an absolute bioavailability of 21-25% for the four doses tested. (*Id.* at ¶ 0319).

9. The '070 Patent

The Phares publication is the publication of U.S. Patent Application No. 10/851,481 ("the '481 application"), which was filed on May 24, 2004, and which ultimately issued as U.S. Patent No. 7.417,070 ("the '070 patent") on August 26, 2008. Accordingly, the disclosure of the '070 patent is the same as that described above with respect to the Phares Publication. Additionally, the '070 patent claims treprostinil diethanolamine salt, as shown below:

1. A compound having the following structure:

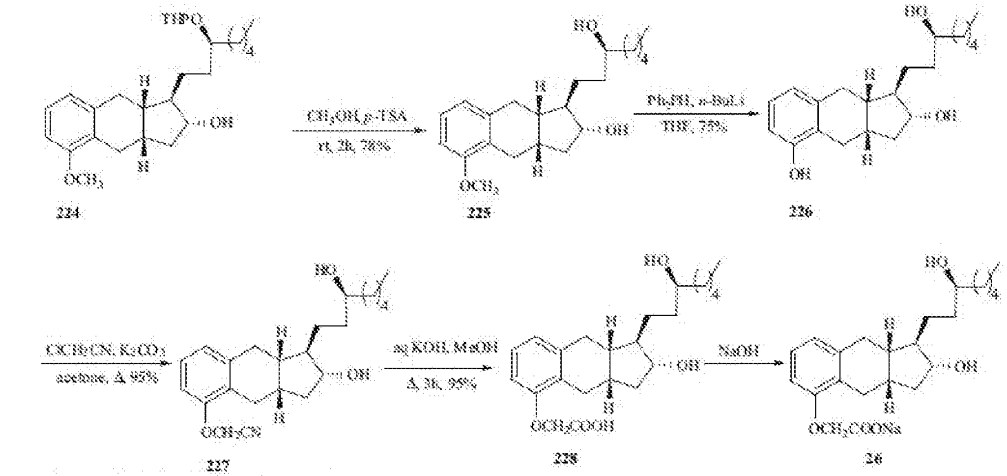


The '070 patent is listed in the Orange Book for UTC's Orenitram product, which is an oral dosage form with treprostinil diethanolamine as the API. (Orenitram Orange Book Listing). The '070 patent is designated as covering the drug substance of Orenitram in the Orange Book. In listing the '070 patent in the Orange Book as covering Orenitram, UTC represented to the FDA that the '070 patent is a patent "with respect to which a claim of patent infringement could

reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product" and that the '070 patent either "claim[s] the drug substance that is the subject of the pending or approved application or that claim[s] a drug substance that is the same as the active ingredient that is the subject of the approved or pending application." 21 C.F.R. 314.53(b)(1).

10. Li

The article "Synthetic Approaches To The 2002 New Drugs" by Jin Li and Kven K.-C. Liu (*Mini-Reviews in Medicinal Chemistry*, Vol. 4 at pp. 207-233 (2004) ("Li")) describes the synthesis of twenty-two drugs brought to market in 2002, including treprostinil. The Li reference discloses a process of making treprostinil that involves alkylating the benzindene triol (compound 226) to obtain the nitrile (compound 227), hydrolyzing the nitrile with a base to form treprostinil acid (compound 228), and then contacting the product of the previous step with a base (NaOH) to form treprostinil sodium salt (compound 26), as shown below:

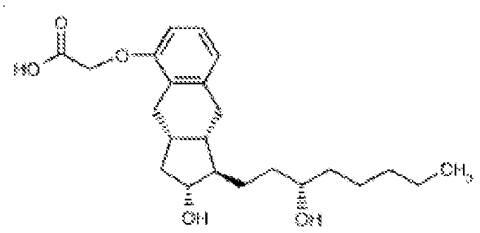


Scheme 28. Synthesis of treprostinil sodium.

(Li at p. 229).

11. Sorbera

Sorbera, *et al.*, "UT-15. Treatment of Pulmonary Hypertension, Treatment of Peripheral Vascular Disease," *Drug of the Future*, Vol. 26(4), pp. 364-374 (2001) ("Sorbera") discloses the treprostinil compound, as shown below, and further discloses several methods of making treprostinil. (*Id.* at 364).



$C_{23}H_{34}O_5$ Mol wt: 390.524

Sorbera further discloses that treprostinil is the active ingredient in Remodulin, and states as follows:

> UT-15 (Remodulin ™), on the other hand, is a chemically stable benzindene analog of prostacyclin that has shown potent preclinical and clinical efficacy and may be a potential treatment for advanced pulmonary hypertension and late-stage vascular disease. The compound is stable at room temperature for up to 5 years and is delivered via s.c. infusion using a MiniMed microinfusion device, thus eliminating the risk of sepsis infection and hospitalization associated with catheters (17). UT-15 has been chosen for further development.

(Sorbera at p. 369). Sorbera then proceeds to describe nonclinical and clinical testing of the Remodulin product. (*Id.* at pp. 369-73).

12. Additional Prior Art References That Disclose Treprostinil

In addition to those discussed above, the treprostinil compound was disclosed in the following references:

- Whittle & Moncada, "Antithrombotic Assessment and Clinical Potential of Prostacyclin Analogues," Chapter 6, Progress in Medicinal Chemistry, Volume 21 (Ellis & West, eds.) pp. 238-279, at p. 238 (1984) ("Whittle 1984")
- Aristoff et al, "Synthesis and Structure - Activity Relationship of Novel Stable Prostacyclin Analogs," Adv. in Prostaglandin, Thromboxane and Leukotriene Research, Vol. 11, pp. 267-74 (1983)) ("Aristoff 1983").
- U.S. Patent No. 4,306,076 (Dec. 15, 1981)
- U.S. Patent No. 5,153,222 (Oct. 6, 1992)
- WO 99/21830 (May 6, 1999)
- Patterson, J. H., *et al.* "Acute Hemodynamic Effects of the Prostacyclin Analog 15AU81 in Severe Congestive Heart Failure," *The American Journal of Cardiology,* Vol. 75, pp. 26A-33A, (1995).

13. Anderson

In 2000, the Academic Press published a book entitled "Practical Process Research & Development: A Guide for Organic Chemists" by Neal Anderson ("Anderson"). Anderson describes various chemical processes for use in development of pharmaceutical compounds, and provides a guide for chemists in the pharmaceutical industry to perform practical and efficient processes. In Chapter 1, entitled "Approaches to Process Development," Anderson explains that "Chromatography is very labor-intensive," and suggests that

> The difficulties of effecting purification by chromatography on scale encourages the process chemist to devise routes with crystalline intermediates, to upgrade quality by recrystallizing. Consequently chromatography is used on scale when other forms of purification are ineffective. Products purified by chromatography have relatively low production volume and high value after processing ….

(Anderson at 13).

Anderson describes the benefits of "telescoping" in a commercial manufacturing process in Chapter 2 as an example of a characteristic of "cost-effective" synthesis routes:

> Isolating intermediates has many potential disadvantages. Isolation is usually costly and invariably leads to some loss of valuable material. On a manufacturing scale, isolating intermediates and API requires about 50% of personnel time and about 75% of equipment financial outlay. The additional handling required increases both exposure of operators to pharmacologically potent materials and opportunities for contamination of batches and loss of valuable product. Intermediates may be isolated to ensure key purifications or to comply with protocols filed with the FDA or other regulatory agencies.
>
> Isolations are avoided by telescoping. Telescoping, also known as concatenation or through-processes, is the process of carrying the product of a reaction without isolation into the next step. Inappropriate telescoping can compound the difficulties in isolating a reaction product that is sufficiently pure from the subsequent step, but appropriate telescoping can greatly increase overall yields.
>
> * * * * *
>
> Unless significant purification or other benefits are realized by isolating intermediates, telescoping is incorporated as part of cost-effective routes.

(Anderson at p. 34).

In Chapter 11, entitled "Tools for Purifying the Product: Column Chromatography, Crystallization and Reslurrying," Anderson adds, "Considering the drawbacks of chromatography on scale, chromatographic purifications are generally used only when reaction optimization and non-chromatographic means of purification prove inadequate to prepare high-quality products." (*Id.* at 223). Alternatively, Anderson goes on to explain that "A good crystallization process reliably provides high-quality product with suitably low levels of impurities." (*Id.* at 226). Further, Anderson teaches that "[s]alt formation may be key for efficient purification of ionizable compounds." (*Id.* at p. 238). Anderson further discloses that "[v]arious salts can display different solubilities and tendencies to crystallize and might possess physicochemical differences that can be exploited for convenient processing on scale. Salt forms

of drug candidates are selected for desired stability, bioavailability, and formulation characteristics." (*Id.*).

Thus, Anderson teaches that one of ordinary skill in the art would have been motivated to use crystallization techniques in lieu of column chromatography, in order to obtain larger volume of product with fewer impurities.

Chapter 3 of Anderson, entitled "Reagent Selection" includes descriptions of "families" of reagents useful for scale-up. (Anderson at p. 61). Amine bases are discussed as one category of reagents for deprotonation. (*Id.* at pp. 61, 63). Diethanolamine is listed in Table 3.7 on page 64 as one of the "Amines Useful for Scale-Up." (*Id.* at p. 64). Anderson further explains that "[t]he solubility of acid salts of the amines (Table 3.7) can provide some operating advantages on scale." (*Id.* at p. 66).

C. Level Of Skill In The Art

A person of ordinary skill in the art would have a Ph.D. in organic or medicinal chemistry, and at least a few years of experience in medicinal chemistry, including in the development of potential drug candidates. A person of ordinary skill in the art would also include a person who has a Bachelor's or Master's degree in organic chemistry or medicinal chemistry if such a person had more years of experience in medicinal chemistry and the development of potential drug candidates.

D. THE LAW APPLICABLE TO THE PATENTABILITY OF THE PRODUCT-BY-PROCESS CLAIMS OF THE '393 PATENT

The claims of the '393 patent are drawn to products comprising treprostinil or related compounds made by a process comprising at least three out of the four steps of (a) alkylation, (b) hydrolysis, (c) salt formation, and (d) optional reformation of the free acid (acidification).

Claims of this type are classified as product-by-process claims. *See Bonito Boats*, 489 U.S. at 159 (A 'product-by-process' claim is "one in which the product is defined at least in part in terms of the method or process by which it is made").

1. The General Rule Is That Process Limitations Are Ignored In Determining The Patentability Of Product-By-Process Claims

A product-by-process claim is anticipated if the product is disclosed in the prior art. *Amgen*, 580 F.3d at 1366; *SmithKline Beecham Corp. v. Apotex Corp.*, 439 F.3d 1312, 1317 (Fed. Cir. 2006) ("It has long been established that one cannot avoid anticipation by an earlier product disclosure by claiming the same product more narrowly, that is, by claiming the product as produced by a particular process"); *Gen. Elec. Co. v. Wabash Appliance Corp.*, 304 U.S. 364, 373 (1938); *Cochrane v. Badische Anilin & Soda Farbrik*, 111 U.S. 293, 311 (1884) ("While a new process for producing [a chemical compound] was patentable, the product itself could not be patented even though it was a product made [by a new process] for the first time because the product was disclosed in the prior art").

"In determining the validity of a product-by-process claim, the focus is on the product and not on the process of making it." *Amgen*, 580 F.3d at 1369-70; *In re Thorpe*, 777 F.2d 695, 697 (Fed. Cir. 1985) ("Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production."); *Smithkline*, 439 F.3d at 1317-19; *see also* Manual of Patent Examining Procedure § 2113 (8th ed. Rev. 8 July 2010). As the Federal Circuit explained in *Amgen*:

> That is because of . . . the long-standing rule that an old product is not patentable even if it is made by a new process. * * * As a result, a product-by-process claim can be anticipated by a prior art product that does not adhere to the claim's process limitation. * * * Because validity

> is determined based on the requirements of patentability, a patent is invalid if a product made by the process recited in a product-by-process claim is anticipated by or obvious from prior art products, even if those prior art products are made by different processes.

580 F.3d at 1370.

Thus, the general rule is that process limitations are ignored for purposes of determining the validity of product-by-process claims. Accordingly, for determining the patentability of the Asserted Claims of the '393 patent, the question is whether the claimed product is disclosed in, or obvious from, the prior art.

As noted *supra*, except for asserted claim 2, the product of the '393 Asserted Claims is a product comprising the treprostinil compound or a pharmaceutically acceptable salt thereof, without further limitations as to the composition of the product. Thus, any product comprising treprostinil compound in any amount, with any other types or amounts of impurities, falls within the scope of the claimed product. For claim 2, the product is a product comprising the treprostinil compound or its salt having a purity of at least 99.5%, without any limitation as to the composition of the impurities.

As noted above and discussed in detail below, products comprising treprostinil compound have been known in the art since the 1981 disclosure of treprostinil in the '075 patent to Aristoff. Other references disclosing products comprising treprostinil include the following:

- The'814 patent
- EP '784
- The Remodulin Product sold prior to December 17, 2006
- The 2006 Remodulin package insert
- The '117 patent
- The Moriarty JOC Article
- The Phares Patent Publication
- The Li article
- The Sorbera Article
- The '070 Patent

- Whittle & Moncada, "Antithrombotic Assessment and Clinical Potential of Prostacyclin Analogues," Chapter 6, Progress in Medicinal Chemistry, Volume 21 (Ellis & West, eds.) pp. 238-279, at p. 238 (1984) ("Whittle 1984")
- Aristoff et al, "Synthesis and Structure - Activity Relationship of Novel Stable Prostacyclin Analogs," Adv. in Prostaglandin, Thromboxane and Leukotriene Research, Vol. 11, pp. 267-74 (1983)) ("Aristoff 1983").
- U.S. Patent No. 4,306,076 (Dec. 15, 1981)
- U.S. Patent No. 5,153,222 (Oct. 6, 1992)
- WO 99/21830 (May 6, 1999)
- Patterson, J. H., et al. "Acute Hemodynamic Effects of the Prostacyclin Analog 15AU81 in Severe Congestive Heart Failure," The American Journal of Cardiology, Vol. 75, pp. 26A-33A, (1995).

These prior art disclosures of treprostinil render the Asserted Claims of the '393 patent invalid as anticipated under 35 U.S.C. § 102(b), except for claim 2, which adds the further limitation that the treprostinil must be at least 99.5% pure. However, the Moriarty JOC Article discloses a sample of treprostinil having a purity level of 99.7%, which anticipates claim 2. Accordingly, all of the Asserted Claims of the '393 patent are anticipated by the disclosure of products comprising treprostinil in these prior art references.

2. There Is An Exception To The General Rule If The Process Imparts Structure And Functional Differences To The Claimed Product

There is an exception to the general rule that the process by which the product made is irrelevant. If the process by which a product is made imparts "structural and functional differences" distinguishing the claimed product from the prior art, then a new process can impart patentability. *See Greenliant Sys., Inc. v. Xicor LLC*, 692 F.3d 1261, 1268 (Fed. Cir. 2012).

The only Federal Circuit case that has applied this exception is *Amgen Inc. v. F. Hoffman-La Roche, Ltd.,* 580 F.3d 1340, 1366-67 (Fed. Cir. 2009). In *Amgen*, the patents at issue related to the production of the protein erythropoietin ("EPO") using recombinant DNA technology. Like the claims of the '393 patent, the claims at issue in *Amgen* were drawn to a product or composition comprising EPO (or a DNA sequence encoding EPO). The prior art

process involved obtaining EPO from natural sources such as human urine. The defendant argued the prior art disclosure of the urinary EPO (i.e. EPO obtained by purifying human urine) anticipated the product-by-process claims to the recombinant EPO. The court found it did not. The reason was simple: The prior art urinary EPO was not the same as recombinant EPO.

In making the recombinant EPO, "carbohydrates are attached to certain sites on EPO in a process called glycosylation, which results in a glycoprotein." *Amgen*, 580 F.3d at 1347. The recombinant EPO had substantial amounts of carbohydrates attached to the EPO, making it a different compound from urinary EPO. The court relied on the fact that the recombinant EPO is a different compound from the prior art urinary EPO, with a "higher molecular weight and different charge than urinary EPO due to differences in carbohydrate composition," *id.* at 1367, to conclude that the product-by-process claims to compositions comprising recombinant EPO were not anticipated by the disclosure of urinary EPO in the prior art.

3. The '393 Patent Does Not Fall Within The Exception To The General Rule That An Old Product Is Not Patentable Based On A New Way Of Making It

Here, unlike *Amgen*, the process of the '393 patent does not impart structural and functional differences in the claimed product. The treprostinil compound is a single, specific stereoisomer and is identical whether made by the '393 patent process or by any of the processes for making treprostinil disclosed in the prior art. Thus, there is no structural difference in the treprostinil compound imparted by the '393 patent process. Nor is there a functional difference between the treprostinil compound produced by the prior art processes and the treprostinil compound produced by the '393 patent process, given that the treprostinil compound produced by any of these processes is identical. *In re Papesch*, 315 F.2d 381, 391 (CCPA 1963) ("From the standpoint of patent law, a compound and all of its properties are inseparable").

As explained above, during prosecution, UTC traversed an anticipation rejection based on the Moriarty JOC Article by arguing that the process recited in the '393 patent claims results in a product that is different from the product disclosed in the Moriarty JOC Article. Specifically, UTC alleged that treprostinil prepared by the process disclosed in the Moriarty JOC Article contains four different impurities (benzindene triol, treprostinil methyl ester, 1AU90 treprostinil stereoisomer and 2AU90 treprostinil stereoisomer) that are not present in the treprostinil product produced by the '393 patent process. The '393 patent issued after UTC submitted information regarding the alleged difference in the impurity profile of products made by the '393 patent process as compared to the product of the Moriarty JOC Article process. UTC's argument does not render the Asserted Claims patentable over the prior art disclosure of treprostinil, for at least two reasons.

a. Differences In Impurities Produced Along With The Claimed Compound Are Irrelevant To Patentability

First, even if it were true that the '393 patent process results in a product that contains different detectible amounts of four impurities from the product of the Moriarty JOC Article (which is not the case, as discussed *infra*), a difference in impurities does not impart patentability to the '393 patent claims.

A difference in the impurity profile of an old compound produced by a new process is not, and cannot be, sufficient to overcome the longstanding rule that an old product is not patentable based on a new process for making it. *BASF*, 111 U.S. at 311 (holding that "an old article" made by a new process is not patentable). In *Amgen,* which as noted is the only Federal Circuit case to apply the exception to the rule, the court looked to the difference imparted to the erythropoietin compound itself by the new synthetic process for making erythropoietin. While

claim 1 of the '422 patent at issue in *Amgen* recited "a pharmaceutical composition comprising" EPO –written in virtually the same form as the claims to "a product comprising" treprostinil in the '393 patent -- the "structural difference" which formed the basis for the patentability of the claim was a difference in the erythropoietin compound itself, not in the impurity profile of the composition. 580 F.3d at 1367. Thus, under *Amgen* a "structural difference" which would be relevant to patentability would be a structural difference in the claimed chemical compound, not a difference in the impurities produced when making the compound.

There is no Federal Circuit precedent holding that a product-by-process claim to a product or composition comprising an old chemical compound made by a new process can be patentable on grounds that the new process results in different impurities than the product of the prior art process. This is hardly surprising. Different processes for making chemical compounds often result in the creation of different impurities along with the compound. If the creation of different impurities through a new process for making an old chemical compound were sufficient to impart patentability, the exception would swallow the century-old rule, tracing its roots to the Supreme Court's 1884 decision in *BASF*, that an old compound is not patentable based on a new process for making it.

This is particularly true where, as here, the Asserted Claims do not contain any limitations regarding the composition of impurities in the claimed product. While claim 2 does recite that the *overall* purity must be greater than 99.5%, claim 2 does not limit the *types* of impurities that can or cannot be present along with treprostinil in the claimed product. There is no indication that elimination of any specific impurities is critical or otherwise significant with respect to treprostinil and its function as a medication for use in treating pulmonary hypertension. And apart from the overall purity limitation of claim 2, none of the other Asserted

Claims contain any limitations at all regarding the composition of the claimed product, other than that it must include the treprostinil compound or its salt.

b. The '393 Process Does Not Necessarily Result In An Improved Impurity Profile Over The Prior Art

Second, even assuming, *arguendo*, the presence or absence of certain impurities resulting from the '393 patent process for making treprostinil were relevant to patentability, the '393 patent process does not necessarily result in a product with different impurities than the Moriarty JOC process. During prosecution, UTC submitted a declaration by David Walsh, Executive Vice President of Chemical Research and Development at United Therapeutics Corporation, providing data from "representative Certificates of Analysis" with impurity profiles for treprostinil free acid prepared according to the process of Moriarty, and treprostinil diethanolamine and treprostinil free acid prepared according to the process of the '393 patent. UTC relied upon the Walsh declaration to argue that the product prepared by the '393 patent process is physically different than the product prepared by the Moriarty JOC process. However, as UTC's documents show, this is factually untrue.

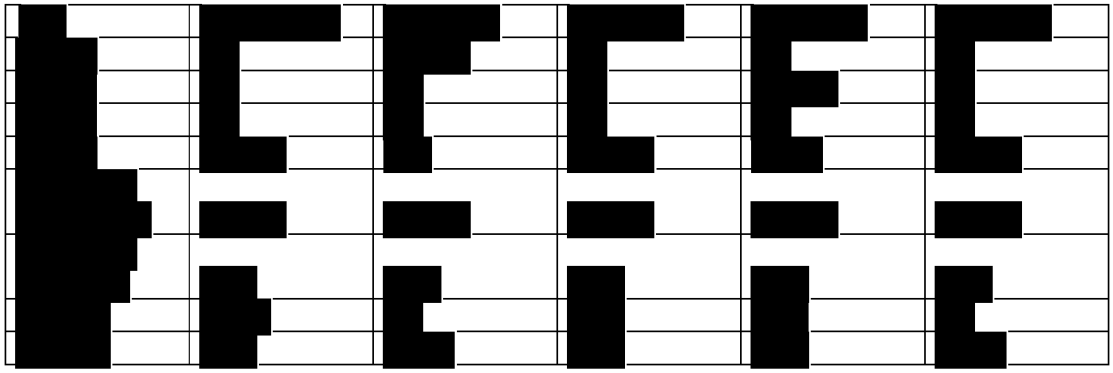
In his declaration, Dr. Walsh evaluates the levels of eight impurities: 1AU90, 2AU90, 3AU90 (isomers of treprostinil), 97W86 (triol intermediate), treprostinil methyl ester, treprostinil ethyl ester, and 750W93 and 751W93 (dimers). The Walsh declaration asserts that while treprostinil free acid made through the Moriarty method contains detectable amounts of seven of the eight impurities, treprostinil free acid made through the process set forth in the '393 patent claims only contains detectable levels of three of the eight impurities. The Walsh declaration further asserts that treprostinil diethanolamine made in accordance with the '393 process contains detectable levels of only one of the eight impurities.

Based on this information, the Walsh declaration concludes that each of treprostinil as the free acid and treprostinil diethanolamine prepared according to the process of the '393 patent "is physically different from treprostinil prepared according to the process of 'Moriarty' at least because neither of them contains a detectable amount of any 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.'" (Walsh Declaration ¶ 8).

The Walsh declaration is misleading, however, because these statements are true only with respect to the three specific batches of treprostinil UTC and Dr. Walsh selected for presentation to the Patent Office. As demonstrated by UTC's own internal documents, these statements do not hold true with respect to other batches of treprostinil made by the Moriarty JOC process and by the '393 patent process. Not surprisingly, UTC's documents reveal batch-to-batch variation in the composition of impurities contained in batches of treprostinil made by both processes. For example, three out of four impurities UTC told the Patent Office were avoided by the '393 patent process *are* present in detectible amounts in batches made by the '393 patent process (1AU90, 2AU90 and treprostinil methyl ester), while the fourth impurity (benzindene triol (97W86)), which UTC had said was avoided by the '393 patent process, was *not* present in detectible amounts in some batches made by the Moriarty JOC process. In short, even based on the limited sample of batches disclosed in UTC's documents, there is no impurity that is always present in treprostinil made by the Moriarty JOC process that is always avoided by the '393 patent process.

UTC's documents show that treprostinil free acid made through the process claimed in the '393 patent may contain detectable amounts of any seven of the eight impurities identified in

the Walsh declaration, and may further contain detectable amounts six of the eight in a single lot. UTC's Dev-00194 report, which is entitled "Silver Spring Process Optimization Report for The Conversion of UT-15C Intermediate To UT-15 API (Treprostinil)" ("UT-15C Optimization Report") discloses a process optimization study in which five lots of treprostinil diethanolamine salt were converted to treprostinil free acid. As is detailed on page UTC-Sand-Rem01096532, the treprostinil diethanolamine lots used in making the five lots of treprostinil free acid were made through the process steps claimed in the '393 patent. The UT-15C Optimization Report provides analytical data for the five lots of treprostinil free acid made by the '393 patent process, as shown in the chart below.



(UTC-Sand-Rem01096532).

[3] The benzindene triol is identified as "97W86" in the charts identifying impurities contained in the Walsh declaration.

[redacted]

At least until January 2006, UTC used the process described in the Moriarty JOC Article as its commercial process. (Attachment 13 to DTX 459, sNDA No. S0006 at UTC-Sand-Rem01096399, 1096406). UTC's documents provide purity information for various batches of treprostinil drug substance made according to the Moriarty JOC process. For example, UTC submitted an NDA Annual Report dated July 21, 2003 which included analytical data for a number of lots of treprostinil drug substance manufactured between 2001 and 2003. (PTX 894 at UTC-Sand-Rem01104231-33). Purity data for 13 batches are shown in the tables below:

Treprostinil Drug Substance Lot Release Analytical Data: 2001-2002 Reporting Period							
Test	UT15-020101	UT15-020201	UT15-020202	UT15-020203	UT15-020301	UT15-020302	UT15-020303
1AU90	ND	ND	ND	ND	ND	ND	ND
2AU90	<0.05%	<0.05%	<0.05%	ND	<0.05%	<0.05%	<0.05%
97W86	ND	ND	<0.05%	ND	ND	ND	ND
3AU90	0.2%	0.2%	0.1%	0.05%	0.2%	0.2%	0.2%
treprostinil methyl ester	ND	ND	ND	<0.05%	ND	ND	ND
treprostinil ethyl ester	<0.05%	0.1%	0.2%	0.1%	0.1%	0.1%	0.1%
750W93	<0.05%	0.09%	0.2%	0.08%	<0.05%	0.06%	<0.05%
751W93	<0.05%	0.1%	0.1%	<0.05%	<0.05%	<0.05%	<0.05%

(PTX 894 at UTC-Sand-Rem01104232).

Treprostinil Drug Substance Lot Release Analytical Data: 2002-2003 Reporting Period

Test	UT15-021001	UT15-021002	UT15-021003	UT15-021101	UT15-021102	UT15-030401
1AU90	ND	ND	ND	ND	ND	ND
2AU90	ND	<0.05%	ND	ND	ND	ND
97W86	<0.05%	<0.05%	ND	ND	0.07%	ND
3AU90	0.4%	0.3%	0.4%	0.2%	0.1%	0.3%
treprostinil methyl ester	<0.05%	<0.05%	<0.05%	ND	ND	<0.05%
treprostinil ethyl ester	0.1%	0.2%	0.1%	0.1%	0.1%	0.2%
750W93	0.1%	0.06%	<0.05%	0.09%	0.2%	0.06%
751W93	0.08%	<0.05%	<0.05%	0.06%	0.1%	<0.05%

(PTX 894 at UTC-Sand-Rem01104232). These data reflect that treprostinil free acid made through the Moriarty JOC process may contain detectable levels of four, five or six of the eight impurities, while one batch included detectable levels of seven of the eight.

It is important to note that nine of the 13 batches made by the Moriarty 2004 process had *no* detectible amounts of benzindene triol (97W86), [redacted]

[redacted] Selection of these two batches shows a *better* impurity profile resulting from the Moriarty JOC process than from the '393 patent process, rather than the other way around as represented by UTC.

These data reflect that there are significant batch-to-batch variations in the composition of impurities, both between batches made by the same process and between batches made by the different processes.[4] So even if the composition of impurities were relevant to patentability, which it is not, there is no factual basis for contending that the product made by the Moriarty JOC process necessarily has a different composition of impurities than the product made by the '393 patent process.

Moreover, even if the different processes resulted in product with different impurities, there is no *functional* difference between the treprostinil product made by the Moriarty JOC process and the treprostinil product made by the '393 patent process. Under *Amgen*, a new process must result in both structural *and* functional changes in the product to fall within the exception to the general rule that an old product is not patentable based on a new process for making it. *Amgen*, 580 F.3d at 1366-67; *Greenliant*, 692 F.3d at 1268 ("As we recognized in

[4] Other batches made by the Moriarty JOC process and the '393 patent process reflect similar batch-to-batch variation. (*See, e.g.,* January 2, 2009 FDA Correspondence regarding switch from Moriarty JOC method to '393 patent method (UTC-Sand-Rem00097567-75); Release Testing Data Range For Treprostinil Drug Substance API Lots Comparison Of Lots From 2000-2006 Manufactured produced at Chicago Facility (UTC-Sand-Rem00097711-713); July 21, 2007 UTC Annual Report at UTC-Sand-Rem000961770-785; July 21, 2005 NDA Annual Report at UTC-Sand-Rem01093128-142; July 21, 2004 NDA Annual Report at UTC-Sand-Rem01093008-3021; Treprostinil Drug Substance Annual Quality Review, May 2006- April 2007 (UTC-Sand-Rem00805081-805109); Analytical Results Of Treprostinil Drug Substance (UTC-Sand-Rem00804964-977).

Amgen, if the process by which a product is made imparts 'structural and functional differences' distinguishing the claimed product from the prior art, then those difference 'are relevant as evidence of no anticipation' . . . "). UTC used the Moriarty JOC process to make treprostinil for its commercial Remodulin® product until 2006. By mid-2008, UTC had modified its manufacturing process to include the process steps claimed in the '393 patent. There was no functional difference reported for the Remodulin® product following UTC's change-over to the '393 patent process in 2008. Thus, even if the composition of impurities were relevant to patentability, any alleged difference resulting from the '393 patent process would fail to establish patentability on this ground as well.

E. The Asserted Claims Are Anticipated By And/Or Obvious In View Of Prior Art That Discloses Products Comprising Treprostinil

For the reasons described above, claims 1, 4, 8, 9 and 16 of the '393 patent are directed to a product that includes the treprostinil compound in any amount with any level of impurities. Accordingly, these claims are anticipated by the disclosure of a product comprising treprostinil or a pharmaceutically acceptable salt of treprostinil in the prior art. Further, claim 2 is directed to a product that includes treprostinil having a purity level of at least 99.5%, and is thus anticipated by or rendered obvious in view of a disclosure of a product comprising treprostinil having such a level of purity in the prior art.

1. The '075 Patent

The '075 patent issued on December 15, 1981 and is thus prior art to the '393 patent under Section 102(b). As described above, the '075 patent discloses and claims treprostinil. Further, the '393 patent itself states that treprostinil was disclosed in the '075 patent. ('393 patent at Col. 1: 22-23) ("Treprostinil, the active ingredient in Remodulin®, was first described

in U.S. Pat. NO. 4,306,075."). Accordingly, because the '075 patent discloses a product comprising the treprostinil compound, the '075 patent anticipates claims 1, 4, 8, 9 and 16 of the '393 patent.

Also, the skilled artisan would have been motivated to obtain a sample of treprostinil having a high level of purity. Accordingly, it would have been obvious for the skilled artisan to purify the treprostinil disclosed in the '075 patent to a purity level of 99.5% or greater, particularly in view of the disclosure in the Moriarty JOC article of treprostinil having a purity level of 99.7%. Further, purification techniques are common practice in the chemical arts. Accordingly, claim 2 would have been obvious in view of the disclosure of treprostinil in the '075 patent.

2. The '814 Patent

The '814 patent issued in 1987 and is thus prior art to the '393 patent under Section 102(b). As described above, the '814 patent discloses treprostinil and pharmaceutically acceptable salts of treprostinil. Accordingly, because the '814 patent discloses products comprising the treprostinil compound and products comprising pharmaceutically acceptable salts of treprostinil, the '814 patent anticipates claims 1, 4, 8, 9 and 16 of the '393 patent.

Also, the skilled artisan would have been motivated to obtain a sample of treprostinil having a high level of purity. As noted above, the 1.2 gram sample of treprostinil disclosed in Example 3 of the '814 patent has a purity level of about 95%. It would have been obvious for the skilled artisan to further purify the treprostinil disclosed in the '814 patent using known techniques, such as column chromatography or crystallization, to a purity level of 99.5% or greater, particularly in view of the disclosure in the Moriarty JOC article of treprostinil having a purity level of 99.7%. Further, purification techniques are common practice in the chemical arts.

Accordingly, claim 2 would have been obvious in view of the disclosure of treprostinil in the '814 patent.

3. EP '784

EP '784 was published in 1985 and is thus prior art to the '393 patent under Section 102(b). As described above, EP '784 discloses treprostinil. Accordingly, because EP '784 discloses products comprising treprostinil compound, EP '784 anticipates claims 1, 4, 8, 9 and 16 of the '393 patent.

Also, the skilled artisan would have been motivated to obtain a sample of treprostinil having a high level of purity. Accordingly, it would have been obvious for the skilled artisan to purify the treprostinil disclosed in EP '784 to a purity level of 99.5% or greater, particularly in view of the disclosure in the Moriarty JOC article of treprostinil having a purity level of 99.7%. Further, purification techniques are common practice in the chemical arts. Accordingly, claim 2 would have been obvious in view of the disclosure of treprostinil in EP '784.

4. The '117 Patent

The '117 patent was issued on July 20, 2004 and is thus is thus prior art to the '393 patent under Section 102(b). As described above, the '117 patent discloses the treprostinil compound and pharmaceutically acceptable salts thereof as well as a method of making treprostinil. Further, the '117 patent is listed in the Orange Book as covering UTC's Remodulin Product along with the '393 patent. Also, the '393 patent specification states that the '117 patent discloses a method of making treprostinil. ('393 patent at Col. 1:23-26). Accordingly, because the '117 patent discloses a product comprising the treprostinil compound and salts thereof, the '117 patent anticipates claims 1, 4, 8, 9 and 16 of the '393 patent.

Also, the skilled artisan would have been motivated to obtain a sample of treprostinil having a high level of purity. Accordingly, it would have been obvious for the skilled artisan to purify the treprostinil disclosed in the '117 patent to a purity level of 99.5% or greater, particularly in view of the disclosure in the Moriarty JOC article of treprostinil having a purity level of 99.7%. Further, purification techniques are common practice in the chemical arts. Accordingly, claim 2 would have been obvious in view of the disclosure of treprostinil in the '117 patent.

5. The Remodulin Package Insert

The 2006 Remodulin Package Insert was published in March 2006 and is thus is thus prior art to the '393 patent under Section 102(b). As explained above, the 2006 Remodulin Package Insert describes UTC's commercial Remodulin product, which includes treprostinil sodium salt as the API. Further, as described above, the '393 patent is listed on the Orange Book as covering UTC's Remodulin Product. Accordingly, because 2006 Remodulin Product Insert discloses a product comprising treprostinil sodium and further describes the commercial product that UTC admits is an embodiment of the product claimed in the '393 patent, the 2006 Remodulin Package Insert anticipates claims 1, 4, 8, 9 and 16 of the '393 patent.

Claim 2 is directed to a product that includes treprostinil having a purity level of at least 99.5%, and is thus anticipated by or rendered obvious in view of a disclosure of a product comprising treprostinil having such a level of purity in the prior art. To the extent that UTC contends that Sandoz's ANDA Product infringes claim 2 of the '393 patent, then claim 2 of the '393 patent is anticipated by the Remodulin product as disclosed in the 2006 Remodulin Package Insert.

6. The Sale Of Remodulin

As explained above, the API in UTC's Remodulin product is treprostinil sodium. Further, as explained above, the '393 patent is listed in the Orange Book as covering UTC's Remodulin Product, and is designated in the Orange Book as containing claims to the drug substance. Accordingly, UTC has represented to the FDA that the '393 patent covers its Remodulin® product. The Remodulin product has been on the market since 2002, and the '393 patent ultimately claims priority to a provisional application filed on December 17, 2007. Accordingly, Remodulin® product sold prior to December 17, 2006 is prior art for the purposes of an on-sale bar under Section 102(b). Because by UTC's own admission the '393 patent covers the Remodulin product and because the Remodulin product was on sale more than one year before the earliest date to which the '393 patent claims priority, claims 1, 4, 8, 9 and 16 of the '393 patent are invalid as anticipated by the sale of UTC's Remodulin product.

Further, claim 2 is directed to a product that includes treprostinil having a purity level of at least 99.5%, and is thus anticipated by or rendered obvious in view of a disclosure of a product comprising treprostinil having such a level of purity in the prior art. To the extent that UTC contends that Sandoz's ANDA Product infringes claim 2 of the '393 patent, then claim 2 of the '393 patent is anticipated by the sale of the Remodulin product as described above.

7. The Moriarty JOC Article

The Moriarty JOC Article was published in 2004 and is thus prior art to the '393 patent under 35 U.S.C. § 102(b). As explained above, the Moriarty JOC Article discloses treprostinil free acid. Also, the '393 patent specification states that the Moriarty JOC Article discloses a method of making treprostinil. ('393 patent at Col. 1:23-26). Further, the Moriarty JOC Article

discloses a sample of treprostinil acid having a purity level of 99.7% Thus, the Moriarty JOC Article anticipates all of the Asserted Claims of the '393 patent.

8. The Phares Publication

The Phares Publication was published on April 21, 2005 and is thus prior art to the '393 patent under Section 102(b). As described above, the Phares Publication discloses treprostinil diethanolamine salt, which is a pharmaceutically acceptable salt of treprostinil. Accordingly, because the Phares Publication discloses a product comprising a pharmaceutically acceptable salt of treprostinil, the Phares Publication anticipates claims 1, 4, 8, 9 and 16 of the '393 patent.

Also, the skilled artisan would have been motivated to obtain a sample of treprostinil having a high level of purity. Accordingly, it would have been obvious for the skilled artisan to purify the treprostinil disclosed in the Phares Publication to a purity level of 99.5% or greater, particularly in view of the disclosure in the Moriarty JOC Article of treprostinil having a purity level of 99.7%. Also, purification techniques are common practice in the chemical arts. Accordingly, claim 2 would have been obvious in view of the disclosure of treprostinil diethanolamine in Phares.

Further, Phares teaches that recrystallizing the diethanolamine salt of treprostinil results in the formation of two crystalline polymorphs of treprostinil diethanolamine, Forms A and B. (Phares Publication at ¶ 0327). Phares teaches that Form A, a metastable form, can be prepared using the crystallization methods shown in Table 15 at ¶ 0327. Phares then provides that the thermodynamically stable polymorph, Form B, can be made from Form A using the crystallization procedures in Table 16 at ¶ 0328. Although Phares does not indicate the purity of polymorph Form B, Phares notes that the melting point is 107°C and provides an XRPD pattern of Form B in Figure 20. (*Id.* at ¶ 0337). The specification of the '393 patent indicates that the

treprostinil diethanolamine compound produced according to the claimed procedures yields treprostinil diethanolamine polymorph Form B that has a melting point of at least 104°C. For example, the table provided at Col. 12:60- Col. 13:12 in the '393 patent shows that Batch 2 of treprostinil diethanolamine salt had a melting point of 105.5-107.2°C. The '393 patent thus discloses that treprostinil diethanolamine salt made through the process described in Examples 1-3 (which correspond to claim steps (a)-(c)) has a melting point within the range of 105.5-107.2°C. Because the melting point of the diethanolamine salt disclosed in Phares is greater than 104°C and falls within the range obtained using the '393 patent process, the product comprising the treprostinil diethanolamine salt disclosed in Phares falls within the scope of the Asserted Claims. Further, the treprostinil diethanolamine salt disclosed in Phares inherently exhibits the same purity level as that described in the '393 patent examples. Thus, the Asserted Claims, including claim 2, are anticipated by Phares

9. The Li Article

The Li article was published in 2004 and is thus prior art to the '393 patent under 35 U.S.C. § 102(b). As explained above, the Li reference discloses a product comprising treprostinil sodium salt. Accordingly, because Li discloses a product comprising treprostinil sodium salt, Li anticipates claims 1, 4, 8, 9 and 16 of the '393 patent.

Also, the skilled artisan would have been motivated to obtain a sample of treprostinil having a high level of purity. Accordingly, it would have been obvious for the skilled artisan to purify the treprostinil disclosed in Li to a purity level of 99.5% or greater, especially in view of the disclosure in the Moriarty JOC Article of treprostinil having a purity of 99.7%. Also, purification techniques are common practice in the chemical arts. Accordingly, claim 2 would have been obvious in view of the disclosure of treprostinil sodium in Li.

10. The Sorbera Article

The Sorbera article was published in 2001 and is thus prior art to the '393 patent under 35 U.S.C. § 102(b). Also, the '393 patent specification states that the Sorbera reference discloses a method of making treprostinil. ('393 patent at Col. 1:23-26). As explained above, the Sorbera reference discloses treprostinil, and further discloses that treprostinil is the active ingredient in Remodulin. Accordingly, because Sorbera discloses a product comprising treprostinil, Sorbera anticipates claims 1, 4, 8, 9 and 16 of the '393 patent.

Also, the skilled artisan would have been motivated to obtain a sample of treprostinil having a high level of purity. Accordingly, it would have been obvious for the skilled artisan to purify the treprostinil disclosed in Sorbera to a purity level of 99.5% or greater, especially in view of the disclosure in the Moriarty JOC Article of treprostinil having a purity of 99.7%. Also, purification techniques are common practice in the chemical arts. Accordingly, claim 2 would have been obvious in view of the disclosure of treprostinil in Sorbera.

11. The Disclosure Of Treprostinil In Additional Prior Art References

As explained above, products comprising treprostinil are disclosed in the following references:

- Whittle & Moncada, "Antithrombotic Assessment and Clinical Potential of Prostacyclin Analogues," Chapter 6, Progress in Medicinal Chemistry, Volume 21 (Ellis & West, eds.) pp. 238-279, at p. 238 (1984) ("Whittle 1984")
- Aristoff et al, "Synthesis and Structure - Activity Relationship of Novel Stable Prostacyclin Analogs," Adv. in Prostaglandin, Thromboxane and Leukotriene Research, Vol. 11, pp. 267-74 (1983)) ("Aristoff 1983").
- U.S. Patent No. 4,306,076 (Dec. 15, 1981)
- U.S. Patent No. 5,153,222 (Oct. 6, 1992)
- WO 99/21830 (May 6, 1999)
- Patterson, J. H., *et al.* "Acute Hemodynamic Effects of the Prostacyclin Analog 15AU81 in Severe Congestive Heart Failure," *The American Journal of Cardiology,* Vol. 75, pp. 26A-33A, (1995).

Each of these references is prior art to the '393 patent under Section 102(b). Further, each of these references are cumulative to the references discussed above that disclose treprostinil. Accordingly, each of these references anticipates or renders obvious the Asserted Claims of the '393 patent for the reasons recited above.

F. Even Assuming That The Process Limitations Of The Asserted Claims Are Pertinent For Validity Purposes, The Prior Art Discloses And/Or Renders Obvious Products Comprising Treprostinil Made Through The Claimed Process

Even assuming, *arguendo*, that the process limitations of the '393 patent claims are relevant to patentability, Asserted Claims are still not patentable because products comprising treprostinil made by the process claimed in the '393 patent are anticipated by, or rendered obvious in view of, the prior art.

1. The Asserted Claims Are Anticipated By Or Obvious In View Of The Phares Publication

The Phares Publication discloses a product comprising treprostinil diethanolamine salt made through the claimed process, and thus anticipates the Asserted Claims of the '393 patent. The Phares publication also discloses a method of making treprostinil diethanolamine salt from treprostinil free acid, which corresponds to claimed step (c). In particular, Phares discloses contacting treprostinil acid (which is the product of claim step (b)) with a base B (diethanolamine) to produce a salt (treprostinil diethanolamine salt) that falls within the genus depicted in formula Is and formula IVs. Accordingly, because the Phares publication discloses a product comprising treprostinil diethanolamine salt made through the claimed process steps (steps (a)-(c)), the Phares Publication anticipates the Asserted Claims.

In the alternative, the disclosure of the Phares publication renders obvious products comprising treprostinil diethanolamine salt made through the claimed process. In particular, as

explained above, the Phares publication discloses treprostinil diethanolamine salt as a preferred embodiment and further discloses the improved oral bioavailability achieved with treprostinil diethanolamine salt as compared to the treprostinil in Remodulin®. Accordingly, the skilled artisan would have been motivated to make treprostinil diethanolamine salt as disclosed in Phares in view of the improved bioavailability profile disclosed in Phares. The starting material for the salt formation step disclosed in Phares is treprostinil free acid, so the skilled artisan would have been motivated to obtain treprostinil free acid in order to make treprostinil diethanolamine as disclosed in Phares.

Phares further discloses that treprostinil free acid can be obtained by alkylating the benzindene triol with an alkylating agent (chloroacetonitrile) to obtain the benzindene nitrile intermediate, and then hydrolyzing the benzindene nitrile intermediate with a base (potassium hydroxide) to obtain treprostinil acid. (Phares at ¶¶ 143-145). Accordingly, because the skilled artisan would have been motivated to make treprostinil acid to use in the diethanolamine salt formation step, the skilled artisan would have been further motivated to use the process described in Phares to make treprostinil free acid that could be used as the starting material in the salt formation step. In doing so, the skilled artisan would obtain a pharmaceutically acceptable salt of treprostinil (treprostinil diethanolamine salt) using the claimed process steps (steps (a)-(c)). Thus, the Phares publication renders obvious the Asserted Claims.

Additionally, asserted claim 2 requires that the product obtained have a purity level of at least 99.5%. As explained above, although Phares does not indicate the purity of polymorph Form B, Phares notes that the melting point is 107°C and provides an XRPD pattern of Form B in Figure 20. (*Id.* at ¶ 0337). The specification of the '393 patent indicates that the treprostinil diethanolamine compound produced according to the claimed procedures yields treprostinil

diethanolamine polymorph Form B that has a melting point of at least 104°C. For example, the table provided at Col. 12:60- Col. 13:12 in the '393 patent shows that Batch 2 of treprostinil diethanolamine salt had a melting point of 105.5-107.2°C. The '393 patent thus discloses that treprostinil diethanolamine salt made through the process described in Examples 1-3 (which correspond to claim steps (a)-(c)) has a melting point within the range of 105.5-107.2°C. Because the melting point of the diethanolamine salt disclosed in Phares is greater than 104°C and falls within the range obtained using the '393 patent process, the product comprising the treprostinil diethanolamine salt disclosed in Phares falls within the scope of the Asserted Claims. Further, the treprostinil diethanolamine salt disclosed in Phares inherently exhibits the same purity level as that described in the '393 patent examples. Thus, the Asserted Claims, including claim 2, are anticipated by Phares

2. The Asserted Claims Are Obvious In View Of The Phares Publication In Combination With The Moriarty JOC Article

In the alternative, the skilled artisan would have been motivated to make treprostinil free acid using the process described in the Moriarty JOC Article and then use the treprostinil free acid as the starting material in the salt formation step. First, the Moriarty JOC Article discloses that the synthetic process described therein is efficient, economical, and superior to methods disclosed in the prior art. Second, the Moriarty JOC Article discloses that the process disclosed therein produces treprostinil free acid having a purity of 99.7%. There is a general desire in the art to obtain drug substance samples having a high purity level through processes that are efficient and economical, so the skilled artisan would have been motivated to use the 99.7% pure sample of treprostinil produced as disclosed in the Moriarty JOC Article as the starting material in the treprostinil diethanolamine formation step disclosed in the Phares Publication.

The Moriarty JOC Article discloses that treprostinil free acid is obtained through a process that includes alkylating the triol intermediate with an alkylating agent (chloroacetonitrile) to obtain the benzindene nitrile intermediate, which is then hydrolyzed with a base (potassium hydroxide) to obtain treprostinil free acid. Thus, the Moriarty JOC Article discloses treprostinil free acid made through the claimed steps (a) and (b). Using the treprostinil free acid obtained in Moriarty in the diethanolamine salt formation step described in the Phares publication would accomplish claimed process step (c) and provide a product comprising pharmaceutically acceptable salt of treprostinil made through the claimed process. Accordingly, Phares in combination with the Moriarty JOC Article renders obvious the Asserted Claims.

Additionally, asserted claim 2 requires that the product obtained have a purity level of at least 99.5%. It is well-known in the art that a salt formation step can be used as a purification step. Given that the treprostinil free acid obtained in the Moriarty JOC Article has a purity level of 99.7%, the skilled artisan would expect that the treprostinil diethanolamine salt produced through the process in the Phares Publication would have a purity level comparable to or greater than the starting material. Accordingly, the skilled artisan would have a reasonable expectation of success in obtaining a batch of treprostinil diethanolamine salt having a purity level of at least 99.5% when performing the salt formation step disclosed in the Phares Publication using the treprostinil free acid disclosed in the Moriarty JOC Article as a starting material.

3. The Asserted Claims Are Obvious Over The Moriarty JOC Article In View Of Phares And Anderson

As discussed above, both the JOC Article and the Phares Publication describe a process for preparing treprostinil that involve alkylation of benzindene triol followed by hydrolysis with a base, and thereby satisfy claimed process steps (a) and (b). The process disclosed in the

Moriarty JOC Article involves purification of the benzindene triol intermediate, the benzindene nitrile intermediate, and treprostinil free acid. In particular, the JOC Article further discloses that the benzindene triol intermediate is obtained having a purity of 99.5% following crystallization. (Moriarty JOC Article at pp. 1901-2). Then, following the alkylation step, the benzindene nitrile intermediate is purified through column chromatography. (Moriarty JOC Article at p. 1902). Treprostinil free acid is then purified through recrystallization to obtain a product that is 99.7% pure. (*Id.*).

Anderson explains that a person of ordinary skill in the art would have been motivated to avoid the "drawbacks" of column chromatography, which is a "labor-intensive" process that is used generally as a last resort. (Anderson at pp. 13, 223, and 226). Instead, Anderson teaches that better results are obtained using salt formation and recrystallization techniques. (*Id.*). Further, Anderson teaches that "[s]alt formation may be key for efficient purification of ionizable compounds." (*Id.* at p. 238). Anderson also discloses that in general, the practice of "telescoping," which is of carrying the product of a reaction without isolation into the next step, can greatly increase overall yields and is usually incorporated as part of a cost-effective route unless significant benefits are obtained from isolation of the intermediate. (Anderson at p. 34).

The skilled artisan would thus have been motivated to improve the Moriarty JOC method by removing the column chromatography step following producing of the nitrile intermediate. In order to obtain a comparable level of purity in the final treprostinil product, the skilled artisan would have been motivated to replace the final crystallization step disclosed in the Moriarty JOC Article with a salt formation step.

The skilled artisan would further have been motivated to use the salt formation step disclosed in the Phares publication, which involves formation of treprostinil diethanolamine salt,

because the use of an amine salt would be expected to provide an improved impurity profile. In particular, the skilled artisan would have been motivated to replace the final recrystallization step in Moriarty with a salt formation step in the hopes of obtaining a better impurity profile. The skilled artisan would understand, as is discussed in Anderson, that basic amines can be used to form salts with acidic compounds and that diethanolamine is a particularly useful amine for scale-up purposes. The skilled artisan would also be aware of the disclosure of the sodium and potassium salts of treprostinil in the prior art. In seeking a new salt of treprostinil, the skilled artisan would have reviewed the Phares reference, which discloses various salts and pro-drugs of treprostinil. Upon review of Phares, the skilled artisan would have learned that treprostinil diethanolamine was a particularly preferred salt that was amenable to crystallization in a variety of conditions and produced a stable polymorph. Accordingly, the skilled artisan would have been motivated to substitute the salt formation step in Phares for the final recrystallization step in Moriarty in an attempt to further improve the purity profile of the treprostinil compound obtained after removing the chromatography step following the nitrile formation step.

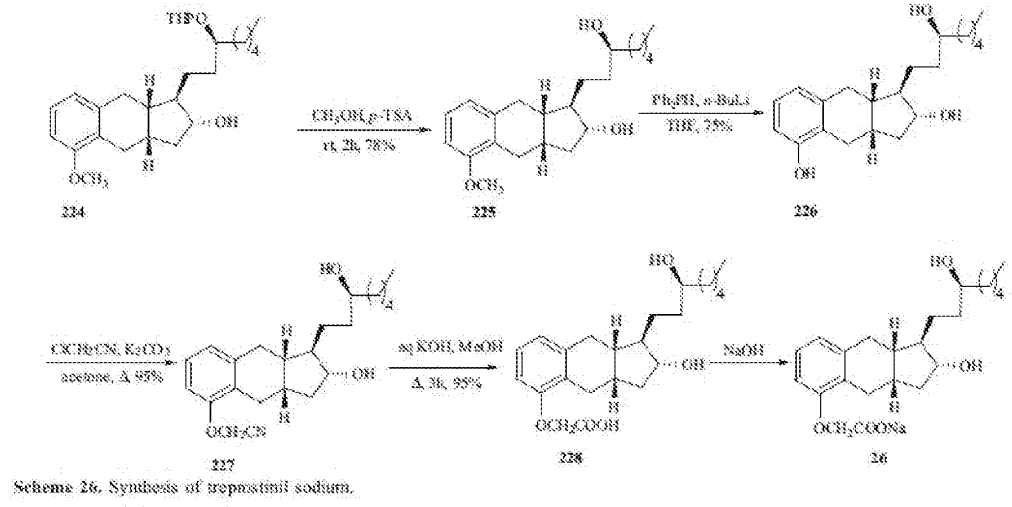
Accordingly, the skilled artisan would have been motivated to improve the process disclosed in the Moriarty JOC Article by using the salt formation step disclosed in Phares as a purification step and would thereby obtain a producing comprising pharmaceutically acceptable salt of treprostinil using the claimed method. Further, this optimized method would not involve a purification step following formation of the benzindene nitrile intermediate, as required by claims 8 and 16.

4. The Asserted Claims Are Anticipated By The Disclosure Of Treprostinil In The Moriarty JOC Article That Is Made Through The Claimed Process Steps (a)-(d)

Further, the Moriarty JOC Article anticipates the Asserted Claims because it discloses treprostinil free acid made by a process that includes claimed steps (a)-(d). As explained above, the Moriarty JOC Article discloses alkylation of the benzindene triol intermediate to obtain the nitrile intermediate (step (a)) followed by hydrolysis of the benzindene nitrile intermediate with a base (potassium hydroxide) (step (b)). The Moriarty JOC Article inherently discloses step (c) because it inherently discloses the formation of treprostinil potassium, which is formed inevitably during the hydrolysis of the benzindene nitrile. Moriarty teaches the performance of the hydrolysis step by reacting the nitrile with potassium hydroxide (KOH) at extremely high pH and elevated temperature. (Moriarty JOC Article at 1902). During this process, some molecules of treprostinil acid necessarily and unavoidably react again with KOH to form treprostinil potassium, which is then converted back to treprostinil acid by the subsequent addition of hydrochloric acid. (*See id.*). That some salt is formed and needs to be converted back to free acid—Moriarty sets out to achieve free acid as its final product—is evidenced by the extraction step that immediately follows the reflux reaction. Salts, being ionic, are found in the aqueous layer of the water:ethyl acetate system; free acid, being non-polar, is found in the non-polar ethyl acetate layer. When Moriarty retains the aqueous layer, acidifies it to pH 2-3 by addition, and then extracts again with ethyl acetate, the result is recovery of free acid that would otherwise have been lost as salt. This is step (d), which involves reacting the salt formed in step (c) (treprostinil potassium salt) with an acid (hydrochloric acid) to form treprostinil free acid. Accordingly, because Moriarty JOC discloses a product comprising treprostinil acid made through the claimed process, the Moriarty JOC Article anticipates the Asserted Claims.

5. To The Extent That The Claims Are Construed Such That Step (c) Covers Formation Of Treprostinil Sodium Salt, Then The Asserted Claims Are Anticipated By, Or Would Have Been Obvious In View Of, Li

As explained above, the Li reference discloses a process of making treprostinil that involves alkylating the benzindene triol (compound 226) to obtain the nitrile (compound 227), hydrolyzing the nitrile with a base to form treprostinil acid (compound 228), and then contacting the product of the previous step with a base (NaOH) to form treprostinil sodium salt (compound 26). This process is shown below:



Scheme 26. Synthesis of treprostinil sodium.

(Li at p. 229). Accordingly, Li discloses claimed process steps (a), alkylation of benzindene triol with an alkylating agent to produce benzindene nitrile, and (b), hydrolyzing the benzindene nitrile intermediate with a base to obtain treprostinil free acid. Li also discloses converting treprostinil acid into treprostinil sodium salt by contacting the product of the previous step (treprostinil acid) with a base (sodium hydroxide). Treprostinil sodium is not a salt that includes the HB+ cation as depicted in claim step (c). However, to the extent that the Asserted Claims are

construed as not limited to a salt that includes an HB+ cation as required by the claims, then the Asserted Claims 1, 4, 8, 9 and 16 are anticipated by the disclosure of a product comprising treprostinil sodium in Li.

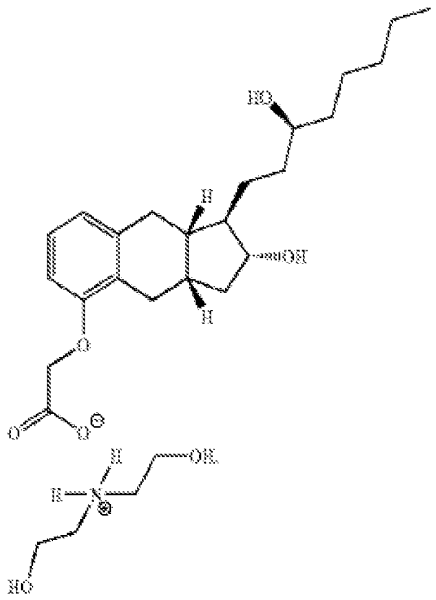
Also, the skilled artisan would have been motivated to obtain a sample of treprostinil having a high level of purity. Accordingly, it would have been obvious for the skilled artisan to purify the treprostinil disclosed in Li to a purity level of 99.5% or greater, especially in view of the disclosure in the Moriarty JOC Article of treprostinil having a purity of 99.7%. Also, purification techniques are common practice in the chemical arts. Accordingly, claim 2 would have been obvious in view of the disclosure of treprostinil sodium in Li.

G. The Asserted Claims Are Invalid For Obviousness-Type Double Patenting Over The '070 Patent

The '070 patent issued on August 26, 2008, well before the application leading to the '393 patent was filed on July 13, 2012, and well before the '393 patent issued on July 30, 2013. The '070 patent is also assigned to UTC. Accordingly, to the extent that the Asserted Claims of the '393 patent are not patentably distinct over the claims of the '070 patent, the Asserted Claims are invalid for obviousness-type double patenting. *See Eli Lilly*, 251 F.3d at 968 (A later claim that is not patentably distinct from an earlier claim in a commonly owned patent is invalid for obvious-type double patenting."). "A later patent claim is not patentably distinct from an earlier patent claim if the later claim is obvious over, or anticipated by, the earlier claim." *Id.*

UTC has already obtained patent coverage of treprostinil diethanolamine salt in the '070 patent. Claim 1 of the '070 patent reads as follows:

1. A compound having the following structure:



Further, the '070 patent is listed on the Orange Book as covering UTC's Orenitram product along with the '393 patent.

Because the treprostinil diethanolamine compound claimed in the '070 patent is a species of the genus of products claimed in the '393 patent, the treprostinil diethanolamine compound claimed in claim 1 of the '070 patent anticipates claims 1, 4, 8, 9 and 16 of the '393 patent. Accordingly, claims 1, 4, 8, 9 and 16 of the '393 patent are not patentably distinct over claim 1 of the '070 patent and are thus invalid for obviousness-type double-patenting.

Also, the skilled artisan would have been motivated to obtain a sample of treprostinil having a high level of purity. Accordingly, it would have been obvious for the skilled artisan to

purify the treprostinil diethanolamine disclosed and claimed in the '070 patent to a purity level of 99.5% or greater, particularly in view of the disclosure in the Moriarty JOC Article of treprostinil having a purity level of 99.7%. Also, purification techniques are common practice in the chemical arts. Accordingly, claim 2 is not patentably distinct over claim 1 of the '070 patent and is invalid for obviousness-type double patenting.

Further, the disclosure of the '070 patent, which is the same as the disclosure of the Phares Publication, discloses a method of making treprostinil diethanolamine salt that satisfies steps (a)-(c) of the Asserted Claims either alone or in combination with the Moriarty JOC Article. Accordingly, to the extent that the claimed process steps are material in the validity analysis, which they are not, then the Asserted Claims are invalid for obviousness-type double patenting over claim 1 of the '070 patent.

H. The Asserted Claims Are Invalid For Obviousness-Type Double Patenting Over the '117 Patent

The '117 patent was issued on July 20, 2004, well before the application leading to the '393 patent was filed on July 13, 2012, and well before the '393 patent issued on July 30, 2013. The '117 patent is also assigned to UTC. Accordingly, to the extent that the Asserted Claims of the '393 patent are not patentably distinct over the claims of the '117 patent, the Asserted Claims are invalid for obviousness-type double patenting. *See Eli Lilly*, 251 F.3d at 968 (A later claim that is not patentably distinct from an earlier claim in a commonly owned patent is invalid for obvious-type double patenting."). A later patent claim is not patentably distinct from an earlier patent claim if the later claim is obvious over, or anticipated by, the earlier claim." *Id.*

The '117 patent includes product-by-process claims directed to the treprostinil compound and pharmaceutically acceptable salts thereof. Further, the '117 patent is listed in the Orange

Book as covering UTC's Remodulin product and UTC's Orenitram product along with the '393 patent. Accordingly, because the '117 patent claims treprostinil compound and salts thereof, claims 1, 4, 8, 9 and 16 of the '393 patent are not patentably distinct over the '117 patent claims.

Also, the skilled artisan would have been motivated to obtain a sample of treprostinil having a high level of purity. Accordingly, it would have been obvious for the skilled artisan to purify the treprostinil disclosed and claimed in the '117 patent to a purity level of 99.5% or greater, especially in view of the disclosure in the Moriarty JOC Article of treprostinil having a purity level of 99.7%. Also, purification techniques are common practice in the chemical arts. Accordingly, claim 2 is not patentably distinct over the '117 patent claims. Thus, the Asserted Claims are invalid for obviousness-type double patenting over the '117 patent claims.

I. Secondary Considerations Do Not Mitigate or Negate the Obviousness of the Invention Claimed in the '393 Patent

UTC bears the burden of providing evidence of objective indicia of non-obviousness. *In re Huang*, 100 F.3d 135, 139 (Fed. Cir. 1996). "Evidence of secondary considerations does not always overcome a strong *prima facie* showing of obviousness." *Asyst Technologies, Inc. v. Emtrak, Inc.*, 544 F.3d 1310, 1316 (Fed. Cir. 2008); *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010); *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 417 (2007)).

Sandoz is unaware of any secondary considerations that negate the obviousness of the inventions of the asserted claims of the '393 patent. It is impossible for Sandoz to anticipate what secondary considerations UTC may rely upon in rebutting Sandoz's obviousness defenses. Consequently, Sandoz reserves the right to amend its invalidity contentions to address the evidence of alleged secondary considerations that UTC may hereafter raise. Sandoz will also address secondary considerations in its expert disclosures once it has the opportunity to assess

UTC's secondary considerations, to the extent it relies on any, and supporting evidence.

1. Long-Felt Need and Failed Attempts by Others

There is no evidence of a long-felt need or failed attempts by others with respect to the claimed inventions of the '393 patent. As explained above, treprostinil sodium produced through the prior art process was used in UTC's Remodulin product until at least 2006. There is no evidence that Remodulin formulated with treprostinil produced through the '393 patent method is in any way different than Remodulin formulated with treprostinil produced through the prior art method.

2. Unexpected Results

To prove unexpected results, the patentee must first show what was expected. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1371 (Fed. Cir. 2007). Then, the patentee must show that the results obtained with the claimed invention, even if superior than what was taught in the prior art, were truly surprising. *Id.* The patentee must show that the results obtained were unexpected as compared with the closest prior art compound. *Pfizer*, 480 F.3d at 1370 (citing *Kao Corp. v. Unilever U. S., Inc.*, 441 F.3d 963, 970 (Fed. Cir. 2006)). In particular, the patentee must show that the claimed invention exhibits unexpected results over the prior art reference supporting the *prima facie* evidence of obviousness. *Aventis Pharma Deutschland GMBH v. Lupin, Ltd.*, 499 F.3d 1293, 1302 (Fed. Cir. 2007).

A showing of unexpected results requires that the results obtained differ "in kind and not merely in degree" when compared with the results obtained with the closest prior art reference. *Iron Grip Barbell Co., Inc. v. USA Sports, Inc.*, 392 F.3d 1317, 1322 (Fed. Cir. 2004) (quoting *In re Huang*, 100 F.3d 135, 139 (Fed. Cir. 1996)). Thus, the patentee must "produce evidence demonstrating 'substantially improved' results that are unexpected in light of the prior art."

Santarus, Inc. v. Par Pharm., Inc., 720 F. Supp. 2d 427, 457 (D. Del. 2010) (quoting *In re Soni*, 54 F.3d 746, 751 (Fed. Cir. 1995)). Then, any such evidence must be "weighed against contrary evidence indicating that the results were not unexpected or not a substantial improvement over the prior art." *Id.*

There is no evidence of unexpected results because the method disclosed and claimed in the '393 patent proceeds exactly as expected and produces treprostinil diethanolamine salt exactly as described in the prior art. *See Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293,1302 (Fed. Cir. 2007) (explaining that the patentee had "failed to show unexpected results that would tend to rebut a prima facie case of obviousness" where the results obtained were "precisely what one would expect"). Further, as explained above, there is no evidence that production of treprostinil using the claimed method provides any difference, let alone any material difference, in impurity profiles. Accordingly, the results are not unexpected.

3. Commercial Success

There is no evidence of a long-felt need or failed attempts by others with respect to the claimed inventions of the '393 patent. Commercial success is probative of non-obviousness "only if there is proof that the sales were a direct result of the unique characteristics of the claimed invention—as opposed to other economic and commercial factors unrelated to the quality of the patented subject matter." *In re Huang*, 100 F.3d at 140. Further, the commercial success must be "attributable to something disclosed in the patent that was not readily available in the prior art." *J.T. Eaton & Co., Inc. v. Atlantic Paste & Glue Co.*, 106 F.3d 1563, 1571 (Fed. Cir. 1997). Thus, commercial success is not probative of non-obviousness if the success "was due to unclaimed or non-novel features of the [claimed invention]". *Ormco Corp. v. Align Technology, Inc.*, 463 F.3d 1299k, 1312 (Fed. Cir. 2006). Moreover, commercial success must

be due to "the subject matter that [the patentee] contends is nonobvious." *Friskit, Inc. v. Realnetworks, Inc.*, 306 F.3d Appx. 610, 617 (Fed. Cir. 2009).

As explained above, treprostinil sodium produced through the prior art process was used in UTC's Remodulin product until at least 2006. There is no evidence that Remodulin formulated with treprostinil produced through the '393 patent method is in any way different than Remodulin formulated with treprostinil produced through the prior art method. Further, there is no evidence that any improvement in Remodulin sales was the result of the change in manufacturing process from the prior art method to the claimed '393 patent method.

4. Acclaim and Acknowledgement of Success

Sandoz is unaware that Remodulin has been subject to any measure of acclaim that results from the change in manufacturing process from the prior art method to the '393 patent method.

5. Copying

Copying is not a secondary consideration germane to ANDA litigation. "[A] showing of copying is not compelling evidence of non-obviousness in Hatch-Waxman cases due to the nature of the ANDA process." *Santarus, Inc. v. Par Pharm., Inc.*, 720 F.Supp.2d 427, 458 (D. Del. 2010); *see also Purdue Pharma Prods. L.P. v. Par Pharm., Inc.*, 642 F.Supp.2d 329, 373-74 (D. Del. 2009). "[T]he ANDA procedures established by the Hatch-Waxman Act require generic drug manufacturers to copy the approved drug. Variations undermine the FDA's ability to assume that if the patented drug is safe and effective, the generic competitor will also be safe and effective." *Eli Lilly & Co. v. Zenith Goldline Pharm., Inc.*, No. IP 99-38-C H/K, 2001 WL 1397403, at * 14 (S.D. Ind., Oct. 29, 2001). Thus, any evidence of copying is entitled to no probative value, and in any case, cannot overcome Sandoz's strong showing of obviousness.

6. Teaching Away

Teaching away requires an affirmative criticism or disparagement of the claimed invention, and a mere statement that a certain embodiment is preferred or optimal is insufficient. "A reference does not teach away, however, if it merely expresses a general preference of an alternative invention but does not criticize, discredit, or otherwise discourage investigation into the invention claimed." *Depuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1327 (Fed. Cir. 2009); *see also In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004); *Syntex (U.S.A.) LLC v. Apotex, Inc.*, 407 F.3d 1371, 1380 (Fed. Cir. 2005). In considering whether a prior art reference teaches away, "all disclosures of the prior art, including unpreferred embodiments, must be considered." *Merck & Co., Inc. v. Biocraft Labs., Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989). Sandoz is unaware of any prior art reference that teaches away from using the features of the manufacturing process identified in the product by process claims of the '393 patent.

IV. CONCLUSION

For the reasons set forth above, the Asserted Claims of the '393 patent are invalid. Sandoz expressly reserves the right to amend or supplement its contentions to address arguments raised in UTC's validity contentions and to address additional issues raised by discovery or any claim construction order entered in this action.

Dated: February 5, 2015

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CERTIFICATE OF SERVICE

I certify that on February 5, 2015, a copy of the foregoing DEFENDANT SANDOZ INC.'S INITIAL DISCLOSURE PURSUANT TO FED. R. CIV. P. 26(a)(1) was served on principal counsel of record as set forth below via email.

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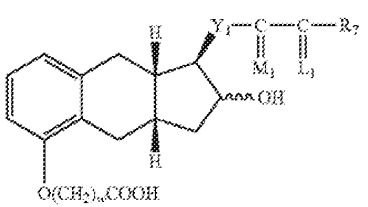
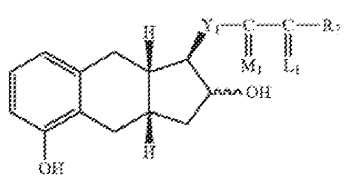
INVALIDITY CONTENTION CLAIM CHART FOR U.S. PATENT NO. 8,497,393

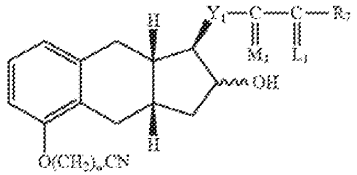
I. THE ASSERTED CLAIMS ARE ANTICIPATED BY AND/OR OBVIOUS IN VIEW OF PRIOR ART THAT DISCLOSES PRODUCTS COMPRISING TREPROSTINIL

A. The Asserted Claims Are Anticipated By, Or Would Have Been Obvious In View Of, U.S. Patent No. 4,306,075 ("The '075 Patent")

Claim 1	Prior Art Disclosure
Element [A] A product comprising a compound of formula I:  (I) or a pharmaceutically acceptable salt thereof, wherein said product is prepared by a process comprising	A product-by-process claim is anticipated if the product is disclosed in the prior art. *Amgen*, 580 F.3d at 1366; *SmithKline Beecham Corp. v. Apotex Corp.*, 439 F.3d 1312, 1317 (Fed. Cir. 2006) ("It has long been established that one cannot avoid anticipation by an earlier product disclosure by claiming the same product more narrowly, that is, by claiming the product as produced by a particular process"); *Gen. Elec. Co. v. Wabash Appliance Corp.*, 304 U.S. 364, 373 (1938); *Cochrane v. Badische Anilin & Soda Farbrik*, 111 U.S. 293, 311 (1884) ("While a new process for producing [a chemical compound] was patentable, the product itself could not be patented even though it was a product made [by a new process] for the first time because the product was disclosed in the prior art"). "In determining the validity of a product-by-process claim, the focus is on the product and not on the process of making it." *Amgen*, 580 F.3d at 1369-70; *In re Thorpe*, 777 F.2d 695, 697 (Fed. Cir. 1985) ("Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production."); *Smithkline*, 439 F.3d at 1317-19; *see also* Manual of Patent Examining Procedure § 2113 (8th ed. Rev. 8 July 2010). Accordingly, for determining the patentability of the Asserted Claims of the '393 patent, the question is whether the claimed product is disclosed in, or obvious from, the prior art. The product of claim 1 the '393 patent is a product comprising a member of the recited genus of compounds that includes the treprostinil compound or a pharmaceutically acceptable salt thereof, without further limitations as to the composition of the product. Thus, any product comprising treprostinil compound in any amount, with any other types or amounts of impurities, falls within the scope of

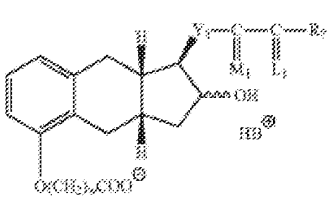
	the claimed product. The '075 patent issued on December 15, 1981 and is thus prior art to the '393 patent under Section 102(b). The '075 patent describes a method of making treprostinil in Example 33, and also claims the treprostinil compound. ('075 patent at Col. 56:15-Col. 59:15, Col. 62:4-39, Col. 97:46-47; *see also* Civil Action No. 12-1617 Trial Tr. at 1850:10-21). Example 33 discloses 0.096 g of treprostinil final product. ('075 patent at Col. 62:34-35). The '075 patent also discloses pharmacologically acceptable salts of the compounds disclosed therein. ('075 patent at Col. 14:56-Col. 15:42, Col. 30:41-62). Further, the '393 patent itself states that treprostinil was disclosed in the '075 patent. ('393 patent at Col. 1: 22-23) ("Treprostinil, the active ingredient in Remodulin®, was first described in U.S. Pat. No. 4,306,075."). Moreover, there are no structural and functional differences between the product of the '075 patent (the treprostinil compound) and the claimed product (a product including the treprostinil compound). Accordingly, because the '075 patent discloses a product comprising the treprostinil compound, the '075 patent anticipates claim 1.
Element [B] (a) alkylating a compound of structure II with an alkylating agent to produce a compound of formula III, (II) 	*See* Element [A] above.

(III)



wherein
w=1, 2, or 3;
Y_1 is trans-CH=CH—, cis-CH=CH—, —$CH_2(CH_2)_m$—, or —C≡C—; m is 1, 2, or 3;
R_2 is
(1) —C_pH_{2p}—CH_3, wherein p is an integer from 1 to 5, inclusive,
(2) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3) alkyl, or (C_1-C_3) alkoxy, with the proviso that not more than two substituents are other than alkyl, with the proviso that R_2 is phenoxy or substituted phenoxy, only when R_3 and R_4 are hydrogen or methyl, being the same or different,
(3) phenyl, benzyl, phenylethyl, or phenylpropyl optionally substituted on the aromatic ring by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3)alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl,
(4) cis-CH=CH—CH_2—CH_3,
(5) —$(CH_2)_2$—CH(OH)—CH_3, or
(6) —$(CH_2)_2$—CH=C(CH_3)$_2$;
—$C(L_1)$—R_7 taken together is
(1) (C_4-C_7)cycloalkyl optionally substituted by 1 to 3 (C_1-C_3) alkyl;

(2) 2-(2-furyl)ethyl,
(3) 2-(3-thienyl)ethoxy, or
(4) 3-thienyloxymethyl;
M_1 is α-OH:β-R_5 or α-R_5β-OH or α-OR_2:β-R_5 or α-R_5:β-OR_2, wherein R_5 is hydrogen or methyl, R_2 is an alcohol protecting group, and
L_1 is α-R_3:β-R_4, α-R_4:β-R_3, or a mixture of α-R_3:β-R_4 and α-R_4:β-R_3, wherein R_3 and R_4 are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R_3 and R_4 is fluoro only when the other is hydrogen or fluoro.

Element [C] (b) hydrolyzing the product of formula III of step (a) with a base,	*See* Element [A] above.
Element [D] (c) contacting the product of step (h) with a base B to form a salt of formula Is.  and	*See* Element [A] above.
Element [E] (d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula I.	*See* Element [A] above.

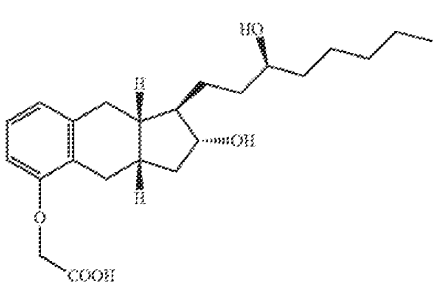
Claim 2	**Prior Art Disclosure**
The product of claim 1, wherein the purity of compound of formula I in said product is at least 99.5%.	*See* Claim 1. The skilled artisan would have been motivated to obtain a sample of treprostinil having a high level of purity. Moriarty, et al in *J. Org. Chem.* 2004, 69, 1890-1902 ("Moriarty JOC Article") includes an experimental section which describes in detail the synthesis of 441 grams

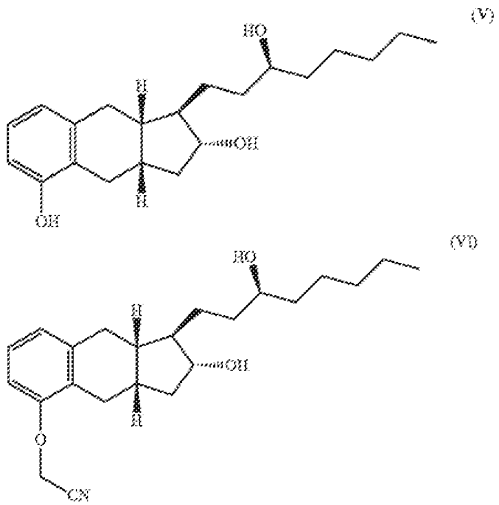
	of treprostinil acid having a purity of 99.7%. (*Id.* at 1902). Accordingly, it would have been obvious for the skilled artisan to purify the treprostinil disclosed in the '075 patent to a purity level of 99.5% or greater, particularly in view of the disclosure in the Moriarty JOC article of treprostinil having a purity level of 99.7%. Further, purification techniques are common practice in the chemical arts. Accordingly, claim 2 would have been obvious in view of the disclosure of treprostinil in the '075 patent.

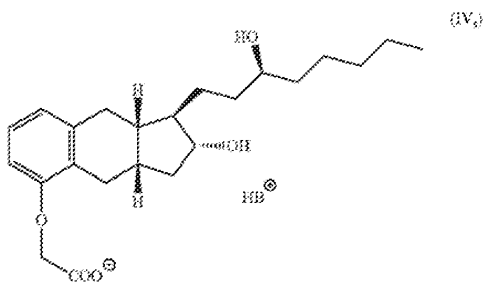
Claim 4	**Prior Art Disclosure**
The product of claim 1, wherein the base in step (b) is KOH or NaOH.	*See* Claim 1.

Claim 8	**Prior Art Disclosure**
The product of claim 1, wherein the process does not include purifying the compound of formula (III) produced in step (a).	*See* Claim 1.

Claim 9	**Prior Art Disclosure**
Element [A] A product comprising a compound having formula IV	A product-by-process claim is anticipated if the product is disclosed in the prior art. *Amgen*, 580 F.3d at 1366; *SmithKline Beecham Corp. v. Apotex Corp.*, 439 F.3d 1312, 1317 (Fed. Cir. 2006) ("It has long been established that one cannot avoid anticipation by an earlier product disclosure by claiming the same product more narrowly, that is, by claiming the product as produced by a particular process"); *Gen. Elec. Co. v. Wabash Appliance Corp.*, 304 U.S. 364, 373 (1938); *Cochrane v. Badische Anilin & Soda Farbrik*, 111 U.S. 293, 311 (1884) ("While a new process for producing [a chemical compound] was patentable, the product itself could not be patented even though it was a product made [by a new process] for the first time because the product was disclosed in the prior art").

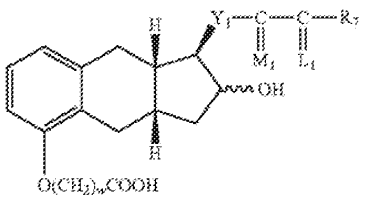
 (IV) or a pharmaceutically acceptable salt thereof, wherein the product is prepared by the process comprising	"In determining the validity of a product-by-process claim, the focus is on the product and not on the process of making it." *Amgen*, 580 F.3d at 1369-70; *In re Thorpe*, 777 F.2d 695, 697 (Fed. Cir. 1985) ("Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production."); *Smithkline*, 439 F.3d at 1317-19; *see also* Manual of Patent Examining Procedure § 2113 (8th ed. Rev. 8 July 2010). Accordingly, for determining the patentability of the Asserted Claims of the '393 patent, the question is whether the claimed product is disclosed in, or obvious from, the prior art. The product of claim 9 the '393 patent is a product comprising the treprostinil compound or a pharmaceutically acceptable salt thereof, without further limitations as to the composition of the product. Thus, any product comprising treprostinil compound in any amount, with any other types or amounts of impurities, falls within the scope of the claimed product. The '075 patent issued on December 15, 1981 and is thus prior art to the '393 patent under 102(b). The '075 patent describes a method of making treprostinil in Example 33, and also claims the treprostinil compound. ('075 patent at Col. 56:15-Col. 59:15, Col. 62:4-39, Col. 97:46-47; *see also* Civil Action No. 12-1617 Trial Tr. at 1850:10-21). Example 33 discloses 0.096 g of treprostinil final product. ('075 patent at Col. 62:34-35). The '075 patent also discloses pharmacologically acceptable salts of the compounds disclosed therein. ('075 patent at Col. 14:56-Col. 15:42, Col. 30:41-62). Further, the '393 patent itself states that treprostinil was disclosed in the '075 patent. ('393 patent at Col. 1: 22-23) ("Treprostinil, the active ingredient in Remodulin®, was first described in U.S. Pat. No. 4,306,075."). Moreover, there are no structural and functional differences between the product of the '075 patent (the treprostinil compound) and the claimed product (a product including the treprostinil compound).

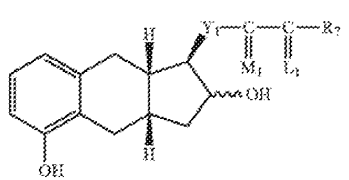
	Accordingly, because the '075 patent discloses a product comprising the treprostinil compound, the '075 patent anticipates claim 9.
Element [B] (a) alkylating a compound of formula V with an alkylating agent to produce a compound of formula VI,  	*See* Element [A] above.
Element [C] (b) hydrolyzing the product of formula VI of step (a) with a base,	*See* Element [A] above.
Element [D] (c) contacting the product of step (h) with a base B to form a salt of formula IVs, and	*See* Element [A] above.

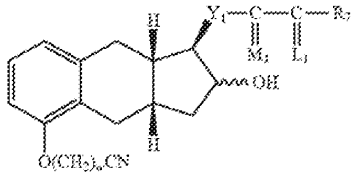
	
Element [E] (d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula IV.	*See* Element [A] above.

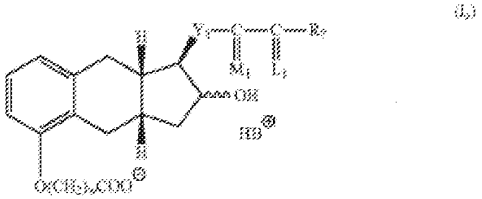
Claim 16	**Prior Art Disclosure**
The product of claim 9, wherein the process does not include purifying the compound of formula (VI) produced in step (a).	*See* Claim 9.

B. The Asserted Claims Are Anticipated By, Or Would Have Been Obvious In View Of, U.S. Patent No. 4,668,814 ("The '814 Patent")

Claim 1	Prior Art Disclosure
Element [A] A product comprising a compound of formula I:  (I) or a pharmaceutically acceptable salt thereof, wherein said product is prepared by a process comprising	A product-by-process claim is anticipated if the product is disclosed in the prior art. *Amgen*, 580 F.3d at 1366; *SmithKline Beecham Corp. v. Apotex Corp.*, 439 F.3d 1312, 1317 (Fed. Cir. 2006) ("It has long been established that one cannot avoid anticipation by an earlier product disclosure by claiming the same product more narrowly, that is, by claiming the product as produced by a particular process"); *Gen. Elec. Co. v. Wabash Appliance Corp.*, 304 U.S. 364, 373 (1938); *Cochrane v. Badische Anilin & Soda Farbrik*, 111 U.S. 293, 311 (1884) ("While a new process for producing [a chemical compound] was patentable, the product itself could not be patented even though it was a product made [by a new process] for the first time because the product was disclosed in the prior art"). "In determining the validity of a product-by-process claim, the focus is on the product and not on the process of making it." *Amgen*, 580 F.3d at 1369-70; *In re Thorpe*, 777 F.2d 695, 697 (Fed. Cir. 1985) ("Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production."); *Smithkline*, 439 F.3d at 1317-19; *see also* Manual of Patent Examining Procedure § 2113 (8th ed. Rev. 8 July 2010). Accordingly, for determining the patentability of the Asserted Claims of the '393 patent, the question is whether the claimed product is disclosed in, or obvious from, the prior art. The product of claim 1 the '393 patent is a product comprising a member of the recited genus of compounds that includes the treprostinil compound or a pharmaceutically acceptable salt thereof, without further limitations as to the composition of the product. Thus, any product comprising treprostinil compound in any amount, with any other types or amounts of impurities, falls within the scope of the claimed product. The '814 patent issued in 1987 and is thus prior art to the '393 patent under Section

	102(b). The '814 patent discloses pharmacologically acceptable salts of treprostinil. (Civil Action No. 12-1617, D.I. 218, Ex. 1, at Stipulated Fact No. 44). The '814 patent discloses an improved process of making treprostinil. (Civil Action No. 12-1617, Trial Tr. at 1850:22-1851:6). The product obtained at the end of Example 3 of the '814 patent is 1.2 grams of the treprostinil compound. (*Id.* at 1856:12-15). The 1.2 grams of treprostinil obtained is about 95% pure. (*Id.* at 1856:16-22). As described above, the '814 patent discloses treprostinil and pharmaceutically acceptable salts of treprostinil. There are no structural and functional differences between the product of the '814 patent (the treprostinil compound and pharmaceutically acceptable salts thereof) and the claimed product (a product including the treprostinil compound and pharmaceutically acceptable salts thereof). Accordingly, because the '814 patent discloses products comprising the treprostinil compound and pharmaceutically acceptable salts of treprostinil, the '814 patent anticipates claim 1.
Element [B] (a) alkylating a compound of structure II with an alkylating agent to produce a compound of formula III, (III) 	*See* Element [A] above.

(IID)  wherein w=1, 2, or 3; Y_1 is trans-CH=CH—, cis-CH=CH—, —$CH_2(CH_2)_m$—, or —C≡C—; m is 1, 2, or 3; R_2 is (1) —C_pH_{2p}—CH_3, wherein p is an integer from 1 to 5, inclusive, (2) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3) alkyl, or (C_1-C_3) alkoxy, with the proviso that not more than two substituents are other than alkyl, with the proviso that R_2 is phenoxy or substituted phenoxy, only when R_3 and R_4 are hydrogen or methyl, being the same or different, (3) phenyl, benzyl, phenylethyl, or phenylpropyl optionally substituted on the aromatic ring by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3)alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl, (4) cis-CH=CH—CH_2—CH_3, (5) —$(CH_2)_2$—CH(OH)—CH_3, or (6) —$(CH_2)_2$—CH=C$(CH_3)_2$; —$C(L_1)$—R_2 taken together is (1) (C_4-C_7)cycloalkyl optionally substituted by 1 to 3 (C_1-C_3) alkyl; (2) 2-(2-furyl)ethyl, (3) 2-(3-thienyl)ethoxy, or (4) 3-thienyloxymethyl; M_1 is α-OH:β-R_3 or α-R_3β-OH or α-OR_2:β-R_3 or α-R_3:β-OR_2, wherein R_3 is hydrogen or methyl, R_2 is an alcohol protecting group, and L_1 is α-R_3:β-R_3, α-R_4:β-R_3, or a mixture of α-R_3:β-R_4 and α-R_4:β-R_3, wherein R_3 and R_4 are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R_3 and R_4 is fluoro only when the other is hydrogen or fluoro.	

Element [C] (b) hydrolyzing the product of formula III of step (a) with a base,	*See* Element [A] above.
Element [D] (c) contacting the product of step (h) with a base B to form a salt of formula Is.  and	*See* Element [A] above.
Element [D] (d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula I.	*See* Element [A] above.

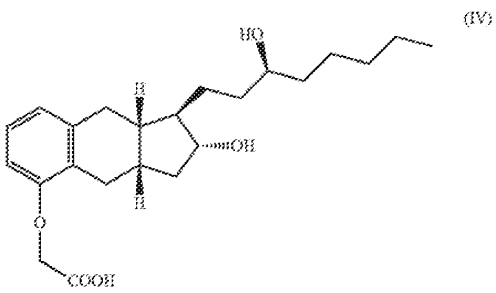
Claim 2	**Prior Art Disclosure**
The product of claim 1, wherein the purity of compound of formula I in said product is at least 99.5%.	*See* Claim 1. The skilled artisan would have been motivated to obtain a sample of treprostinil having a high level of purity. The Moriarty JOC Article includes an experimental section which describes in detail the synthesis of 441 grams of treprostinil acid having a purity of 99.7%. (*Id.* at 1902).

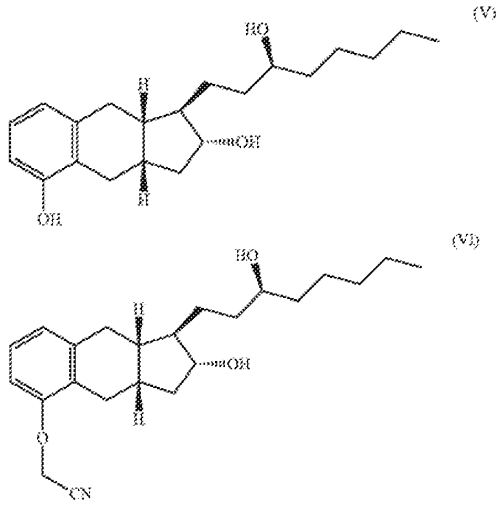
	As noted above, the 1.2 gram sample of treprostinil disclosed in Example 3 of the '814 patent has a purity level of about 95%. It would have been obvious for the skilled artisan to further purify the treprostinil disclosed in the '814 patent to a purity level of 99.5% or greater, particularly in view of the disclosure in the Moriarty JOC article of treprostinil having a purity level of 99.7%. Further, purification techniques are common practice in the chemical arts. Accordingly, claim 2 would have been obvious in view of the disclosure of treprostinil in the '814 patent.

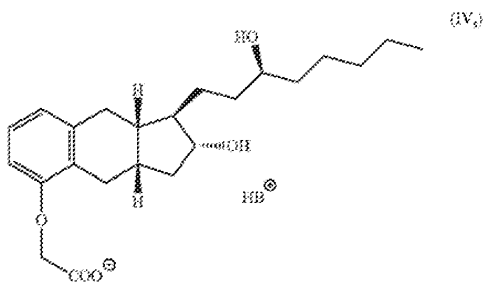
Claim 4	**Prior Art Disclosure**
The product of claim 1, wherein the base in step (b) is KOH or NaOH.	*See* Claim 1.

Claim 8	**Prior Art Disclosure**
The product of claim 1, wherein the process does not include purifying the compound of formula (III) produced in step (a).	*See* Claim 1.

Claim 9	**Prior Art Disclosure**
Element [A] A product comprising a compound having formula IV	A product-by-process claim is anticipated if the product is disclosed in the prior art. *Amgen*, 580 F.3d at 1366; *SmithKline Beecham Corp. v. Apotex Corp.*, 439 F.3d 1312, 1317 (Fed. Cir. 2006) ("It has long been established that one cannot avoid anticipation by an earlier product disclosure by claiming the same product more narrowly, that is, by claiming the product as produced by a particular process"); *Gen. Elec. Co. v. Wabash Appliance Corp.*, 304 U.S. 364, 373 (1938); *Cochrane v. Badische Anilin & Soda Farbrik*, 111 U.S. 293, 311 (1884) ("While a new process for producing [a chemical compound] was patentable, the product itself could not be patented even though it was a product made [by a new process] for the first time because the product was disclosed in the prior art").

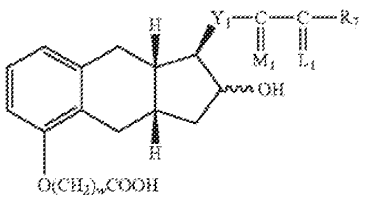
 (IV) or a pharmaceutically acceptable salt thereof, wherein the product is prepared by the process comprising	"In determining the validity of a product-by-process claim, the focus is on the product and not on the process of making it." *Amgen*, 580 F.3d at 1369-70; *In re Thorpe*, 777 F.2d 695, 697 (Fed. Cir. 1985) ("Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production."); *Smithkline*, 439 F.3d at 1317-19; *see also* Manual of Patent Examining Procedure § 2113 (8th ed. Rev. 8 July 2010). Accordingly, for determining the patentability of the Asserted Claims of the '393 patent, the question is whether the claimed product is disclosed in, or obvious from, the prior art. The product of claim 9 the '393 patent is a product comprising the treprostinil compound or a pharmaceutically acceptable salt thereof, without further limitations as to the composition of the product. Thus, any product comprising treprostinil compound in any amount, with any other types or amounts of impurities, falls within the scope of the claimed product. The '814 patent issued in 1987 and is thus prior art to the '393 patent under Section 102(b). The '814 patent discloses pharmacologically acceptable salts of treprostinil. (Civil Action No. 12-1617, D.I. 218, Ex. 1, at Stipulated Fact No. 44). The '814 patent discloses an improved process of making treprostinil. (Civil Action No. 12-1617, Trial Tr. at 1850:22-1851:6). The product obtained at the end of Example 3 of the '814 patent is 1.2 grams of the treprostinil compound. (*Id.* at 1856:12-15). The 1.2 grams of treprostinil obtained is about 95% pure. (*Id.* at 1856:16-22). As described above, the '814 patent discloses treprostinil and pharmaceutically acceptable salts of treprostinil. Moreover, there are no structural and functional differences between the product of the '814 patent (the treprostinil compound and pharmaceutically acceptable salts thereof) and the claimed product (a product including the treprostinil compound and pharmaceutically acceptable salts thereof). Accordingly, because the '814 patent discloses products comprising the treprostinil compound and pharmaceutically acceptable salts of treprostinil, the '814 patent

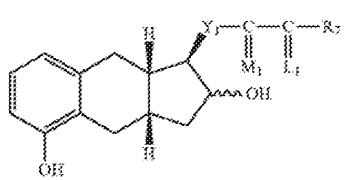
	anticipates claim 9.
Element [B] (a) alkylating a compound of formula V with an alkylating agent to produce a compound of formula VI, 	*See* Element [A] above.
Element [C] (b) hydrolyzing the product of formula VI of step (a) with a base,	*See* Element [A] above.
Element [D] (c) contacting the product of step (h) with a base B to form a salt of formula IVs, and	*See* Element [A] above.

	
Element [E] (d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula IV.	*See* Element [A] above.

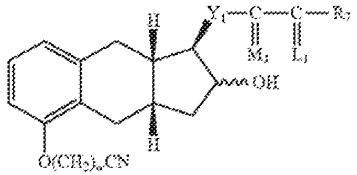
Claim 16	**Prior Art Disclosure**
The product of claim 9, wherein the process does not include purifying the compound of formula (VI) produced in step (a).	*See* Claim 9.

C. The Asserted Claims Are Anticipated By, Or Would Have Been Obvious In View Of, European Patent Publication No. 0159784A1 ("EP '784")

Claim 1	Prior Art Disclosure
Element [A] A product comprising a compound of formula I:  (I) or a pharmaceutically acceptable salt thereof, wherein said product is prepared by a process comprising	A product-by-process claim is anticipated if the product is disclosed in the prior art. *Amgen*, 580 F.3d at 1366; *SmithKline Beecham Corp. v. Apotex Corp.*, 439 F.3d 1312, 1317 (Fed. Cir. 2006) ("It has long been established that one cannot avoid anticipation by an earlier product disclosure by claiming the same product more narrowly, that is, by claiming the product as produced by a particular process"); *Gen. Elec. Co. v. Wabash Appliance Corp.*, 304 U.S. 364, 373 (1938); *Cochrane v. Badische Anilin & Soda Farbrik*, 111 U.S. 293, 311 (1884) ("While a new process for producing [a chemical compound] was patentable, the product itself could not be patented even though it was a product made [by a new process] for the first time because the product was disclosed in the prior art"). "In determining the validity of a product-by-process claim, the focus is on the product and not on the process of making it." *Amgen*, 580 F.3d at 1369-70; *In re Thorpe*, 777 F.2d 695, 697 (Fed. Cir. 1985) ("Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production."); *Smithkline*, 439 F.3d at 1317-19; *see also* Manual of Patent Examining Procedure § 2113 (8th ed. Rev. 8 July 2010). Accordingly, for determining the patentability of the Asserted Claims of the '393 patent, the question is whether the claimed product is disclosed in, or obvious from, the prior art. The product of claim 1 the '393 patent is a product comprising a member of the recited genus of compounds that includes the treprostinil compound or a pharmaceutically acceptable salt thereof, without further limitations as to the composition of the product. Thus, any product comprising treprostinil compound in any amount, with any other types or amounts of impurities, falls within the scope of the claimed product. EP '784 was published in 1985 and is thus prior art to the '393 patent under Section

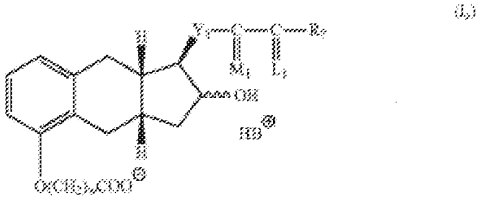
	102(b). Example 9 of EP '784 discloses the chemical formula 9-Deoxy-13,14-dihydro-2',9α-methano-3-oxa-4,5,6-trinor-3,7-(1',3'-interphenylene)-PGF_1 (EP '784 at 66:23-71:29). The compound represented by chemical formula 9-Deoxy-13,14-dihydro-2',9α-methano-3-oxa-4,5,6-trinor-3,7-(1',3'-interphenylene)-PGF_1 is the treprostinil compound. EP '784 teaches that the compounds of Formula 1 or 1(a), wherein Q is $COOR_1$ (which includes treprostinil), may be used in the free acid form or in pharmacologically acceptable salt form. (EP '784 at 20:21-23). The method for making treprostinil disclosed in EP '784 is identical to the method disclosed in the '814 patent. (Civil Action No. 12-1617, D.I. 218, Ex. 1, Stipulated Fact No. 45). There are no structural and functional differences between the product of EP '784 (the treprostinil compound and pharmaceutically acceptable salts thereof) and the claimed product (a product including the treprostinil compound and pharmaceutically acceptable salts thereof). Accordingly, because EP '784 discloses products comprising treprostinil compound and pharmaceutically acceptable salts of treprostinil, EP '784 anticipates claim 1.
Element [B] (a) alkylating a compound of structure II with an alkylating agent to produce a compound of formula III, (II) 	*See* Element [A] above.

(IID)



wherein
w=1, 2, or 3;
Y_1 is trans-CH=CH—, cis-CH=CH—, —$CH_2(CH_2)_m$—, or —C≡C—; m is 1, 2, or 3;
R_2 is
(1) —C_pH_{2p}—CH_3, wherein p is an integer from 1 to 5, inclusive,
(2) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3) alkyl, or (C_1-C_3) alkoxy, with the proviso that not more than two substituents are other than alkyl, with the proviso that R_2 is phenoxy or substituted phenoxy, only when R_3 and R_4 are hydrogen or methyl, being the same or different,
(3) phenyl, benzyl, phenylethyl, or phenylpropyl optionally substituted on the aromatic ring by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3)alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl,
(4) cis-CH=CH—CH_2—CH_3,
(5) —$(CH_2)_2$—CH(OH)—CH_3, or
(6) —$(CH_2)_2$—CH=C(CH_3)$_2$;
—$C(L_1)$—R_2 taken together is
(1) (C_4-C_7)cycloalkyl optionally substituted by 1 to 3 (C_1-C_3) alkyl;

(2) 2-(2-furyl)ethyl,
(3) 2-(3-thienyl)ethoxy, or
(4) 3-thienyloxymethyl;
M_1 is α-OH:β-R_5 or α-R_5β-OH or α-OR_2:β-R_5 or α-R_5:β-OR_2, wherein R_5 is hydrogen or methyl, R_2 is an alcohol protecting group, and
L_1 is α-R_3:β-R_4, α-R_4:β-R_3, or a mixture of α-R_3:β-R_4 and α-R_4:β-R_3, wherein R_3 and R_4 are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R_3 and R_4 is fluoro only when the other is hydrogen or fluoro.

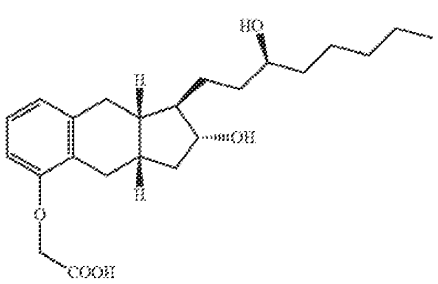
Element [C] (b) hydrolyzing the product of formula III of step (a) with a base,	*See* Element [A] above.
Element [D] (c) contacting the product of step (h) with a base B to form a salt of formula Is.  And	*See* Element [A] above.
Element [E] (d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula I.	*See* Element [A] above.

Claim 2	**Prior Art Disclosure**
The product of claim 1, wherein the purity of compound of formula I in said product is at least 99.5%.	*See* Claim 1. The skilled artisan would have been motivated to obtain a sample of treprostinil having a high level of purity. The Moriarty JOC Article includes an experimental section which describes in detail the synthesis of 441 grams of treprostinil acid having a purity of 99.7%. (*Id.* at 1902).

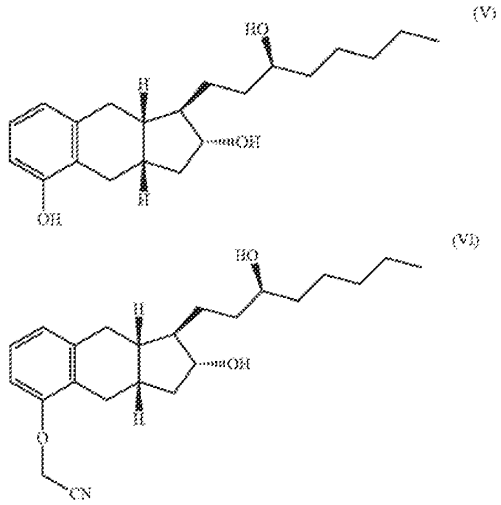
	Accordingly, it would have been obvious for the skilled artisan to purify the treprostinil disclosed in EP '784 to a purity level of 99.5% or greater, particularly in view of the disclosure in the Moriarty JOC article of treprostinil having a purity level of 99.7%. Further, purification techniques are common practice in the chemical arts. Accordingly, claim 2 would have been obvious in view of the disclosure of treprostinil in EP '784.

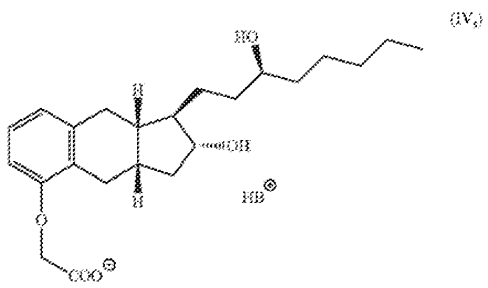
Claim 4	**Prior Art Disclosure**
The product of claim 1, wherein the base in step (b) is KOH or NaOH.	*See* Claim 1.

Claim 8	**Prior Art Disclosure**
The product of claim 1, wherein the process does not include purifying the compound of formula (III) produced in step (a).	*See* Claim 1.

Claim 9	**Prior Art Disclosure**
Element [A] A product comprising a compound having formula IV  	A product-by-process claim is anticipated if the product is disclosed in the prior art. *Amgen*, 580 F.3d at 1366; *SmithKline Beecham Corp. v. Apotex Corp.*, 439 F.3d 1312, 1317 (Fed. Cir. 2006) ("It has long been established that one cannot avoid anticipation by an earlier product disclosure by claiming the same product more narrowly, that is, by claiming the product as produced by a particular process"); *Gen. Elec. Co. v. Wabash Appliance Corp.*, 304 U.S. 364, 373 (1938); *Cochrane v. Badische Anilin & Soda Farbrik*, 111 U.S. 293, 311 (1884) ("While a new process for producing [a chemical compound] was patentable, the product itself could not be patented even though it was a product made [by a new process] for the first time because the product was disclosed in the prior art"). "In determining the validity of a product-by-process claim, the focus is on the product and not on the process of making it." *Amgen*, 580 F.3d at 1369-70; *In re Thorpe*, 777 F.2d 695, 697 (Fed. Cir. 1985) ("Even though product-by-process

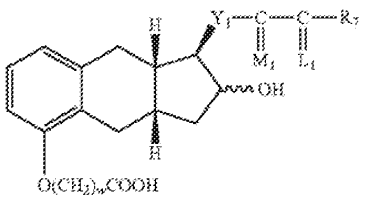
or a pharmaceutically acceptable salt thereof, wherein the product is prepared by the process comprising	claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production."); *Smithkline*, 439 F.3d at 1317-19; *see also* Manual of Patent Examining Procedure § 2113 (8th ed. Rev. 8 July 2010). Accordingly, for determining the patentability of the Asserted Claims of the '393 patent, the question is whether the claimed product is disclosed in, or obvious from, the prior art. The product of claim 9 the '393 patent is a product comprising the treprostinil compound or a pharmaceutically acceptable salt thereof, without further limitations as to the composition of the product. Thus, any product comprising treprostinil compound in any amount, with any other types or amounts of impurities, falls within the scope of the claimed product. EP '784 was published in 1985 and is thus prior art to the '393 patent under Section 102(b). Example 9 of EP '784 discloses the chemical formula 9-Deoxy-13,14-dihydro-2',9α-methano-3-oxa-4,5,6-trinor-3,7-(1',3'-interphenylene)-PGF_1 (EP '784 at 66:23-71:29). The compound represented by chemical formula 9-Deoxy-13,14-dihydro-2',9α-methano-3-oxa-4,5,6-trinor-3,7-(1',3'-interphenylene)-PGF_1 is the treprostinil compound. EP '784 teaches that the compounds of Formula 1 or 1(a), wherein Q is $COOR_1$ (which includes treprostinil), may be used in the free acid form or in pharmacologically acceptable salt form. (EP '784 at 20:21-23). The method for making treprostinil disclosed in EP '784 is identical to the method disclosed in the '814 patent. (Civil Action No. 12-1617, D.I. 218, Ex. 1, Stipulated Fact No. 45). There are no structural and functional differences between the product of EP '784 (the treprostinil compound and pharmaceutically acceptable salts thereof) and the claimed product (a product including the treprostinil compound and pharmaceutically acceptable salts thereof). Accordingly, because EP '784 discloses products comprising the treprostinil compound and pharmaceutically acceptable salts of treprostinil, EP '784 anticipates

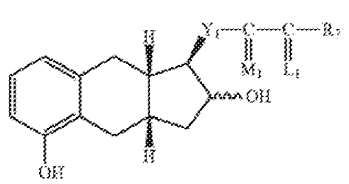
	claim 9.
Element [B] (a) alkylating a compound of formula V with an alkylating agent to produce a compound of formula VI, 	*See* Element [A] above.
Element [C] (b) hydrolyzing the product of formula VI of step (a) with a base,	*See* Element [A] above.
Element [D] (c) contacting the product of step (h) with a base B to form a salt of formula IVs, and	*See* Element [A] above.

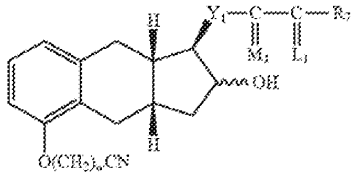
	
Element [E] (d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula IV.	*See* Element [A] above.

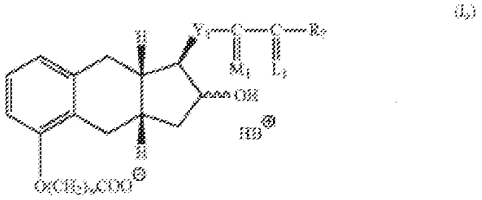
Claim 16	**Prior Art Disclosure**
The product of claim 9, wherein the process does not include purifying the compound of formula (VI) produced in step (a).	*See* Claim 9.

D. The Asserted Claims Are Anticipated By, Or Would Have Been Obvious In View Of, U.S. Patent No. 6,765,117 ("The '117 Patent")

Claim 1	Prior Art Disclosure
Element [A] A product comprising a compound of formula I:  (I) or a pharmaceutically acceptable salt thereof, wherein said product is prepared by a process comprising	A product-by-process claim is anticipated if the product is disclosed in the prior art. *Amgen*, 580 F.3d at 1366; *SmithKline Beecham Corp. v. Apotex Corp.*, 439 F.3d 1312, 1317 (Fed. Cir. 2006) ("It has long been established that one cannot avoid anticipation by an earlier product disclosure by claiming the same product more narrowly, that is, by claiming the product as produced by a particular process"); *Gen. Elec. Co. v. Wabash Appliance Corp.*, 304 U.S. 364, 373 (1938); *Cochrane v. Badische Anilin & Soda Farbrik*, 111 U.S. 293, 311 (1884) ("While a new process for producing [a chemical compound] was patentable, the product itself could not be patented even though it was a product made [by a new process] for the first time because the product was disclosed in the prior art"). "In determining the validity of a product-by-process claim, the focus is on the product and not on the process of making it." *Amgen*, 580 F.3d at 1369-70; *In re Thorpe*, 777 F.2d 695, 697 (Fed. Cir. 1985) ("Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production."); *Smithkline*, 439 F.3d at 1317-19; *see also* Manual of Patent Examining Procedure § 2113 (8th ed. Rev. 8 July 2010). Accordingly, for determining the patentability of the Asserted Claims of the '393 patent, the question is whether the claimed product is disclosed in, or obvious from, the prior art. The product of claim 1 of the '393 patent is a product comprising a member of the recited genus of compounds that includes the treprostinil compound or a pharmaceutically acceptable salt thereof, without further limitations as to the composition of the product. Thus, any product comprising treprostinil compound in any amount, with any other types or amounts of impurities, falls within the scope of the claimed product. The '117 patent was issued on July 20, 2004 and is thus is thus prior art to the '393

	patent under Section 102(b). The '117 patent discloses a method of synthesizing treprostinil. ('117 patent at Col. 11:55-21:12). The final step of Example 1 describes a process of obtaining crude treprostinil and then purifying the crude product by silica gel chromatography using a dichloromethane solution containing 3% methanol and 0.1% acetic acid as eluent to yield 0.076 g of product (95%). ('117 patent at Col. 21:8-11). The '117 patent claims are product-by-process claims directed to treprostinil (claims 1-3) and a pharmaceutically acceptable salt of treprostinil (claim 4) produced through a process that includes the Pauson-Khand cyclization step. The '117 patent is listed in the Orange Book in connection with NDA No. 21-272 for Remodulin. (Civil Action No. 12-1617, D.I. 218, Ex. 1, Stipulated Fact No. 11). Further, the '393 patent specification states that the '117 patent discloses a method of making treprostinil. ('393 patent at Col. 1:23-26). There are no structural and functional differences between the product of the '117 patent (the treprostinil compound and pharmaceutically acceptable salts thereof) and the claimed product (a product including the treprostinil compound and pharmaceutically acceptable salts thereof). Accordingly, because the '117 patent discloses products comprising the treprostinil compound and salts thereof, the '117 patent anticipates claim 1.
Element [B] (a) alkylating a compound of structure II with an alkylating agent to produce a compound of formula III, (II) 	*See* Element [A] above.

(IID)  wherein w=1, 2, or 3; Y_1 is trans-CH=CH—, cis-CH=CH—, —$CH_2(CH_2)_m$—, or —C≡C—; m is 1, 2, or 3; R_2 is (1) —C_pH_{2p}—CH_3, wherein p is an integer from 1 to 5, inclusive, (2) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3) alkyl, or (C_1-C_3) alkoxy, with the proviso that not more than two substituents are other than alkyl, with the proviso that R_2 is phenoxy or substituted phenoxy, only when R_3 and R_4 are hydrogen or methyl, being the same or different, (3) phenyl, benzyl, phenylethyl, or phenylpropyl optionally substituted on the aromatic ring by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3)alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl, (4) cis-CH=CH—CH_2—CH_3, (5) —$(CH_2)_2$—CH(OH)—CH_3, or (6) —$(CH_2)_2$—CH=C(CH_3)$_2$; —$C(L_1)$—R_2 taken together is (1) (C_4-C_7)cycloalkyl optionally substituted by 1 to 3 (C_1-C_3) alkyl; (2) 2-(2-furyl)ethyl, (3) 2-(3-thienyl)ethoxy, or (4) 3-thienyloxymethyl; M_1 is α-OH:β-R_4 or α-R_4:β-OH or α-OR_2:β-R_4 or α-R_4:β-OR_2, wherein R_4 is hydrogen or methyl, R_2 is an alcohol protecting group, and L_1 is α-R_3:β-R_3, α-R_4:β-R_3, or a mixture of α-R_3:β-R_4 and α-R_4:β-R_3, wherein R_3 and R_4 are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R_3 and R_4 is fluoro only when the other is hydrogen or fluoro.	

Element [C] (b) hydrolyzing the product of formula III of step (a) with a base,	*See* Element [A] above.
Element [D] (c) contacting the product of step (h) with a base B to form a salt of formula Is.  and	*See* Element [A] above.
Element [E] (d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula I.	*See* Element [A] above.

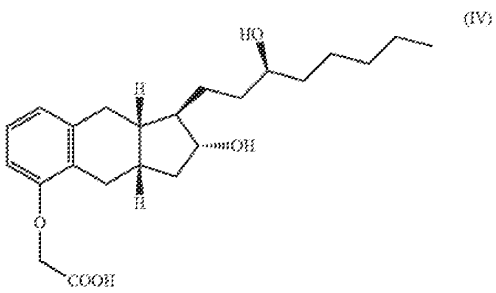
Claim 2	**Prior Art Disclosure**
The product of claim 1, wherein the purity of compound of formula I in said product is at least 99.5%.	*See* Claim 1. The skilled artisan would have been motivated to obtain a sample of treprostinil having a high level of purity. The Moriarty JOC Article includes an experimental section which describes in detail the synthesis of 441 grams of treprostinil acid having a purity of 99.7%. (*Id.* at 1902).

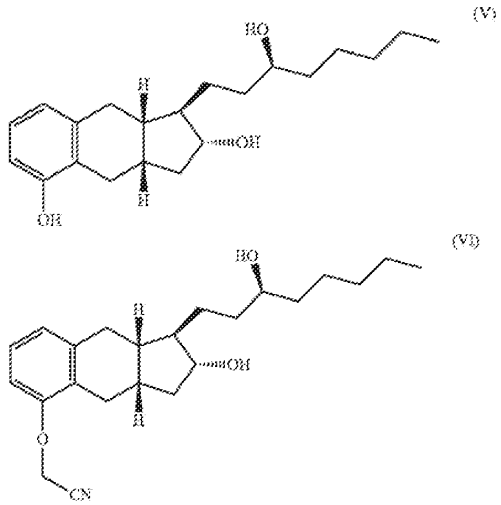
	Accordingly, it would have been obvious for the skilled artisan to purify the treprostinil disclosed in the '117 patent to a purity level of 99.5% or greater, particularly in view of the disclosure in the Moriarty JOC article of treprostinil having a purity level of 99.7%. Further, purification techniques are common practice in the chemical arts. Accordingly, claim 2 would have been obvious in view of the disclosure of treprostinil in the '117 patent.

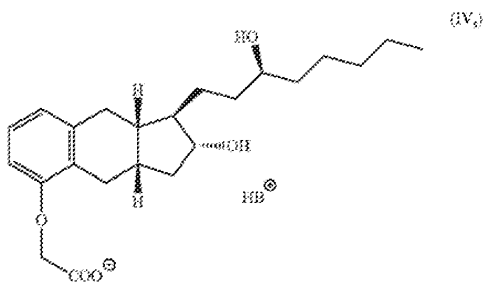
Claim 4	**Prior Art Disclosure**
The product of claim 1, wherein the base in step (b) is KOH or NaOH.	*See* Claim 1.

Claim 8	**Prior Art Disclosure**
The product of claim 1, wherein the process does not include purifying the compound of formula (III) produced in step (a).	*See* Claim 1.

Claim 9	**Prior Art Disclosure**
Element [A] A product comprising a compound having formula IV	A product-by-process claim is anticipated if the product is disclosed in the prior art. *Amgen*, 580 F.3d at 1366; *SmithKline Beecham Corp. v. Apotex Corp.*, 439 F.3d 1312, 1317 (Fed. Cir. 2006) ("It has long been established that one cannot avoid anticipation by an earlier product disclosure by claiming the same product more narrowly, that is, by claiming the product as produced by a particular process"); *Gen. Elec. Co. v. Wabash Appliance Corp.*, 304 U.S. 364, 373 (1938); *Cochrane v. Badische Anilin & Soda Farbrik*, 111 U.S. 293, 311 (1884) ("While a new process for producing [a chemical compound] was patentable, the product itself could not be patented even though it was a product made [by a new process] for the first time because the product was disclosed in the prior art"). "In determining the validity of a product-by-process claim, the focus is on the

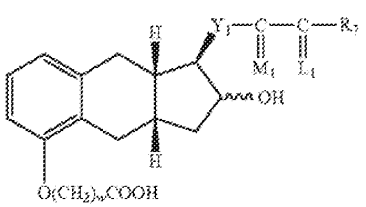
 (IV) or a pharmaceutically acceptable salt thereof, wherein the product is prepared by the process comprising	product and not on the process of making it." *Amgen*, 580 F.3d at 1369-70; *In re Thorpe*, 777 F.2d 695, 697 (Fed. Cir. 1985) ("Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production."); *Smithkline*, 439 F.3d at 1317-19; *see also* Manual of Patent Examining Procedure § 2113 (8th ed. Rev. 8 July 2010). Accordingly, for determining the patentability of the Asserted Claims of the '393 patent, the question is whether the claimed product is disclosed in, or obvious from, the prior art. The product of claim 9 of the '393 patent is a product comprising the treprostinil compound or a pharmaceutically acceptable salt thereof, without further limitations as to the composition of the product. Thus, any product comprising treprostinil compound in any amount, with any other types or amounts of impurities, falls within the scope of the claimed product. The '117 patent was issued on July 20, 2004 and is thus is thus prior art to the '393 patent under Section 102(b). The '117 patent discloses a method of synthesizing treprostinil. ('117 patent at Col. 11:55-21:12). The final step of Example 1 describes a process of obtaining crude treprostinil and then purifying the crude product by silica gel chromatography using a dichloromethane solution containing 3% methanol and 0.1% acetic acid as eluent to yield 0.076 g of product (95%). ('117 patent at Col. 21:8-11). The '117 patent claims are product-by-process claims directed to treprostinil (claims 1-3) and a pharmaceutically acceptable salt of treprostinil (claim 4) produced through a process that includes the Pauson-Khand cyclization step. The '117 patent is listed in the Orange Book in connection with NDA No. 21-272 for Remodulin. (Civil Action No. 12-1617, D.I. 218, Ex. 1, Stipulated Fact No. 11). There are no structural and functional differences between the product of the '117 patent (the treprostinil compound and pharmaceutically acceptable salts thereof) and the claimed product (a product including the treprostinil compound and pharmaceutically acceptable salts thereof).

	Accordingly, because the '117 patent discloses products comprising the treprostinil compound and salts thereof, the '117 patent anticipates claim 9.
Element [B] (a) alkylating a compound of formula V with an alkylating agent to produce a compound of formula VI,  	*See* Element [A] above.
Element [C] (b) hydrolyzing the product of formula VI of step (a) with a base,	*See* Element [A] above.
Element [D] (c) contacting the product of step (h) with a base B to form a salt of formula IVs, and	*See* Element [A] above.

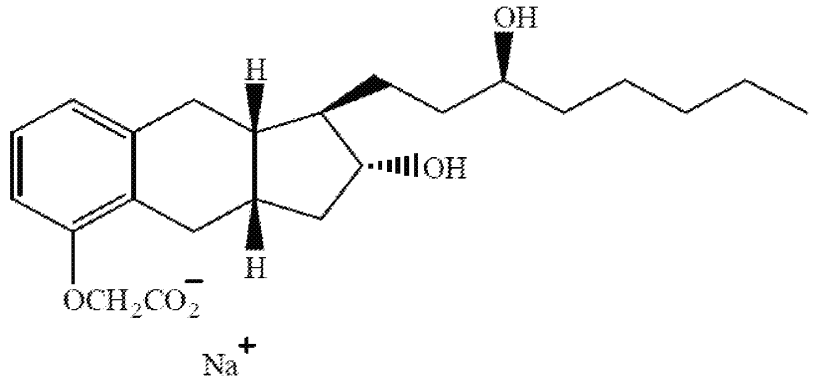
	
Element [E] (d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula IV.	*See* Element [A] above.

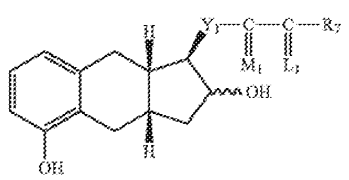
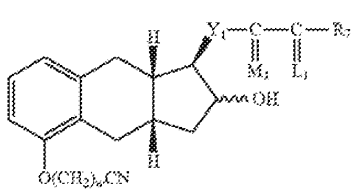
Claim 16	**Prior Art Disclosure**
The product of claim 9, wherein the process does not include purifying the compound of formula (VI) produced in step (a).	*See* Claim 9.

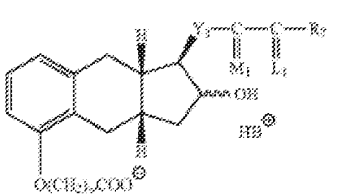
E. The Remodulin Package Insert Anticipates The Asserted Claims

Claim 1	Prior Art Disclosure
Element [A] A product comprising a compound of formula I:  (I) or a pharmaceutically acceptable salt thereof, wherein said product is prepared by a process comprising	A product-by-process claim is anticipated if the product is disclosed in the prior art. *Amgen*, 580 F.3d at 1366; *SmithKline Beecham Corp. v. Apotex Corp.*, 439 F.3d 1312, 1317 (Fed. Cir. 2006) ("It has long been established that one cannot avoid anticipation by an earlier product disclosure by claiming the same product more narrowly, that is, by claiming the product as produced by a particular process"); *Gen. Elec. Co. v. Wabash Appliance Corp.*, 304 U.S. 364, 373 (1938); *Cochrane v. Badische Anilin & Soda Farbrik*, 111 U.S. 293, 311 (1884) ("While a new process for producing [a chemical compound] was patentable, the product itself could not be patented even though it was a product made [by a new process] for the first time because the product was disclosed in the prior art"). "In determining the validity of a product-by-process claim, the focus is on the product and not on the process of making it." *Amgen*, 580 F.3d at 1369-70; *In re Thorpe*, 777 F.2d 695, 697 (Fed. Cir. 1985) ("Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production."); *Smithkline*, 439 F.3d at 1317-19; *see also* Manual of Patent Examining Procedure § 2113 (8th ed. Rev. 8 July 2010). Accordingly, for determining the patentability of the Asserted Claims of the '393 patent, the question is whether the claimed product is disclosed in, or obvious from, the prior art. The product of claim 1 of the '393 patent is a product comprising a member of the recited genus of compounds that includes the treprostinil compound or a pharmaceutically acceptable salt thereof, without further limitations as to the composition of the product. Thus, any product comprising treprostinil compound in any amount, with any other types or amounts of impurities, falls within the scope of the claimed product. The 2006 Remodulin Package Insert was published in March 2006 and is thus is thus

	prior art to the '393 patent under Section 102(b). The Package Insert states as follows: > Remodulin® (treprostinil sodium) Injection is a sterile sodium salt formulated for subcutaneous or intravenous administration. Remodulin is supplied in 20 mL multi-use vials in four strengths, containing 1 mg/mL, 2.5 mg/mL, 5 mg/mL or 10 mg/mL of treprostinil. Each mL also contains 5.3 mg sodium chloride (except for the 10 mg/mL strength which contains 4.0 mg sodium chloride), 3.0 mg metacresol, 6.3 mg sodium citrate, and water for injection. Sodium hydroxide and hydrochloric acid may be added to adjust pH between 6.0 and 7.2. (Package Insert at 1). The Package Insert also provides the chemical name for treprostinil sodium as "(1R,2R,3aS,9aS)-[[2,3,3a,4,9,9a-Hexahydro-2-hydroxy-1-[(3S)-3-hydroxyoctyl]-1Hbenz[f]inden-5-yl]oxy]acetic acid monosodium salt" and discloses that "[t]reprostinil sodium has a molecular weight of 412.49 and a molecular formula of $C_{23}H_{33}NaO_5$." (*Id.*). Further, the Package Insert discloses that the "structural formula of treprostinil sodium" is as follows:

	 (*Id.*). Accordingly, the 2006 Remodulin Package Insert describes UTC's commercial Remodulin product, which includes treprostinil sodium salt as the API. Further, the '393 patent is listed on the Orange Book as covering UTC's Remodulin Product. Accordingly, because 2006 Remodulin Product Insert discloses products comprising the treprostinil sodium API and further describes the commercial product that UTC admits is an embodiment of the product claimed in the '393 patent, the 2006 Remodulin Package Insert anticipates claim 1.
Element [B] (a) alkylating a compound of structure II with an alkylating agent to produce a compound of formula III,	*See* Element [A] above.

(II)  (III)  wherein w=1, 2, or 3; Y_1 is trans-CH=CH—, cis-CH=CH—, —$CH_2(CH_2)_m$—, or —C≡C—; m is 1, 2, or 3; R_7 is (1) —C_pH_{2p}—CH_3, wherein p is an integer from 1 to 5, inclusive, (2) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3) alkyl, or (C_1-C_3) alkoxy, with the proviso that not more than two substituents are other than alkyl, with the proviso that R_7 is phenoxy or substituted phenoxy, only when R_3 and R_4 are hydrogen or methyl, being the same or different, (3) phenyl, benzyl, phenylethyl, or phenylpropyl optionally substituted on the aromatic ring by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3)alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl, (4) cis-CH=CH—CH_2—CH_3, (5) —$(CH_2)_2$—CH(OH)—CH_3, or (6) —$(CH_2)_2$—CH=C$(CH_3)_2$; —$C(L_1)$—R_7 taken together is (1) (C_4-C_7)cycloalkyl optionally substituted by 1 to 3 (C_1-C_3) alkyl;	

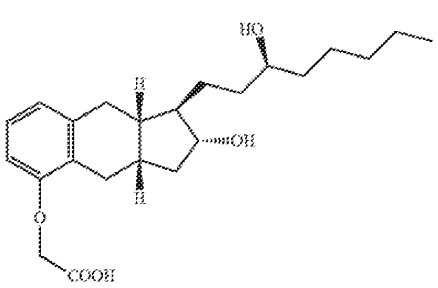
(2) 2-(2-furyl)ethyl, (3) 2-(3-thienyl)ethoxy, or (4) 3-thienyloxymethyl; M_1 is α-OH:β-R_3 or α-R_3:β-OH or α-OR_1:β-R_3 or α-R_3:β-OR_2, wherein R_3 is hydrogen or methyl, R_2 is an alcohol protecting group, and L_1 is α-R_3:β-R_4, α-R_4:β-R_3, or a mixture of α-R_3:β-R_4 and α-R_4:β-R_3, wherein R_3 and R_4 are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R_3 and R_4 is fluoro only when the other is hydrogen or fluoro,	
Element [C] (b) hydrolyzing the product of formula III of step (a) with a base,	*See* Element [A] above.
Element [D] (c) contacting the product of step (h) with a base B to form a salt of formula Is.  and	*See* Element [A] above.
Element [E] (d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula I.	*See* Element [A] above.

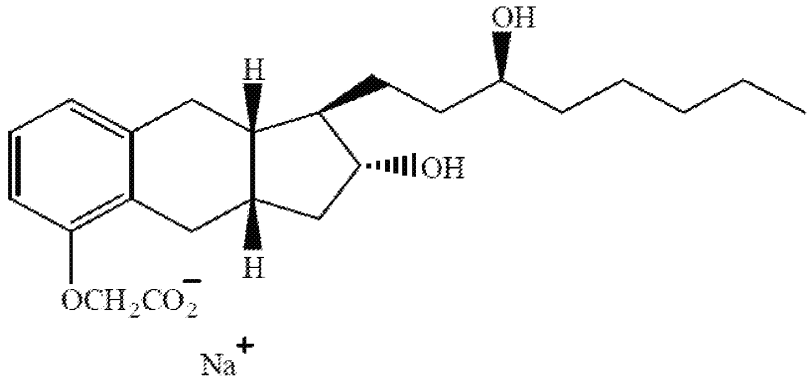
Claim 2	Prior Art Disclosure
The product of claim 1, wherein the purity of compound of formula I in said product is at least 99.5%.	*See* Claim 1. As noted above, the '393 patent is listed on the Orange Book as covering UTC's Remodulin Product. To the extent that UTC contends that Sandoz's ANDA Product infringes claim 2 of the '393 patent, then claim 2 of the '393 patent is anticipated by the Remodulin product as disclosed in the 2006 Remodulin Package Insert.

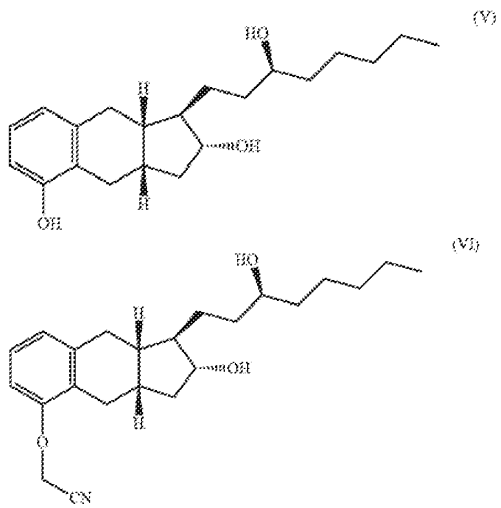
Claim 4	Prior Art Disclosure
The product of claim 1, wherein the base in step (b) is KOH or NaOH.	*See* Claim 1.

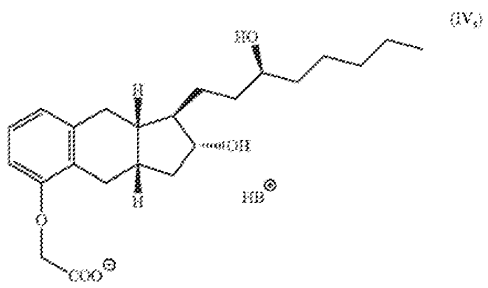
Claim 8	Prior Art Disclosure
The product of claim 1, wherein the process does not include purifying the compound of formula (III) produced in step (a).	*See* Claim 1.

Claim 9	Prior Art Disclosure
Element [A] A product comprising a compound having formula IV	A product-by-process claim is anticipated if the product is disclosed in the prior art. *Amgen*, 580 F.3d at 1366; *SmithKline Beecham Corp. v. Apotex Corp.*, 439 F.3d 1312, 1317 (Fed. Cir. 2006) ("It has long been established that one cannot avoid anticipation by an earlier product disclosure by claiming the same product more narrowly, that is, by claiming the product as produced by a particular process"); *Gen. Elec. Co. v. Wabash Appliance Corp.*, 304 U.S. 364, 373 (1938); *Cochrane v. Badische Anilin & Soda Farbrik*, 111 U.S. 293, 311 (1884) ("While a new process for producing [a chemical compound] was patentable, the product itself could not be patented even though it was a product made [by a new process] for the first time because the product was disclosed in the prior art").

 (IV) or a pharmaceutically acceptable salt thereof, wherein the product is prepared by the process comprising	"In determining the validity of a product-by-process claim, the focus is on the product and not on the process of making it." *Amgen*, 580 F.3d at 1369-70; *In re Thorpe*, 777 F.2d 695, 697 (Fed. Cir. 1985) ("Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production."); *Smithkline*, 439 F.3d at 1317-19; *see also* Manual of Patent Examining Procedure § 2113 (8th ed. Rev. 8 July 2010). Accordingly, for determining the patentability of the Asserted Claims of the '393 patent, the question is whether the claimed product is disclosed in, or obvious from, the prior art. The product of claim 9 of the '393 patent is a product comprising the treprostinil compound or a pharmaceutically acceptable salt thereof, without further limitations as to the composition of the product. Thus, any product comprising treprostinil compound in any amount, with any other types or amounts of impurities, falls within the scope of the claimed product. The 2006 Remodulin Package Insert was published in March 2006 and is thus is thus prior art to the '393 patent under Section 102(b). The Package Insert states as follows: Remodulin® (treprostinil sodium) Injection is a sterile sodium salt formulated for subcutaneous or intravenous administration. Remodulin is supplied in 20 mL multi-use vials in four strengths, containing 1 mg/mL, 2.5 mg/mL, 5 mg/mL or 10 mg/mL of treprostinil. Each mL also contains 5.3 mg sodium chloride (except for the 10 mg/mL strength which contains 4.0 mg sodium chloride), 3.0 mg metacresol, 6.3 mg sodium citrate, and water for injection. Sodium hydroxide and hydrochloric acid may be added to adjust pH between 6.0 and 7.2. (Package Insert at 1). The Package Insert also provides the chemical name for treprostinil sodium as "(1R,2R,3aS,9aS)-[[2,3,3a,4,9,9a-Hexahydro-2-hydroxy-1-

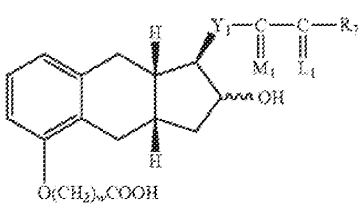
	[(3S)-3-hydroxyoctyl]-1Hbenz[f]inden-5-yl]oxy]acetic acid monosodium salt" and discloses that "[t]reprostinil sodium has a molecular weight of 412.49 and a molecular formula of $C_{23}H_{33}NaO_5$." (*Id.*). Further, the Package Insert discloses that the "structural formula of treprostinil sodium" is as follows:  (*Id.*). Accordingly, the 2006 Remodulin Package Insert describes UTC's commercial Remodulin product, which includes treprostinil sodium salt as the API. Further, the '393 patent is listed on the Orange Book as covering UTC's Remodulin Product. Accordingly, because 2006 Remodulin Product Insert discloses products comprising the treprostinil sodium API and further describes the commercial product that UTC admits is an embodiment of the product claimed in the '393 patent, the 2006 Remodulin Package Insert anticipates claim 9.
Element [B] (a) alkylating a compound of formula V with	*See* Element [A] above.

an alkylating agent to produce a compound of formula VI, 	
Element [C] (b) hydrolyzing the product of formula VI of step (a) with a base,	*See* Element [A] above.
Element [D] (c) contacting the product of step (h) with a base B to form a salt of formula IVs, and	*See* Element [A] above.

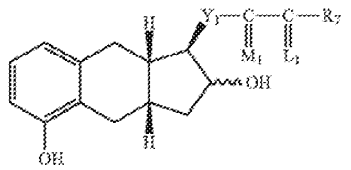
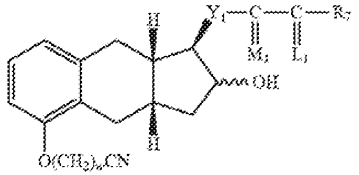
	
Element [E] (d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula IV.	*See* Element [A] above.

Claim 16	**Prior Art Disclosure**
The product of claim 9, wherein the process does not include purifying the compound of formula (VI) produced in step (a).	*See* Claim 9.

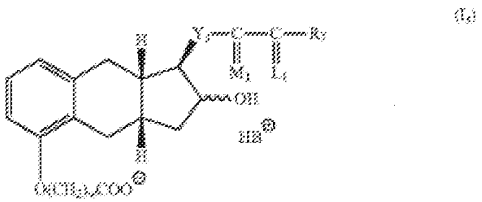
F. The Sale Of UTC's Remodulin Product Anticipates The Asserted Claims

Claim 1	Prior Art Disclosure
[Element A] A product comprising a compound of formula I:  (I) or a pharmaceutically acceptable salt thereof, wherein said product is prepared by a process comprising	"The on-sale bar applies when the invention is the subject of a commercial offer for sale, and is ready for patenting before the critical date." *Netscape Communications Corp. v. Konrad*, 295 F.3d 1315, 1323 (Fed. Cir. 2002)(citing *Pfaff v. Wells*, 525 U.S. 55, 67 (1998)). "A single sale or offer to sell suffices to bar patentability." *Atlantic Thermoplastics Co., Inc. v. Faytex Corp.*, 970 F.2d 834, 836 (Fed. Cir. 1992). "To invoke the on-sale bar, a defendant must prove that the complete claimed invention is embodied in or obvious in view of the thing sold or offered for sale before the critical date." *Atlantic Thermoplastics*, 787 F.2d at 836. In determining whether an on-sale bar invalidates a patent claim, "the court should determine whether the subject of the barring activity met each of the limitations of the claim, and thus was an embodiment of the claimed invention." *Netscape*, 295 F.3d at 1323. A product-by-process claim is anticipated if the product is disclosed in the prior art. *Amgen*, 580 F.3d at 1366; *SmithKline Beecham Corp. v. Apotex Corp.*, 439 F.3d 1312, 1317 (Fed. Cir. 2006) ("It has long been established that one cannot avoid anticipation by an earlier product disclosure by claiming the same product more narrowly, that is, by claiming the product as produced by a particular process"); *Gen. Elec. Co. v. Wabash Appliance Corp.*, 304 U.S. 364, 373 (1938); *Cochrane v. Badische Anilin & Soda Farbrik*, 111 U.S. 293, 311 (1884) ("While a new process for producing [a chemical compound] was patentable, the product itself could not be patented even though it was a product made [by a new process] for the first time because the product was disclosed in the prior art"). "In determining the validity of a product-by-process claim, the focus is on the product and not on the process of making it." *Amgen*, 580 F.3d at 1369-70; *In re Thorpe*, 777 F.2d 695, 697 (Fed. Cir. 1985) ("Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its

	method of production."); *Smithkline*, 439 F.3d at 1317-19; *see also* Manual of Patent Examining Procedure § 2113 (8th ed. Rev. 8 July 2010). Accordingly, for determining the patentability of the Asserted Claims of the '393 patent in the context of an on-sale bar under Section 102(b), the question is whether an embodiment of the claimed product was sold more than a year before the '393 patent priority date. The product of claim 1 of the '393 patent is a product comprising a member of the recited genus of compounds that includes the treprostinil compound or a pharmaceutically acceptable salt thereof, without further limitations as to the composition of the product. Thus, any product comprising treprostinil compound in any amount, with any other types or amounts of impurities, falls within the scope of the claimed product. The Remodulin® product is the subject of UTC's NDA No. 21-272, and has treprostinil sodium as its active ingredient. (Civil Action No. 12-1617, D.I. 218, Ex. 1, Stipulated Fact No. 3; Package Insert). Remodulin was first approved in the United States in May 2002, and is indicated for the treatment of pulmonary arterial hypertension ("PAH"). (*Id.* at Stipulated Fact No. 4). Remodulin is an injectable product approved for sale in concentrations including 1 mg/mL, 2.5 mg/mL, 5 mg/mL, and 10 mg/mL. (*Id.* at Stipulated Fact No. 5). In November 2004, the Food and Drug Administration ("FDA") approved Remodulin for intravenous use. (*Id.* at Stipulated Fact No. 6). UTC has listed the '393 patent on the Orange Book as covering the Remodulin Product. (Remodulin Orange Book Listing). The Remodulin product has been on the market since 2002, and the '393 patent ultimately claims priority to a provisional application filed on December 17, 2007. Accordingly, Remodulin product sold prior to December 17, 2006 is prior art for the purposes of an on-sale bar under Section 102(b). Because by UTC's own admission the '393 patent covers the Remodulin product, and because the Remodulin product was on sale more than one year before the earliest date to which the '393 patent claims priority, claim 1 is invalid as anticipated by the sale of UTC's Remodulin product.

[Element B] (a) alkylating a compound of structure II with an alkylating agent to produce a compound of formula III, (II)  (III) 	*See* Element [A] above.

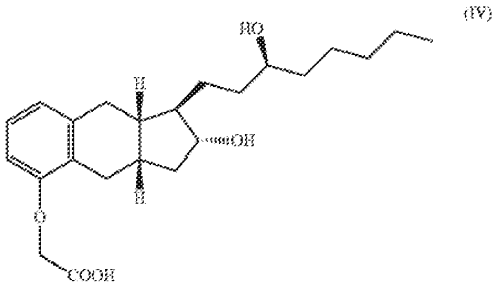
wherein w=1, 2, or 3; Y_1 is trans-CH=CH—, cis-CH=CH—, —$CH_2(CH_2)_m$—, or —C≡C—; m is 1, 2, or 3; R_7 is (1) —C_pH_{2p}—CH_3, wherein p is an integer from 1 to 5, inclusive, (2) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3) alkyl, or (C_1-C_3) alkoxy, with the proviso that not more than two substituents are other than alkyl, with the proviso that R_7 is phenoxy or substituted phenoxy, only when R_3 and R_4 are hydrogen or methyl, being the same or different, (3) phenyl, benzyl, phenylethyl, or phenylpropyl optionally substituted on the aromatic ring by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3)alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl, (4) cis-CH=CH—CH_2—CH_3, (5) —$(CH_2)_2$—CH(OH)—CH_3, or (6) —$(CH_2)_2$—CH=$C(CH_3)_2$; —$C(L_1)$—R_7 taken together is (1) (C_4-C_7)cycloalkyl optionally substituted by 1 to 3 (C_1-C_3) alkyl; (2) 2-(2-furyl)ethyl, (3) 2-(3-thienyl)ethoxy, or (4) 3-thienyloxymethyl; M_1 is α-OH:β-R_5 or α-R_5:β-OH or α-OR_1:β-R_5 or α-R_5:β-OR_2, wherein R_5 is hydrogen or methyl, R_2 is an alcohol protecting group, and L_1 is α-R_3:β-R_4, α-R_4:β-R_3, or a mixture of α-R_3:β-R_4 and α-R_4:β-R_3, wherein R_3 and R_4 are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R_3 and R_4 is fluoro only when the other is hydrogen or fluoro,	
[Element C] (b) hydrolyzing the product of formula III of step (a) with a base,	*See* Element [A] above.
[Element D]	*See* Element [A] above.

(c) contacting the product of step (h) with a base B to form a salt of formula Is.  and	
[Element E] (d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula I.	*See* Element [A] above.

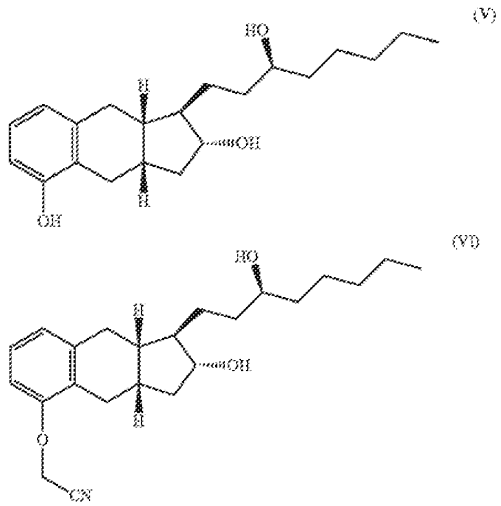
Claim 2	**Prior Art Disclosure**
The product of claim 1, wherein the purity of compound of formula I in said product is at least 99.5%.	*See* Claim 1. As noted above, the '393 patent is listed on the Orange Book as covering UTC's Remodulin Product. To the extent that UTC contends that Sandoz's ANDA Product infringes claim 2 of the '393 patent, then claim 2 of the '393 patent is anticipated by the sale of the Remodulin product as described above.

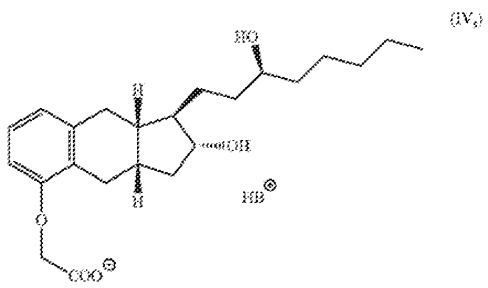
Claim 4	**Prior Art Disclosure**
The product of claim 1, wherein the base in step (b) is KOH or NaOH.	*See* Claim 1.

Claim 8	Prior Art Disclosure
The product of claim 1, wherein the process does not include purifying the compound of formula (III) produced in step (a).	*See* Claim 1.

Claim 9	Prior Art Disclosure
[Element A] A product comprising a compound having formula IV  or a pharmaceutically acceptable salt thereof, wherein the product is prepared by the process comprising	"The on-sale bar applies when the invention is the subject of a commercial offer for sale, and is ready for patenting before the critical date." *Netscape Communications Corp. v. Konrad*, 295 F.3d 1315, 1323 (Fed. Cir. 2002)(citing *Pfaff v. Wells*, 525 U.S. 55, 67 (1998)). "A single sale or offer to sell suffices to bar patentability." *Atlantic Thermoplastics Co., Inc. v. Faytex Corp.*, 970 F.2d 834, 836 (Fed. Cir. 1992). "To invoke the on-sale bar, a defendant must prove that the complete claimed invention is embodied in or obvious in view of the thing sold or offered for sale before the critical date." *Atlantic Thermoplastics*, 787 F.2d at 836. In determining whether an on-sale bar invalidates a patent claim, "the court should determine whether the subject of the barring activity met each of the limitations of the claim, and thus was an embodiment of the claimed invention." *Netscape*, 295 F.3d at 1323. A product-by-process claim is anticipated if the product is disclosed in the prior art. *Amgen*, 580 F.3d at 1366; *SmithKline Beecham Corp. v. Apotex Corp.*, 439 F.3d 1312, 1317 (Fed. Cir. 2006) ("It has long been established that one cannot avoid anticipation by an earlier product disclosure by claiming the same product more narrowly, that is, by claiming the product as produced by a particular process"); *Gen. Elec. Co. v. Wabash Appliance Corp.*, 304 U.S. 364, 373 (1938); *Cochrane v. Badische Anilin & Soda Farbrik*, 111 U.S. 293, 311 (1884) ("While a new process for producing [a chemical compound] was patentable, the product itself could not be patented even though it was a product made [by a new process] for the first time because the product was disclosed in the prior art"). "In determining the validity of a product-by-process claim, the focus is on the product and not on the process of making it." *Amgen*, 580 F.3d at 1369-70; *In re Thorpe*, 777 F.2d 695, 697 (Fed. Cir. 1985) ("Even though product-by-process

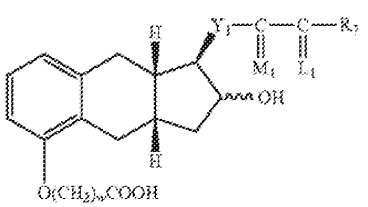
	claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production."); *Smithkline*, 439 F.3d at 1317-19; *see also* Manual of Patent Examining Procedure § 2113 (8th ed. Rev. 8 July 2010). Accordingly, for determining the patentability of the Asserted Claims of the '393 patent in the context of an on-sale bar under Section 102(b), the question is whether an embodiment of the claimed product was sold more than a year before the '393 patent priority date. The product of claim 9 of the '393 patent is a product comprising the treprostinil compound or a pharmaceutically acceptable salt thereof, without further limitations as to the composition of the product. Thus, any product comprising treprostinil compound in any amount, with any other types or amounts of impurities, falls within the scope of the claimed product. The Remodulin® product is the subject of UTC's NDA No. 21-272, and has treprostinil sodium as its active ingredient. (Civil Action No. 12-1617, D.I. 218, Ex. 1, Stipulated Fact No. 3; Package Insert). Remodulin was first approved in the United States in May 2002, and is indicated for the treatment of pulmonary arterial hypertension ("PAH"). (*Id.* at Stipulated Fact No. 4). Remodulin is an injectable product approved for sale in concentrations including 1 mg/mL, 2.5 mg/mL, 5 mg/mL, and 10 mg/mL. (*Id.* at Stipulated Fact No. 5). In November 2004, the Food and Drug Administration ("FDA") approved Remodulin for intravenous use. (*Id.* at Stipulated Fact No. 6). UTC has listed the '393 patent on the Orange Book as covering the Remodulin Product. (Remodulin Orange Book Listing). The Remodulin product has been on the market since 2002, and the '393 patent ultimately claims priority to a provisional application filed on December 17, 2007. Accordingly, Remodulin product sold prior to December 17, 2006 is prior art for the purposes of an on-sale bar under Section 102(b). Because by UTC's own admission the '393 patent covers the Remodulin product, and because the Remodulin product was on sale more than one year before the earliest date to which the '393 patent claims priority, claim 9 is invalid as anticipated by the sale of UTC's Remodulin product.

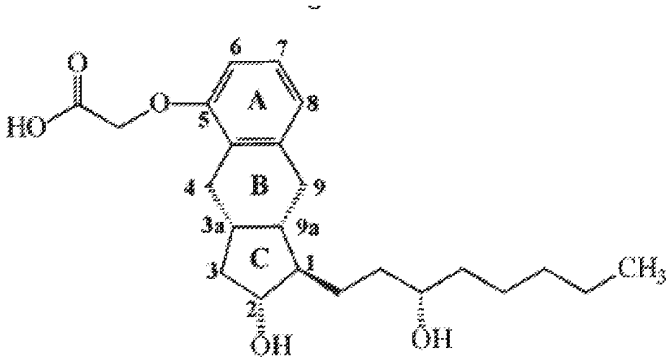
[Element B] (a) alkylating a compound of formula V with an alkylating agent to produce a compound of formula VI,  	*See* Element [A] above.
[Element C] (b) hydrolyzing the product of formula VI of step (a) with a base,	*See* Element [A] above.
[Element D] (c) contacting the product of step (h) with a base B to form a salt of formula IVs, and	*See* Element [A] above.

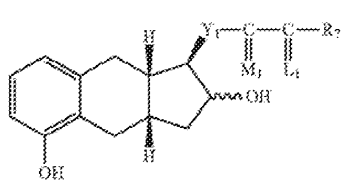
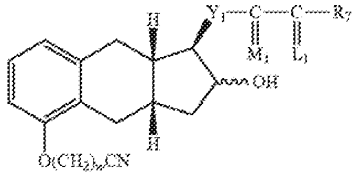
	
[Element E] (d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula IV.	*See* Element [A] above.

Claim 16	**Prior Art Disclosure**
The product of claim 9, wherein the process does not include purifying the compound of formula (VI) produced in step (a).	*See* Claim 9.

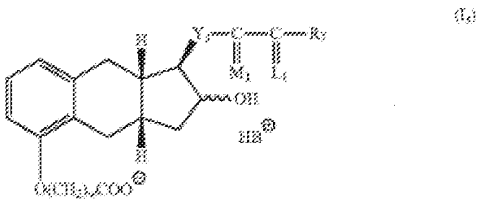
G. The Asserted Claims Are Anticipated By Moriarty, et al in *J. Org. Chem.* 2004, 69, 1890-1902 (2004) ("The Moriarty JOC Article")

Claim 1	Prior Art Disclosure
Element [A] A product comprising a compound of formula I:  (I) or a pharmaceutically acceptable salt thereof, wherein said product is prepared by a process comprising	A product-by-process claim is anticipated if the product is disclosed in the prior art. *Amgen*, 580 F.3d at 1366; *SmithKline Beecham Corp. v. Apotex Corp.*, 439 F.3d 1312, 1317 (Fed. Cir. 2006) ("It has long been established that one cannot avoid anticipation by an earlier product disclosure by claiming the same product more narrowly, that is, by claiming the product as produced by a particular process"); *Gen. Elec. Co. v. Wabash Appliance Corp.*, 304 U.S. 364, 373 (1938); *Cochrane v. Badische Anilin & Soda Farbrik*, 111 U.S. 293, 311 (1884) ("While a new process for producing [a chemical compound] was patentable, the product itself could not be patented even though it was a product made [by a new process] for the first time because the product was disclosed in the prior art"). "In determining the validity of a product-by-process claim, the focus is on the product and not on the process of making it." *Amgen*, 580 F.3d at 1369-70; *In re Thorpe*, 777 F.2d 695, 697 (Fed. Cir. 1985) ("Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production."); *Smithkline*, 439 F.3d at 1317-19; *see also* Manual of Patent Examining Procedure § 2113 (8th ed. Rev. 8 July 2010). Accordingly, for determining the patentability of the Asserted Claims of the '393 patent, the question is whether the claimed product is disclosed in, or obvious from, the prior art. The product of claim 1 of the '393 patent is a product comprising a member of the recited genus of compounds that includes the treprostinil compound or a pharmaceutically acceptable salt thereof, without further limitations as to the composition of the product. Thus, any product comprising treprostinil compound in any amount, with any other types or amounts of impurities, falls within the scope of the claimed product.

	The Moriarty JOC Article was published in 2004 and is thus prior art to the '393 patent under 35 U.S.C. § 102(b). As explained above, the Moriarty JOC Article discloses treprostinil free acid. Further, the Moriarty JOC Article discloses a sample of treprostinil acid having a purity level of 99.7% Thus, the Moriarty JOC Article anticipates all of the Asserted Claims of the '393 patent. Moriarty JOC Article discloses that "[t]o meet the demands of producing multikilogram quantities of UT-15 ([compound] 7) needed in the course of drug development, an efficient and economical synthesis [of treprostinil] had to be devised." (Moriarty JOC Article at 1892). The Moriarty JOC Paper concludes that "[t]the strategy of employing the highly diastereoselective 1,2-asymmetric induction in the PKC using a temporary and readily removable stereodirecting group results in an asymmetric synthesis that is superior to other methods used to date." (*Id.* at 1898). The Moriarty synthesis is depicted in Scheme 4, which results in the production of treprostinil free acid, which is depicted as compound 7.  7 (Moriarty JOC article at 1892, 1895).

	The Moriarty JOC article also includes an experimental section which describes in detail the synthesis of 441 grams of treprostinil acid having a purity of 99.7%. (*Id.* at 1902). Further, the '393 patent specification states that the Moriarty JOC Article discloses a method of making treprostinil. ('393 patent at Col. 1:23-26). There are no structural and functional differences between the product of the Moriarty JOC Article (the treprostinil compound) and the claimed product (a product including the treprostinil compound). Thus, the Moriarty JOC Article anticipates claim 1.
Element [B] (a) alkylating a compound of structure II with an alkylating agent to produce a compound of formula III, (II)  (III) 	*See* Element [A] above.

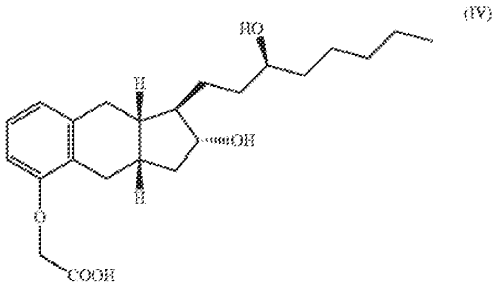
wherein w=1, 2, or 3; Y_1 is trans-CH=CH—, cis-CH=CH—, —$CH_2(CH_2)_m$—, or —C≡C—; m is 1, 2, or 3; R_7 is (1) —C_pH_{2p}—CH_3, wherein p is an integer from 1 to 5, inclusive, (2) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3) alkyl, or (C_1-C_3) alkoxy, with the proviso that not more than two substituents are other than alkyl, with the proviso that R_7 is phenoxy or substituted phenoxy, only when R_3 and R_4 are hydrogen or methyl, being the same or different, (3) phenyl, benzyl, phenylethyl, or phenylpropyl optionally substituted on the aromatic ring by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3)alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl, (4) cis-CH=CH—CH_2—CH_3, (5) —$(CH_2)_2$—CH(OH)—CH_3, or (6) —$(CH_2)_2$—CH=$C(CH_3)_2$; —$C(L_1)$—R_7 taken together is (1) (C_4-C_7)cycloalkyl optionally substituted by 1 to 3 (C_1-C_3) alkyl; (2) 2-(2-furyl)ethyl, (3) 2-(3-thienyl)ethoxy, or (4) 3-thienyloxymethyl; M_1 is α-OH:β-R_5 or α-R_5:β-OH or α-OR_1:β-R_5 or α-R_5:β-OR_2, wherein R_5 is hydrogen or methyl, R_2 is an alcohol protecting group, and L_1 is α-R_3:β-R_4, α-R_4:β-R_3, or a mixture of α-R_3:β-R_4 and α-R_4:β-R_3, wherein R_3 and R_4 are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R_3 and R_4 is fluoro only when the other is hydrogen or fluoro,	
Element [C] (b) hydrolyzing the product of formula III of step (a) with a base,	*See* Element [A] above.
Element [D]	*See* Element [A] above.

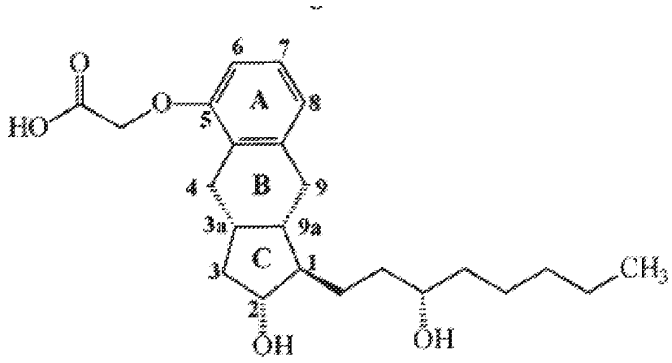
(c) contacting the product of step (h) with a base B to form a salt of formula Is.  And	
Element [E] (d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula I.	*See* Element [A] above.

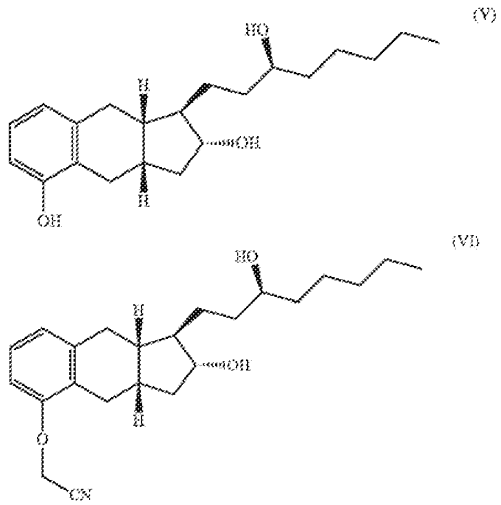
Claim 2	**Prior Art Disclosure**
The product of claim 1, wherein the purity of compound of formula I in said product is at least 99.5%.	*See* Claim 1. The Moriarty JOC article includes an experimental section which describes in detail the synthesis of 441 grams of treprostinil acid having a purity of 99.7%. (*Id.* at 1902). Accordingly, the Moriarty JOC Article anticipates claim 2.

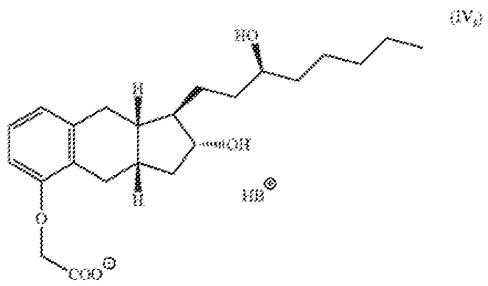
Claim 4	**Prior Art Disclosure**
The product of claim 1, wherein the base in step (b) is KOH or NaOH.	*See* Claim 1.

Claim 8	Prior Art Disclosure
The product of claim 1, wherein the process does not include purifying the compound of formula (III) produced in step (a).	*See* Claim 1.

Claim 9	Prior Art Disclosure
Element [A] A product comprising a compound having formula IV  (IV) or a pharmaceutically acceptable salt thereof, wherein the product is prepared by the process comprising	A product-by-process claim is anticipated if the product is disclosed in the prior art. *Amgen*, 580 F.3d at 1366; *SmithKline Beecham Corp. v. Apotex Corp.*, 439 F.3d 1312, 1317 (Fed. Cir. 2006) ("It has long been established that one cannot avoid anticipation by an earlier product disclosure by claiming the same product more narrowly, that is, by claiming the product as produced by a particular process"); *Gen. Elec. Co. v. Wabash Appliance Corp.*, 304 U.S. 364, 373 (1938); *Cochrane v. Badische Anilin & Soda Farbrik*, 111 U.S. 293, 311 (1884) ("While a new process for producing [a chemical compound] was patentable, the product itself could not be patented even though it was a product made [by a new process] for the first time because the product was disclosed in the prior art"). "In determining the validity of a product-by-process claim, the focus is on the product and not on the process of making it." *Amgen*, 580 F.3d at 1369-70; *In re Thorpe*, 777 F.2d 695, 697 (Fed. Cir. 1985) ("Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production."); *Smithkline*, 439 F.3d at 1317-19; *see also* Manual of Patent Examining Procedure § 2113 (8th ed. Rev. 8 July 2010). Accordingly, for determining the patentability of the Asserted Claims of the '393 patent, the question is whether the claimed product is disclosed in, or obvious from, the prior art. The product of claim 9 of the '393 patent is a product comprising the treprostinil compound or a pharmaceutically acceptable salt thereof, without further limitations as to the composition of the product. Thus, any product comprising treprostinil compound in any amount, with any other types or amounts of impurities, falls within the scope of the claimed product.

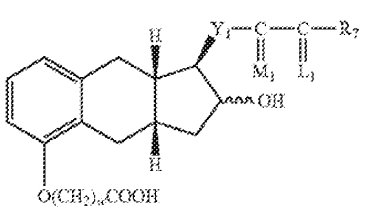
	The Moriarty JOC Article was published in 2004 and is thus prior art to the '393 patent under 35 U.S.C. § 102(b). Moriarty JOC Article discloses that "[t]o meet the demands of producing multikilogram quantities of UT-15 ([compound] 7) needed in the course of drug development, an efficient and economical synthesis [of treprostinil] had to be devised." (Moriarty JOC Article at 1892). The Moriarty JOC Paper concludes that "[t]the strategy of employing the highly diastereoselective 1,2-asymmetric induction in the PKC using a temporary and readily removable stereodirecting group results in an asymmetric synthesis that is superior to other methods used to date." (*Id.* at 1898). The Moriarty synthesis is depicted in Scheme 4, which results in the production of treprostinil free acid, which is depicted as compound 7.  7 (Moriarty JOC article at 1892, 1895). The Moriarty JOC article also includes an experimental section which describes in detail the synthesis of 441 grams of treprostinil acid having a purity of 99.7%. (*Id.* at 1902). There are no structural and functional differences between the product of the

	Moriarty JOC Article (the treprostinil compound) and the claimed product (a product including the treprostinil compound). Thus, the Moriarty JOC Article anticipates claim 9.
Element [B] (a) alkylating a compound of formula V with an alkylating agent to produce a compound of formula VI,  	*See* Element [A] above.
Element [C] (b) hydrolyzing the product of formula VI of step (a) with a base,	*See* Element [A] above.
Element [D] (c) contacting the product of step (h) with a	*See* Element [A] above.

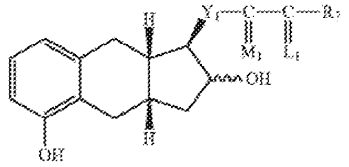
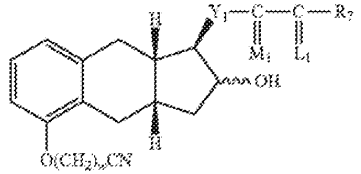
base B to form a salt of formula IVs, and 	
Element [E] (d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula IV.	*See* Element [A] above.

Claim 16	**Prior Art Disclosure**
The product of claim 9, wherein the process does not include purifying the compound of formula (VI) produced in step (a).	*See* Claim 16.

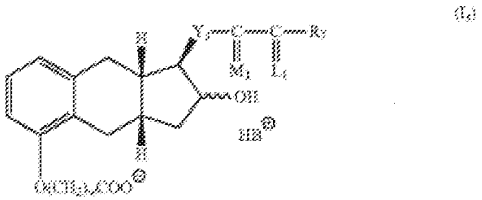
H. The Asserted Claims Are Anticipated By, Or Obvious In View Of, U.S. Patent Application Publication No. 2005/0085540A1 ("The Phares Publication")

Claim 1	Prior Art Disclosure
Element [A] A product comprising a compound of formula I:  (I) or a pharmaceutically acceptable salt thereof, wherein said product is prepared by a process comprising	A product-by-process claim is anticipated if the product is disclosed in the prior art. *Amgen*, 580 F.3d at 1366; *SmithKline Beecham Corp. v. Apotex Corp.*, 439 F.3d 1312, 1317 (Fed. Cir. 2006) ("It has long been established that one cannot avoid anticipation by an earlier product disclosure by claiming the same product more narrowly, that is, by claiming the product as produced by a particular process"); *Gen. Elec. Co. v. Wabash Appliance Corp.*, 304 U.S. 364, 373 (1938); *Cochrane v. Badische Anilin & Soda Farbrik*, 111 U.S. 293, 311 (1884) ("While a new process for producing [a chemical compound] was patentable, the product itself could not be patented even though it was a product made [by a new process] for the first time because the product was disclosed in the prior art"). "In determining the validity of a product-by-process claim, the focus is on the product and not on the process of making it." *Amgen*, 580 F.3d at 1369-70; *In re Thorpe*, 777 F.2d 695, 697 (Fed. Cir. 1985) ("Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production."); *Smithkline*, 439 F.3d at 1317-19; *see also* Manual of Patent Examining Procedure § 2113 (8th ed. Rev. 8 July 2010). Accordingly, for determining the patentability of the Asserted Claims of the '393 patent, the question is whether the claimed product is disclosed in, or obvious from, the prior art. The product of claim 1 of the '393 patent is a product comprising a member of the recited genus of compounds that includes the treprostinil compound or a pharmaceutically acceptable salt thereof, without further limitations as to the composition of the product. Thus, any product comprising treprostinil compound in any amount, with any other types or amounts of impurities, falls within the scope of the claimed product.

	The Phares Publication was published on April 21, 2005 and is thus prior art to the '393 patent under Section 102(b). The Phares Publication discloses that "treprostinil sodium (Remodulin®) is approved by the Food and Drug Administration (FDA) for subcutaneous administration" and that "treprostinil as the free acid has an absolute oral bioavailability of less than 10%." (*Id.* at ¶ 0004). The purpose of the invention was to serve the "clinical interest in providing treprostinil orally," and "increasing systemic availability of treprostinil via administration of treprostinil or treprostinil analogs." (Id. at ¶ 0004-0005). The Phares Publication further provides that "[a] preferred embodiment of the present invention is the diethanolamine salt of treprostinil." (*Id.* at ¶ 0051). Further, Phares teaches that recrystallizing the diethanolamine salt of treprostinil results in the formation of two crystalline polymorphs of treprostinil diethanolamine, Forms A and B. (Phares Publication at ¶ 0327). Phares teaches that Form A, a metastable form, can be prepared using the crystallization methods shown in Table 15 at ¶ 0327. Phares then provides that the thermodynamically stable polymorph, Form B, can be made from Form A using the crystallization procedures in Table 16 at ¶ 0328. Although Phares does not indicate the purity of polymorph Form B, Phares notes that the melting point is 107°C and provides an XRPD pattern of Form B in Figure 20. (*Id.* at ¶ 0337). The specification of the ' 393 patent indicates that the treprostinil diethanolamine compound produced according to the claimed procedures yields treprostinil diethanolamine polymorph Form B that has a melting point of at least 104°C. For example, the table provided at Col. 12:60- Col. 13:12 in the '393 patent shows that Batch 2 of treprostinil diethanolamine salt had a melting point of 105.5-107.2°C. Thus, the diethanolamine treprostinil polymorph Form B formed using the procedures taught by Phares is the same as the diethanolamine treprostinil product produced following the steps recited in the claims of the '393 patent. Finally, Phares discloses animal testing involving administration of treprostinil diethanolamine to rats in Example 1 and clinical trials using treprostinil diethanolamine salt formulations in Example 5. (Phares Publication at ¶¶ 0203-

	0237, 0311-0326). Pharmacokinetic testing of an oral formulation of treprostinil diethanolamine in human patients showed an absolute bioavailability of 21-25% for the four doses tested. (*Id.* at ¶ 0319). There are no structural and functional differences between the product of the Phares Publication (treprostinil diethanolamine salt) and the claimed product (a product including a pharmaceutically acceptable salt of treprostinil). Thus, the Phares Publication anticipates claim 1.
Element [B] (a) alkylating a compound of structure II with an alkylating agent to produce a compound of formula III, (II)  (III) 	*See* Element [A] above.

wherein w=1, 2, or 3; Y_1 is trans-CH=CH—, cis-CH=CH—, —$CH_2(CH_2)_m$—, or —C≡C—; m is 1, 2, or 3; R_7 is (1) —C_pH_{2p}—CH_3, wherein p is an integer from 1 to 5, inclusive, (2) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3) alkyl, or (C_1-C_3) alkoxy, with the proviso that not more than two substituents are other than alkyl, with the proviso that R_7 is phenoxy or substituted phenoxy, only when R_3 and R_4 are hydrogen or methyl, being the same or different, (3) phenyl, benzyl, phenylethyl, or phenylpropyl optionally substituted on the aromatic ring by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3)alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl, (4) cis-CH=CH—CH_2—CH_3, (5) —$(CH_2)_2$—CH(OH)—CH_3, or (6) —$(CH_2)_3$—CH=$C(CH_3)_2$; —$C(L_1)$—R_7 taken together is (1) (C_4-C_7)cycloalkyl optionally substituted by 1 to 3 (C_1-C_3) alkyl; (2) 2-(2-furyl)ethyl, (3) 2-(3-thienyl)ethoxy, or (4) 3-thienyloxymethyl; M_1 is α-OH:β-R_5 or α-R_5:β-OH or α-OR_1:β-R_5 or α-R_5:β-OR_2, wherein R_5 is hydrogen or methyl, R_2 is an alcohol protecting group, and L_1 is α-R_3:β-R_4, α-R_4:β-R_3, or a mixture of α-R_3:β-R_4 and α-R_4:β-R_3, wherein R_3 and R_4 are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R_3 and R_4 is fluoro only when the other is hydrogen or fluoro,	
Element [C] (b) hydrolyzing the product of formula III of step (a) with a base,	*See* Element [A] above.
Element [D]	*See* Element [A] above.

(c) contacting the product of step (h) with a base B to form a salt of formula Is.  And	
Element [E] (d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula I.	*See* Element [A] above.

Claim 2	Prior Art Disclosure
The product of claim 1, wherein the purity of compound of formula I in said product is at least 99.5%.	*See* Claim 1. As noted above, the Phares Publication teaches that recrystallizing the diethanolamine salt of treprostinil results in the formation of two crystalline polymorphs of treprostinil diethanolamine, Forms A and B. (Phares Publication at ¶ 0327). Although Phares does not indicate the purity of polymorph Form B, Phares notes that the melting point is 107°C and provides an XRPD pattern of Form B in Figure 20. (*Id.* at ¶ 0337). The specification of the ' 393 patent indicates that the treprostinil diethanolamine compound produced according to the claimed procedures yields treprostinil diethanolamine polymorph Form B that has a melting point of at least 104°C. For example, the table provided at Col. 12:60- Col. 13:12 in the '393 patent shows that Batch 2 of treprostinil diethanolamine salt had a melting point of 105.5-107.2°C. Thus, the diethanolamine treprostinil polymorph Form B formed

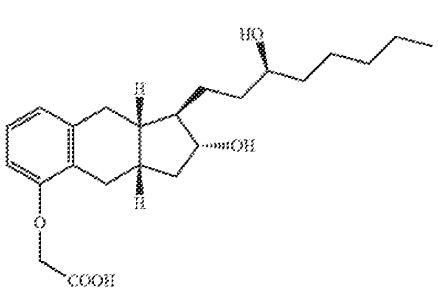
	using the procedures taught by Phares is the same as the diethanolamine treprostinil product produced following the steps recited in the claims of the '393 patent. Accordingly, the treprostinil diethanolamine salt of Form B disclose in Phares anticipates claim 2. Further, Phares teaches a method of making treprostinil diethanolamine salt that includes the same steps as the claimed method: alkylating the triol, hydrolyzing the nitrile with a base, and contacting the product with a base (B) to produce treprostinil diethanolamine salt of polymorph form Form B: The Phares publication discloses a method of making treprostinil involving alkylating benzindene triol to form the nitrile, then hydrolyzing the nitrile with a base (KOH) to obtain the free acid. (Phares publication at ¶¶ 0143-0145). The Phares publication discloses converting treprostinil free acid into treprostinil diethanolamine salt as follows: > Treprostinil acid acid [*sic*] is dissolved in a 1:1 molar ratio mixture of ethanol:water and diethanolamine is added and dissolved. The solution is heated and acetone is added as an antisolvent during cooling. (Phares publication at ¶ 0105). The Phares Publication also teaches that treprostinil diethanolamine can be recrystallized to yield two crystalline polymorphs, including the metastable polymorph A, and the thermodynamically more stable polymorph B. (*Id.* at ¶ 327). According to Phares, the resulting polymorphs have melting points at 103° C (Form A) and 107° C (Form B), respectively. (*Id.* at ¶¶ 0332, 0337). Thus, because the Phares publication discloses using the same process as that claimed to make the same product (treprostinil diethanolamine salt), then the product obtained through the method disclosed in Phares inherently has the claimed purity profile.

	Also, the skilled artisan would have been motivated to obtain a sample of treprostinil having a high level of purity. The Moriarty JOC Article includes an experimental section which describes in detail the synthesis of 441 grams of treprostinil acid having a purity of 99.7%. (*Id.* at 1902). Accordingly, it would have been obvious for the skilled artisan to purify the treprostinil disclosed in the Phares Publication to a purity level of 99.5% or greater, particularly in view of the disclosure in the Moriarty JOC Article of treprostinil having a purity level of 99.7%. Also, purification techniques are common practice in the chemical arts. Accordingly, claim 2 would have been obvious in view of the disclosure of treprostinil diethanolamine in Phares.

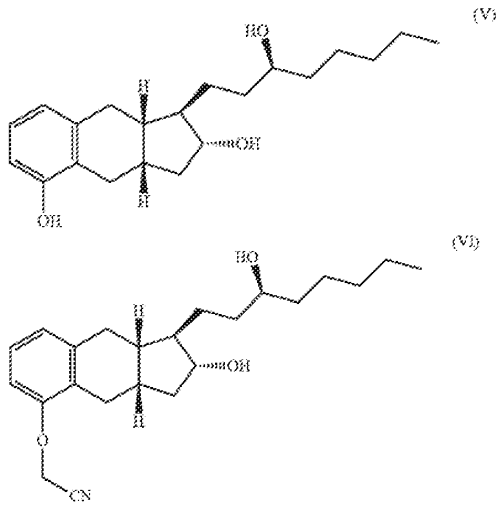
Claim 4	**Prior Art Disclosure**
The product of claim 1, wherein the base in step (b) is KOH or NaOH.	*See* Claim 1.

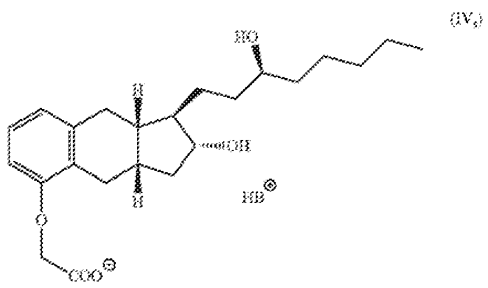
Claim 8	**Prior Art Disclosure**
The product of claim 1, wherein the process does not include purifying the compound of formula (III) produced in step (a).	*See* Claim 1.

Claim 9	**Prior Art Disclosure**
Element [A] A product comprising a compound having formula IV	A product-by-process claim is anticipated if the product is disclosed in the prior art. *Amgen*, 580 F.3d at 1366; *SmithKline Beecham Corp. v. Apotex Corp.*, 439 F.3d 1312, 1317 (Fed. Cir. 2006) ("It has long been established that one cannot avoid anticipation by an earlier product disclosure by claiming the same product more narrowly, that is, by claiming the product as produced by a particular process"); *Gen. Elec. Co. v. Wabash Appliance Corp.*, 304 U.S. 364, 373 (1938); *Cochrane v.*

 (IV) or a pharmaceutically acceptable salt thereof, wherein the product is prepared by the process comprising	*Badische Anilin & Soda Farbrik*, 111 U.S. 293, 311 (1884) ("While a new process for producing [a chemical compound] was patentable, the product itself could not be patented even though it was a product made [by a new process] for the first time because the product was disclosed in the prior art"). "In determining the validity of a product-by-process claim, the focus is on the product and not on the process of making it." *Amgen*, 580 F.3d at 1369-70; *In re Thorpe*, 777 F.2d 695, 697 (Fed. Cir. 1985) ("Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production."); *Smithkline*, 439 F.3d at 1317-19; *see also* Manual of Patent Examining Procedure § 2113 (8th ed. Rev. 8 July 2010). Accordingly, for determining the patentability of the Asserted Claims of the '393 patent, the question is whether the claimed product is disclosed in, or obvious from, the prior art. The product of claim 9 of the '393 patent is a product comprising the treprostinil compound or a pharmaceutically acceptable salt thereof, without further limitations as to the composition of the product. Thus, any product comprising treprostinil compound in any amount, with any other types or amounts of impurities, falls within the scope of the claimed product. The Phares Publication was published on April 21, 2005 and is thus prior art to the '393 patent under Section 102(b). The Phares Publication discloses that "treprostinil sodium (Remodulin®) is approved by the Food and Drug Administration (FDA) for subcutaneous administration" and that "treprostinil as the free acid has an absolute oral bioavailability of less than 10%." (*Id.* at ¶ 0004). The purpose of the invention was to serve the "clinical interest in providing treprostinil orally," and "increasing systemic availability of treprostinil via administration of treprostinil or treprostinil analogs." (Id. at ¶ 0004-0005). The Phares Publication further provides that "[a] preferred embodiment of the present invention is the diethanolamine salt of treprostinil." (*Id.* at ¶ 0051). Further, Phares teaches that recrystallizing the diethanolamine salt of treprostinil

	results in the formation of two crystalline polymorphs of treprostinil diethanolamine, Forms A and B. (Phares Publication at ¶ 0327). Phares teaches that Form A, a metastable form, can be prepared using the crystallization methods shown in Table 15 at ¶ 0327. Phares then provides that the thermodynamically stable polymorph, Form B, can be made from Form A using the crystallization procedures in Table 16 at ¶ 0328. Although Phares does not indicate the purity of polymorph Form B, Phares notes that the melting point is 107°C and provides an XRPD pattern of Form B in Figure 20. (*Id.* at ¶ 0337). The specification of the ' 393 patent indicates that the treprostinil diethanolamine compound produced according to the claimed procedures yields treprostinil diethanolamine polymorph Form B that has a melting point of at least 104°C. For example, the table provided at Col. 12:60- Col. 13:12 in the '393 patent shows that Batch 2 of treprostinil diethanolamine salt had a melting point of 105.5-107.2°C. Thus, the diethanolamine treprostinil polymorph Form B formed using the procedures taught by Phares is the same as the diethanolamine treprostinil product produced following the steps recited in the claims of the '393 patent. Finally, Phares discloses animal testing involving administration of treprostinil diethanolamine to rats in Example 1 and clinical trials using treprostinil diethanolamine salt formulations in Example 5. (Phares Publication at ¶¶ 0203-0237, 0311-0326). Pharmacokinetic testing of an oral formulation of treprostinil diethanolamine in human patients showed an absolute bioavailability of 21-25% for the four doses tested. (*Id.* at ¶ 0319). There are no structural and functional differences between the product of the Phares Publication (treprostinil diethanolamine salt) and the claimed product (a product including a pharmaceutically acceptable salt of treprostinil). Thus, the Phares Publication anticipates claim 9.
Element [B]	*See* Element [A] above.

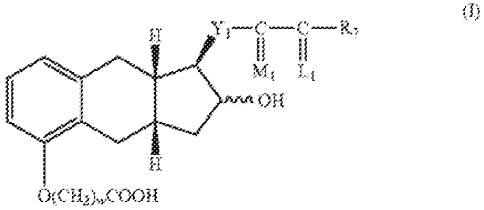
(a) alkylating a compound of formula V with an alkylating agent to produce a compound of formula VI,  	
Element [C] (b) hydrolyzing the product of formula VI of step (a) with a base,	*See* Element [A] above.
Element [D] (c) contacting the product of step (h) with a base B to form a salt of formula IVs, and	*See* Element [A] above.

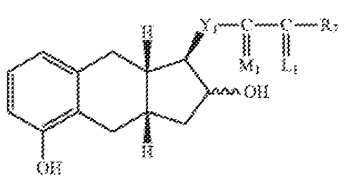
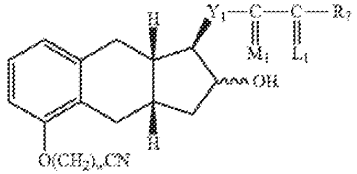
	
Element [E] (d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula IV.	*See* Element [A] above.

Claim 16	**Prior Art Disclosure**
The product of claim 9, wherein the process does not include purifying the compound of formula (VI) produced in step (a).	*See* Claim 9.

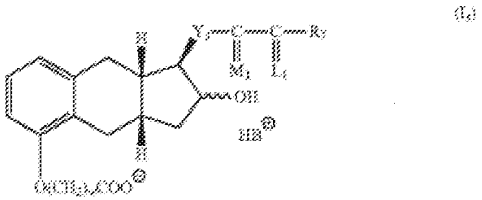
INVALIDITY CONTENTION CLAIM CHART FOR U.S. PATENT NO. 8,497,393

I. The Asserted Claims Are Anticipated By, Or Would Have Been Obvious In View Of, The Disclosure Of Treprostinil Sodium In "Synthetic Approaches To The 2002 New Drugs" by Jin Li and Kven K.-C. Liu (*Mini-Reviews in Medicinal Chemistry*, Vol. 4 at pp. 207-233 (2004) ("Li"))

Claim 1	Prior Art Disclosure
Element [A] A product comprising a compound of formula I:  (I) or a pharmaceutically acceptable salt thereof, wherein said product is prepared by a process comprising	A product-by-process claim is anticipated if the product is disclosed in the prior art. *Amgen*, 580 F.3d at 1366; *SmithKline Beecham Corp. v. Apotex Corp.*, 439 F.3d 1312, 1317 (Fed. Cir. 2006) ("It has long been established that one cannot avoid anticipation by an earlier product disclosure by claiming the same product more narrowly, that is, by claiming the product as produced by a particular process"); *Gen. Elec. Co. v. Wabash Appliance Corp.*, 304 U.S. 364, 373 (1938); *Cochrane v. Badische Anilin & Soda Farbrik*, 111 U.S. 293, 311 (1884) ("While a new process for producing [a chemical compound] was patentable, the product itself could not be patented even though it was a product made [by a new process] for the first time because the product was disclosed in the prior art"). "In determining the validity of a product-by-process claim, the focus is on the product and not on the process of making it." *Amgen*, 580 F.3d at 1369-70; *In re Thorpe*, 777 F.2d 695, 697 (Fed. Cir. 1985) ("Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production."); *Smithkline*, 439 F.3d at 1317-19; *see also* Manual of Patent Examining Procedure § 2113 (8th ed. Rev. 8 July 2010). Accordingly, for determining the patentability of the Asserted Claims of the '393 patent, the question is whether the claimed product is disclosed in, or obvious from, the prior art. The product of claim 1 of the '393 patent is a product comprising a member of the recited genus of compounds that includes the treprostinil compound or a pharmaceutically acceptable salt thereof, without further limitations as to the composition of the product. Thus, any product comprising treprostinil compound in any amount, with any other types or amounts of impurities, falls within the scope of the claimed product.

	The Li article was published in 2004 and is thus prior art to the '393 patent under 35 U.S.C. § 102(b). Li describes the synthesis of twenty-two drugs brought to market in 2002, including treprostinil. There are no structural and functional differences between the product of the Li article (treprostinil sodium) and the claimed product (a product including pharmaceutically acceptable salts of treprostinil). Accordingly, because Li discloses a product comprising treprostinil sodium salt, Li anticipates claim 1.
Element [B] (a) alkylating a compound of structure II with an alkylating agent to produce a compound of formula III, (II)  (III) 	*See* Element [A] above.

wherein w=1, 2, or 3; Y_1 is trans-CH=CH—, cis-CH=CH—, —$CH_2(CH_2)_m$—, or —C≡C—; m is 1, 2, or 3; R_7 is (1) —C_pH_{2p}—CH_3, wherein p is an integer from 1 to 5, inclusive, (2) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3) alkyl, or (C_1-C_3) alkoxy, with the proviso that not more than two substituents are other than alkyl, with the proviso that R_7 is phenoxy or substituted phenoxy, only when R_3 and R_4 are hydrogen or methyl, being the same or different, (3) phenyl, benzyl, phenylethyl, or phenylpropyl optionally substituted on the aromatic ring by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3)alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl, (4) cis-CH=CH—CH_2—CH_3, (5) —$(CH_2)_2$—CH(OH)—CH_3, or (6) —$(CH_2)_2$—CH=$C(CH_3)_2$; —$C(L_1)$—R_7 taken together is (1) (C_4-C_7)cycloalkyl optionally substituted by 1 to 3 (C_1-C_3) alkyl; (2) 2-(2-furyl)ethyl, (3) 2-(3-thienyl)ethoxy, or (4) 3-thienyloxymethyl; M_1 is α-OH:β-R_5 or α-R_5:β-OH or α-OR_1:β-R_5 or α-R_5:β-OR_2, wherein R_5 is hydrogen or methyl, R_2 is an alcohol protecting group, and L_1 is α-R_3:β-R_4, α-R_4:β-R_3, or a mixture of α-R_3:β-R_4 and α-R_4:β-R_3, wherein R_3 and R_4 are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R_3 and R_4 is fluoro only when the other is hydrogen or fluoro,	
Element [C] (b) hydrolyzing the product of formula III of step (a) with a base,	*See* Element [A] above.
Element [D]	*See* Element [A] above.

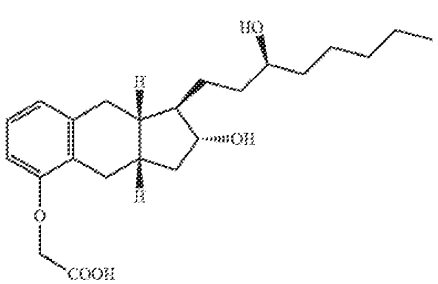
(c) contacting the product of step (h) with a base B to form a salt of formula Is.  and	
Element [E] (d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula I.	*See* Element [A] above.

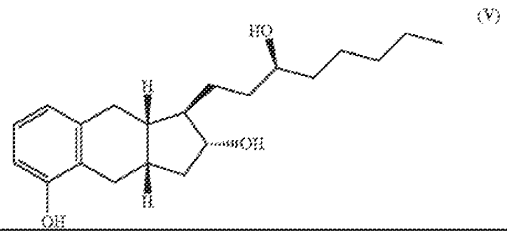
Claim 2	**Prior Art Disclosure**
The product of claim 1, wherein the purity of compound of formula I in said product is at least 99.5%.	*See* Claim 1. The skilled artisan would have been motivated to obtain a sample of treprostinil having a high level of purity. The Moriarty JOC Article includes an experimental section which describes in detail the synthesis of 441 grams of treprostinil acid having a purity of 99.7%. (*Id.* at 1902). Accordingly, it would have been obvious for the skilled artisan to purify the treprostinil disclosed in Li to a purity level of 99.5% or greater, especially in view of the disclosure in the Moriarty JOC Article of treprostinil having a purity of 99.7%. Also, purification techniques are common practice in the chemical arts. Accordingly, claim 2 would have been obvious in view of the disclosure of treprostinil sodium in

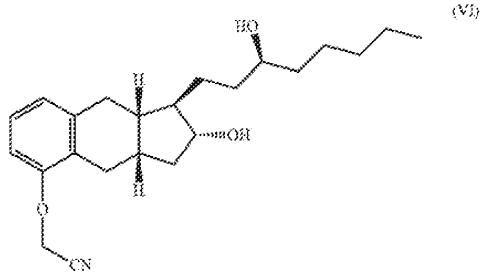
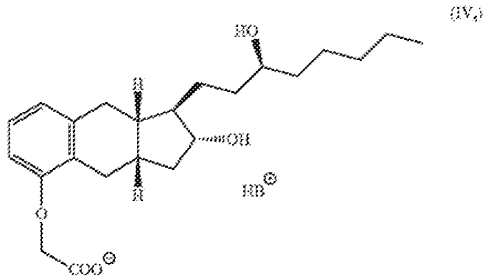
	Li.

Claim 4	Prior Art Disclosure
The product of claim 1, wherein the base in step (b) is KOH or NaOH.	*See* Claim 1.

Claim 8	Prior Art Disclosure
The product of claim 1, wherein the process does not include purifying the compound of formula (III) produced in step (a).	*See* Claim 1.

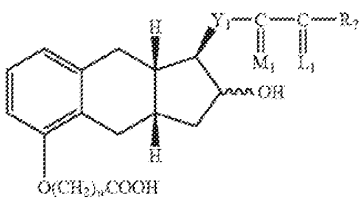
Claim 9	Prior Art Disclosure
Element [A] A product comprising a compound having formula IV  (IV) or a pharmaceutically acceptable salt thereof, wherein the product is prepared by the process comprising	A product-by-process claim is anticipated if the product is disclosed in the prior art. *Amgen*, 580 F.3d at 1366; *SmithKline Beecham Corp. v. Apotex Corp.*, 439 F.3d 1312, 1317 (Fed. Cir. 2006) ("It has long been established that one cannot avoid anticipation by an earlier product disclosure by claiming the same product more narrowly, that is, by claiming the product as produced by a particular process"); *Gen. Elec. Co. v. Wabash Appliance Corp.*, 304 U.S. 364, 373 (1938); *Cochrane v. Badische Anilin & Soda Farbrik*, 111 U.S. 293, 311 (1884) ("While a new process for producing [a chemical compound] was patentable, the product itself could not be patented even though it was a product made [by a new process] for the first time because the product was disclosed in the prior art"). "In determining the validity of a product-by-process claim, the focus is on the product and not on the process of making it." *Amgen*, 580 F.3d at 1369-70; *In re Thorpe*, 777 F.2d 695, 697 (Fed. Cir. 1985) ("Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production."); *Smithkline*, 439 F.3d at 1317-19; *see also* Manual of Patent Examining Procedure § 2113 (8th ed. Rev. 8 July 2010).

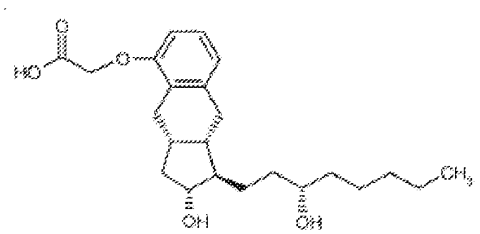
	Accordingly, for determining the patentability of the Asserted Claims of the '393 patent, the question is whether the claimed product is disclosed in, or obvious from, the prior art. The product of claim 9 of the '393 patent is a product comprising the treprostinil compound or a pharmaceutically acceptable salt thereof, without further limitations as to the composition of the product. Thus, any product comprising treprostinil compound in any amount, with any other types or amounts of impurities, falls within the scope of the claimed product. The Li article was published in 2004 and is thus prior art to the '393 patent under 35 U.S.C. § 102(b). Li describes the synthesis of twenty-two drugs brought to market in 2002, including treprostinil. There are no structural and functional differences between the product of the Li article (treprostinil sodium) and the claimed product (a product including pharmaceutically acceptable salts of treprostinil). Accordingly, because Li discloses a product comprising treprostinil sodium salt, Li anticipates claim 9.
Element [B] (a) alkylating a compound of formula V with an alkylating agent to produce a compound of formula VI,  (V)	*See* Element [A] above.

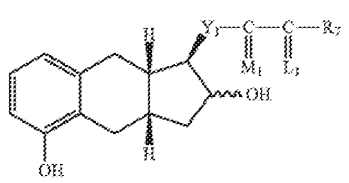
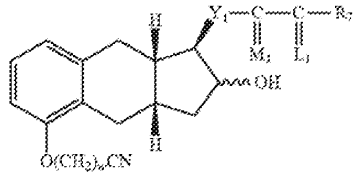
	
Element [C] (b) hydrolyzing the product of formula VI of step (a) with a base,	*See* Element [A] above.
Element [D] (c) contacting the product of step (h) with a base B to form a salt of formula IVs, and 	*See* Element [A] above.
Element [E] (d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula IV.	*See* Element [A] above.

Claim 16	Prior Art Disclosure
The product of claim 9, wherein the process does not include purifying the compound of formula (VI) produced in step (a).	*See* Claim 9.

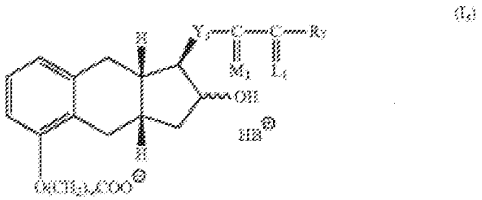
J. The Asserted Claims Are Anticipated By, Or Would Have Been Obvious In View Of, The Disclosure Of Treprostinil In Sorbera, *et al.*, "UT-15. Treatment of Pulmonary Hypertension, Treatment of Peripheral Vascular Disease," *Drug of the Future*, Vol. 26(4), pp. 364-374 (2001) ("Sorbera")

I. CLAIM 1	Prior Art Disclosure
Element [A] A product comprising a compound of formula I:  (I) or a pharmaceutically acceptable salt thereof, wherein said product is prepared by a process comprising	A product-by-process claim is anticipated if the product is disclosed in the prior art. *Amgen*, 580 F.3d at 1366; *SmithKline Beecham Corp. v. Apotex Corp.*, 439 F.3d 1312, 1317 (Fed. Cir. 2006) ("It has long been established that one cannot avoid anticipation by an earlier product disclosure by claiming the same product more narrowly, that is, by claiming the product as produced by a particular process"); *Gen. Elec. Co. v. Wabash Appliance Corp.*, 304 U.S. 364, 373 (1938); *Cochrane v. Badische Anilin & Soda Farbrik*, 111 U.S. 293, 311 (1884) ("While a new process for producing [a chemical compound] was patentable, the product itself could not be patented even though it was a product made [by a new process] for the first time because the product was disclosed in the prior art"). "In determining the validity of a product-by-process claim, the focus is on the product and not on the process of making it." *Amgen*, 580 F.3d at 1369-70; *In re Thorpe*, 777 F.2d 695, 697 (Fed. Cir. 1985) ("Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production."); *Smithkline*, 439 F.3d at 1317-19; *see also* Manual of Patent Examining Procedure § 2113 (8th ed. Rev. 8 July 2010). Accordingly, for determining the patentability of the Asserted Claims of the '393 patent, the question is whether the claimed product is disclosed in, or obvious from, the prior art. The product of claim 1 of the '393 patent is a product comprising a member of the recited genus of compounds that includes the treprostinil compound or a pharmaceutically acceptable salt thereof, without further limitations as to the composition of the product. Thus, any product comprising treprostinil compound in any amount, with any other types or amounts of impurities, falls within the scope of the claimed product.

	The Sorbera article was published in 2001 and is thus prior art to the '393 patent under 35 U.S.C. § 102(b). The Sorbera article discloses the treprostinil compound, as shown below, and further discloses several methods of making treprostinil. (*Id.* at 364).  $C_{23}H_{34}O_5$ Mol wt: 390.524 Sorbera further discloses that treprostinil is the active ingredient in Remodulin, and states as follows: > UT-15 (Remodulin ™), on the other hand, is a chemically stable benzindene analog of prostacyclin that has shown potent preclinical and clinical efficacy and may be a potential treatment for advanced pulmonary hypertension and late-stage vascular disease. The compound is stable at room temperature for up to 5 years and is delivered via s.c. infusion using a MiniMed microinfusion device, thus eliminating the risk of sepsis infection and hospitalization associated with catheters (17). UT-15 has been chosen for further development. (Sorbera at p. 369). Sorbera then proceeds to describe nonclinical and clinical testing

	of the Remodulin product. (*Id.* at pp. 369-73). Also, the '393 patent specification states that the Sorbera reference discloses a method of making treprostinil. ('393 patent at Col. 1:23-26). There are no structural and functional differences between the product of the Sorbera article (treprostinil) and the claimed product (a product including treprostinil or pharmaceutically acceptable salts thereof). Accordingly, because Sorbera discloses a product comprising treprostinil, Sorbera anticipates claim 1.
Element [B] (a) alkylating a compound of structure II with an alkylating agent to produce a compound of formula III, (II)  (III) 	*See* Element [A] above.

wherein w=1, 2, or 3; Y_1 is trans-CH=CH—, cis-CH=CH—, —$CH_2(CH_2)_m$—, or —C≡C—; m is 1, 2, or 3; R_7 is (1) —C_pH_{2p}—CH_3, wherein p is an integer from 1 to 5, inclusive, (2) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3) alkyl, or (C_1-C_3) alkoxy, with the proviso that not more than two substituents are other than alkyl, with the proviso that R_7 is phenoxy or substituted phenoxy, only when R_3 and R_4 are hydrogen or methyl, being the same or different, (3) phenyl, benzyl, phenylethyl, or phenylpropyl optionally substituted on the aromatic ring by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3)alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl, (4) cis-CH=CH—CH_2—CH_3, (5) —$(CH_2)_2$—CH(OH)—CH_3, or (6) —$(CH_2)_2$—CH=$C(CH_3)_2$; —$C(L_1)$—R_7 taken together is (1) (C_3-C_7)cycloalkyl optionally substituted by 1 to 3 (C_1-C_3) alkyl; (2) 2-(2-furyl)ethyl, (3) 2-(3-thienyl)ethoxy, or (4) 3-thienyloxymethyl; M_1 is α-OH:β-R_5 or α-R_5:β-OH or α-OR_1:β-R_5 or α-R_5:β-OR_2, wherein R_5 is hydrogen or methyl, R_2 is an alcohol protecting group, and L_1 is α-R_3:β-R_4, α-R_4:β-R_3, or a mixture of α-R_3:β-R_4 and α-R_4:β-R_3, wherein R_3 and R_4 are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R_3 and R_4 is fluoro only when the other is hydrogen or fluoro,	
Element [C] (b) hydrolyzing the product of formula III of step (a) with a base,	*See* Element [A] above.
Element [D]	*See* Element [A] above.

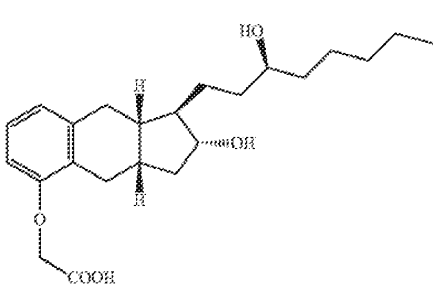
(c) contacting the product of step (h) with a base B to form a salt of formula Is.  and	
Element [E] (d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula I.	*See* Element [A] above.

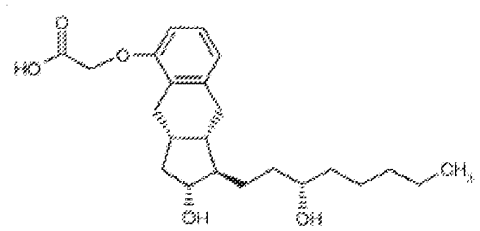
Claim 2	**Prior Art Disclosure**
The product of claim 1, wherein the purity of compound of formula I in said product is at least 99.5%.	*See* Claim 1. The skilled artisan would have been motivated to obtain a sample of treprostinil having a high level of purity. The Moriarty JOC Article includes an experimental section which describes in detail the synthesis of 441 grams of treprostinil acid having a purity of 99.7%. (*Id.* at 1902). Accordingly, it would have been obvious for the skilled artisan to purify the treprostinil disclosed in Sorbera to a purity level of 99.5% or greater, especially in view of the disclosure in the Moriarty JOC Article of treprostinil having a purity of 99.7%. Also, purification techniques are common practice in the chemical arts. Accordingly, claim 2 would have been obvious in view of the disclosure of

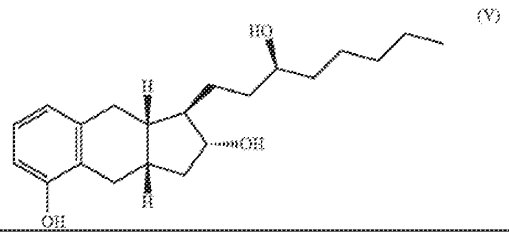
	treprostinil in Sorbera.

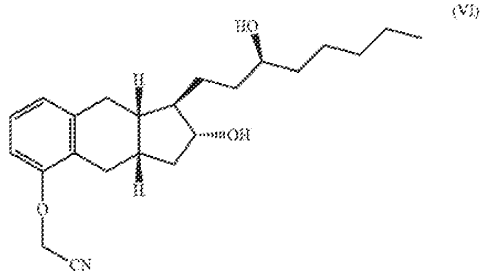
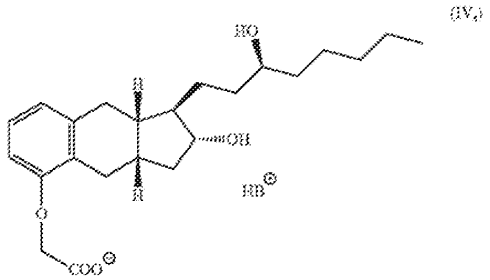
Claim 4	Prior Art Disclosure
The product of claim 1, wherein the base in step (b) is KOH or NaOH.	*See* Claim 1.

Claim 8	Prior Art Disclosure
The product of claim 1, wherein the process does not include purifying the compound of formula (III) produced in step (a).	*See* Claim 1.

Claim 9	Prior Art Disclosure
Element [A] A product comprising a compound having formula IV  (IV) or a pharmaceutically acceptable salt thereof, wherein the product is prepared by the process comprising	A product-by-process claim is anticipated if the product is disclosed in the prior art. *Amgen*, 580 F.3d at 1366; *SmithKline Beecham Corp. v. Apotex Corp.*, 439 F.3d 1312, 1317 (Fed. Cir. 2006) ("It has long been established that one cannot avoid anticipation by an earlier product disclosure by claiming the same product more narrowly, that is, by claiming the product as produced by a particular process"); *Gen. Elec. Co. v. Wabash Appliance Corp.*, 304 U.S. 364, 373 (1938); *Cochrane v. Badische Anilin & Soda Farbrik*, 111 U.S. 293, 311 (1884) ("While a new process for producing [a chemical compound] was patentable, the product itself could not be patented even though it was a product made [by a new process] for the first time because the product was disclosed in the prior art"). "In determining the validity of a product-by-process claim, the focus is on the product and not on the process of making it." *Amgen*, 580 F.3d at 1369-70; *In re Thorpe*, 777 F.2d 695, 697 (Fed. Cir. 1985) ("Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production."); *Smithkline*, 439 F.3d at 1317-19; *see also* Manual of Patent

	Examining Procedure § 2113 (8th ed. Rev. 8 July 2010). Accordingly, for determining the patentability of the Asserted Claims of the '393 patent, the question is whether the claimed product is disclosed in, or obvious from, the prior art. The product of claim 9 of the '393 patent is a product comprising the treprostinil compound or a pharmaceutically acceptable salt thereof, without further limitations as to the composition of the product. Thus, any product comprising treprostinil compound in any amount, with any other types or amounts of impurities, falls within the scope of the claimed product. The Sorbera article was published in 2001 and is thus prior art to the '393 patent under 35 U.S.C. § 102(b). The Sorbera article discloses the treprostinil compound, as shown below, and further discloses several methods of making treprostinil. (*Id.* at 364).  $C_{23}H_{34}O_5$ Mol wt: 390.524 Sorbera further discloses that treprostinil is the active ingredient in Remodulin, and states as follows: UT-15 (Remodulin ™), on the other hand, is a chemically stable benzindene analog of prostacyclin that has shown potent

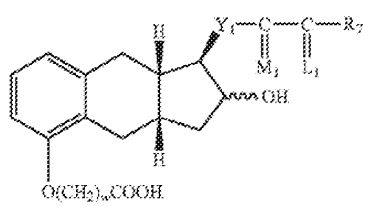
	preclinical and clinical efficacy and may be a potential treatment for advanced pulmonary hypertension and late-stage vascular disease. The compound is stable at room temperature for up to 5 years and is delivered via s.c. infusion using a MiniMed microinfusion device, thus eliminating the risk of sepsis infection and hospitalization associated with catheters (17). UT-15 has been chosen for further development. (Sorbera at p. 369). Sorbera then proceeds to describe nonclinical and clinical testing of the Remodulin product. (*Id.* at pp. 369-73). Also, the '393 patent specification states that the Sorbera reference discloses a method of making treprostinil. ('393 patent at Col. 1:23-26). There are no structural and functional differences between the product of the Sorbera article (treprostinil) and the claimed product (a product including treprostinil or pharmaceutically acceptable salts thereof). Accordingly, because Sorbera discloses a product comprising treprostinil, Sorbera anticipates claim 9.
Element [B] (a) alkylating a compound of formula V with an alkylating agent to produce a compound of formula VI,  	*See* Element [A] above.

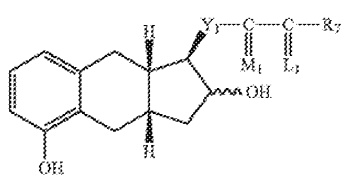
	
Element [C] (b) hydrolyzing the product of formula VI of step (a) with a base,	*See* Element [A] above.
Element [D] (c) contacting the product of step (h) with a base B to form a salt of formula IVs, and 	*See* Element [A] above.
Element [E] (d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula IV.	*See* Element [A] above.

Claim 16	Prior Art Disclosure
The product of claim 9, wherein the process does not include purifying the compound of formula (VI) produced in step (a).	*See* Claim 9.

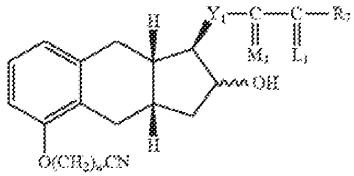
II. EVEN ASSUMING THAT THE PROCESS LIMITATIONS OF THE ASSERTED CLAIMS ARE PERTINENT FOR VALIDITY PURPOSES, THE PRIOR ART DISCLOSES AND/OR RENDERS OBVIOUS PRODUCTS COMPRISING TREPROSTINIL MADE THROUGH THE CLAIMED PROCESS

A. The Asserted Claims Are Anticipated By Or Obvious In View Of Phares

Claim 1	Prior Art Disclosure
[Element A] A product comprising a compound of formula I:  (I) or a pharmaceutically acceptable salt thereof, wherein said product is prepared by a process comprising	To the extent that the process limitations Asserted Claims are pertitent to validity, which they are not, the claimed product is anticipated by Phares because Phares discloses a product comprising treprostinil diethanolamine made through the claimed process. The Phares publication discloses a process of making treprostinil diethanolamine salt. (Phares publication at ¶ 105).
[Element B] (a) alkylating a compound of structure II with an alkylating agent to produce a compound of formula III,	The Phares publication discloses a method of making treprostinil involving alkylating benzindene triol to form the nitrile, then hydrolyzing the nitrile with a base (KOH) to obtain the free acid. (Phares publication at ¶¶ 0143-0145). Phares teaches that chemical derivatives of (+)-treprostinil are included within the scope of the invention:

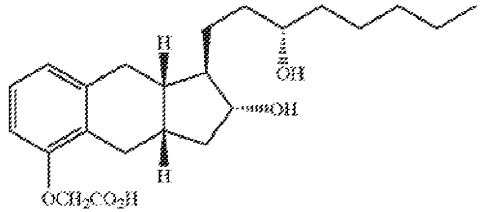


(II)



(III)

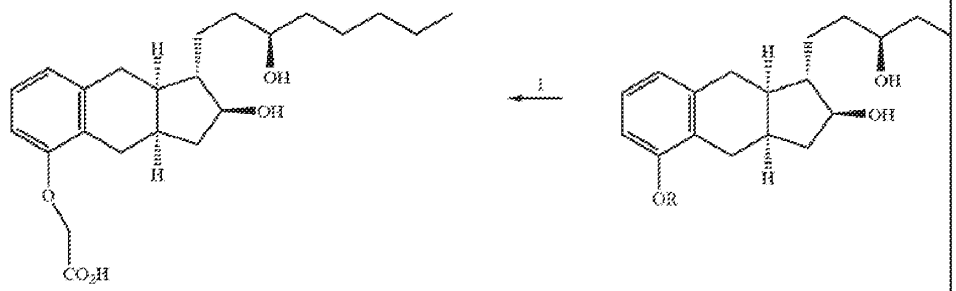
wherein
w=1, 2, or 3;
Y_1 is trans-CH=CH—, cis-CH=CH—, $—CH_2(CH_2)_m—$, or —C≡C—; m is 1, 2, or 3;
R_7 is
(1) $—C_pH_{2p}—CH_3$, wherein p is an integer from 1 to 5, inclusive,
(2) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3) alkyl, or (C_1-C_3) alkoxy, with the proviso that not more than two substituents are other than alkyl, with the proviso that R_7 is phenoxy or substituted phenoxy, only when R_3 and R_4 are hydrogen or methyl, being the same or different,
(3) phenyl, benzyl, phenylethyl, or phenylpropyl optionally substituted on the aromatic ring by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3)alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl,
(4) cis-CH=CH—CH_2—CH_3,
(5) —$(CH_2)_2$—CH(OH)—CH_3, or
(6) —$(CH_2)_2$—CH=C$(CH_3)_2$;
—$C(L_1)$—R_7 taken together is
(1) (C_4-C_7)cycloalkyl optionally substituted by 1 to 3 (C_1-C_3) alkyl;

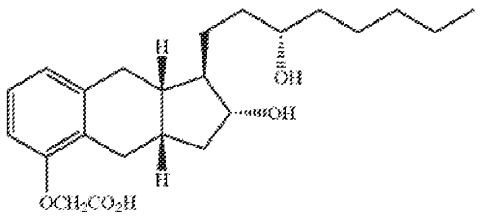


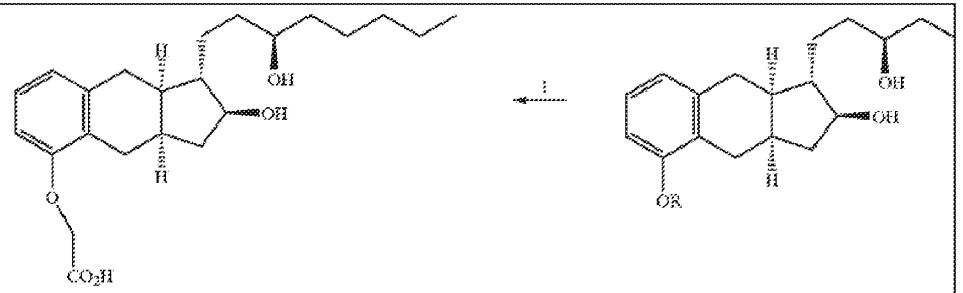
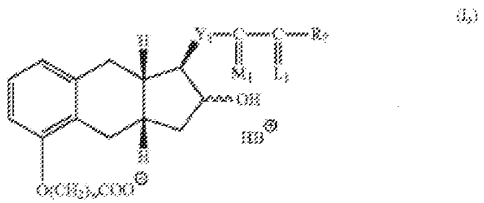
(+)-treprostinil

(*Id.* at ¶ 0050). Phares teaches the preparation of (-)-treprostinil but notes that (+)-treprostinil can be prepared in the same manner. (*Id.* at ¶¶ 0143-0145).

According to Phares, (-)-treprostinil can be prepared by alkylating the benzindene triol compound shown below (note R= H) with chloroacetonitrile to form a benzindene nitrile compound:



(2) 2-(2-furyl)ethyl, (3) 2-(3-thienyl)ethoxy, or (4) 3-thienyloxymethyl; M_1 is α-OH:β-R_3 or α-R_3:β-OH or α-OR_1:β-R_3 or α-R_3:β-OR_2, wherein R_3 is hydrogen or methyl, R_2 is an alcohol protecting group, and L_1 is α-R_3:β-R_4, α-R_4:β-R_3, or a mixture of α-R_3:β-R_4 and α-R_4:β-R_3, wherein R_3 and R_4 are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R_3 and R_4 is fluoro only when the other is hydrogen or fluoro,	(a) (S)-2-methyl-CBS-oxazaborolidine, BH_3•SMe_2, THF, -30° C., 85%. (b) TBDMSCl, imadazole, CH_2Cl_2, 95%. (c) $Co_2(CO)_8$, CH_2Cl_2, 2 hr. r.t., then CH_3CN, 2 hr. 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, DEAD, TPP, benzene. (i) CH_3OH, KOH, 94%. (j) Pd/C (10%), EtOH, 50 psi/2 hr. quant. (k) Ph_3PLi, THF. (l) i. $ClCH_2CN$, K_2CO_3; ii. KOH, CH_3OH, reflux, 83% (2 steps). (*Id.* at ¶ 0144).
[Element C] (b) hydrolyzing the product of formula III of step (a) with a base,	The Phares publication discloses a method of making treprostinil involving alkylating benzindene triol to form the nitrile, then hydrolyzing the nitrile with a base (KOH) to obtain the free acid. (Phares publication at ¶¶ 0143-0145). Phares teaches that chemical derivatives of (+)-treprostinil are included within the scope of the invention:  **(+)-treprostinil** (*Id.* at ¶ 0050). Phares teaches the preparation of (-)-treprostinil but notes that (+)-treprostinil can be prepared in the same manner. (*Id.* at ¶¶ 0143-0145). According to Phares, (-)-treprostinil can be prepared by forming a benzindene nitrile compound which can then be hydrolyzed to the free acid of treprostinil using KOH:

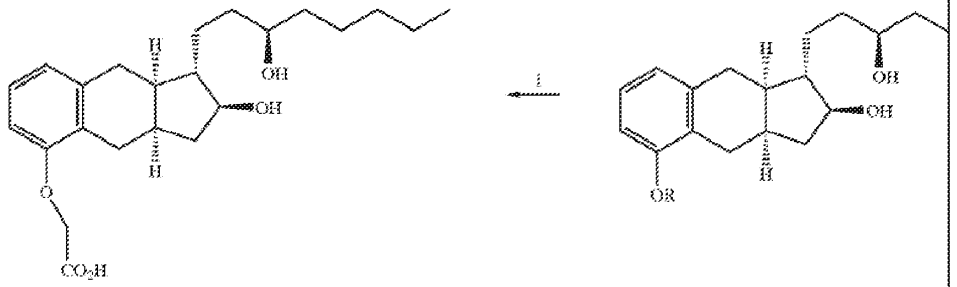
	 (a) (S)-2-methyl-CBS-oxazaborolidine, BH_3•SMe_2, THF, -30° C., 85%. (b) TBDMSCl, imadazole, CH_2Cl_2, 95%. (c) $Co_2(CO)_8$, CH_2Cl_2, 2 hr. r.t., then CH_3CN, 2 hr. reflux. 98%. (d) K_2CO_3, Pd/C (10%), EtOH, 50 psi/24 hr. 78% (e) NaOH, EtOH, $NaBH_4$, 95%. (f) BnBr, NaH, THF, 98%. (g) CH_3OH, $TsOH$, 96%. (h) i, p-nitrobenzoic acid, DEAD, TPP, benzene. (i) CH_3OH, KOH, 94%. (j) Pd/C (10%), EtOH, 50 psi/2 hr. quant. (k) Ph_3P.I, THF. (l) i. $ClCH_2CN$, K_2CO_3, ii, KOH, CH_3OH, reflux, 83% (2 steps). (*Id.* at ¶ 0144).
[Element D] (c) contacting the product of step (h) with a base B to form a salt of formula Is.  and	The Phares publication discloses converting treprostinil free acid into treprostinil diethanolamine salt as follows: Treprostinil acid acid [*sic*] is dissolved in a 1:1 molar ratio mixture of ethanol:water and diethanolamine is added and dissolved. The solution is heated and acetone is added as an antisolvent during cooling. (Phares publication at ¶ 0105). The Phares Publication also teaches that treprostinil diethanolamine can be recrystallized to yield two crystalline polymorphs, including the metastable polymorph A, and the thermodynamically more stable polymorph B. (*Id.* at ¶ 327).

	According to Phares, the resulting polymorphs have melting points at 103° C (Form A) and 107° C (Form B), respectively. (*Id.* at ¶¶ 0332, 0337).
[Element E] (d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula I.	

Claim 2	**Prior Art Disclosure**
The product of claim 1, wherein the purity of compound of formula I in said product is at least 99.5%.	*See* Claim 1. As noted above, the Phares Publication teaches that recrystallizing the diethanolamine salt of treprostinil results in the formation of two crystalline polymorphs of treprostinil diethanolamine, Forms A and B. (Phares Publication at ¶ 0327). Although Phares does not indicate the purity of polymorph Form B, Phares notes that the melting point is 107°C and provides an XRPD pattern of Form B in Figure 20. (*Id.* at ¶ 0337). The specification of the ' 393 patent indicates that the treprostinil diethanolamine compound produced according to the claimed procedures yields treprostinil diethanolamine polymorph Form B that has a melting point of at least 104°C. For example, the table provided at Col. 12:60- Col. 13:12 in the '393 patent shows that Batch 2 of treprostinil diethanolamine salt had a melting point of 105.5-107.2°C. Thus, the diethanolamine treprostinil polymorph Form B formed using the procedures taught by Phares is the same as the diethanolamine treprostinil product produced following the steps recited in the claims of the '393 patent. Accordingly, the treprostinil diethanolamine salt of Form B disclose in Phares anticipates claim 2. Further, Phares teaches a method of making treprostinil diethanolamine salt that

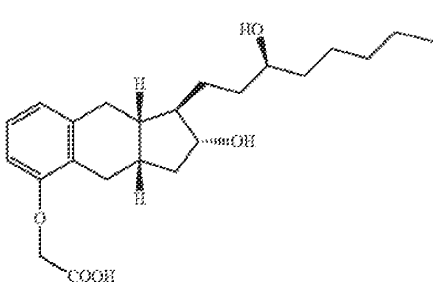
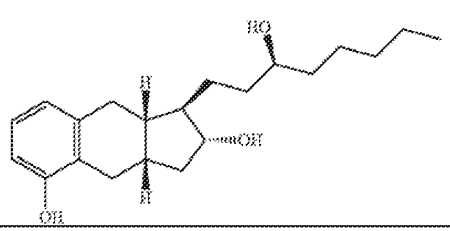
	includes the same steps as the claimed method: alkylating the triol, hydrolyzing the nitrile with a base, and contacting the product with a base (B) to produce treprostinil diethanolamine salt of polymorph form Form B: The Phares publication discloses a method of making treprostinil involving alkylating benzindene triol to form the nitrile, then hydrolyzing the nitrile with a base (KOH) to obtain the free acid. (Phares publication at ¶¶ 0143-0145). The Phares publication discloses converting treprostinil free acid into treprostinil diethanolamine salt as follows: > Treprostinil acid acid [*sic*] is dissolved in a 1:1 molar ratio mixture of ethanol:water and diethanolamine is added and dissolved. The solution is heated and acetone is added as an antisolvent during cooling. (Phares publication at ¶ 0105). The Phares Publication also teaches that treprostinil diethanolamine can be recrystallized to yield two crystalline polymorphs, including the metastable polymorph A, and the thermodynamically more stable polymorph B. (*Id.* at ¶ 327). According to Phares, the resulting polymorphs have melting points at 103° C (Form A) and 107° C (Form B), respectively. (*Id.* at ¶¶ 0332, 0337). Thus, because the Phares publication discloses using the same process as that claimed to make the same product (treprostinil diethanolamine salt), then the product obtained through the method disclosed in Phares inherently has the claimed purity profile. Also, the skilled artisan would have been motivated to obtain a sample of treprostinil having a high level of purity. The Moriarty JOC Article includes an experimental section which describes in detail the synthesis of 441 grams of treprostinil acid having a purity of 99.7%. (*Id.* at 1902).

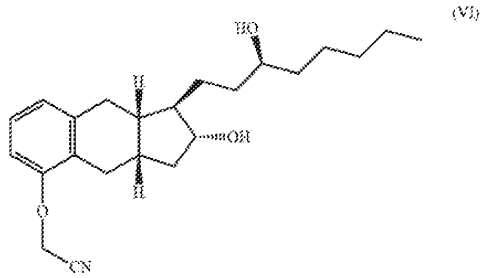
	It is well-known in the art that a salt formation step can be used as a purification step. Given that the treprostinil free acid obtained in the Moriarty JOC Article has a purity level of 99.7%, the skilled artisan would expect that the treprostinil diethanolamine salt produced through the process in the Phares Publication would have a purity level comparable to or greater than the starting material. Accordingly, the skilled artisan would have a reasonable expectation of success in obtaining a batch of treprostinil diethanolamine salt having a purity level of at least 99.5% when performing the salt formation step disclosed in the Phares Publication using the treprostinil free acid disclosed in the Moriarty JOC Article as a starting material. Moreover, it would have been obvious for the skilled artisan to purify the treprostinil disclosed in the Phares Publication to a purity level of 99.5% or greater, particularly in view of the disclosure in the Moriarty JOC Article of treprostinil having a purity level of 99.7%. Also, purification techniques are common practice in the chemical arts. Accordingly, claim 2 would have been obvious.

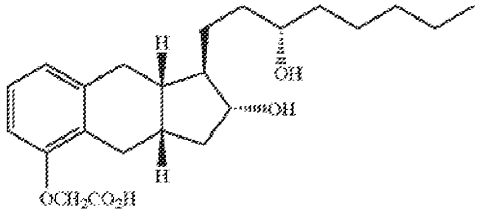
Claim 4	**Prior Art Disclosure**
The product of claim 1, wherein the base in step (b) is KOH or NaOH.	*See* Claim 1. According to Phares, (-)-treprostinil can be prepared by forming a benzindene nitrile compound which can then be hydrolyzed to the free acid of treprostinil using KOH: 

	(a) (S)-2-methyl-CBS-oxazaborolidine, BH_3•SMe_2, THF, -30° C., 85%. (b) TBDMSCl, imadazole, CH_2Cl_2, 95%. (c) $Co_2(CO)_8$, CH_2Cl_2, 2 hr. r.t., then CH_3CN, 2 hr. 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, DEAD, TPP, benzene. (i) CH_3OH, KOH, 94%. (j) Pd/C (10%), EtOH, 50 psi/2 hr, quant. (k) Ph_3PLi, THF. (l) i. $ClCH_2CN$, K_2CO_3; ii. KOH, CH_3OH, reflux, 83% (2 steps). (*Id.* at ¶ 0144).

Claim 8	Prior Art Disclosure
The product of claim 1, wherein the process does not include purifying the compound of formula (III) produced in step (a).	*See* Claim 1. In general, there is a motivation in the art to optimize the efficiency of reaction processes. Further, a person of ordinary skill in the art would have been motivated to avoid the "drawbacks" of column chromatography, which is a "labor-intensive" process that is used generally as a last resort. (Anderson, N. "*Practical Process Research & Development: A Guide for Organic Chemists*" at pp. 13, 223, 226 (2000) ("Anderson"). Anderson also discloses that in general, the practice of "telescoping," which is of carrying the product of a reaction without isolation into the next step, can greatly increase overall yields and is usually incorporated as part of a cost-effective route unless significant benefits are obtained from isolation of the intermediate. Accordingly, here, the skilled artisan would have been motivated to carry the product of step (a) through without isolation or purification with the goal of obtaining a pure final product after step (c) following crystallization of the diethanolamine salt.

Claim 9	Prior Art Disclosure
[Element A] A product comprising a compound having formula IV  or a pharmaceutically acceptable salt thereof, wherein the product is prepared by the process comprising	To the extent that the process limitations Asserted Claims are pertitent to validity, which they are not, the claimed product is anticipated by Phares because Phares discloses a product comprising treprostinil diethanolamine made through the claimed process. The Phares publication discloses a process of making treprostinil diethanolamine salt. (Phares publication at ¶ 105).
[Element B] (a) alkylating a compound of formula V with an alkylating agent to produce a compound of formula VI, 	The Phares publication discloses a method of making treprostinil involving alkylating benzindene triol to form the nitrile, then hydrolyzing the nitrile with a base (KOH) to obtain the free acid. (Phares publication at ¶¶ 0143-0145). Phares teaches that chemical derivatives of (+)-treprostinil are included within the scope of the invention:

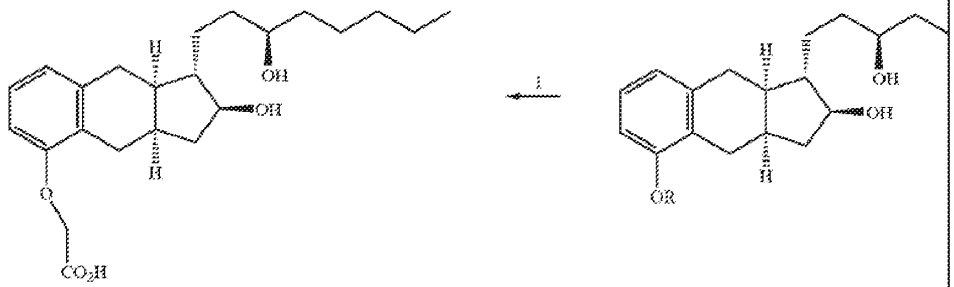


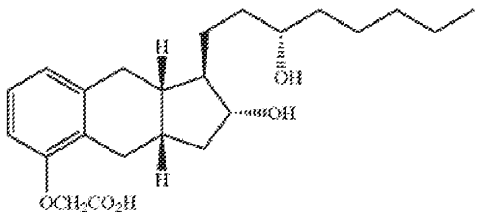


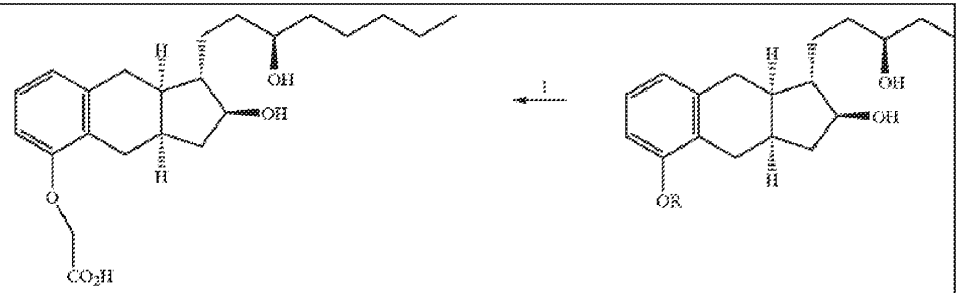
(+)-treprostinil

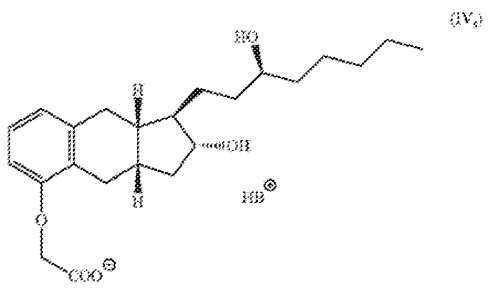
(*Id.* at ¶ 0050). Phares teaches the preparation of (-)-treprostinil but notes that (+)-treprostinil can be prepared in the same manner. (*Id.* at ¶¶ 0143-0145).

According to Phares, (-)-treprostinil can be prepared by alkylating the benzindene triol compound shown below (note R= H) with chloroacetonitrile to form a benzindene nitrile compound:



	(a) (S)-2-methyl-CBS-oxazaborolidine, BH_3•SMe_2, THF, -30° C., 85%. (b) TBDMSCl, imadazole, CH_2Cl_2, 95%. (c) $Co_2(CO)_8$, CH_2Cl_2, 2 hr. r.t., then CH_3CN, 2 hr. 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, DEAD, TPP, benzene. (i) CH_3OH, KOH, 94%. (j) Pd/C (10%), EtOH, 50 psi/2 hr, quant. (k) Ph_3PLi, THF. (l) i. $ClCH_2CN$, K_2CO_3; ii. KOH, CH_3OH, reflux, 83% (2 steps). (*Id.* at ¶ 0144).
[Element C] (b) hydrolyzing the product of formula VI of step (a) with a base,	The Phares publication discloses a method of making treprostinil involving alkylating benzindene triol to form the nitrile, then hydrolyzing the nitrile with a base (KOH) to obtain the free acid. (Phares publication at ¶¶ 0143-0145). Phares teaches that chemical derivatives of (+)-treprostinil are included within the scope of the invention:  **(+)-treprostinil** (*Id.* at ¶ 0050). Phares teaches the preparation of (-)-treprostinil but notes that (+)-treprostinil can be prepared in the same manner. (*Id.* at ¶¶ 0143-0145). According to Phares, (-)-treprostinil can be prepared by forming a benzindene nitrile compound which can then be hydrolyzed to the free acid of treprostinil using KOH:

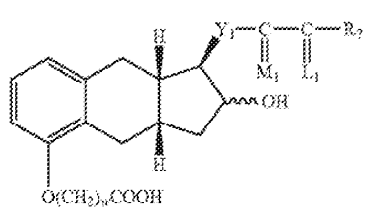
	 (a) (S)-2-methyl-CBS-oxazaborolidine, BH_3•SMe_2, THF, -30° C., 85%. (b) TBDMSCl, imadazole, CH_2Cl_2, 95%. (c) $Co_2(CO)_8$, CH_2Cl_2, 2 hr. r.t., then CH_3CN, 2 hr. reflux. 98%. (d) K_2CO_3, Pd/C (10%), EtOH, 50 psi/24 hr. 78% (e) NaOH, EtOH, $NaBH_4$, 95%. (f) BnBr, NaH, THF, 98%. (g) CH_3OH, $TsOH$, 96%. (h) i, p-nitrobenzoic acid, DEAD, TPP, benzene. (i) CH_3OH, KOH, 94%. (j) Pd/C (10%), EtOH, 50 psi/2 hr. quant. (k) Ph_3PI, i, THF. (l) i. $ClCH_2CN$, K_2CO_3, ii, KOH, CH_3OH, reflux, 83% (2 steps). (*Id.* at ¶ 0144).
[Element D] (c) contacting the product of step (h) with a base B to form a salt of formula IVs, and	The Phares publication discloses converting treprostinil free acid into treprostinil diethanolamine salt as follows: > Treprostinil acid acid [*sic*] is dissolved in a 1:1 molar ratio mixture of ethanol:water and diethanolamine is added and dissolved. The solution is heated and acetone is added as an antisolvent during cooling. (Phares publication at ¶ 0105). The Phares Publication also teaches that treprostinil diethanolamine can be recrystallized to yield two crystalline polymorphs, including the metastable polymorph A, and the thermodynamically more stable polymorph B. (*Id.* at ¶ 327).

	According to Phares, the resulting polymorphs have melting points at 103° C (Form A) and 107° C (Form B), respectively. (*Id.* at ¶¶ 0332, 0337).
[Element E] (d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula IV.	

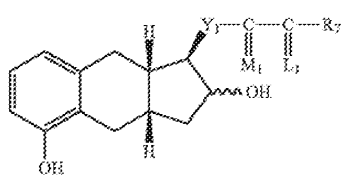
Claim 16	**Prior Art Disclosure**
The product of claim 9, wherein the process does not include purifying the compound of formula (VI) produced in step (a).	*See* Claim 9. In general, there is a motivation in the art to optimize the efficiency of reaction processes. Further, a person of ordinary skill in the art would have been motivated to avoid the "drawbacks" of column chromatography, which is a "labor-intensive" process that is used generally as a last resort. (Anderson, N. "*Practical Process Research & Development: A Guide for Organic Chemists*" at pp. 13, 223, 226 (2000) ("Anderson"). Anderson also discloses that in general, the practice of "telescoping," which is of carrying the product of a reaction without isolation into the next step, can greatly increase overall yields and is usually incorporated as part of a cost-effective route unless significant benefits are obtained from isolation of the intermediate. (Anderson at p. 34). Accordingly, here, the skilled artisan would have been motivated to carry the

	product of step (a) through without isolation or purification with the goal of obtaining a pure final product after step (c) following crystallization of the diethanolamine salt.

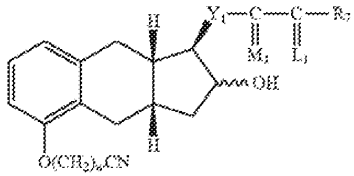
B. The Asserted Claims Are Obvious In View Of Phares In Combination With The Moriarty JOC Article

Claim 1	Prior Art Disclosure
[Element A] A product comprising a compound of formula I:  (I) or a pharmaceutically acceptable salt thereof, wherein said product is prepared by a process comprising	To the extent that the Asserted Claims are not anticipated by Phares, then the Asserted Claims are invalid as obvious in view of Phares, alone or in combination with the Moriarty JOC Article. Because the Asserted Claims are product-by-process claims, it is not necessary to consider the claimed method steps as part of an invalidity analysis. However, to the extent that the claimed process steps are material to validity, which they are not, the Asserted Claims are invalid because the prior art discloses a process of making treprostinil diethanolamine salt using the claimed process steps. The Phares Publication discloses that "treprostinil sodium (Remodulin®) is approved by the Food and Drug Administration (FDA) for subcutaneous administration" and that "treprostinil as the free acid has an absolute oral bioavailability of less than 10%." (*Id.* at ¶ 0004). The purpose of the invention was to serve the "clinical interest in providing treprostinil orally," and "increasing systemic availability of treprostinil via administration of treprostinil or treprostinil analogs." (Id. at ¶ 0004-0005). The Phares Publication further provides that "[a] preferred embodiment of the present invention is the diethanolamine salt of treprostinil." (*Id.* at ¶ 0051). Phares discloses animal testing involving administration of treprostinil diethanolamine to rats in Example 1 and clinical trials using treprostinil diethanolamine salt formulations in Example 5. (Phares Publication at ¶¶ 0203-0237, 0311-0326). Pharmacokinetic testing of an oral formulation of treprostinil diethanolamine in human patients showed an absolute bioavailability of 21-25% for the four doses tested. (*Id.* at ¶ 0319).

	The skilled artisan would have been motivated to make treprostinil diethanolamine salt as disclosed in Phares in view of the improved bioavailability profile disclosed in Phares. The starting material for the salt formation step disclosed in Phares is treprostinil free acid, so the skilled artisan would have been motivated to obtain treprostinil free acid in order to make treprostinil diethanolamine as disclosed in Phares. Because the skilled artisan would have been motivated to make treprostinil acid to use in the diethanolamine salt formation step, the skilled artisan would have been further motivated to use the process described in Phares to make treprostinil free acid that could be used as the starting material in the salt formation step. In the alternative, the skilled artisan would have been motivated to make treprostinil free acid using the process described in the Moriarty JOC Article and then use the treprostinil free acid as the starting material in the salt formation step. First, the Moriarty JOC Article discloses that the synthesis process described therein is efficient, economical, and superior to methods disclosed in the prior art. Second, the Moriarty JOC Article discloses that the process disclosed therein produces treprostinil free acid having a purity of 99.7%. There is a general desire in the art to obtain drug substance samples having a high purity level through processes that are efficient and economical, so the skilled artisan would have been motivated to use the 99.7% pure sample of treprostinil produced as disclosed in the Moriarty JOC Article as the starting material in the treprostinil diethanolamine formation step disclosed in the Phares Publication.
[Element B] (a) alkylating a compound of structure II with an alkylating agent to produce a compound of formula III,	The Phares publication discloses a method of making treprostinil involving alkylating benzindene triol to form the nitrile, then hydrolyzing the nitrile with a base (KOH) to obtain the free acid. (Phares publication at ¶¶ 0143-0145). Phares teaches that chemical derivatives of (+)-treprostinil are included within the scope of the invention:

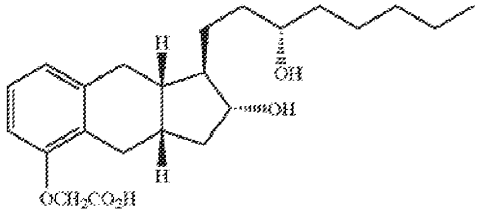


(II)



(III)

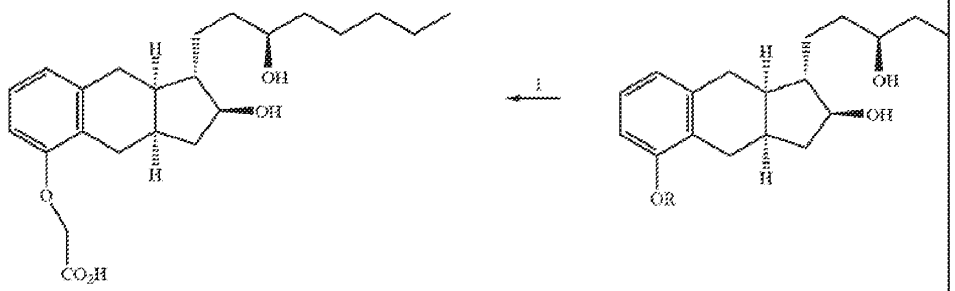
wherein
w=1, 2, or 3;
Y_1 is trans-CH=CH—, cis-CH=CH—, $—CH_2(CH_2)_m—$, or —C≡C—; m is 1, 2, or 3;
R_7 is
(1) $—C_pH_{2p}—CH_3$, wherein p is an integer from 1 to 5, inclusive,
(2) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3) alkyl, or (C_1-C_3) alkoxy, with the proviso that not more than two substituents are other than alkyl, with the proviso that R_7 is phenoxy or substituted phenoxy, only when R_3 and R_4 are hydrogen or methyl, being the same or different,
(3) phenyl, benzyl, phenylethyl, or phenylpropyl optionally substituted on the aromatic ring by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3)alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl,
(4) cis-CH=CH—CH_2—CH_3,
(5) —$(CH_2)_2$—CH(OH)—CH_3, or
(6) —$(CH_2)_2$—CH=C(CH_3)$_2$;
—$C(L_1)$—R_7 taken together is
(1) (C_4-C_7)cycloalkyl optionally substituted by 1 to 3 (C_1-C_3) alkyl;

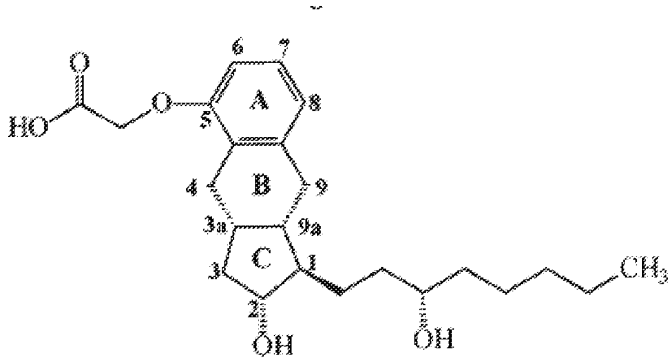


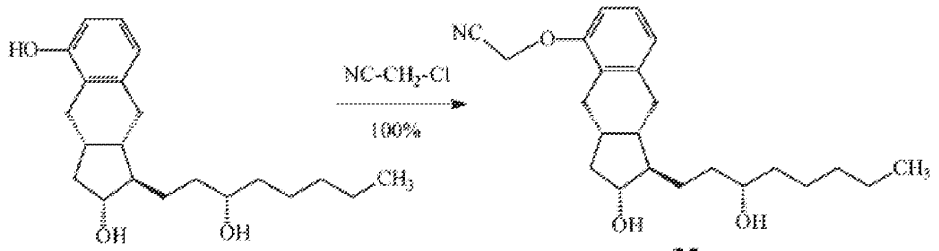
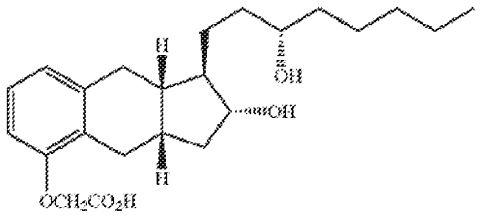
(+)-treprostinil

(*Id.* at ¶ 0050). Phares teaches the preparation of (-)-treprostinil but notes that (+)-treprostinil can be prepared in the same manner. (*Id.* at ¶¶ 0143-0145).

According to Phares, (-)-treprostinil can be prepared by alkylating the benzindene triol compound shown below (note R= H) with chloroacetonitrile to form a benzindene nitrile compound:

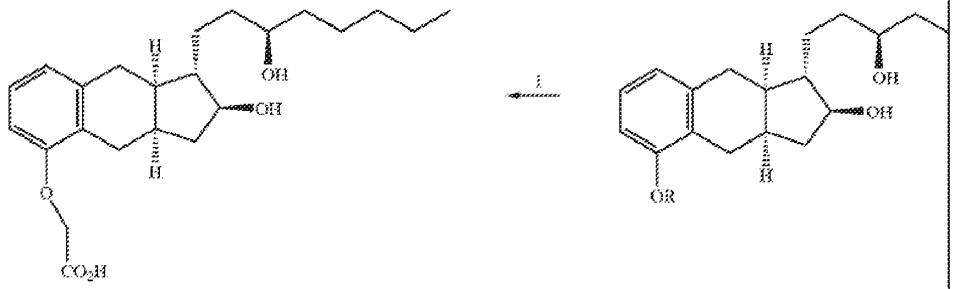


(2) 2-(2-furyl)ethyl, (3) 2-(3-thienyl)ethoxy, or (4) 3-thienyloxymethyl; M_1 is α-OH:β-R_3 or α-R_3:β-OH or α-OR_1:β-R_3 or α-R_3:β-OR_2, wherein R_3 is hydrogen or methyl, R_2 is an alcohol protecting group, and L_1 is α-R_3:β-R_4, α-R_4:β-R_3, or a mixture of α-R_3:β-R_4 and α-R_4:β-R_3, wherein R_3 and R_4 are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R_3 and R_4 is fluoro only when the other is hydrogen or fluoro,	(a) (S)-2-methyl-CBS-oxazaborolidine, BH_3•SMe_2, THF, -30° C., 85%. (b) TBDMSCl, imadazole, CH_2Cl_2, 95%. (c) $Co_2(CO)_8$, CH_2Cl_2, 2 hr. r.t., then CH_3CN, 2 hr. 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, DEAD, TPP, benzene. (i) CH_3OH, KOH, 94%. (j) Pd/C (10%), EtOH, 50 psi/2 hr. quant. (k) Ph_3PLi, THF. (l) i. $ClCH_2CN$, K_2CO_3; ii. KOH, CH_3OH, reflux, 83% (2 steps). (*Id.* at ¶ 0144). The Moriarty synthesis is depicted in Scheme 4, which results in the production of treprostinil free acid, which is depicted as compound 7.  7 (Moriarty JOC article at 1892, 1895). The process disclosed in the Moriarty JOC article includes the step of alkylating the benzindene triol (compound 34) to make the nitrile intermediate (compound 35)

	 (*Id.* at 1895). The above process step is described in the Moriarty JOC article as follows: "[t]riol **34** was alkylated at the phenolic hydroxyl group with use of chloroacetonitrile in refluxing acetone with potassium carbonate (**34** → **35**)…" (*Id.* at 1897).
[Element C] (b) hydrolyzing the product of formula III of step (a) with a base,	The Phares publication discloses a method of making treprostinil involving alkylating benzindene triol to form the nitrile, then hydrolyzing the nitrile with a base (KOH) to obtain the free acid. (Phares publication at ¶¶ 0143-0145). Phares teaches that chemical derivatives of (+)-treprostinil are included within the scope of the invention: 

(+)-treprostinil

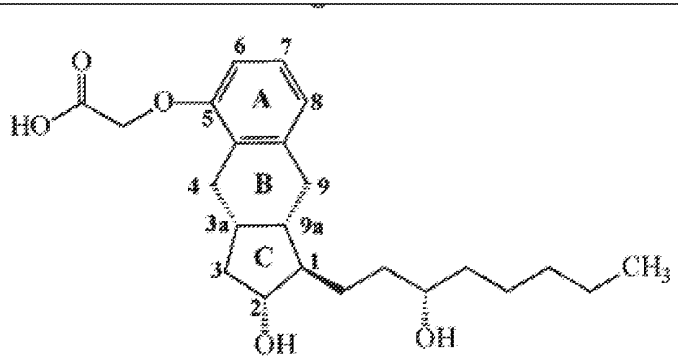
(*Id.* at ¶ 0050). Phares teaches the preparation of (-)-treprostinil but notes that (+)-treprostinil can be prepared in the same manner. (*Id.* at ¶¶ 0143-0145). According to Phares, (-)-treprostinil can be prepared by forming a benzindene nitrile compound which can then be hydrolyzed to the free acid of treprostinil using KOH:



(a) (S)-2-methyl-CBS-oxazaborolidine, BH_3•SMe_2, THF, -30° C., 85%.
(b) TBDMSCl, imadazole, CH_2Cl_2, 95%.
(c) $Co_2(CO)_8$, CH_2Cl_2, 2 hr. r.t., then CH_3CN, 2 hr. 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, DEAD, TPP, benzene.
(i) CH_3OH, KOH, 94%.
(j) Pd/C (10%), EtOH, 50 psi/2 hr. quant.
(k) Ph_3PLi, THF.
(l) i. $ClCH_2CN$, K_2CO_3, ii. KOH, CH_3OH, reflux, 83% (2 steps).

(*Id.* at ¶ 0144).

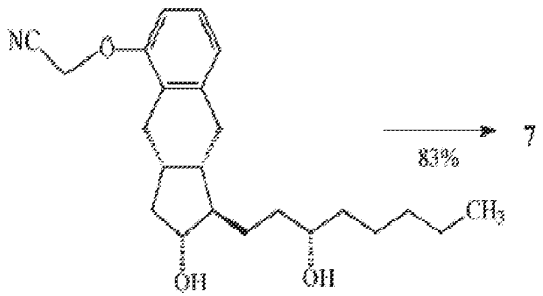
The Moriarty synthesis is depicted in Scheme 4, which results in the production of treprostinil free acid, which is depicted as compound 7.



7

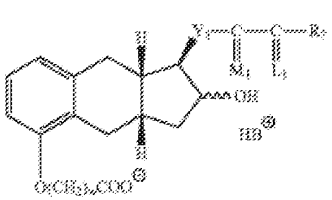
(Moriarty JOC article at 1892, 1895).

The process disclosed in the Moriarty JOC article includes the step of hydrolyzing the nitrile intermediate (compound 35) with a base to form treprostinil free acid:



35

(*Id.* at 1895). The above process step is described in the Moriarty JOC article as

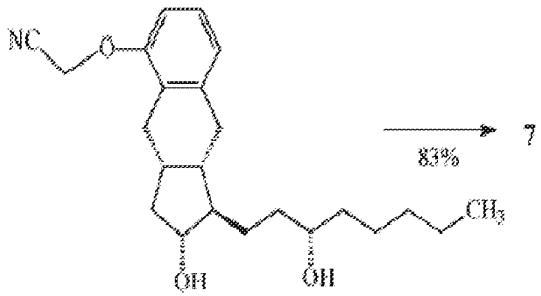
	follows: "…and nitrile **35** was hydrolyzed with ethanolic potassium hydroxide to yield UT-15 (**7**) in 9% overall yield." (*Id.* at 1897). The Moriarty JOC article also includes an experimental section which describes in detail the synthesis of 441 grams of treprostinil acid having a purity of 99.7%. (*Id.* at 1902).
[Element D] (c) contacting the product of step (h) with a base B to form a salt of formula Is. (I$_S$)  and	The Phares publication discloses converting treprostinil free acid into treprostinil diethanolamine salt as follows: > Treprostinil acid acid [*sic*] is dissolved in a 1:1 molar ratio mixture of ethanol:water and diethanolamine is added and dissolved. The solution is heated and acetone is added as an antisolvent during cooling. (Phares publication at ¶ 0105). The Phares Publication also teaches that treprostinil diethanolamine can be recrystallized to yield two crystalline polymorphs, including the metastable polymorph A, and the thermodynamically more stable polymorph B. (*Id.* at ¶ 327). According to Phares, the resulting polymorphs have melting points at 103° C (Form A) and 107° C (Form B), respectively. (*Id.* at ¶¶ 0332, 0337). As explained above with respect to Element [A], the skilled artisan would have been motivated to make treprostinil diethanolamine salt as disclosed in Phares in view of the improved bioavailability profile disclosed in Phares. The starting material for the salt formation step disclosed in Phares is treprostinil free acid, so the skilled artisan would have been motivated to obtain treprostinil free acid in order to make treprostinil diethanolamine as disclosed in Phares. Further, as explained above with respect to Element [A], the skilled artisan would have been motivated to make the treprostinil acid starting material using the method disclosed in Phares, or in the alternative, using the method disclosed in the Moriarty

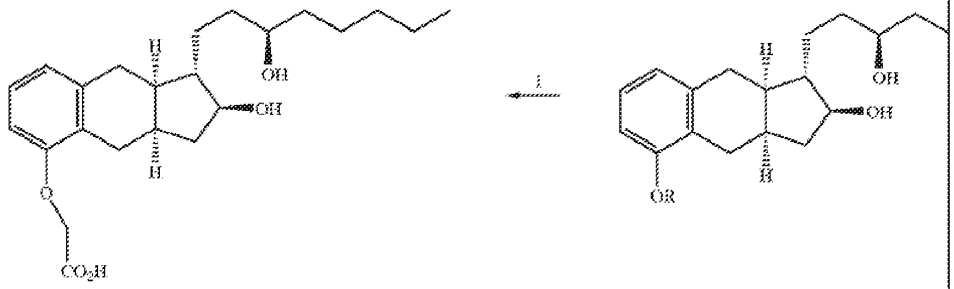
	JOC Article.
[Element E] (d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula I.	

Claim 2	**Prior Art Disclosure**
The product of claim 1, wherein the purity of compound of formula I in said product is at least 99.5%.	*See* Claim 1. As noted above, the Phares Publication teaches that recrystallizing the diethanolamine salt of treprostinil results in the formation of two crystalline polymorphs of treprostinil diethanolamine, Forms A and B. (Phares Publication at ¶ 0327). Although Phares does not indicate the purity of polymorph Form B, Phares notes that the melting point is 107°C and provides an XRPD pattern of Form B in Figure 20. (*Id.* at ¶ 0337). The specification of the ' 393 patent indicates that the treprostinil diethanolamine compound produced according to the claimed procedures yields treprostinil diethanolamine polymorph Form B that has a melting point of at least 104°C. For example, the table provided at Col. 12:60- Col. 13:12 in the '393 patent shows that Batch 2 of treprostinil diethanolamine salt had a melting point of 105.5-107.2°C. Thus, the diethanolamine treprostinil polymorph Form B formed using the procedures taught by Phares is the same as the diethanolamine treprostinil product produced following the steps recited in the claims of the '393 patent. Accordingly, the treprostinil diethanolamine salt of Form B disclose in Phares anticipates claim 2. Further, Phares teaches a method of making treprostinil diethanolamine salt that includes the same steps as the claimed method: alkylating the triol, hydrolyzing the nitrile with a base, and contacting the product with a base (B) to produce treprostinil diethanolamine salt of polymorph form Form B:

	The Phares publication discloses a method of making treprostinil involving alkylating benzindene triol to form the nitrile, then hydrolyzing the nitrile with a base (KOH) to obtain the free acid. (Phares publication at ¶¶ 0143-0145). The Phares publication discloses converting treprostinil free acid into treprostinil diethanolamine salt as follows: > Treprostinil acid acid [*sic*] is dissolved in a 1:1 molar ratio mixture of ethanol:water and diethanolamine is added and dissolved. The solution is heated and acetone is added as an antisolvent during cooling. (Phares publication at ¶ 0105). The Phares Publication also teaches that treprostinil diethanolamine can be recrystallized to yield two crystalline polymorphs, including the metastable polymorph A, and the thermodynamically more stable polymorph B. (*Id.* at ¶ 327). According to Phares, the resulting polymorphs have melting points at 103° C (Form A) and 107° C (Form B), respectively. (*Id.* at ¶¶ 0332, 0337). Thus, because the Phares publication discloses using the same process as that claimed to make the same product (treprostinil diethanolamine salt), then the product obtained through the method disclosed in Phares inherently has the claimed purity profile. Also, the skilled artisan would have been motivated to obtain a sample of treprostinil having a high level of purity. The Moriarty JOC Article includes an experimental section which describes in detail the synthesis of 441 grams of treprostinil acid having a purity of 99.7%. (*Id.* at 1902). It is well-known in the art that a salt formation step can be used as a purification step. Given that the treprostinil free acid obtained in the Moriarty JOC Article has a purity

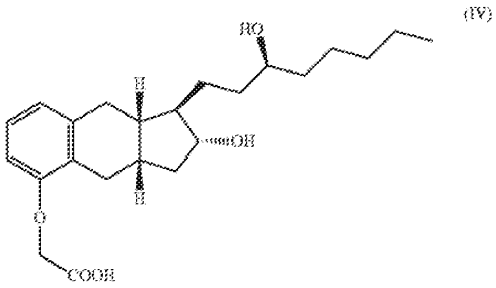
	level of 99.7%, the skilled artisan would expect that the treprostinil diethanolamine salt produced through the process in the Phares Publication would have a purity level comparable to or greater than the starting material. Accordingly, the skilled artisan would have a reasonable expectation of success in obtaining a batch of treprostinil diethanolamine salt having a purity level of at least 99.5% when performing the salt formation step disclosed in the Phares Publication using the treprostinil free acid disclosed in the Moriarty JOC Article as a starting material. Moreover, it would have been obvious for the skilled artisan to purify the treprostinil disclosed in the Phares Publication to a purity level of 99.5% or greater, particularly in view of the disclosure in the Moriarty JOC Article of treprostinil having a purity level of 99.7%. Also, purification techniques are common practice in the chemical arts. Accordingly, claim 2 would have been obvious.

Claim 4	**Prior Art Disclosure**
The product of claim 1, wherein the base in step (b) is KOH or NaOH.	*See* Claim 1. The process disclosed in the Moriarty JOC article includes the step of hydrolyzing the nitrile intermediate (compound 35) with a base to form treprostinil free acid:  35

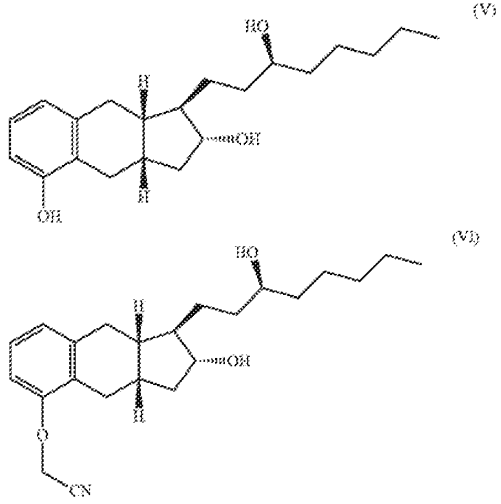
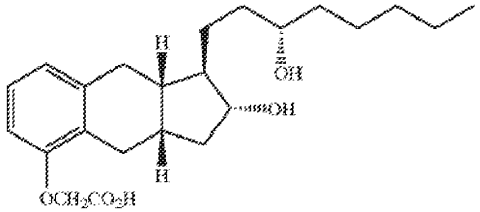
	(*Id.* at 1895). The above process step is described in the Moriarty JOC article as follows: "…and nitrile **35** was hydrolyzed with ethanolic potassium hydroxide to yield UT-15 (**7**) in 9% overall yield." (*Id.* at 1897). According to Phares, (-)-treprostinil can be prepared by forming a benzindene nitrile compound which can then be hydrolyzed to the free acid of treprostinil using KOH:  (a) (S)-2-methyl-CBS-oxazaborolidine, BH_3•SMe_2, THF, -30° C., 85%. (b) TBDMSCl, imadazole, CH_2Cl_2, 95%. (c) $Co_2(CO)_8$, CH_2Cl_2, 2 hr. r.t., then CH_3CN, 2 hr. 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-nitrobenzeic acid, DEAD, TPP, benzene. (i) CH_3OH, KOH, 94%. (j) Pd/C (10%), EtOH, 50 psi/2 hr, quant. (k) Ph_3PLi, THF. (l) i. $ClCH_2CN$, K_2CO_3, ii. KOH, CH_3OH, reflux, 83% (2 steps). (*Id.* at ¶ 0144).

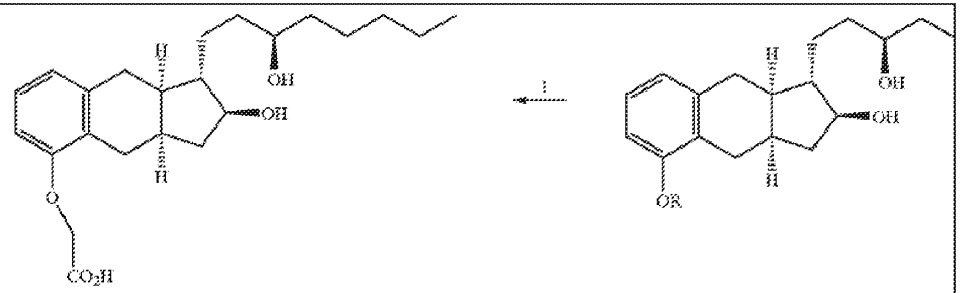
Claim 8	Prior Art Disclosure
The product of claim 1, wherein the process	*See* Claim 1.

does not include purifying the compound of formula (III) produced in step (a).	In general, there is a motivation in the art to optimize the efficiency of reaction processes. Further, a person of ordinary skill in the art would have been motivated to avoid the "drawbacks" of column chromatography, which is a "labor-intensive" process that is used generally as a last resort. (Anderson, N. "*Practical Process Research & Development: A Guide for Organic Chemists*" at pp. 13, 223, 226 (2000) ("Anderson"). Anderson also discloses that in general, the practice of "telescoping," which is of carrying the product of a reaction without isolation into the next step, can greatly increase overall yields and is usually incorporated as part of a cost-effective route unless significant benefits are obtained from isolation of the intermediate. Accordingly, here, the skilled artisan would have been motivated to carry the product of step (a) through without isolation or purification with the goal of obtaining a pure final product after step (c) following crystallization of the diethanolamine salt.

Claim 9	**Prior Art Disclosure**
[Element A] A product comprising a compound having formula IV 	To the extent that the Asserted Claims are not anticipated by Phares, then the Asserted Claims are invalid as obvious in view of Phares, alone or in combination with the Moriarty JOC Article. Because the Asserted Claims are product-by-process claims, it is not necessary to consider the claimed method steps as part of an invalidity analysis. However, to the extent that the claimed process steps are material to validity, which they are not, the Asserted Claims are invalid because the prior art discloses a process of making treprostinil diethanolamine salt using the claimed process steps. The Phares Publication discloses that "treprostinil sodium (Remodulin®) is approved by the Food and Drug Administration (FDA) for subcutaneous administration" and that "treprostinil as the free acid has an absolute oral bioavailability of less than 10%." (*Id.* at ¶ 0004). The purpose of the invention was to serve the "clinical interest in providing treprostinil orally," and "increasing systemic availability of

or a pharmaceutically acceptable salt thereof, wherein the product is prepared by the process comprising	treprostinil via administration of treprostinil or treprostinil analogs." (Id. at ¶ 0004-0005). The Phares Publication further provides that "[a] preferred embodiment of the present invention is the diethanolamine salt of treprostinil." (*Id.* at ¶ 0051). Phares discloses animal testing involving administration of treprostinil diethanolamine to rats in Example 1 and clinical trials using treprostinil diethanolamine salt formulations in Example 5. (Phares Publication at ¶¶ 0203-0237, 0311-0326). Pharmacokinetic testing of an oral formulation of treprostinil diethanolamine in human patients showed an absolute bioavailability of 21-25% for the four doses tested. (*Id.* at ¶ 0319). The skilled artisan would have been motivated to make treprostinil diethanolamine salt as disclosed in Phares in view of the improved bioavailability profile disclosed in Phares. The starting material for the salt formation step disclosed in Phares is treprostinil free acid, so the skilled artisan would have been motivated to obtain treprostinil free acid in order to make treprostinil diethanolamine as disclosed in Phares. Because the skilled artisan would have been motivated to make treprostinil acid to use in the diethanolamine salt formation step, the skilled artisan would have been further motivated to use the process described in Phares to make treprostinil free acid that could be used as the starting material in the salt formation step. In the alternative, the skilled artisan would have been motivated to make treprostinil free acid using the process described in the Moriarty JOC Article and then use the treprostinil free acid as the starting material in the salt formation step. First, the Moriarty JOC Article discloses that the synthesis process described therein is efficient, economical, and superior to methods disclosed in the prior art. Second, the Moriarty JOC Article discloses that the process disclosed therein produces treprostinil free acid having a purity of 99.7%. There is a general desire in the art to obtain drug substance samples having a high purity level through processes that are efficient and economical, so the skilled artisan would have been motivated to use the 99.7% pure sample of treprostinil produced as disclosed in the Moriarty JOC Article as the starting material in the treprostinil diethanolamine formation step disclosed in

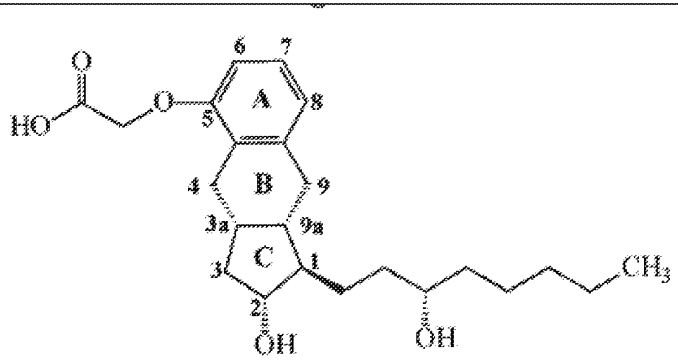
	the Phares Publication.
[Element B] (a) alkylating a compound of formula V with an alkylating agent to produce a compound of formula VI, 	The Phares publication discloses a method of making treprostinil involving alkylating benzindene triol to form the nitrile, then hydrolyzing the nitrile with a base (KOH) to obtain the free acid. (Phares publication at ¶¶ 0143-0145). Phares teaches that chemical derivatives of (+)-treprostinil are included within the scope of the invention:  **(+)-treprostinil** (*Id.* at ¶ 0050). Phares teaches the preparation of (-)-treprostinil but notes that (+)-treprostinil can be prepared in the same manner. (*Id.* at ¶¶ 0143-0145). According to Phares, (-)-treprostinil can be prepared by alkylating the benzindene triol compound shown below (note R= H) with chloroacetonitrile to form a benzindene nitrile compound:



(a) (S)-2-methyl-CBS-oxazaborolidine, BH_3•SMe_2, THF, -30° C., 85%.
(b) TBDMSCl, imadazole, CH_2Cl_2, 95%.
(c) $Co_2(CO)_8$, CH_2Cl_2, 2 hr. r.t., then CH_3CN, 2 hr. 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, DEAD, TPP, benzene.
(i) CH_3OH, KOH, 94%.
(j) Pd/C (10%), EtOH, 50 psi/2 hr. quant.
(k) Ph_3P.I, THF.
(l) i. $ClCH_2CN$, K_2CO_3, ii, KOH, CH_3OH, reflux, 83% (2 steps).

(*Id.* at ¶ 0144).

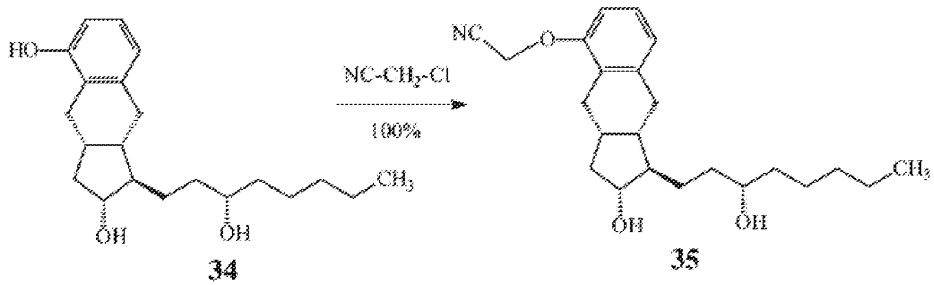
The Moriarty synthesis is depicted in Scheme 4, which results in the production of treprostinil free acid, which is depicted as compound 7.



7

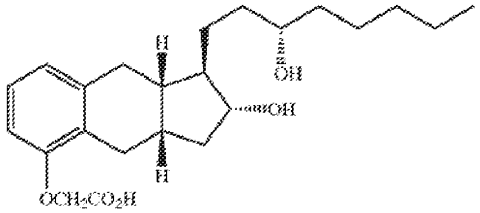
(Moriarty JOC article at 1892, 1895).

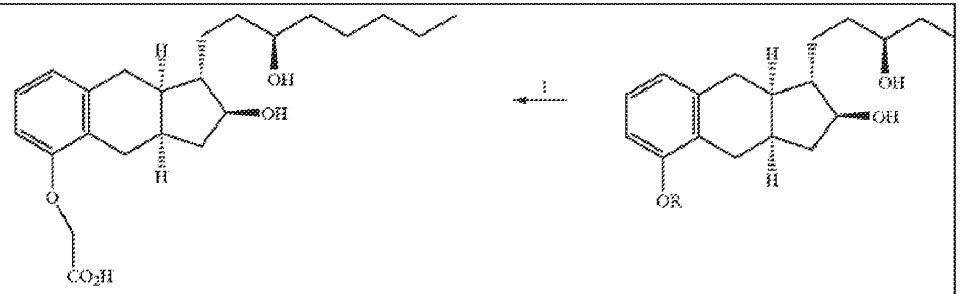
The process disclosed in the Moriarty JOC article includes the step of alkylating the benzindene triol (compound 34) to make the nitrile intermediate (compound 35)



34 35

(*Id.* at 1895).

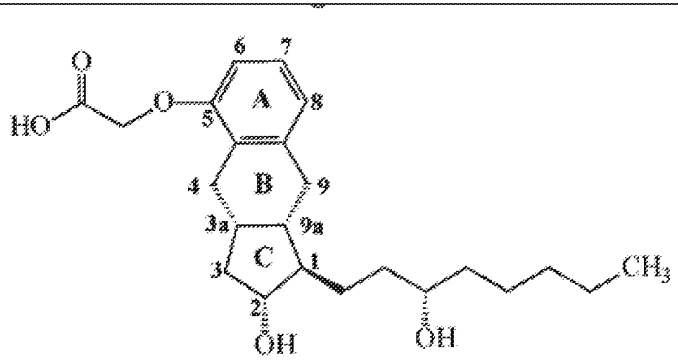
	The above process step is described in the Moriarty JOC article as follows: "[t]riol **34** was alkylated at the phenolic hydroxyl group with use of chloroacetonitrile in refluxing acetone with potassium carbonate (**34** → **35**)…" (*Id.* at 1897).
[Element C] (b) hydrolyzing the product of formula VI of step (a) with a base,	The Phares publication discloses a method of making treprostinil involving alkylating benzindene triol to form the nitrile, then hydrolyzing the nitrile with a base (KOH) to obtain the free acid. (Phares publication at ¶¶ 0143-0145). Phares teaches that chemical derivatives of (+)-treprostinil are included within the scope of the invention:  **(+)-treprostinil** (*Id.* at ¶ 0050). Phares teaches the preparation of (-)-treprostinil but notes that (+)-treprostinil can be prepared in the same manner. (*Id.* at ¶¶ 0143-0145). According to Phares, (-)-treprostinil can be prepared by forming a benzindene nitrile compound which can then be hydrolyzed to the free acid of treprostinil using KOH:



(a) (S)-2-methyl-CBS-oxazaborolidine, BH_3•SMe_2, THF, -30° C., 85%.
(b) TBDMSCl, imadazole, CH_2Cl_2, 95%.
(c) $Co_2(CO)_8$, CH_2Cl_2, 2 hr. r.t., then CH_3CN, 2 hr. 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, DEAD, TPP, benzene.
(i) CH_3OH, KOH, 94%.
(j) Pd/C (10%), EtOH, 50 psi/2 hr. quant.
(k) Ph_3P.I, THF.
(l) i. $ClCH_2CN$, K_2CO_3, ii, KOH, CH_3OH, reflux, 83% (2 steps).

(*Id.* at ¶ 0144).

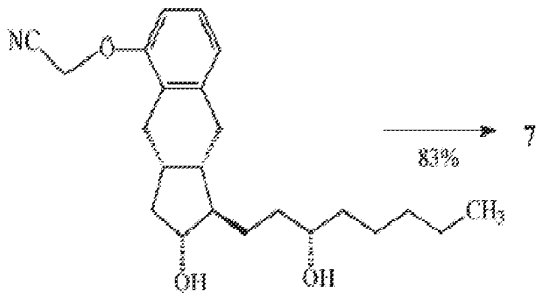
The Moriarty synthesis is depicted in Scheme 4, which results in the production of treprostinil free acid, which is depicted as compound 7.



7

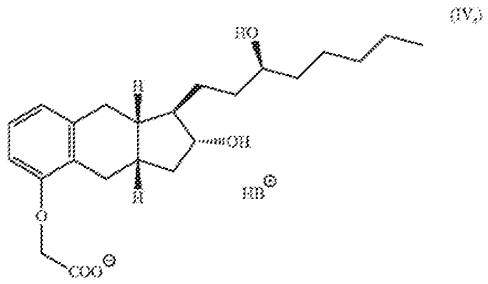
(Moriarty JOC article at 1892, 1895).

The process disclosed in the Moriarty JOC article includes the step of hydrolyzing the nitrile intermediate (compound 35) with a base to form treprostinil free acid:



35

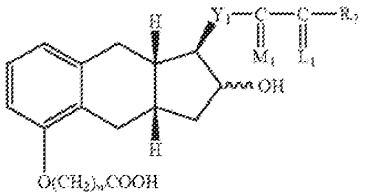
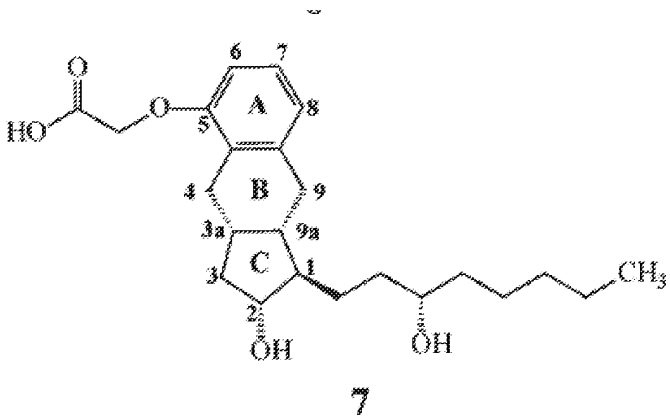
(*Id.* at 1895). The above process step is described in the Moriarty JOC article as

	follows: "…and nitrile **35** was hydrolyzed with ethanolic potassium hydroxide to yield UT-15 (**7**) in 9% overall yield." (*Id.* at 1897). The Moriarty JOC article also includes an experimental section which describes in detail the synthesis of 441 grams of treprostinil acid having a purity of 99.7%. (*Id.* at 1902).
[Element D] (c) contacting the product of step (h) with a base B to form a salt of formula IVs, and 	The Phares publication discloses converting treprostinil free acid into treprostinil diethanolamine salt as follows: > Treprostinil acid acid [*sic*] is dissolved in a 1:1 molar ratio mixture of ethanol:water and diethanolamine is added and dissolved. The solution is heated and acetone is added as an antisolvent during cooling. (Phares publication at ¶ 0105). The Phares Publication also teaches that treprostinil diethanolamine can be recrystallized to yield two crystalline polymorphs, including the metastable polymorph A, and the thermodynamically more stable polymorph B. (*Id.* at ¶ 327). According to Phares, the resulting polymorphs have melting points at 103° C (Form A) and 107° C (Form B), respectively. (*Id.* at ¶¶ 0332, 0337). As explained above with respect to Element [A], the skilled artisan would have been motivated to make treprostinil diethanolamine salt as disclosed in Phares in view of the improved bioavailability profile disclosed in Phares. The starting material for the salt formation step disclosed in Phares is treprostinil free acid, so the skilled artisan would have been motivated to obtain treprostinil free acid in order to make treprostinil diethanolamine as disclosed in Phares. Further, as explained above with respect to Element [A], the skilled artisan would have been motivated to make the treprostinil acid starting material using the method disclosed in Phares, or in the alternative, using the method disclosed in the Moriarty

	JOC Article.
[Element E] (d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula IV.	

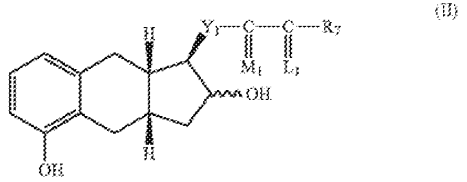
Claim 16	**Prior Art Disclosure**
The product of claim 9, wherein the process does not include purifying the compound of formula (VI) produced in step (a).	*See* Claim 9. In general, there is a motivation in the art to optimize the efficiency of reaction processes. Further, a person of ordinary skill in the art would have been motivated to avoid the "drawbacks" of column chromatography, which is a "labor-intensive" process that is used generally as a last resort. (Anderson, N. "*Practical Process Research & Development: A Guide for Organic Chemists*" at pp. 13, 223, 226 (2000) ("Anderson"). Anderson also discloses that in general, the practice of "telescoping," which is of carrying the product of a reaction without isolation into the next step, can greatly increase overall yields and is usually incorporated as part of a cost-effective route unless significant benefits are obtained from isolation of the intermediate. (Anderson at p. 34). Accordingly, here, the skilled artisan would have been motivated to carry the product of step (a) through without isolation or purification with the goal of obtaining a pure final product after step (c) following crystallization of the diethanolamine salt.

C. The Asserted Claims Are Obvious Over The Moriarty JOC Article In View Of Phares And Anderson

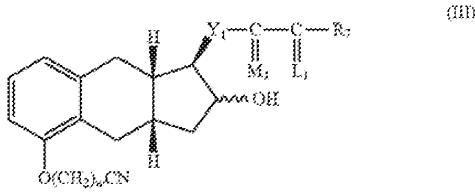
Claim 1	Prior Art Disclosure
[Element A] A product comprising a compound of formula I:  or a pharmaceutically acceptable salt thereof, wherein said product is prepared by a process comprising	The Moriarty synthesis is depicted in Scheme 4, which results in the production of treprostinil free acid, which is depicted as compound 7.  7 (Moriarty JOC article at 1892, 1895). As discussed above, both the JOC Article and the Phares Publication describe a process for preparing treprostinil that involve alkylation of benzindene triol followed by hydrolysis with a base, and thereby satisfy claimed process steps (a) and (b). The process disclosed in the Moriarty JOC Article involves purification of the benzindene triol intermediate, the benzindene nitrile intermediate, and treprostinil free acid. In particular, the JOC Article further discloses that the benzindene triol intermediate is obtained having a purity of 99.5% following crystallization. (Moriarty JOC Article at pp. 1901-2). Then, following the alkylation step, the benzindene nitrile intermediate is purified through column chromatography. (Moriarty JOC Article at p.

	1902). Treprostinil free acid is then purified through recrystallization to obtain a product that is 99.7% pure. (*Id.*). Anderson explains that a person of ordinary skill in the art would have been motivated to avoid the "drawbacks" of column chromatography, which is a "labor-intensive" process that is used generally as a last resort. (Anderson at pp. 13, 223, and 226). Instead, Anderson teaches that better results are obtained using salt formation and recrystallization techniques. (*Id.*). Further, Anderson teaches that "[s]alt formation may be key for efficient purification of ionizable compounds." (*Id.* at p. 238). Anderson further discloses that "[v]arious salts can display different solubilities and tendencies to crystallize and might possess physicochemical differences that can be exploited for convenient processing on scale. Salt forms of drug candidates are selected for desired stability, bioavailability, and formulation characteristics." (*Id.*). Anderson also discloses that in general, the practice of "telescoping," which is of carrying the product of a reaction without isolation into the next step, can greatly increase overall yields and is usually incorporated as part of a cost-effective route unless significant benefits are obtained from isolation of the intermediate. (Anderson at p. 34). Chapter 3 of Anderson, entitled "Reagent Selection" includes descriptions of "families" of reagents useful for scale-up. (Anderson at p. 61). Amine bases are discussed as one category of reagents for deprotonation. (*Id.* at pp. 61, 63). Diethanolamine is listed in Table 3.7 on page 64 as one of the "Amines Useful for Scale-Up." (*Id.* at p. 64). Anderson further explains that "[t]he solubility of acid salts of the amines (Table 3.7) can provide some operating advantages on scale." (*Id.* at p. 66). The skilled artisan would thus have been motivated to improve the Moriarty JOC method by removing the column chromatography step following producing of the nitrile intermediate. In order to obtain a comparable level of purity in the final treprostinil product, the skilled artisan would have been motivated to replace the final

	crystallization step disclosed in the Moriarty JOC Article with a salt formation step. The skilled artisan would further have been motivated to use the salt formation step disclosed in the Phares publication, which involves formation of treprostinil diethanolamine salt, because the use of an amine salt would be expected to provide an improved impurity profile. In particular, the skilled artisan would have been motivated to replace the final recrystallization step in Moriarty with a salt formation step in the hopes of obtaining a better impurity profile. The skilled artisan would understand, as is discussed in Anderson, that basic amines can be used to form salts with acidic compounds, and that diethanolamine is a particularly useful amine for scale-up purposes. The skilled artisan would also be aware of the disclosure of the sodium and potassium salts of treprostinil the prior art. In seeking a new salt of treprostinil, the skilled artisan would review the Phares reference, which discloses various salts and pro-drugs of treprostinil. Upon review of Phares, the skilled artisan would learn that treprostinil diethanolamine was a particularly preferred salt that was amenable to crystallization in a variety of conditions and produced a stable polymorph. Accordingly, the skilled artisan would be motivated to substitute the salt formation step in Phares for the final recrystallization step in Moriarty in an attempt to further improve the purity profile of the treprostinil compound obtained after removing the chromatography step following the nitrile formation step. Accordingly, the skilled artisan would have been motivated to improve the process disclosed in the Moriarty JOC Article by using the salt formation step disclosed in Phares as a purification step and would thereby obtain a pharmaceutically acceptable salt of treprostinil using the claimed method.
[Element B] (a) alkylating a compound of structure II with an alkylating agent to produce a compound of formula III,	The process disclosed in the Moriarty JOC article includes the step of alkylating the benzindene triol (compound 34) to make the nitrile intermediate (compound 35)

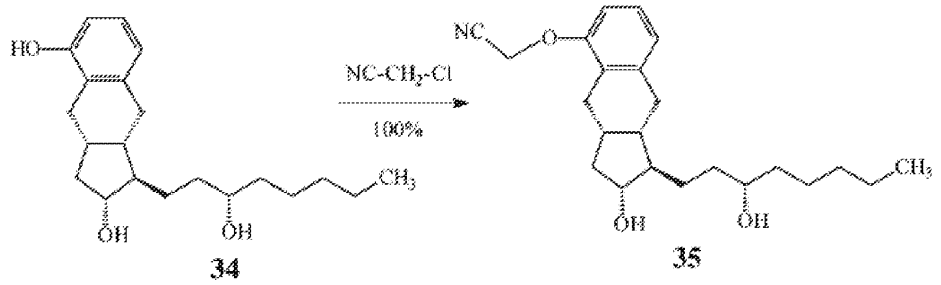


(II)



(III)

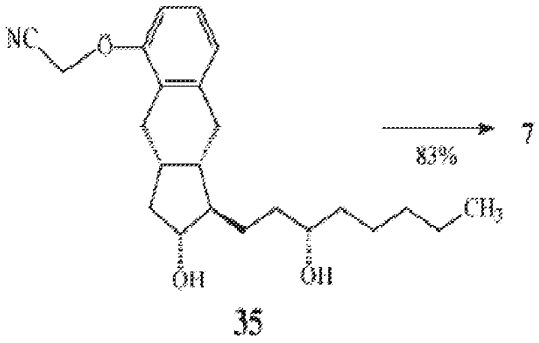
wherein
w=1, 2, or 3;
Y_1 is trans-CH=CH—, cis-CH=CH—, —$CH_2(CH_2)_m$—, or —C≡C—; m is 1, 2, or 3;
R_7 is
(1) —C_pH_{2p}—CH_3, wherein p is an integer from 1 to 5, inclusive,
(2) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3) alkyl, or (C_1-C_3) alkoxy, with the proviso that not more than two substituents are other than alkyl, with the proviso that R_7 is phenoxy or substituted phenoxy, only when R_3 and R_4 are hydrogen or methyl, being the same or different,
(3) phenyl, benzyl, phenylethyl, or phenylpropyl optionally substituted on the aromatic ring by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3)alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl,
(4) cis-CH=CH—CH_2—CH_3,
(5) —$(CH_2)_2$—CH(OH)—CH_3, or
(6) —$(CH_2)_2$—CH=C$(CH_3)_2$;
—$C(L_1)$—R_7 taken together is
(1) (C_4-C_7)cycloalkyl optionally substituted by 1 to 3 (C_1-C_3) alkyl;

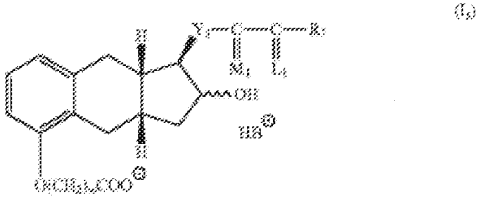


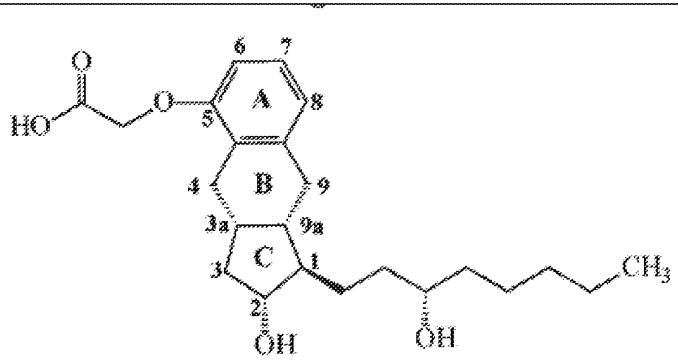
34 **35**

(*Id.* at 1895).

The above process step is described in the Moriarty JOC article as follows: "[t]riol **34** was alkylated at the phenolic hydroxyl group with use of chloroacetonitrile in refluxing acetone with potassium carbonate (**34** → **35**)…" (*Id.* at 1897).

(2) 2-(2-furyl)ethyl, (3) 2-(3-thienyl)ethoxy, or (4) 3-thienyloxymethyl; M_1 is α-OH:β-R_3 or α-R_3:β-OH or α-OR_1:β-R_3 or α-R_3:β-OR_2, wherein R_3 is hydrogen or methyl, R_2 is an alcohol protecting group, and L_1 is α-R_3:β-R_4, α-R_4:β-R_3, or a mixture of α-R_3:β-R_4 and α-R_4:β-R_3, wherein R_3 and R_4 are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R_3 and R_4 is fluoro only when the other is hydrogen or fluoro,	
[Element C] (b) hydrolyzing the product of formula III of step (a) with a base,	The process disclosed in the Moriarty JOC article includes the step of hydrolyzing the nitrile intermediate (compound 35) with a base to form treprostinil free acid:  35 (*Id.* at 1895). The above process step is described in the Moriarty JOC article as follows: "…and nitrile **35** was hydrolyzed with ethanolic potassium hydroxide to yield UT-15 (**7**) in 9% overall yield." (*Id.* at 1897). The Moriarty JOC article also includes an experimental section which describes in detail the synthesis of 441 grams of treprostinil acid having a purity of 99.7%. (*Id.* at

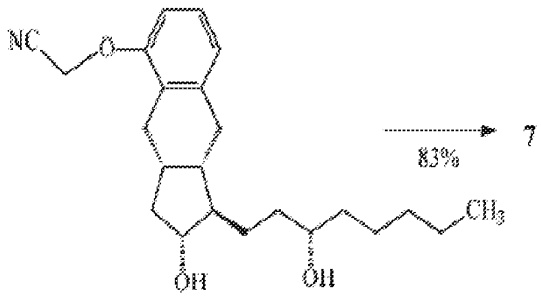
	1902).
[Element D] (c) contacting the product of step (h) with a base B to form a salt of formula Is.  and	The Phares publication discloses converting treprostinil free acid into treprostinil diethanolamine salt as follows: > Treprostinil acid acid [*sic*] is dissolved in a 1:1 molar ratio mixture of ethanol:water and diethanolamine is added and dissolved. The solution is heated and acetone is added as an antisolvent during cooling. (Phares publication at ¶ 0105). The Phares Publication also teaches that treprostinil diethanolamine can be recrystallized to yield two crystalline polymorphs, including the metastable polymorph A, and the thermodynamically more stable polymorph B. (*Id.* at ¶ 327). According to Phares, the resulting polymorphs have melting points at 103° C (Form A) and 107° C (Form B), respectively. (*Id.* at ¶¶ 0332, 0337).
[Element E] (d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula I.	In the experimental section, the Moriarty JOC article further discloses that the hydrolysis step involved adding a solution of potassium hydroxide to a solution of nitrile in methanol and then refluxing the mixture for three hours, after which point the reaction mixture was cooled to 0°C. (Moriarty JOC Article at p. 1902). Then, hydrochloric acid was added to adjust the pH to 10-12, and the solvent was removed in vacuo, at which point the solution was extracted with ethyl acetate. (*Id.*). The aqueous layer was retained and acidified to pH 2-3 by addition of hydrochloric acid. (*Id.*). The Moriarty synthesis is depicted in Scheme 4, which results in the production of treprostinil free acid, which is depicted as compound 7.

	 7 (Moriarty JOC article at 1892, 1895).

Claim 2	Prior Art Disclosure
The product of claim 1, wherein the purity of compound of formula I in said product is at least 99.5%.	*See* Claim 1. As noted above, the Phares Publication teaches that recrystallizing the diethanolamine salt of treprostinil results in the formation of two crystalline polymorphs of treprostinil diethanolamine, Forms A and B. (Phares Publication at ¶ 0327). Although Phares does not indicate the purity of polymorph Form B, Phares notes that the melting point is 107°C and provides an XRPD pattern of Form B in Figure 20. (*Id.* at ¶ 0337). The specification of the ' 393 patent indicates that the treprostinil diethanolamine compound produced according to the claimed procedures yields treprostinil diethanolamine polymorph Form B that has a melting point of at least 104°C. For example, the table provided at Col. 12:60- Col. 13:12 in the '393

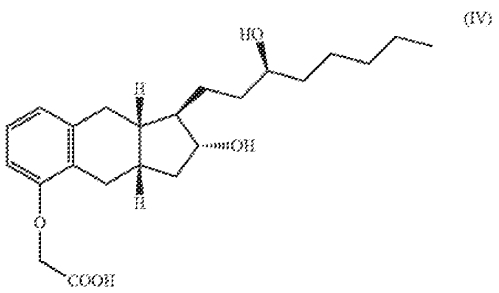
	patent shows that Batch 2 of treprostinil diethanolamine salt had a melting point of 105.5-107.2°C. Thus, the diethanolamine treprostinil polymorph Form B formed using the procedures taught by Phares is the same as the diethanolamine treprostinil product produced following the steps recited in the claims of the '393 patent. Accordingly, the treprostinil diethanolamine salt of Form B disclose in Phares anticipates claim 2. Also, the skilled artisan would have been motivated to obtain a sample of treprostinil having a high level of purity. The Moriarty JOC Article includes an experimental section which describes in detail the synthesis of 441 grams of treprostinil acid having a purity of 99.7%. (*Id.* at 1902). Given that the treprostinil free acid obtained in the Moriarty JOC Article has a purity level of 99.7%, the skilled artisan would expect that the treprostinil diethanolamine salt produced through the process in the Phares Publication would have a purity level comparable to or greater than the starting material. Accordingly, the skilled artisan would have a reasonable expectation of success in obtaining a batch of treprostinil diethanolamine salt having a purity level of at least 99.5% when performing the salt formation step disclosed in the Phares Publication using the treprostinil free acid disclosed in the Moriarty JOC Article as a starting material. Moreover, it would have been obvious for the skilled artisan to purify the treprostinil disclosed in the Phares Publication to a purity level of 99.5% or greater, particularly in view of the disclosure in the Moriarty JOC Article of treprostinil having a purity level of 99.7%. Also, purification techniques are common practice in the chemical arts. Accordingly, claim 2 would have been obvious.

Claim 4	**Prior Art Disclosure**
The product of claim 1, wherein the base in step (b) is KOH or NaOH.	*See* Claim 1.

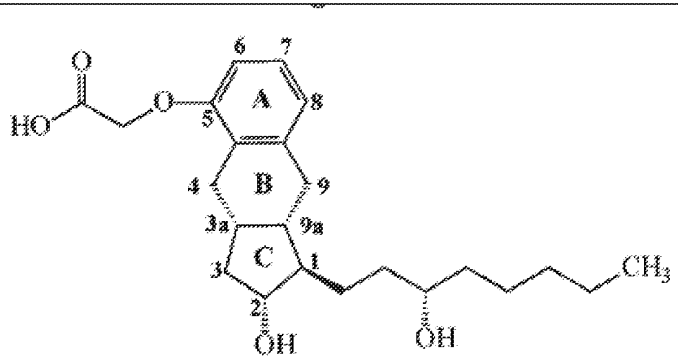
	The process disclosed in the Moriarty JOC article includes the step of hydrolyzing the nitrile intermediate (compound 35) with a base to form treprostinil free acid:  35 (*Id.* at 1895). The above process step is described in the Moriarty JOC article as follows: "…and nitrile **35** was hydrolyzed with ethanolic potassium hydroxide to yield UT-15 (**7**) in 9% overall yield." (*Id.* at 1897).

Claim 8	**Prior Art Disclosure**
The product of claim 1, wherein the process does not include purifying the compound of formula (III) produced in step (a).	*See* Claim 1.

Claim 9	**Prior Art Disclosure**
[Element A] A product comprising a compound having formula IV	The Moriarty synthesis is depicted in Scheme 4, which results in the production of treprostinil free acid, which is depicted as compound 7.



or a pharmaceutically acceptable salt thereof, wherein the product is prepared by the process comprising



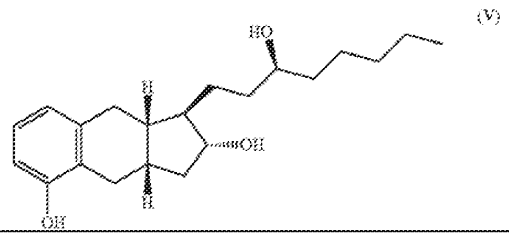
7

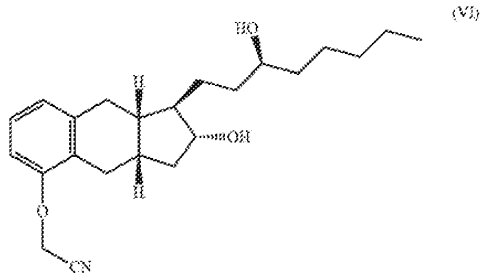
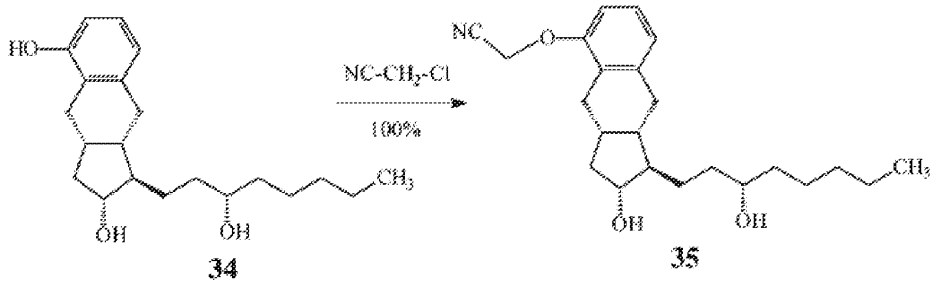
(Moriarty JOC article at 1892, 1895).

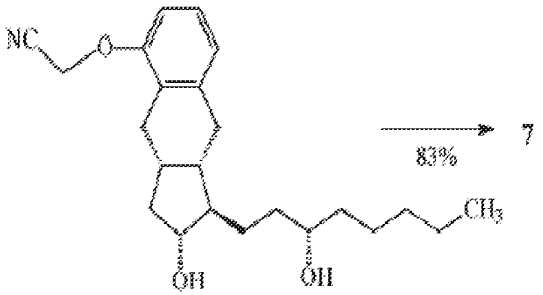
As discussed above, both the JOC Article and the Phares Publication describe a process for preparing treprostinil that involve alkylation of benzindene triol followed by hydrolysis with a base, and thereby satisfy claimed process steps (a) and (b). The process disclosed in the Moriarty JOC Article involves purification of the benzindene triol intermediate, the benzindene nitrile intermediate, and treprostinil free acid. In particular, the JOC Article further discloses that the benzindene triol intermediate is obtained having a purity of 99.5% following crystallization. (Moriarty JOC Article at pp. 1901-2). Then, following the alkylation step, the benzindene nitrile intermediate is purified through column chromatography. (Moriarty JOC Article at p. 1902). Treprostinil free acid is then purified through recrystallization to obtain a product that is 99.7% pure. (*Id.*).

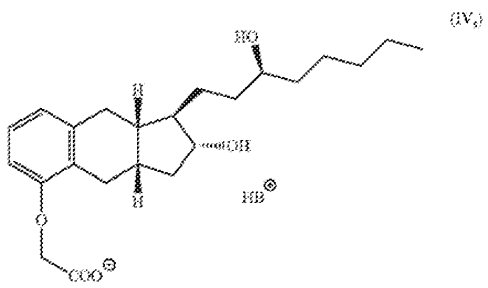
Anderson explains that a person of ordinary skill in the art would have been motivated to avoid the "drawbacks" of column chromatography, which is a "labor-intensive" process that is used generally as a last resort. (Anderson at pp. 13, 223, and 226). Instead, Anderson teaches that better results are obtained using salt formation and recrystallization techniques. (*Id.*). Further, Anderson teaches that

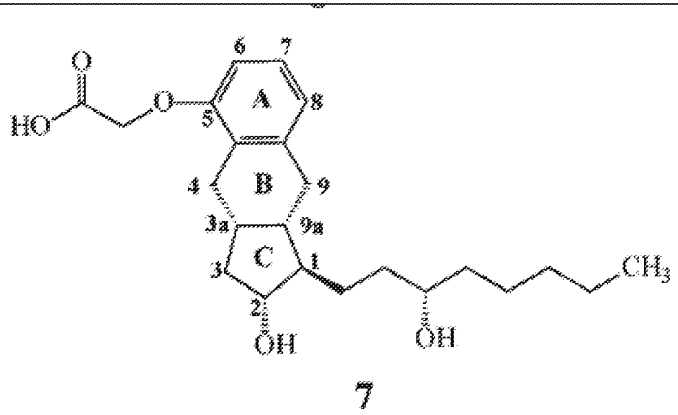
	"[s]alt formation may be key for efficient purification of ionizable compounds." (*Id.* at p. 238). Anderson further discloses that "[v]arious salts can display different solubilities and tendencies to crystallize and might possess physicochemical differences that can be exploited for convenient processing on scale. Salt forms of drug candidates are selected for desired stability, bioavailability, and formulation characteristics." (*Id.*). Anderson also discloses that in general, the practice of "telescoping," which is of carrying the product of a reaction without isolation into the next step, can greatly increase overall yields and is usually incorporated as part of a cost-effective route unless significant benefits are obtained from isolation of the intermediate. (Anderson at p. 34). Chapter 3 of Anderson, entitled "Reagent Selection" includes descriptions of "families" of reagents useful for scale-up. (Anderson at p. 61). Amine bases are discussed as one category of reagents for deprotonation. (*Id.* at pp. 61, 63). Diethanolamine is listed in Table 3.7 on page 64 as one of the "Amines Useful for Scale-Up." (*Id.* at p. 64). Anderson further explains that "[t]he solubility of acid salts of the amines (Table 3.7) can provide some operating advantages on scale." (*Id.* at p. 66). The skilled artisan would thus have been motivated to improve the Moriarty JOC method by removing the column chromatography step following producing of the nitrile intermediate. In order to obtain a comparable level of purity in the final treprostinil product, the skilled artisan would have been motivated to replace the final crystallization step disclosed in the Moriarty JOC Article with a salt formation step. The skilled artisan would further have been motivated to use the salt formation step disclosed in the Phares publication, which involves formation of treprostinil diethanolamine salt, because the use of an amine salt would be expected to provide an improved impurity profile. In particular, the skilled artisan would have been motivated to replace the final recrystallization step in Moriarty with a salt formation step in the hopes of obtaining

	a better impurity profile. The skilled artisan would understand, as is discussed in Anderson, that basic amines can be used to form salts with acidic compounds, and that diethanolamine is a particularly useful amine for scale-up purposes. The skilled artisan would also be aware of the disclosure of the sodium and potassium salts of treprostinil the prior art. In seeking a new salt of treprostinil, the skilled artisan would review the Phares reference, which discloses various salts and pro-drugs of treprostinil. Upon review of Phares, the skilled artisan would learn that treprostinil diethanolamine was a particularly preferred salt that was amenable to crystallization in a variety of conditions and produced a stable polymorph. Accordingly, the skilled artisan would be motivated to substitute the salt formation step in Phares for the final recrystallization step in Moriarty in an attempt to further improve the purity profile of the treprostinil compound obtained after removing the chromatography step following the nitrile formation step. Accordingly, the skilled artisan would have been motivated to improve the process disclosed in the Moriarty JOC Article by using the salt formation step disclosed in Phares as a purification step and would thereby obtain a pharmaceutically acceptable salt of treprostinil using the claimed method.
[Element B] (a) alkylating a compound of formula V with an alkylating agent to produce a compound of formula VI, 	The process disclosed in the Moriarty JOC article includes the step of alkylating the benzindene triol (compound 34) to make the nitrile intermediate (compound 35)

	 34 35 (*Id.* at 1895). The above process step is described in the Moriarty JOC article as follows: "[t]riol **34** was alkylated at the phenolic hydroxyl group with use of chloroacetonitrile in refluxing acetone with potassium carbonate (**34** → **35**)…" (*Id.* at 1897).
[Element C] (b) hydrolyzing the product of formula VI of step (a) with a base,	The process disclosed in the Moriarty JOC article includes the step of hydrolyzing the nitrile intermediate (compound 35) with a base to form treprostinil free acid.

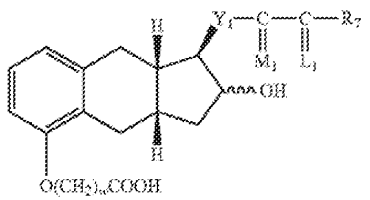
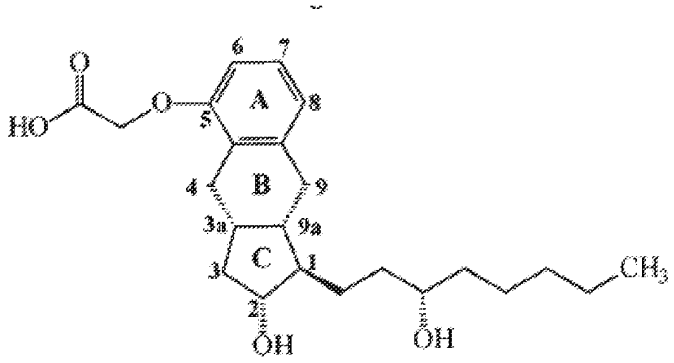
	 35 (*Id.* at 1895). The above process step is described in the Moriarty JOC article as follows: "…and nitrile **35** was hydrolyzed with ethanolic potassium hydroxide to yield UT-15 (**7**) in 9% overall yield." (*Id.* at 1897). The Moriarty JOC article also includes an experimental section which describes in detail the synthesis of 441 grams of treprostinil acid having a purity of 99.7%. (*Id.* at 1902).
[Element D] (c) contacting the product of step (h) with a base B to form a salt of formula IVs, and	The Phares publication discloses converting treprostinil free acid into treprostinil diethanolamine salt as follows: > Treprostinil acid acid [*sic*] is dissolved in a 1:1 molar ratio mixture of ethanol:water and diethanolamine is added and dissolved. The solution is heated and acetone is added as an antisolvent during cooling. (Phares publication at ¶ 0105). The Phares Publication also teaches that treprostinil diethanolamine can be recrystallized to yield two crystalline polymorphs, including the metastable polymorph A, and the thermodynamically more stable polymorph B. (*Id.* at ¶ 327).

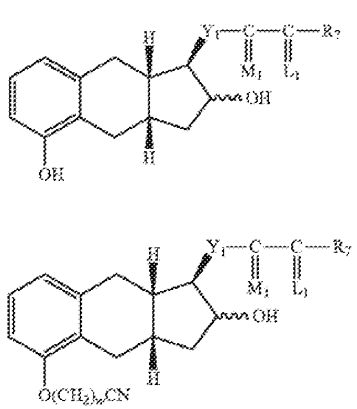
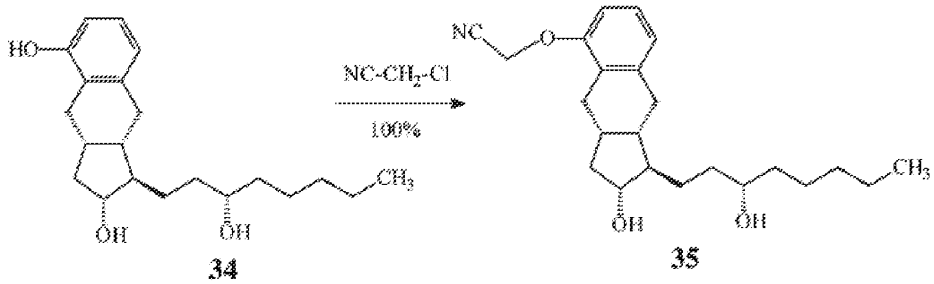
	According to Phares, the resulting polymorphs have melting points at 103° C (Form A) and 107° C (Form B), respectively. (*Id.* at ¶¶ 0332, 0337).
[Element E] (d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula IV.	In the experimental section, the Moriarty JOC article further discloses that the hydrolysis step involved adding a solution of potassium hydroxide to a solution of nitrile in methanol and then refluxing the mixture for three hours, after which point the reaction mixture was cooled to 0°C. (Moriarty JOC Article at p. 1902). Then, hydrochloric acid was added to adjust the pH to 10-12, and the solvent was removed in vacuo, at which point the solution was extracted with ethyl acetate. (*Id.*). The aqueous layer was retained and acidified to pH 2-3 by addition of hydrochloric acid. (*Id.*). The Moriarty synthesis is depicted in Scheme 4, which results in the production of treprostinil free acid, which is depicted as compound 7.

	 7 (Moriarty JOC article at 1892, 1895).

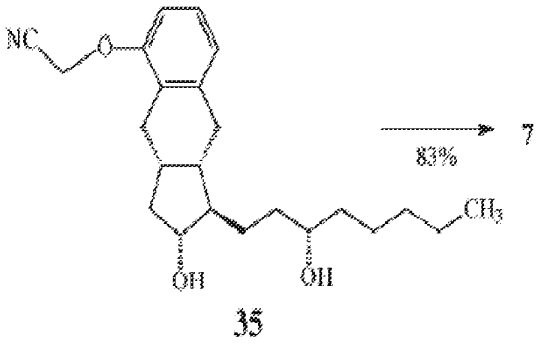
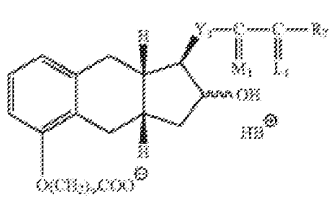
Claim 16	
The product of claim 9, wherein the process does not include purifying the compound of formula (VI) produced in step (a).	*See* Claim 9.

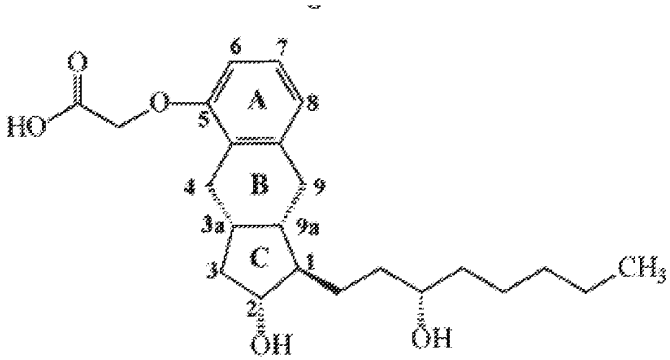
D. The Asserted Claims Are Anticipated By The Disclosure Of Products Comprising Treprostinil Made Through The Claimed Process Steps (a)-(d) In The Moriarty JOC Article

Claim 1	Prior Art Disclosure
[Element A] A product comprising a compound of formula I:  (I) or a pharmaceutically acceptable salt thereof, wherein said product is prepared by a process comprising	To the extent that the process steps recited in the Asserted Claims are material to patentability, which they are not, the Moriarty JOC Article anticipates the Asserted Claims because it discloses treprostinil free acid made by a process that includes claimed steps (a)-(d). The Moriarty synthesis is depicted in Scheme 4, which results in the production of treprostinil free acid, which is depicted as compound 7.  7 (Moriarty JOC article at 1892, 1895).
[Element B]	The process disclosed in the Moriarty JOC article includes the step of alkylating the

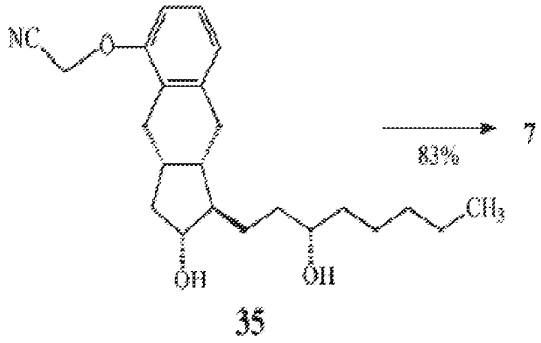
(a) alkylating a compound of structure II with an alkylating agent to produce a compound of formula III, 	benzindene triol (compound 34) to make the nitrile intermediate (compound 35)  (*Id.* at 1895). The above process step is described in the Moriarty JOC article as follows: "[t]riol **34** was alkylated at the phenolic hydroxyl group with use of chloroacetonitrile in refluxing acetone with potassium carbonate (**34** → **35**)…" (*Id.* at 1897).

wherein w=1, 2, or 3; Y_1 is trans-CH=CH—, cis-CH=CH—, —$CH_2(CH_2)_m$—, or —C≡C—; m is 1, 2, or 3; R_7 is (1) —C_pH_{2p}—CH_3, wherein p is an integer from 1 to 5, inclusive, (2) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3) alkyl, or (C_1-C_3) alkoxy, with the proviso that not more than two substituents are other than alkyl, with the proviso that R_7 is phenoxy or substituted phenoxy, only when R_3 and R_4 are hydrogen or methyl, being the same or different, (3) phenyl, benzyl, phenylethyl, or phenylpropyl optionally substituted on the aromatic ring by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3)alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl, (4) cis-CH=CH—CH_2—CH_3, (5) —$(CH_2)_2$—CH(OH)—CH_3, or (6) —$(CH_2)_2$—CH=$C(CH_3)_2$; —$C(L_1)$—R_7 taken together is (1) (C_4-C_7)cycloalkyl optionally substituted by 1 to 3 (C_1-C_3) alkyl; (2) 2-(2-furyl)ethyl, (3) 2-(3-thienyl)ethoxy, or (4) 3-thienyloxymethyl; M_1 is α-OH:β-R_5 or α-R_5:β-OH or α-OR_1:β-R_5 or α-R_5:β-OR_2, wherein R_5 is hydrogen or methyl, R_2 is an alcohol protecting group, and L_1 is α-R_3:β-R_4, α-R_4:β-R_3, or a mixture of α-R_3:β-R_4 and α-R_4:β-R_3, wherein R_3 and R_4 are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R_3 and R_4 is fluoro only when the other is hydrogen or fluoro,	
[Element C] (b) hydrolyzing the product of formula III of step (a) with a base,	The process disclosed in the Moriarty JOC article includes the step of hydrolyzing the nitrile intermediate (compound 35) with a base to form treprostinil free acid:

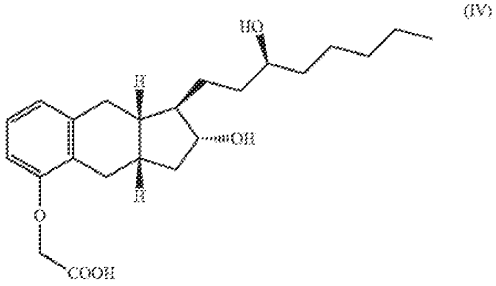
	 35 (*Id.* at 1895). The above process step is described in the Moriarty JOC article as follows: "…and nitrile **35** was hydrolyzed with ethanolic potassium hydroxide to yield UT-15 (**7**) in 9% overall yield." (*Id.* at 1897). The Moriarty JOC article also includes an experimental section which describes in detail the synthesis of 441 grams of treprostinil acid having a purity of 99.7%. (*Id.* at 1902).
[Element D] (c) contacting the product of step (h) with a base B to form a salt of formula Is.  and	The Moriarty JOC Article inherently discloses step (c) because it inherently discloses the formation of treprostinil potassium, which is formed inevitably during the hydrolysis of the benzindene nitrile. Moriarty teaches the performance of the hydrolysis step by reacting the nitrile with potassium hydroxide (KOH) at extremely high pH and elevated temperature. (Moriarty JOC Article at 1902). During this process, some molecules of treprostinil acid necessarily and unavoidably react again with KOH to form treprostinil potassium, which is then converted back to treprostinil acid by the subsequent addition of hydrochloric acid. (*See id.*). That some salt is formed and needs to be converted back to free acid—Moriarty sets out to achieve free acid as its final product—is evidence by the extraction step that immediately follows reflux reaction. Salts, being ionic, are found in the aqueous layer of the water:ethyl acetate system; free acid, being non-polar, is found in the non-polar ethyl acetate layer. When Moriarty retains the aqueous layer, acidifies it to pH 2-3 by addition, and

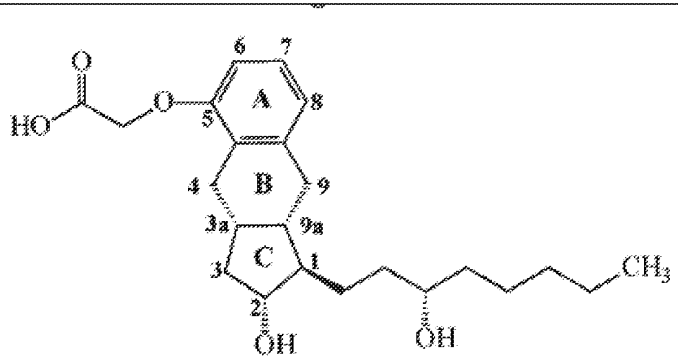
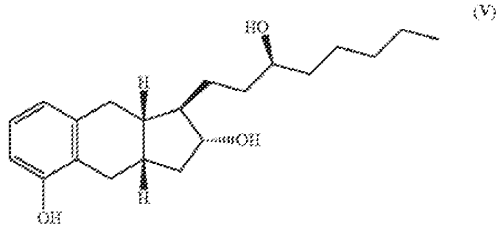
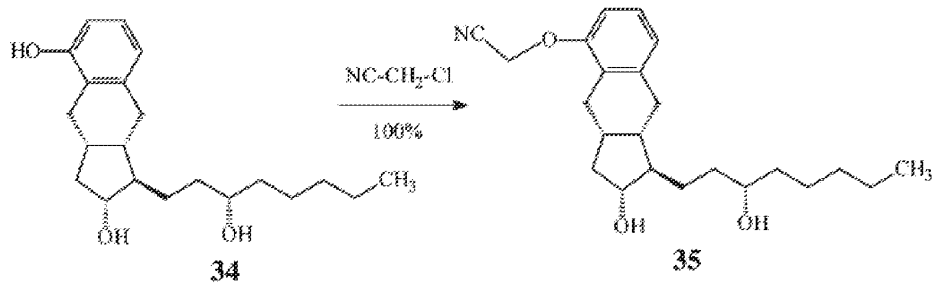
	then extracts again with ethyl acetate, the result is recovery of free acid that would otherwise have been lost as salt.
[Element E] (d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula I.	In the experimental section, the Moriarty JOC article further discloses that the hydrolysis step involved adding a solution of potassium hydroxide to a solution of nitrile in methanol and then refluxing the mixture for three hours, after which point the reaction mixture was cooled to 0°C. (Moriarty JOC Article at p. 1902). Then, hydrochloric acid was added to adjust the pH to 10-12, and the solvent was removed in vacuo, at which point the solution was extracted with ethyl acetate. (*Id.*). The aqueous layer was retained and acidified to pH 2-3 by addition of hydrochloric acid. (*Id.*). The Moriarty synthesis is depicted in Scheme 4, which results in the production of treprostinil free acid, which is depicted as compound 7.  7 (Moriarty JOC article at 1892, 1895).

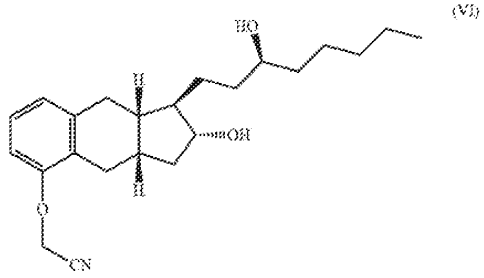
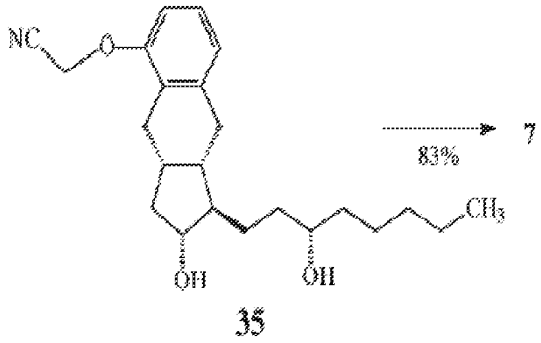
Claim 2	Prior Art Disclosure
The product of claim 1, wherein the purity of compound of formula I in said product is at least 99.5%.	*See* Claim 1. The Moriarty JOC article also includes an experimental section which describes in detail the synthesis of 441 grams of treprostinil acid having a purity of 99.7%. (*Id.* at 1902).

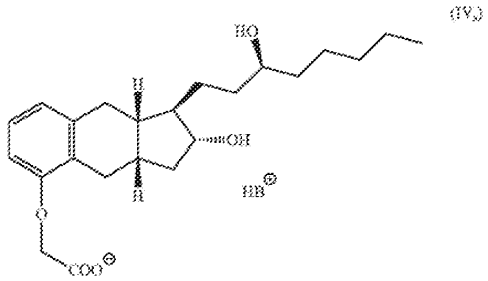
Claim 4	Prior Art Disclosure
The product of claim 1, wherein the base in step (b) is KOH or NaOH.	*See* Claim 1. The process disclosed in the Moriarty JOC article includes the step of hydrolyzing the nitrile intermediate (compound 35) with a base to form treprostinil free acid:  35 (*Id.* at 1895). The above process step is described in the Moriarty JOC article as follows: "…and nitrile **35** was hydrolyzed with ethanolic potassium hydroxide to yield UT-15 (**7**) in 9% overall yield." (*Id.* at 1897).

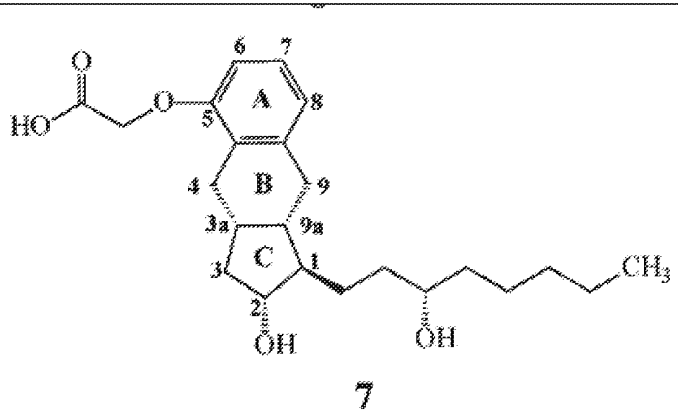
Claim 8	Prior Art Disclosure
The product of claim 1, wherein the process does not include purifying the compound of formula (III) produced in step (a).	*See* Claim 1. In general, there is a motivation in the art to optimize the efficiency of reaction processes. Further, a person of ordinary skill in the art would have been motivated to avoid the "drawbacks" of column chromatography, which is a "labor-intensive" process that is used generally as a last resort. (Anderson, N. "*Practical Process Research & Development: A Guide for Organic Chemists*" at pp. 13, 223, 226 (2000) ("Anderson"). Anderson also discloses that in general, the practice of "telescoping," which is of carrying the product of a reaction without isolation into the next step, can greatly increase overall yields and is usually incorporated as part of a cost-effective route unless significant benefits are obtained from isolation of the intermediate.

Claim 9	Prior Art Disclosure
[Element A] A product comprising a compound having formula IV  (IV) or a pharmaceutically acceptable salt thereof, wherein the product is prepared by the process comprising	To the extent that the process steps recited in the Asserted Claims are material to patentability, which they are not, the Moriarty JOC Article anticipates the Asserted Claims because it discloses treprostinil free acid made by a process that includes claimed steps (a)-(d). The Moriarty synthesis is depicted in Scheme 4, which results in the production of treprostinil free acid, which is depicted as compound 7.

	 7 (Moriarty JOC article at 1892, 1895).
[Element B] (a) alkylating a compound of formula V with an alkylating agent to produce a compound of formula VI, 	The process disclosed in the Moriarty JOC article includes the step of alkylating the benzindene triol (compound 34) to make the nitrile intermediate (compound 35)  34 35

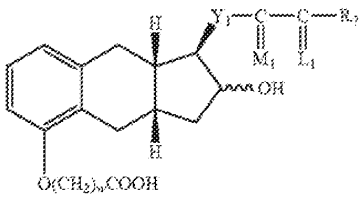
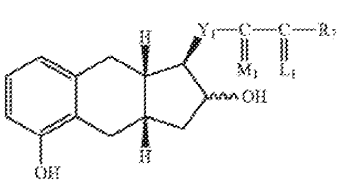
 (VI)	(*Id.* at 1895). The above process step is described in the Moriarty JOC article as follows: "[t]riol **34** was alkylated at the phenolic hydroxyl group with use of chloroacetonitrile in refluxing acetone with potassium carbonate (**34** → **35**)…" (*Id.* at 1897).
[Element C] (b) hydrolyzing the product of formula VI of step (a) with a base,	The process disclosed in the Moriarty JOC article includes the step of hydrolyzing the nitrile intermediate (compound 35) with a base to form treprostinil free acid:  (*Id.* at 1895). The above process step is described in the Moriarty JOC article as follows: "…and nitrile **35** was hydrolyzed with ethanolic potassium hydroxide to yield UT-15 (**7**) in 9% overall yield." (*Id.* at 1897). The Moriarty JOC article also includes an experimental section which describes in detail the synthesis of 441 grams of treprostinil acid having a purity of 99.7%. (*Id.* at 1902).
[Element D]	The Moriarty JOC Article inherently discloses step (c) because it inherently discloses

(c) contacting the product of step (h) with a base B to form a salt of formula IVs, and 	the formation of treprostinil potassium, which is formed inevitably during the hydrolysis of the benzindene nitrile. Moriarty teaches the performance of the hydrolysis step by reacting the nitrile with potassium hydroxide (KOH) at extremely high pH and elevated temperature. (Moriarty JOC Article at 1902). During this process, some molecules of treprostinil acid necessarily and unavoidably react again with KOH to form treprostinil potassium, which is then converted back to treprostinil acid by the subsequent addition of hydrochloric acid. (*See id.*). That some salt is formed and needs to be converted back to free acid—Moriarty sets out to achieve free acid as its final product—is evidence by the extraction step that immediately follows reflux reaction. Salts, being ionic, are found in the aqueous layer of the water:ethyl acetate system; free acid, being non-polar, is found in the non-polar ethyl acetate layer. When Moriarty retains the aqueous layer, acidifies it to pH 2-3 by addition, and then extracts again with ethyl acetate, the result is recovery of free acid that would otherwise have been lost as salt.
[Element E] (d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula IV.	In the experimental section, the Moriarty JOC article further discloses that the hydrolysis step involved adding a solution of potassium hydroxide to a solution of nitrile in methanol and then refluxing the mixture for three hours, after which point the reaction mixture was cooled to 0°C. (Moriarty JOC Article at p. 1902). Then, hydrochloric acid was added to adjust the pH to 10-12, and the solvent was removed in vacuo, at which point the solution was extracted with ethyl acetate. (*Id.*). The aqueous layer was retained and acidified to pH 2-3 by addition of hydrochloric acid. (*Id.*). The Moriarty synthesis is depicted in Scheme 4, which results in the production of treprostinil free acid, which is depicted as compound 7.

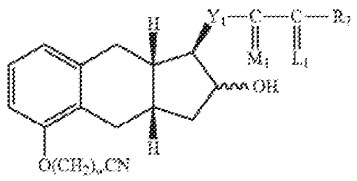
	 7 (Moriarty JOC article at 1892, 1895).

Claim 16	
The product of claim 9, wherein the process does not include purifying the compound of formula (VI) produced in step (a).	*See* Claim 9. In general, there is a motivation in the art to optimize the efficiency of reaction processes. Further, a person of ordinary skill in the art would have been motivated to avoid the "drawbacks" of column chromatography, which is a "labor-intensive" process that is used generally as a last resort. (Anderson, N. "*Practical Process Research & Development: A Guide for Organic Chemists*" at pp. 13, 223, 226 (2000) ("Anderson"). Anderson also discloses that in general, the practice of "telescoping," which is of carrying the product of a reaction without isolation into the next step, can greatly increase overall yields and is usually incorporated as part of a cost-effective route unless significant benefits are obtained from isolation of the intermediate.

E. To The Extent That The Claims Are Construed Such That Step (c) Covers Formation Of Treprostinil Sodium Salt, Then The Asserted Claims Are Anticipated By, Or Would Have Been Obvious In View Of, Li

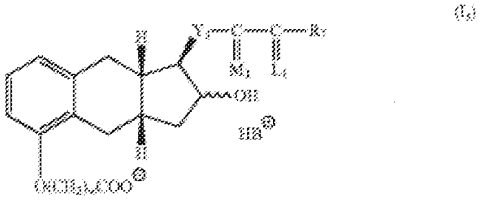
Claim 1	Prior Art Disclosure
Element [A] A product comprising a compound of formula I: (I)  or a pharmaceutically acceptable salt thereof, wherein said product is prepared by a process comprising	The Li article was published in 2004 and is thus prior art to the '393 patent under 35 U.S.C. § 102(b). To the extent that the process steps are pertinent to validity, which they are not, and to the extent that claim step (c) covers formation of treprostinil sodium salt, which it does not, then the asserted claims are anticipated by or rendered obvious in view of Li, which discloses a product comprising treprostinil sodium made through the claimed process steps. .
Element [B] (a) alkylating a compound of structure II with an alkylating agent to produce a compound of formula III, (II) 	The Li reference discloses alkylation of the triol intermediate with chloroacetonitrile to produce the nitrile intermediate. (Li at p. 229).

(III)



wherein
w=1, 2, or 3;
Y_1 is trans-CH=CH—, cis-CH=CH—, —$CH_2(CH_2)_m$—, or —C≡C—; m is 1, 2, or 3;
R_2 is
(1) —C_pH_{2p}—CH_3, wherein p is an integer from 1 to 5, inclusive,
(2) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3) alkyl, or (C_1-C_3) alkoxy, with the proviso that not more than two substituents are other than alkyl, with the proviso that R_2 is phenoxy or substituted phenoxy, only when R_3 and R_4 are hydrogen or methyl, being the same or different,
(3) phenyl, benzyl, phenylethyl, or phenylpropyl optionally substituted on the aromatic ring by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3)alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl,
(4) cis-CH=CH—CH_2—CH_3,
(5) —$(CH_2)_2$—CH(OH)—CH_3, or
(6) —$(CH_2)_3$—CH=C(CH_3)$_2$;
—$C(L_1)$—R_2 taken together is
(1) (C_4-C_7)cycloalkyl optionally substituted by 1 to 3 (C_1-C_3) alkyl;

(2) 2-(2-furyl)ethyl,
(3) 2-(3-thienyl)ethoxy, or
(4) 3-thienyloxymethyl;
M_1 is α-OH:β-R_5 or α-R_5:β-OH or α-OR_2:β-R_5 or α-R_5:β-OR_2, wherein R_5 is hydrogen or methyl, R_2 is an alcohol protecting group, and
L_1 is α-R_3:β-R_4, α-R_4:β-R_3, or a mixture of α-R_3:β-R_4 and α-R_4:β-R_3, wherein R_3 and R_4 are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R_3 and R_4 is fluoro only when the other is hydrogen or fluoro.

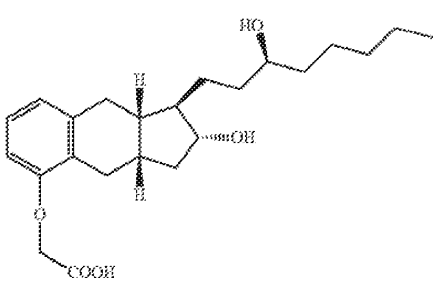
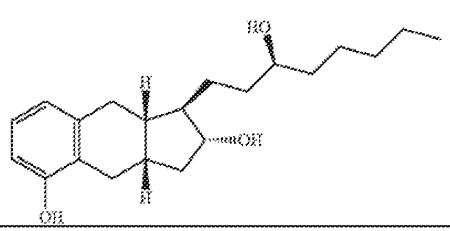
Element [C] (b) hydrolyzing the product of formula III of step (a) with a base,	The Li reference discloses hydrolysis of the nitrile intermediate with potassium hydroxide. (Li at p. 229).
Element [D] (c) contacting the product of step (h) with a base B to form a salt of formula Is.  and	To the extent that step (c) is construed to cover the formation of treprostinil sodium, which it does not, then the Li reference also anticipates because it discloses formation of treprostinil sodium salt following the hydrolysis step. (Li at p. 229).
Element [E] (d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula I.	

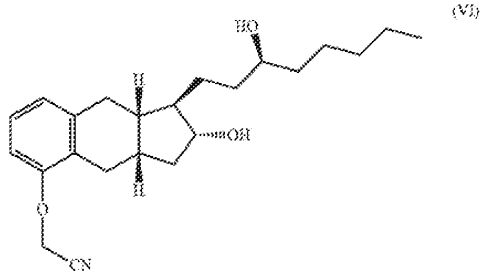
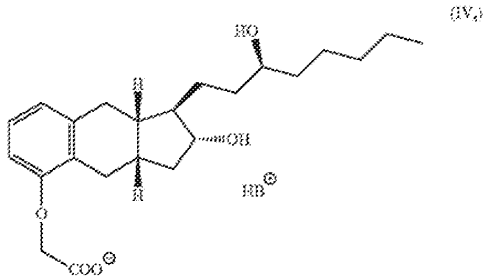
Claim 2	**Prior Art Disclosure**
The product of claim 1, wherein the purity of compound of formula I in said product is at least 99.5%.	*See* Claim 1. The skilled artisan would have been motivated to obtain a sample of treprostinil having a high level of purity. The Moriarty JOC Article includes an experimental section which describes in detail the synthesis of 441 grams of treprostinil acid having a purity of 99.7%. (*Id.* at

	1902). Accordingly, it would have been obvious for the skilled artisan to purify the treprostinil disclosed in Li to a purity level of 99.5% or greater, especially in view of the disclosure in the Moriarty JOC Article of treprostinil having a purity of 99.7%. Also, purification techniques are common practice in the chemical arts. Accordingly, claim 2 would have been obvious in view of the disclosure of treprostinil sodium in Li.

Claim 4	**Prior Art Disclosure**
The product of claim 1, wherein the base in step (b) is KOH or NaOH.	*See* Claim 1. Further, the Li reference discloses hydrolysis of the nitrile intermediate with potassium hydroxide. (Li at p. 229).

Claim 8	**Prior Art Disclosure**
The product of claim 1, wherein the process does not include purifying the compound of formula (III) produced in step (a).	*See* Claim 1. In general, there is a motivation in the art to optimize the efficiency of reaction processes. Further, a person of ordinary skill in the art would have been motivated to avoid the "drawbacks" of column chromatography, which is a "labor-intensive" process that is used generally as a last resort. (Anderson, N. "*Practical Process Research & Development: A Guide for Organic Chemists*" at pp. 13, 223, 226 (2000) ("Anderson"). Anderson also discloses that in general, the practice of "telescoping," which is of carrying the product of a reaction without isolation into the next step, can greatly increase overall yields and is usually incorporated as part of a cost-effective route unless significant benefits are obtained from isolation of the intermediate. Accordingly, here, the skilled artisan would have been motivated to carry the product of step (a) through without isolation or purification with the goal of obtaining a pure final product after step (c) following crystallization of the treprostinil salt.

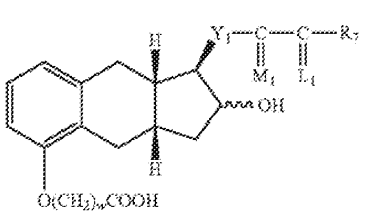
Claim 9	Prior Art Disclosure
Element [A] A product comprising a compound having formula IV  (IV) or a pharmaceutically acceptable salt thereof, wherein the product is prepared by the process comprising	The Li article was published in 2004 and is thus prior art to the '393 patent under 35 U.S.C. § 102(b). To the extent that the process steps are pertinent to validity, which they are not, and to the extent that claim step (c) covers formation of treprostinil sodium salt, which it does not, then the asserted claims are anticipated by or rendered obvious in view of Li, which discloses a product comprising treprostinil sodium made through the claimed process steps.
Element [B] (a) alkylating a compound of formula V with an alkylating agent to produce a compound of formula VI,  (V)	The Li reference discloses hydrolysis of the nitrile intermediate with potassium hydroxide. (Li at p. 229).

	
Element [C] (b) hydrolyzing the product of formula VI of step (a) with a base,	The Li reference discloses hydrolysis of the nitrile intermediate with potassium hydroxide. (Li at p. 229).
Element [D] (c) contacting the product of step (h) with a base B to form a salt of formula IVs, and 	To the extent that step (c) is construed to cover the formation of treprostinil sodium, which it does not, then the Li reference also anticipates because it discloses formation of treprostinil sodium salt following the hydrolysis step. (Li at p. 229).
Element [E] (d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula IV.	

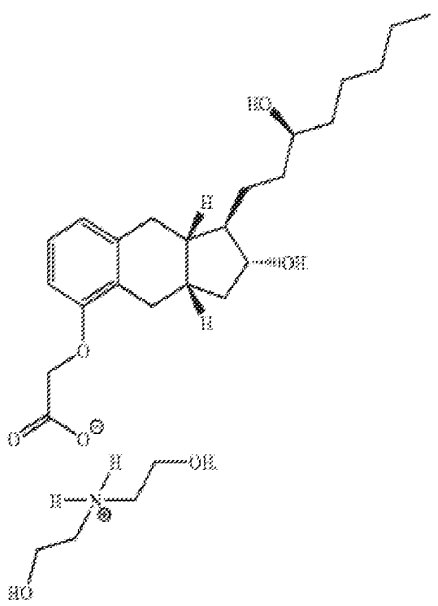
Claim 16	Prior Art Disclosure
The product of claim 9, wherein the process does not include purifying the compound of formula (VI) produced in step (a).	*See* Claim 9. In general, there is a motivation in the art to optimize the efficiency of reaction processes. Further, a person of ordinary skill in the art would have been motivated to avoid the "drawbacks" of column chromatography, which is a "labor-intensive" process that is used generally as a last resort. (Anderson, N. "*Practical Process Research & Development: A Guide for Organic Chemists*" at pp. 13, 223, 226 (2000) ("Anderson"). Anderson also discloses that in general, the practice of "telescoping," which is of carrying the product of a reaction without isolation into the next step, can greatly increase overall yields and is usually incorporated as part of a cost-effective route unless significant benefits are obtained from isolation of the intermediate. Accordingly, here, the skilled artisan would have been motivated to carry the product of step (a) through without isolation or purification with the goal of obtaining a pure final product after step (c) following crystallization of the treprostinil salt.

III. THE ASSERTED CLAIMS ARE INVALID FOR OBVIOUSNESS-TYPE DOUBLE PATENTING

A. The Asserted Claims Are Not Patentably Distinct Over Claim 1 Of U.S. Patent No. 7.417,070 ("The '070 Patent") And Are Thus Invalid For Obviousness-Type Double Patenting

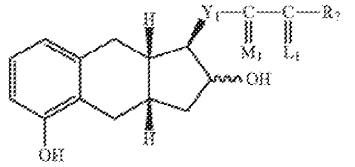
Claim 1	Prior Art Disclosure
[Element A] A product comprising a compound of formula I:  (I) or a pharmaceutically acceptable salt thereof, wherein said product is prepared by a process comprising	The '070 patent issued on August 26, 2008, well before the application leading to the '393 patent was filed on July 13, 2012, and well before the '393 patent issued on July 30, 2013. The '070 patent is also assigned to UTC. Accordingly, to the extent that the Asserted Claims of the '393 patent are not patentably distinct over the claims of the '070 patent, the Asserted Claims are invalid for obviousness-type double patenting. *See Eli Lilly*, 251 F.3d at 968 (A later claim that is not patentably distinct from an earlier claim in a commonly owned patent is invalid for obvious-type double patenting."). "A later patent claim is not patentably distinct from an earlier patent claim if the later claim is obvious over, or anticipated by, the earlier claim." *Id.* A product-by-process claim is anticipated if the product is disclosed in the prior art. *Amgen*, 580 F.3d at 1366; *SmithKline Beecham Corp. v. Apotex Corp.*, 439 F.3d 1312, 1317 (Fed. Cir. 2006) ("It has long been established that one cannot avoid anticipation by an earlier product disclosure by claiming the same product more narrowly, that is, by claiming the product as produced by a particular process"); *Gen. Elec. Co. v. Wabash Appliance Corp.*, 304 U.S. 364, 373 (1938); *Cochrane v. Badische Anilin & Soda Farbrik*, 111 U.S. 293, 311 (1884) ("While a new process for producing [a chemical compound] was patentable, the product itself could not be patented even though it was a product made [by a new process] for the first time because the product was disclosed in the prior art"). "In determining the validity of a product-by-process claim, the focus is on the product and not on the process of making it." *Amgen*, 580 F.3d at 1369-70; *In re Thorpe*, 777 F.2d 695, 697 (Fed. Cir. 1985) ("Even though product-by-process claims are limited by and defined by the process, determination of patentability is

	based on the product itself. The patentability of a product does not depend on its method of production."); *Smithkline*, 439 F.3d at 1317-19; *see also* Manual of Patent Examining Procedure § 2113 (8th ed. Rev. 8 July 2010). Accordingly, for determining the patentability of the Asserted Claims of the '393 patent, the question is whether the claimed product is disclosed in, or obvious from, the prior art. The product of claim 1 of the '393 patent is a product comprising a member of the recited genus of compounds that includes the treprostinil compound or a pharmaceutically acceptable salt thereof, without further limitations as to the composition of the product. Thus, any product comprising treprostinil compound in any amount, with any other types or amounts of impurities, falls within the scope of the claimed product. Claim 1 of the '070 patent reads as follows:

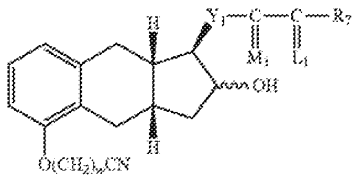
	1. A compound having the following structure:  Further, the '070 patent is listed on the Orange Book as covering UTC's Orenitram product along with the '393 patent. Because the treprostinil diethanolamine compound claimed in the '070 patent is a species of the genus of products claimed in the '393 patent, the treprostinil diethanolamine compound claimed in claim 1 of the '070 patent anticipates claim 1 of the '393 patent. Accordingly, claim 1of the '393 patent is not patentably distinct over claim 1 of the '070 patent.
[Element B]	*See* Element [A] above.

(a) alkylating a compound of structure II with an alkylating agent to produce a compound of formula III,	

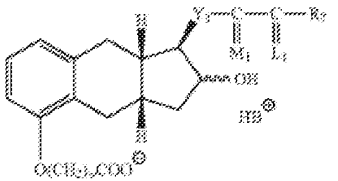
(II)



(III)



wherein
w=1, 2, or 3;
Y_1 is trans-CH=CH—, cis-CH=CH—, —$CH_2(CH_2)_m$—, or —C≡C—; m is 1, 2, or 3;
R_7 is
(1) —C_pH_{2p}—CH_3, wherein p is an integer from 1 to 5, inclusive,
(2) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3) alkyl, or (C_1-C_3) alkoxy, with the proviso that not more than two substituents are other than alkyl, with the proviso that R_7 is phenoxy or substituted phenoxy, only when R_3 and R_4 are hydrogen or methyl, being the same or different,
(3) phenyl, benzyl, phenylethyl, or phenylpropyl optionally substituted on the aromatic ring by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3)alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl,
(4) cis-CH=CH—CH_2—CH_3,
(5) —$(CH_2)_2$—CH(OH)—CH_3, or
(6) —$(CH_2)_3$—CH=$C(CH_3)_2$;
—$C(L_1)$—R_7 taken together is
(1) (C_4-C_7)cycloalkyl optionally substituted by 1 to 3 (C_1-C_3) alkyl;

(2) 2-(2-furyl)ethyl, (3) 2-(3-thienyl)ethoxy, or (4) 3-thienyloxymethyl; M_1 is α-OH:β-R_3 or α-R_3:β-OH or α-OR_1:β-R_3 or α-R_3:β-OR_2, wherein R_3 is hydrogen or methyl, R_2 is an alcohol protecting group, and L_1 is α-R_3:β-R_4, α-R_4:β-R_3, or a mixture of α-R_3:β-R_4 and α-R_4:β-R_3, wherein R_3 and R_4 are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R_3 and R_4 is fluoro only when the other is hydrogen or fluoro,	
[Element C] (b) hydrolyzing the product of formula III of step (a) with a base,	*See* Element [A] above.
[Element D] (c) contacting the product of step (h) with a base B to form a salt of formula Is. (I$_s$)  and	*See* Element [A] above.
[Element E] (d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula I.	*See* Element [A] above.

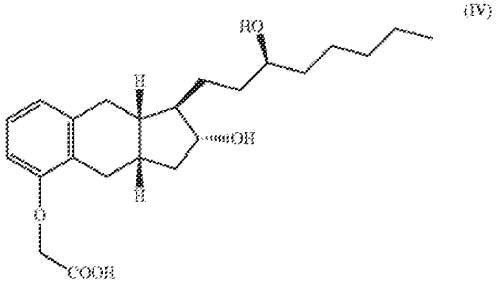
Claim 2	
The product of claim 1, wherein the purity of compound of formula I in said product is at least 99.5%.	*See* Claim 1. Further, The '070 patent teaches a method of making treprostinil diethanolamine salt that includes the same steps as the claimed method: alkylating the triol, hydrolyzing the nitrile with a base, and contacting the product with a base (B) to produce treprostinil diethanolamine salt of polymorph form Form B: The '070 paent discloses a method of making treprostinil involving alkylating benzindene triol to form the nitrile, then hydrolyzing the nitrile with a base (KOH) to obtain the free acid. ('070 patent at Col. 34:7-Col. 35:43, Col. 36:1-38). The '070 patent discloses converting treprostinil free acid into treprostinil diethanolamine salt as follows: > Treprostinil acid acid [*sic*] is dissolved in a 1:1 molar ratio mixture of ethanol:water and diethanolamine is added and dissolved. The solution is heated and acetone is added as an antisolvent during cooling. ('070 patent at Col. 15:32-37). The '070 patent also teaches that treprostinil diethanolamine can be recrystallized to yield two crystalline polymorphs, including the metastable polymorph A, and the thermodynamically more stable polymorph B. (*Id.* at Col. 66:36-Col. 67:35). According to Phares, the resulting polymorphs have melting points at 103° C (Form A) and 107° C (Form B), respectively. (*Id.* at Col. 67:59-61, Col. 68:50-52). Thus, because the '070 patent discloses using the same process as that claimed to make the same product (treprostinil diethanolamine salt), then the treprostinil diethanolamine salt claimed in the '070 patent, when produced through the disclosed

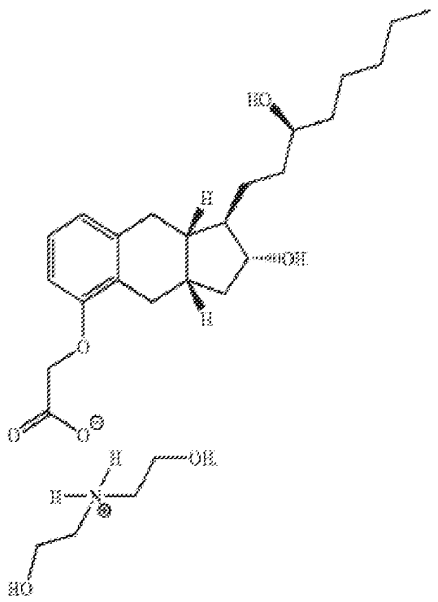
	process, inherently has the claimed purity profile. The skilled artisan would have been motivated to obtain a sample of treprostinil having a high level of purity. The Moriarty JOC Article includes an experimental section which describes in detail the synthesis of 441 grams of treprostinil acid having a purity of 99.7%. (*Id.* at 1902). Accordingly, it would have been obvious for the skilled artisan to purify the treprostinil disclosed and claimed in the '070 patent to a purity level of 99.5% or greater, particularly in view of the disclosure in the Moriarty JOC article of treprostinil having a purity level of 99.7%. Further, purification techniques are common practice in the chemical arts. Accordingly, claim 2 is not patentably distinct over claim 1 of the '070 patent and is invalid for obviousness-type double patenting.

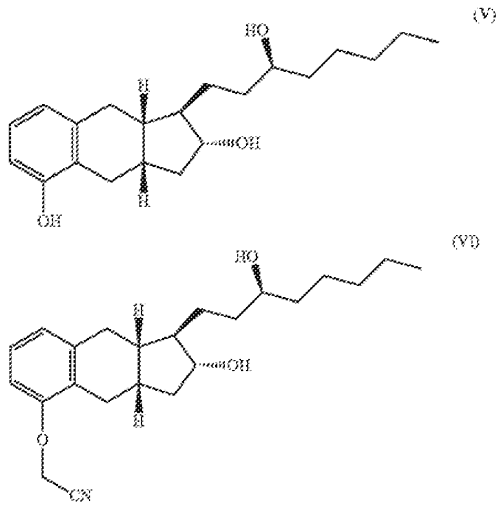
Claim 4	
The product of claim 1, wherein the base in step (b) is KOH or NaOH.	*See* Claim 1.

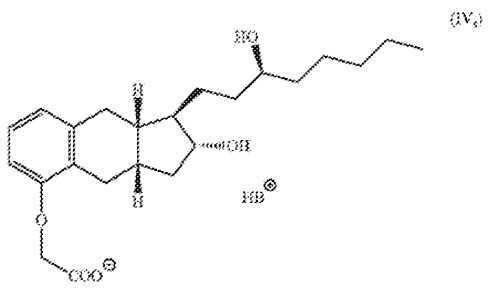
Claim 8	
The product of claim 1, wherein the process does not include purifying the compound of formula (III) produced in step (a).	*See* Claim 1.

Claim 9	**Prior Art Disclosure**
[Element A]	The '070 patent issued on August 26, 2008, well before the application leading to the

A product comprising a compound having formula IV  (IV) or a pharmaceutically acceptable salt thereof, wherein the product is prepared by the process comprising	'393 patent was filed on July 13, 2012, and well before the '393 patent issued on July 30, 2013. The '070 patent is also assigned to UTC. Accordingly, to the extent that the Asserted Claims of the '393 patent are not patentably distinct over the claims of the '070 patent, the Asserted Claims are invalid for obviousness-type double patenting. *See Eli Lilly*, 251 F.3d at 968 (A later claim that is not patentably distinct from an earlier claim in a commonly owned patent is invalid for obvious-type double patenting."). A later patent claim is not patentably distinct from an earlier patent claim if the later claim is obvious over, or anticipated by, the earlier claim." *Id.* A product-by-process claim is anticipated if the product is disclosed in the prior art. *Amgen*, 580 F.3d at 1366; *SmithKline Beecham Corp. v. Apotex Corp.*, 439 F.3d 1312, 1317 (Fed. Cir. 2006) ("It has long been established that one cannot avoid anticipation by an earlier product disclosure by claiming the same product more narrowly, that is, by claiming the product as produced by a particular process"); *Gen. Elec. Co. v. Wabash Appliance Corp.*, 304 U.S. 364, 373 (1938); *Cochrane v. Badische Anilin & Soda Farbrik*, 111 U.S. 293, 311 (1884) ("While a new process for producing [a chemical compound] was patentable, the product itself could not be patented even though it was a product made [by a new process] for the first time because the product was disclosed in the prior art"). "In determining the validity of a product-by-process claim, the focus is on the product and not on the process of making it." *Amgen*, 580 F.3d at 1369-70; *In re Thorpe*, 777 F.2d 695, 697 (Fed. Cir. 1985) ("Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production."); *Smithkline*, 439 F.3d at 1317-19; *see also* Manual of Patent Examining Procedure § 2113 (8th ed. Rev. 8 July 2010). Accordingly, for determining the patentability of the Asserted Claims of the '393 patent, the question is whether the claimed product is disclosed in, or obvious from, the prior art. The product of claim 9 of the '393 patent is a product comprising the treprostinil compound or a pharmaceutically acceptable salt thereof, without further limitations as to the composition of the product. Thus, any product comprising

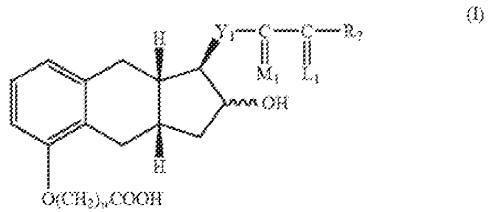
	treprostinil compound in any amount, with any other types or amounts of impurities, falls within the scope of the claimed product. Claim 1 of the '070 patent reads as follows: 1. A compound having the following structure:  Because the treprostinil diethanolamine compound claimed in the '070 patent is a pharmaceutically acceptable salt of the treprostinil compound, as claimed in the '393 patent, the treprostinil diethanolamine compound claimed in claim 1 of the '070 patent anticipates claim 9 of the '393 patent. Accordingly, claim 9 of the '393 patent is not patentably distinct over claim 1 of the '070 patent.

[Element B] (a) alkylating a compound of formula V with an alkylating agent to produce a compound of formula VI,  	*See* Element [A] above.
[Element C] (b) hydrolyzing the product of formula VI of step (a) with a base,	*See* Element [A] above.
[Element D] (c) contacting the product of step (h) with a base B to form a salt of formula IVs, and	*See* Element [A] above.

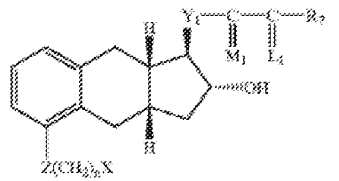
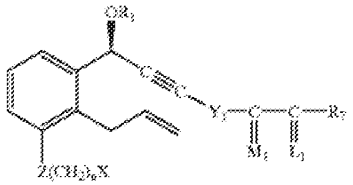
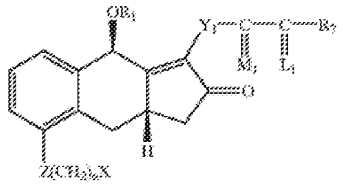
	
[Element E] (d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula IV.	*See* Element [A] above.

Claim 16	
The product of claim 9, wherein the process does not include purifying the compound of formula (VI) produced in step (a).	*See* Claim 9

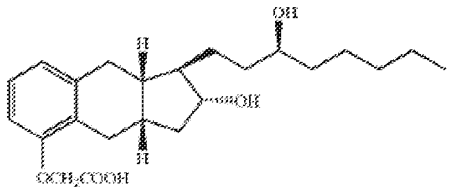
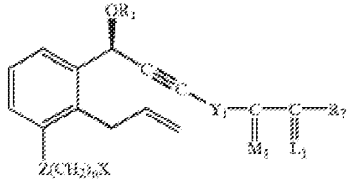
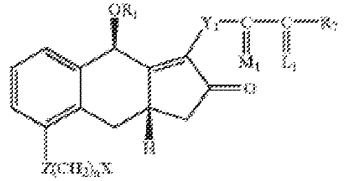
B. The Asserted Claims Are Not Patentably Distinct Over The Claims Of The '117 Patent And Are Thus Invalid For Obviousness-Type Double Patenting

Claim 1	Prior Art Disclosure
[Element A] A product comprising a compound of formula I:  or a pharmaceutically acceptable salt thereof, wherein said product is prepared by a process comprising	The '117 patent was issued on July 20, 2004, well before the application leading to the '393 patent was filed on July 13, 2012, and well before the '393 patent issued on July 30, 2013. The '117 patent is also assigned to UTC. Accordingly, to the extent that the Asserted Claims of the '393 patent are not patentably distinct over the claims of the '117 patent, the Asserted Claims are invalid for obviousness-type double patenting. *See Eli Lilly*, 251 F.3d at 968 (A later claim that is not patentably distinct from an earlier claim in a commonly owned patent is invalid for obvious-type double patenting."). "A later patent claim is not patentably distinct from an earlier patent claim if the later claim is obvious over, or anticipated by, the earlier claim." *Id.* A product-by-process claim is anticipated if the product is disclosed in the prior art. *Amgen*, 580 F.3d at 1366; *SmithKline Beecham Corp. v. Apotex Corp.*, 439 F.3d 1312, 1317 (Fed. Cir. 2006) ("It has long been established that one cannot avoid anticipation by an earlier product disclosure by claiming the same product more narrowly, that is, by claiming the product as produced by a particular process"); *Gen. Elec. Co. v. Wabash Appliance Corp.*, 304 U.S. 364, 373 (1938); *Cochrane v. Badische Anilin & Soda Farbrik*, 111 U.S. 293, 311 (1884) ("While a new process for producing [a chemical compound] was patentable, the product itself could not be patented even though it was a product made [by a new process] for the first time because the product was disclosed in the prior art"). "In determining the validity of a product-by-process claim, the focus is on the product and not on the process of making it." *Amgen*, 580 F.3d at 1369-70; *In re Thorpe*, 777 F.2d 695, 697 (Fed. Cir. 1985) ("Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production."); *Smithkline*, 439 F.3d at 1317-19; *see also* Manual of Patent

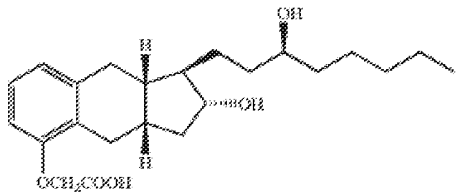
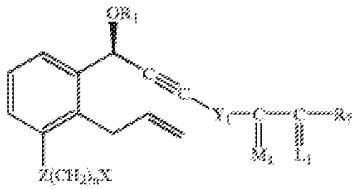
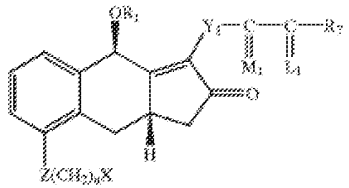
	Examining Procedure § 2113 (8th ed. Rev. 8 July 2010). Accordingly, for determining the patentability of the Asserted Claims of the '393 patent, the question is whether the claimed product is disclosed in, or obvious from, the prior art. The product of claim 1 of the '393 patent is a product comprising a member of the recited genus of compounds that includes the treprostinil compound or a pharmaceutically acceptable salt thereof, without further limitations as to the composition of the product. Thus, any product comprising treprostinil compound in any amount, with any other types or amounts of impurities, falls within the scope of the claimed product. Claim 1 of the '117 patent reads in pertinent part as follows:

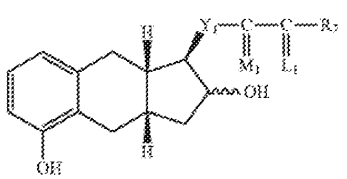
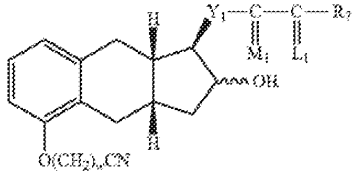
	1. A stereoselectively produced isomeric compound according to the following formula:  that is produced by a process for making 9-deoxy-PGF_2-type compounds, the process comprising cyclizing a starting compound of the formula:  into a compound of the following formula:  by intramolecular cyclization of the enyne. ('117 patent at Col. 21:23-59).

	Claim 3 of the '117 patent reads, in pertinent part, as follows: ('117 patent at Col. 21:23-59).

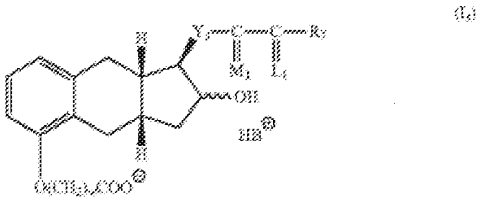
	3. A stereoselectively produced isomeric compound according to the following formula:  that is produced by a process for making 9-deoxy-PGE$_1$-type compounds, the process comprising cyclizing a starting compound of the formula:  into a compound of the following formula:  by intramolecular cyclization of the enyne,

	('117 patent at Col. 22:42-Col. 23:12). Claim 4 of the '117 patent reads in pertinent part as follows:

	4. A stereoselectively produced isomeric compound in pharmacologically acceptable salt form according to the following formula:  that is produced by process for making 9-deoxy-PGF_1-type compounds, the process comprising cyclizing a starting compound of the formula:  into a compound of the following formula:  by intramolecular cyclization of the cyne,

	('117 patent at Col. 23:53-Col. 24:23). The '117 patent includes product-by-process claims directed to the treprostinil compound and pharmaceutically acceptable salts thereof. Further, the '117 patent is listed on the Orange Book as covering UTC's Remodulin product and UTC's Orenitram product along with the '393 patent. Accordingly, because the '117 patent claims treprostinil compound and salts thereof, claim 1 is of the '393 patent is not patentably distinct over the '117 patent claims.
[Element B] (a) alkylating a compound of structure II with an alkylating agent to produce a compound of formula III, (II)  (III) 	*See* Element [A] above.

wherein w=1, 2, or 3; Y_1 is trans-CH=CH—, cis-CH=CH—, —$CH_2(CH_2)_m$—, or —C≡C—; m is 1, 2, or 3; R_7 is (1) —C_pH_{2p}—CH_3, wherein p is an integer from 1 to 5, inclusive, (2) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3) alkyl, or (C_1-C_3) alkoxy, with the proviso that not more than two substituents are other than alkyl, with the proviso that R_7 is phenoxy or substituted phenoxy, only when R_3 and R_4 are hydrogen or methyl, being the same or different, (3) phenyl, benzyl, phenylethyl, or phenylpropyl optionally substituted on the aromatic ring by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3)alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl, (4) cis-CH=CH—CH_2—CH_3, (5) —$(CH_2)_2$—CH(OH)—CH_3, or (6) —$(CH_2)_2$—CH=$C(CH_3)_2$; —$C(L_1)$—R_7 taken together is (1) (C_4-C_7)cycloalkyl optionally substituted by 1 to 3 (C_1-C_3) alkyl; (2) 2-(2-furyl)ethyl, (3) 2-(3-thienyl)ethoxy, or (4) 3-thienyloxymethyl; M_1 is α-OH:β-R_5 or α-R_5:β-OH or α-OR_1:β-R_5 or α-R_5:β-OR_2, wherein R_5 is hydrogen or methyl, R_2 is an alcohol protecting group, and L_1 is α-R_3:β-R_4, α-R_4:β-R_3, or a mixture of α-R_3:β-R_4 and α-R_4:β-R_3, wherein R_3 and R_4 are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R_3 and R_4 is fluoro only when the other is hydrogen or fluoro,	
[Element C] (b) hydrolyzing the product of formula III of step (a) with a base,	*See* Element [A] above.
[Element D]	*See* Element [A] above.

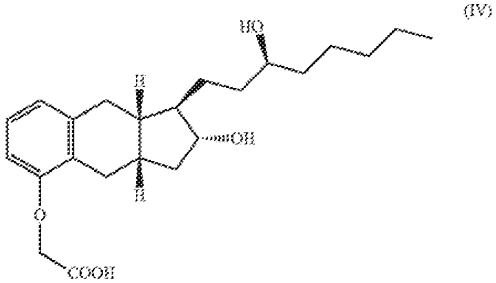
(c) contacting the product of step (h) with a base B to form a salt of formula Is.  and	
[Element E] (d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula I.	*See* Element [A] above.

Claim 2	
The product of claim 1, wherein the purity of compound of formula I in said product is at least 99.5%.	*See* Claim 1. The skilled artisan would have been motivated to obtain a sample of treprostinil having a high level of purity. The Moriarty JOC Article includes an experimental section which describes in detail the synthesis of 441 grams of treprostinil acid having a purity of 99.7%. (*Id.* at 1902). Accordingly, it would have been obvious for the skilled artisan to purify the treprostinil disclosed and claimed in the '117 patent to a purity level of 99.5% or greater, particularly in view of the disclosure in the Moriarty JOC article of treprostinil having a purity level of 99.7%. Further, purification techniques are common practice in the chemical arts. Accordingly, claim 2 is not patentably distinct

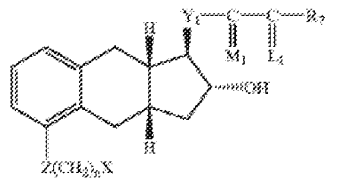
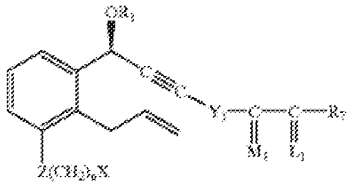
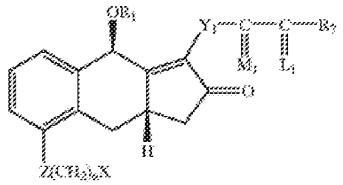
	over the claims of the '117 patent and is invalid for obviousness-type double patenting.

Claim 4	
The product of claim 1, wherein the base in step (b) is KOH or NaOH.	*See* Claim 1.

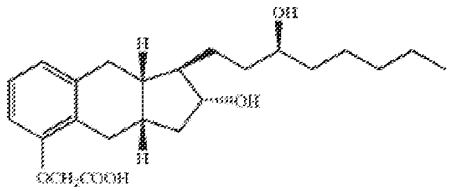
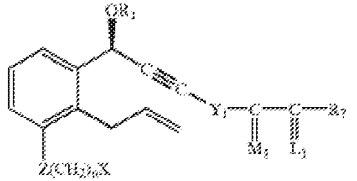
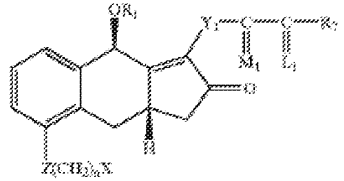
Claim 8	
The product of claim 1, wherein the process does not include purifying the compound of formula (III) produced in step (a).	*See* Claim 1.

Claim 9	**Prior Art Disclosure**
[Element A] A product comprising a compound having formula IV  (IV) or a pharmaceutically acceptable salt thereof, wherein the product is prepared by the process comprising	The '117 patent was issued on July 20, 2004, well before the application leading to the '393 patent was filed on July 13, 2012, and well before the '393 patent issued on July 30, 2013. The '117 patent is also assigned to UTC. Accordingly, to the extent that the Asserted Claims of the '393 patent are not patentably distinct over the claims of the '117 patent, the Asserted Claims are invalid for obviousness-type double patenting. *See Eli Lilly*, 251 F.3d at 968 (A later claim that is not patentably distinct from an earlier claim in a commonly owned patent is invalid for obvious-type double patenting."). A later patent claim is not patentably distinct from an earlier patent claim if the later claim is obvious over, or anticipated by, the earlier claim." *Id.* A product-by-process claim is anticipated if the product is disclosed in the prior art. *Amgen*, 580 F.3d at 1366; *SmithKline Beecham Corp. v. Apotex Corp.*, 439 F.3d 1312, 1317 (Fed. Cir. 2006) ("It has long been established that one cannot avoid anticipation by an earlier product disclosure by claiming the same product more narrowly, that is, by claiming the product as produced by a particular process"); *Gen. Elec. Co. v. Wabash Appliance Corp.*, 304 U.S. 364, 373 (1938); *Cochrane v. Badische Anilin & Soda Farbrik*, 111 U.S. 293, 311 (1884) ("While a new process for producing [a chemical compound] was patentable, the product itself could not be

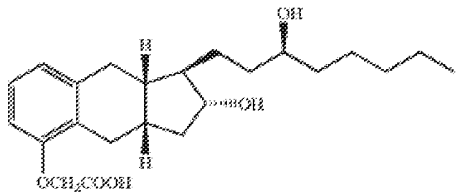
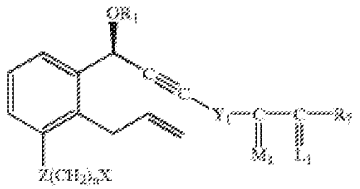
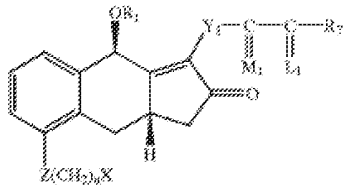
	patented even though it was a product made [by a new process] for the first time because the product was disclosed in the prior art"). "In determining the validity of a product-by-process claim, the focus is on the product and not on the process of making it." *Amgen*, 580 F.3d at 1369-70; *In re Thorpe*, 777 F.2d 695, 697 (Fed. Cir. 1985) ("Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production."); *Smithkline*, 439 F.3d at 1317-19; *see also* Manual of Patent Examining Procedure § 2113 (8th ed. Rev. 8 July 2010). Accordingly, for determining the patentability of the Asserted Claims of the '393 patent, the question is whether the claimed product is disclosed in, or obvious from, the prior art. The product of claim 9 of the '393 patent is a product comprising the treprostinil compound or a pharmaceutically acceptable salt thereof, without further limitations as to the composition of the product. Thus, any product comprising treprostinil compound in any amount, with any other types or amounts of impurities, falls within the scope of the claimed product. Claim 1 of the '117 patent reads in pertinent part as follows:

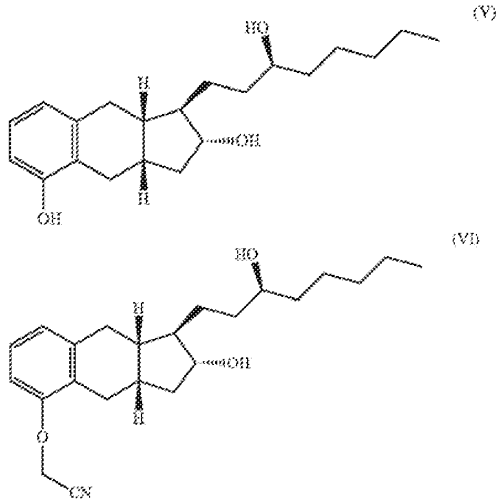
	1. A stereoselectively produced isomeric compound according to the following formula:  that is produced by a process for making 9-deoxy-PGF_2-type compounds, the process comprising cyclizing a starting compound of the formula:  into a compound of the following formula:  by intramolecular cyclization of the enyne. ('117 patent at Col. 21:23-59).

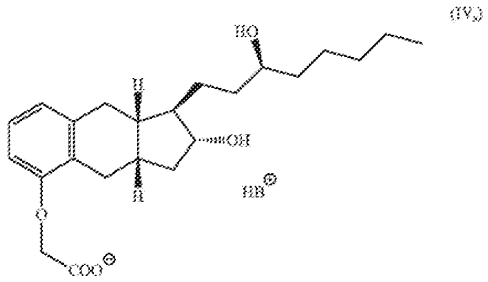
	Claim 3 of the '117 patent reads, in pertinent part, as follows: ('117 patent at Col. 21:23-59).

	3. A stereoselectively produced isomeric compound according to the following formula:  that is produced by a process for making 9-deoxy-PGE$_1$-type compounds, the process comprising cyclizing a starting compound of the formula:  into a compound of the following formula:  by intramolecular cyclization of the enyne,

	('117 patent at Col. 22:42-Col. 23:12). Claim 4 of the '117 patent reads in pertinent part as follows:

	4. A stereoselectively produced isomeric compound in pharmacologically acceptable salt form according to the following formula:  that is produced by process for making 9-deoxy-PGF_1-type compounds, the process comprising cyclizing a starting compound of the formula:  into a compound of the following formula:  by intramolecular cyclization of the cyne,

	('117 patent at Col. 23:53-Col. 24:23). The '117 patent includes product-by-process claims directed to the treprostinil compound and pharmaceutically acceptable salts thereof. Further, the '117 patent is listed on the Orange Book as covering UTC's Remodulin Product along with the '393 patent. Accordingly, because the '117 patent claims treprostinil compound and salts thereof, claim 9 is of the '393 patent is not patentably distinct over the '117 patent claims.
[Element B] (a) alkylating a compound of formula V with an alkylating agent to produce a compound of formula VI,  	*See* Element [A] above.
[Element C]	*See* Element [A] above.

(b) hydrolyzing the product of formula VI of step (a) with a base,	
[Element D] (c) contacting the product of step (h) with a base B to form a salt of formula IVs, and 	*See* Element [A] above.
[Element E] (d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula IV.	*See* Element [A] above.

Claim 16	
The product of claim 9, wherein the process does not include purifying the compound of formula (VI) produced in step (a).	*See* Claim 9.

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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

UNITED THERAPEUTICS CORPORATION, and SUPERNUS PHARMACEUTICALS, INC., Plaintiff, v. ACTAVIS LABORATORIES FL, INC., Defendant.	Civil Action No. 3:16-cv-01816-PGS-LHG Civil Action No. 3:16-cv-03642-PGS-LHG

DEFENDANT ACTAVIS LABORATORIES FL, INC.'S
PRELIMINARY INVALIDITY CONTENTIONS

Pursuant to Local Patent Rules 3.3 and 3.6 and the pretrial scheduling order (D.E. 28), Actavis Laboratories FL, Inc. (hereinafter "Actavis") submits the following preliminary invalidity contentions for the asserted claims of United States Patent Nos. 8,497,393, 7,417,070,

8,252,839, 7,544,713, 8,410,169, 9,050,311, 8,747,897, 8,349,892, 9,278,901 (the "patents-in-suit").[1]

Actavis reserves the right to supplement and/or amend these preliminary contentions in response to any contentions by plaintiffs United Therapeutics Corporation and Supernus Pharmaceuticals, Inc. (hereinafter collectively, "plaintiffs"). Actavis further reserves the right to supplement and/or amend these contentions as discovery proceeds, including based on fact or expert discovery disclosures and on any discovery materials that have not yet been produced or provided to Actavis, or upon further investigation. Actavis further reserves the right to supplement and/or amend these contentions based on any Court decisions in any related cases (including the *United Therapeutics Corp. v. Watson Laboratories, Inc.*, case (case no. 3:15-cv-05723-PGS-LHG) and *United Therapeutics Corp. v. Teva Pharm., USA, Inc.* (case no. 3:14-cv-5498-PGS-LHG)). Actavis also reserves the right to supplement and/or amend these contentions when plaintiff provides its infringement allegations, or to the extent, any claim construction ruling by the Court modifies Actavis's positions herein and/or provides the basis for additional invalidity contentions. Actavis otherwise reserves the right to supplement and/or amend these contentions as necessary and appropriate and as provided under the Local Patent Rules or any other applicable rules or order of the Court.

These contentions are made pursuant to Federal Rule of Evidence 502. To the extent, these contentions contain any information that may be protected from discovery under the attorney-client privilege, the attorney work-product immunity, the common interest privilege, or any other applicable privilege or immunity, such disclosure is inadvertent and does not constitute a waiver of any such privilege or immunity. The information set forth in these contentions is

[1] Nothing in this statement of contentions should be construed as limiting Actavis' statutory rights pursuant to 35 U.S.C. § 282.

provided without waiving: (1) the right to object to the use of any statement for any purpose, in this action or any other, on the grounds of privilege, relevance, materiality, or any other appropriate grounds; (2) the right to object to any request involving or relating to the subject matter of the statements herein; or (3) the right to revise, correct, supplement, or clarify any of the statements provided below at any time.

These contentions should not be taken as an indication of Actavis's position with regard to the proper construction of any claim term.[2] Rather, Actavis has made reasonable assumptions, to the extent necessary and appropriate, as to the meaning of claim terms for the purpose of these contentions only and has used those meanings to prepare these contentions. To the extent that Actavis determines that a different meaning is appropriate for any claim term, it will assert that meaning in connection with the claim construction proceedings, and Actavis reserves the right to amend these contentions as a result of the *Markman* hearing, or any other subsequent clarification or alteration of the meaning of claim terms.

Actavis's invalidity positions in these contentions and the accompanying charts may be in the alternative and do not constitute any concession by Actavis for purposes of infringement. *See, e.g.*, *Vanmoor v. Wal-Mart Stores, Inc.*, 201 F.3d 1363, 1366 (Fed. Cir. 2000).

In accordance with 21 U.S.C. § 355(j)(2)(B)(ii), Actavis provided notice in the form of "notice letters" to UTC that it sought FDA approval to market drug products under its Abbreviated New Drug Application before the expiration date of the patents-in-suit. The notice letters set forth, among other things, the factual and legal bases that the claims of the patents are not infringed, invalid, and/or unenforceable by the proposed treprostinil products described in the

[2] Any reference in these contentions to the preamble of any claim of the patents-in-suit, including any word or any phrase appearing in such preamble, shall not be taken as an admission that the referenced language of the preamble is or is not a claim limitation. Actavis reserves the right to contend that any word or any phrase in the preamble of any claim of the patents-in-suit is or is not a claim limitation.

ANDA at issue in this case. Actavis hereby incorporates by reference the full contents of these notice letters.

As discussed in more detail below, at this early stage of the litigation, Actavis contends that the relevant prior art—standing alone or in combination with the knowledge of a person of ordinary skill in the art—renders the asserted claims of the patents-in-suit invalid as anticipated under 35 U.S.C. § 102 and/or obvious under 35 U.S.C. § 103.

While Actavis has endeavored to identify the most relevant portions of the prior art references in the accompanying claim charts, the cited references may contain other or additional support for particular claim limitations. Actavis may rely upon these portions that have not been specifically identified, any documents or statements identified in the cited references, any documents that claim priority to the cited references, any foreign counterparts to the cited references, their file histories (as applicable), or fact and expert testimony/documents not yet in evidence to provide context in understanding the references.

Pursuant to Local Patent Rules 3.6(c) and 3.3(a)–(b), Actavis herein identifies each item of prior art known at this time that allegedly renders each claim invalid as anticipated and/or obvious, and includes an explanation of why the prior art renders the claim invalid. Charts relevant to the patents-in-suit, setting forth the information required under Local Patent Rules 3.6(c) and 3.3(c), are included herein. Further pursuant to Local Patent Rules 3.6(c) and 3.3(c), Actavis currently contends that no claim elements are subject to 35 U.S.C. § 112, sixth paragraph. Contemporaneously with this submission, Actavis is also producing the documents required under Local Patent Rules 3.6(d) and 3.4, to the extent the same are not already in the possession of plaintiff or have not been otherwise previously produced. Actavis reserves the right

to supplement this identification should additional documents become relevant during the continuing course of discovery.

I. THE PATENTS-IN-SUIT

Actavis incorporates by reference all contents of the asserted patents, including their file histories. Below are representative summaries of the claims and specifications of the patents-in-suit.

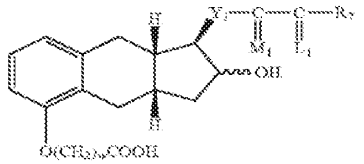
A. '393 Patent

U.S. Patent No. 8,497,393 ("the '393 patent"), titled "PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN™," issued on July 30, 2013 from U.S. Patent Application No. 13/548,446, filed on July 13, 2012, which is a continuation of U.S. Patent Application No. 12/334,731, filed on December 15, 2008, which issued as U.S. Patent No. 8,242,305. The '393 patent claims priority to U.S. Provisional No. 61/014,232, filed on December 17, 2007. Therefore, according to the face of the '393 patent, the earliest possible priority date and also the earliest effective filing date for the '393 patent is December 17, 2007. The '393 patent names as inventors Hitesh Batra, Sudersan M. Tuladhar, Raju Penmasta, and David A. Walsh. The '393 patent is assigned on its face to United Therapeutics Corporation. The USPTO's online assignment records have no assignment data available for the '393 patent. The '393 patent's term has been adjusted under 35 U.S.C. § 154(b) by 0 days. *See* '393 patent, cover page; *see also* Issue Notification (July 10, 2013). Accordingly, the '393 patent is due to expire on December 15, 2028.

The '393 patent has 22 claims, including independent claims 1 and 9, all of which are asserted against Actavis. Claims 1-22 are product-by-process claims directed to treprostinil or its pharmaceutically acceptable salt. The claimed process involves the alkylation of a triol compound to a benzindene nitrile compound, hydrolysis of the nitrile compound, formation of a

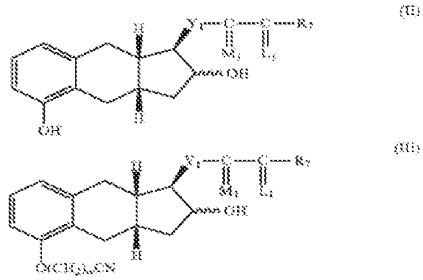
salt using "a base B," and optionally reacting the salt with an acid to form treprostinil. Claim 1 is exemplary:

A product comprising a compound of formula I



or a pharmaceutically acceptable salt thereof, wherein said product is prepared by a process comprising

(a) alkylating a compound of structure II with an alkylating agent to produce a compound of formula III,



wherein w=1, 2, or 3; Y_1 is trans-CH=CH—, cis-CH=CH—, —$CH_2(CH_2)_m$—, or —C≡C—; m is 1, 2, or 3; R_7 is

(1) —C_pH_{2p}—CH_3, wherein p is an integer from 1 to 5, inclusive,

(2) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3) alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl, with the proviso that R_7 is phenoxy or substituted phenoxy, only when R_3 and R_4 are hydrogen or methyl, being the same or different,

(3) phenyl, benzyl, phenylethyl, or phenylpropyl optionally substituted on the aromatic ring by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3)alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl,

(4) cis-CH=CH—CH_2—CH_3,

(5) —$(CH_2)_2$—CH(OH)—CH_3, or

(6) —$(CH_2)_3$—CH=C(CH_3)$_2$; —$C(L_1)$—R_7 taken together is (1) (C_4-C_7)cycloalkyl optionally substituted by 1 to 3 (C_1-C_5)alkyl;

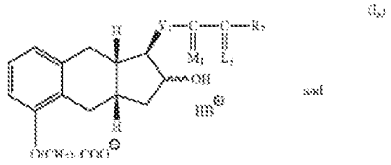
(2) 2-(2-furyl)ethyl,

(3) 2-(3-thienyl)ethoxy, or

(4) 3-thienyloxymethyl; M_1 is α-OH:β-R_5 or α-R_5β-OH or α-OR_1:β-R_5 or α-R_5:β-OR_2, wherein R_5 is hydrogen or methyl, R_2 is an alcohol protecting group, and L_1 is α-R_3:β-R_4, α-R_4:β-R_3, or a mixture of α-R_3:β-R_4 and α-R_4:β-R_3, wherein R_3 and R_4 are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R_3 and R_4 is fluoro only when the other is hydrogen or fluoro,

(b) hydrolyzing the product of formula III of step (a) with a base,

(c) contacting the product of step (h) with a base B to form a salt of formula I_5.



(d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula I.

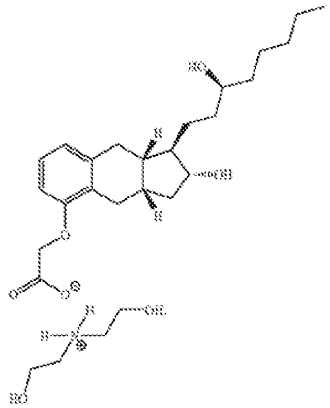
See '393 patent at claim 1.

B. '070 Patent

U.S. Patent No. 7,417,070 ("the '070 patent"), titled "COMPOUNDS AND METHODS FOR DELIVERY OF PROSTACYCLIN ANALOGS," issued on August 26, 2008 from U.S. Patent Application No. 10/851,481 ("the '481 application"), filed on May 24, 2004. U.S. Patent Nos. 7,384,978, 8,252,839, and 7,544,713 also descend from the '481 application. The '070 patent claims priority to U.S. Provisional No. 60/472,407, filed on May 22, 2003, the earliest potential priority date for the '070 patent. The '070 patent names as inventors Ken Phares and David Mottola. It is assigned on its face to United Therapeutics Corporation, which agrees with the USPTO's online assignment records. The '070 patent's term has been adjusted under 35 U.S.C. § 154(b) by 797 days. *See* '070 patent, Certificate of Correction (April 13, 2010); *see also* '481 Application, Petition Decision (March 9, 2010). Accordingly, the '070 patent is due to expire on July 30, 2026.

The '070 patent has three claims, of which only claim 1 is independent. All three claims are reproduced below.

1. A compound having the following structure:



2. The compound of claim 1, wherein the compound melts at about 107° C.

3. The compound of claim 1, wherein the compound has an x-ray powder diffraction pattern having a pattern peak at about 17.2 degrees 2 theta.

C. '839 Patent

U.S. Patent No. 8,252,839 ("the '839 patent"), titled "COMPOUNDS AND METHODS FOR DELIVERY OF PROSTACYCLIN ANALOGS," issued on August 28, 2012, from U.S. Patent Application No. 12/078,955 ("the '955 application"), filed on April 8, 2008, as a divisional U.S. Patent Application No. 11/603,124 (filed on November 22, 2006, issued as U.S. Patent No. 7,384,978, which was a continuation of the '481 application, which was filed on May 24, 2004, and issued as the '070 patent, addressed above). The '839 patent claims priority to U.S. Provisional No. 60/472,407, filed on May 22, 2003, the earliest potential priority date for the '839 patent. The '839 patent names as inventors Ken Phares and David Mottola. It is assigned on

its face to United Therapeutics Corporation. Assignment information for the '839 patent is not available from the USPTO's online assignment database. According to the Orange Book, the '839 patent is set to expire May 24, 2024.

The '839 patent has five claims, of which only claim 1 is independent. Claims 1 and 3–5, which UTC has asserted in this litigation, are reproduced below.

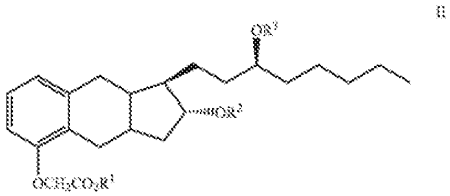
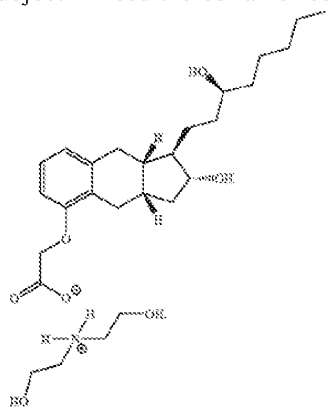
> 1. A pharmaceutical formulation comprising a therapeutically effective amount of a diethanolamine salt of treprostinil and a pharmaceutically acceptable carrier.
> 3. The pharmaceutical formulation according to claim 1, wherein the formulation exists in a dosage form selected from a capsule, tablet, liquid, or suspension.
> 4. The pharmaceutical formulation of claim 1, wherein the diethanolamine salt of treprostinil comprises a diethanolamine salt of (+)-treprostinil.
> 5. The pharmaceutical formulation of claim 1, wherein the diethanolamine salt of treprostinil comprises a polymorph of a diethanolamine salt of (+)- treprostinil, which polymorph melts at 107° C.

D. '713 Patent

U.S. Patent No. 7,544,713 ("the '713 patent"), titled "COMPOUNDS AND METHODS FOR DELIVERY OF PROSTACYCLIN ANALOGS," issued on June 9, 2009, from U.S. Patent Application No. 11/603,116 ("the '116 application"), filed on November 22, 2006, as a divisional of the '481 application, which was filed on May 24, 2004, and issued as the '070 patent, addressed above. The '713 patent claims priority to U.S. Provisional No. 60/472,407, filed on May 22, 2003, the earliest potential priority date for the '713 patent. The '713 patent names as inventors Ken Phares and David Mottola. It is assigned on its face to United Therapeutics Corporation. Assignment information for the '713 patent is not available from the USPTO's online assignment database. The '713 patent's term has been adjusted under 35 U.S.C. § 154(b) by fifty-one days. Accordingly, the '713 patent is due to expire on July 14, 2024. This agrees with the Orange Book listing.

A Certificate of Correction issued that changes independent claims 1 and 26 and dependent claims 2, 4, 6, 9, 12, 13, and 19. *See* Certificate of Correction (September 11, 2011).

The '713 patent has twenty-six claims, of which only claims 1, 23 and 26 are independent. UTC has asserted claims 23–25 in this litigation. Exemplary independent claims are reproduced below.

> 1. A method of treating pulmonary hypertension comprising orally administering a pharmaceutically effective amount of a compound of structure II to a subject in need thereof:
>
> 
>
> wherein,
>
> R_1 is independently selected from the group consisting of H, substituted and unsubstituted alkyl groups, arylalkyl groups and groups wherein OR_1 form a substituted or unsubstituted glycolamide ester;
>
> R_2 and R_3 may be the same or different and are independently selected from the group consisting of H, phosphate and groups wherein OR_2 and OR_3 form esters of amino acids or proteins, with the proviso that all of R_1, R_2 and R_3 are not H;
>
> an enantiomer thereof; or
>
> a pharmaceutically acceptable salt of the compound.
>
> 23. A method of treating pulmonary hypertension comprising orally administering to a subject in need thereof an effective amount of a compound of the following structure:
>
> 

E. '169 Patent

U.S. Patent No. 8,410,169 ("the '169 patent"), titled "COMPOUNDS AND METHODS FOR DELIVERY OF PROSTACYCLIN ANALOGS," issued on April 2, 2013 from U.S. Patent Application No. 11/189,072 ("the '072 application"), filed on July 26, 2005, which is a continuation of U.S. Patent Application No. 10/851,481 ("the '481 application"), filed on May 24, 2004, which issued as U.S. Patent No. 7,417,070 ("the '070 patent"). U.S. Patent Nos. 7,384,978, 8,252,839, and 7,544,713 also descend from the '481 application. The '169 patent claims priority to U.S. Provisional No. 60/472,407, filed on May 22, 2003, the earliest possible priority date for the '169 patent. The '169 patent names as inventors Ken Phares and David Mottola. The '169 patent is assigned on its face to United Therapeutics Corporation. The USPTO's online assignment records have no assignment data available for the '169 patent. The '169 patent's term has been adjusted under 35 U.S.C. § 154(b) by 2,091 days. *See* '169 patent, cover page; *see also* Issue Notification (March 13, 2013). Accordingly, the '169 patent is due to expire on February 13, 2030.

The '169 patent has eleven claims, of which claims 1, 2, 4, 6 and 8 are independent. UTC has asserted claims 8–11 in this litigation. The independent claims and dependent claims 9-11 are reproduced below.

> 1. A therapeutic composition comprising a diethanolamine salt of treprostinil in combination with at least one additional cardiovascular agent selected from the group consisting of a calcium channel blocker, a phosphodiesterase inhibitor, and an endothelial antagonist.
>
> 2. A method of treating pulmonary hypertension comprising administering to a subject in need thereof an effective amount of a therapeutic composition comprising a diethanolamine salt of treprostinil in combination with at least one additional cardiovascular agent.
>
> 4. A composition comprising a therapeutically effective amount of treprostinil, wherein said composition is a liposome.
>
> 6. A method of treating pulmonary hypertension comprising administering to a subject in need thereof an effective amount of the composition of claim 4.

8. A pharmaceutical composition for oral administration comprising a therapeutically effective amount of a salt or ester of treprostinil, wherein said composition provides an oral bioavailability of treprostinil at least 50% greater than the oral bioavailability of a composition with treprostinil as a free acid.

9. The composition of claim 8, wherein said composition provides an oral bioavailability of treprostinil at least 100% greater than the oral bioavailability of a composition with treprostinil as a free acid.

10. The composition of claim 8, wherein the ester is selected from the group consisting of a benzyl ester and an amino acid ester.

11. The composition of claim 8, wherein the ester is selected from the group consisting of a benzyl ester and a diglycine ester.

The dependent claims recite additional requirements relating to the class of the additional cardiovascular agent and the salt of treprostinil.

F. '311 Patent

U.S. Patent No. 9,050,311 ("the '311 patent"), titled "COMPOUNDS AND METHODS FOR DELIVERY OF PROSTACYCLIN ANALOGS," issued on June 9, 2015, from U.S. Patent Application No. 13/906,585 ("the '585 application"), filed on May 31, 2013. The '585 application purports to be a division of U.S. Patent Application No. 13/558,757 (filed July 26, 2012), which is a continuation of 12/078,955 (filed April 8, 2008), which purports to be a division of 11/603,124 (filed November 22, 2006), which is a continuation of 10/851,481 (filed May 24, 2004). The predecessor applications issued as U.S. Patent Nos. 8,536,363, 8,252,839, 7,384,978, and 7,417,070, respectively. The '311 patent claims priority to U.S. Provisional No. 60/472,407, filed on May 22, 2003, the earliest possible priority date for the '311 patent. The '311 patent names as inventors Ken Phares, David Mottola, and Hitesh Batra. It is assigned on its face to United Therapeutics Corporation, which agrees with the USPTO's online assignment records. The '311 patent is terminally disclaimed over the '070, '839, and '169 patents. *See* Terminal Disclaimer (December 16, 2014), Terminal Disclaimer Review Decision (December 31, 2014). Its term has been adjusted under 35 U.S.C. § 154(b) by 0 days. *See* Issue Notification

(May 20, 2015). Accordingly, the '311 patent is due to expire on May 24, 2024, twenty years after the earliest claimed non-provisional application filing date.

The '311 patent has eleven claims, of which claims 1, 10 and 11 are independent. All eleven claims are reproduced below.

> 1. A method of producing a pharmaceutically acceptable salt of treprostinil comprising dissolving treprostinil in a solvent, adding a base, heating, and cooling in an antisolvent to form a pharmaceutically acceptable salt of treprostinil as a crystalline solid.
>
> 2. The method of claim 1, wherein the base is an inorganic base.
>
> 3. The method of claim 2, wherein the base is an alkali metal.
>
> 4. The method of claim 3, wherein the alkali metal is sodium or potassium.
>
> 5. The method of claim 1, wherein the base is an organic base.
>
> 6. The method of claim 5, wherein the organic base is diethanolamine.
>
> 7. The method of claim 3, wherein the solvent comprises ethanol and water.
>
> 8. The method of claim 5, wherein the solvent comprises ethanol and water.
>
> 9. The method of claim 1, wherein the antisolvent comprises acetone.
>
> 10. A pharmaceutically acceptable crystalline salt of treprostinil produced by the method of claim 1.
>
> 11. A pharmaceutical composition prepared by combining a pharmaceutically acceptable salt of treprostinil produced according to the method of claim 1 and a pharmaceutically acceptable carrier.

G. '897 Patent

U.S. Patent No. 8,747,897 ("the '897 patent"), titled "OSMOTIC DRUG DELIVERY SYSTEM," issued on June 10, 2014, from U.S. Patent Application No. 11/412,100 ("the '100 application"), filed on April 27, 2006, the earliest potential priority date for the '897 patent. No earlier priority is claimed. The '897 patent names as inventors Argaw Kidane and Padmanabh P. Bhatt. The '897 patent is assigned on its face to Supernus Pharmaceuticals, Inc. which, according to the USPTO's online assignment records, is the current assignee. The '897 patent's term has been adjusted under 35 U.S.C. § 154(b) by 1,260 days. *See* '897 patent, cover page; *see also*

Issue Notification (May 21, 2014). Accordingly, the '897 patent is due to expire on October 8, 2029.[3]

The '897 patent has sixty claims, of which claims 1, 20, and 33 are independent. The independent claims are reproduced below.

> 1. An oral osmotic pharmaceutical dosage form of treprostinil, comprising an osmotically active drug core surrounded by a semi-permeable membrane, wherein the osmotically active drug core comprises
>
> A) at least one release enhancing agent selected from a group consisting of wicking agents, complexing agents, and micelle-forming agents, wherein
>
> i) the wicking agents are selected from the group consisting of high HLB surfactants, ionic surfactants, and non-swelling hydrophilic polymers,
>
> ii) the complexing agents are selected from the group consisting of polyvinyl pyrrolidone, cyclodextrins, and non-ionic surface active agents, and
>
> iii) the micelle-forming agents are selected from the group consisting of poly(ethylene oxide) modified sorbitan monoesters, fatty acid sorbitan esters, sodium lauryl sulfate, and sodium docusate,
>
> and
>
> B) treprostinil as treprostinil diethanolamine, and wherein the semi-permeable membrane includes at least one opening suitable for providing for the osmotic delivery of the treprostinil from the osmotically active drug core.
>
> 20. A method of oral delivery of treprostinil comprising administering to a human patient in need thereof an oral osmotic pharmaceutical dosage form of claim 1.
>
> 33. A method of treating a disease selected from the group consisting of pulmonary hypertension, pulmonary arterial hypertension (PAH), peripheral vascular disease (PVD), ischemic diseases, heart failure, conditions requiring anticoagulation, thrombotic microangiopathy, extracorporeal circulation, central retinal vein occlusion, atherosclerosis, inflammatory diseases, hypertension, cancer and other conditions of unregulated cell growth, comprising administering to a patient in need thereof an oral osmotic pharmaceutical dosage form of claim 1.

[3] The USPTO initially calculated a PTA of 1,414 days. *See* Determination of Patent Term Adjustment (February 4, 2014). The Applicants have petitioned the USPTO to recalculate the PTA to equal 2,030 days. *See* Request for Reconsideration of Patent Term Adjustment (August 5, 2014).

The dependent claims recite additional characteristics of the treprostinil diethanolamine (such as solubility and half-life), the pharmaceutical dosage form (such as pharmacokinetic parameters, release enhancing agent identity and concentration), and the condition being treated (such as pulmonary arterial hypertension).

H. '892 Patent

U.S. Patent No. 8,349,892 ("the '892 patent"), titled "SOLID FORMULATIONS OF PROSTACYCLIN ANALOGS," issued January 8, 2013, from U.S. Patent Application No. 12/775,102 ("the '102 application"), filed May 6, 2010. The '102 application claimed the benefit of U.S. Provisional Application No. 61/176,268, filed May 7, 2009, the earliest potential priority date for the '892 patent.

The listed inventor of the '892 patent is Kenneth R. Phares. The '892 patent is assigned on its face to United Therapeutics Corp. The USPTO's assignment database confirms the assignment from the inventor to United Therapeutics Corp. and indicates that United Therapeutics Corp. has an address of 1040 Spring Street, Silver Springs, Maryland 20910 and a correspondence address of Stephen B. Maebius, Foley & Lardner LLP, 3000 K Street, N.W. 61 Floor, Washington, D.C. 20007.

The '892 patent has 33 claims, of which claims 1, 9, 15, and 25 are independent. UTC has asserted claims 1–6, 9–23, and 25–32 in this litigation. The independent claims are produced below:

> 1. A pharmaceutical product comprising a pharmaceutical packaging; and a solid formulation inside the packaging, wherein the formulation comprises an active agent that is treprostinil diethanolamine, wherein the packaging is configured to maintain a moisture level in the solid formulation of greater than 3% and no more than 7%.
>
> 9. A pharmaceutical product comprising: (a) a pharmaceutical packaging; (b) a solid formulation inside the packaging, wherein the formulation comprises a active agent that is treprostinil diethanolamine; and (c) a desiccant inside the packaging, wherein an amount of the desiccant in the packaging is less than an effective amount for maintaining

a relative humidity level inside the packaging for a storage time of the formulation below 40%.

15. A storage method comprising: storing a solid formulation inside a pharmaceutical packaging, wherein the formulation comprises an active agent that is treprostinil diethanolamine; wherein a moisture level in the solid formulation after said storing is greater than 3% and no more than 7%.

25. A storage method comprising: storing a solid formulation and a desiccant inside a pharmaceutical packaging, wherein the formulation comprises an active agent that is treprostinil diethanolamine; wherein an amount of the desiccant is less that [sic] an effective amount for maintaining a relative humidity level inside the packaging during said storing below 40%.

I. '901 Patent

U.S. Patent No. 9,278,901 ("the '901 patent"), titled "COMPOUNDS AND METHODS FOR DELIVERY OF PROSTACYCLIN ANALOGS," issued on March 8, 2016 from U.S. Patent Application No. 14/710,694 ("the '694 application"), filed on May 13, 2015. The '694 application descends from a series of continuation and division applications: the '694 application is a continuation of application No. 14/490,014, filed on September 18, 2014, which is a continuation of application No. 13/906,585, filed on May 31, 2013, now Patent No. 9,050,311, which is a division of application No. 13/558,757, filed on July 26, 2012, now Patent No. 8,536,363, which is a continuation of application No. 12/078,955, filed on April 8, 2008, now Patent No. 8,252,839, which is a division of application No. 11/603,124, filed on November 22, 2006, now Patent No. 7,384,978, which is a continuation of application No. 10/851,481, filed on May 24, 2004, now Patent No. 7,417,070. The '070 patent claims priority to U.S. Provisional application No. 60/472,407, filed on May 22, 2003, the earliest potential priority date for the '901 patent. (U.S. Patent Nos. 7,384,978, 8,252,839, and 7,544,713 also descend from the '481 application.)

The '901 patent names as inventors Ken Phares, David Mottola, and Roger Jeffs. The '901 patent is assigned on its face to United Therapeutics Corporation. The USPTO's online

assignment records have no assignment data available for the '901 patent. The '901 patent's term has been adjusted under 35 U.S.C. § 154(b) by 0 days. *See* '901 patent, cover page; *see also* Issue Notification (February 17, 2016). Accordingly, the '901 patent is due to expire on May 24, 2024.

The '901 patent has twelve claims, of which claims 1 and 7 are independent. The independent claims are reproduced below.

> 1. A method of treating pulmonary hypertension comprising administering to a subject in needed thereof an oral pharmaceutical formulation comprising a pharmaceutically acceptable salt or ester of treprostinil which has an absolute bioavailability of at least 15%, wherein a Cmax in a plasma of the subject increases in a linear fashion with a dose of at least 0.05 mg administered to the subject and wherein a concentration of treprostinil in the plasma of the subject is at least 50 pg/ml for at least 8 hours.
>
> 7. A method of treating pulmonary hypertension comprising administering to a subject in needed thereof an oral pharmaceutical formulation comprising a pharmaceutically acceptable salt or ester of treprostinil which has an absolute bioavailability of at least 15%, wherein an AUCinf in a plasma of the subject increases in a linear fashion with a dose of at least 0.05 mg administered to the subject and wherein a concentration of treprostinil in the plasma of the subject is at least 50 pg/ml for at least 8 hours.

The dependent claims recite additional requirements listed below.

Claim no.	Claim no. dependent from	Additional limitation
2	1	the absolute bioavailability of said salt or ester ranges from 21 to 25%
3	1	the oral bioavailability of the salt or ester is at least 50% greater than the oral bioavailability of treprostinil as free acid
4	1	the oral bioavailability of the salt or ester is at least 100% greater than the oral bioavailability of treprostinil as free acid
5	1	the pharmaceutically acceptable salt or ester is the diethanolamine salt of treprostinil
6	1	the subject is a human
8	7	the absolute bioavailability of said salt or ester ranges from 21 to 25%
9	7	the oral bioavailability of the salt or ester is at least 50% greater than the oral bioavailability of treprostinil as free acid
10	7	the oral bioavailability of the salt or ester is at least 100%

		greater than the oral bioavailability of treprostinil as free acid
11	7	the pharmaceutically acceptable salt or ester is the diethanolamine salt of treprostinil
12	7	the subject is a human

I. IDENTIFICATION OF PRIOR ART UNDER L. PAT. R. 3.3(a)

Actavis relies on at least the following prior art in support of its invalidity contentions. Actavis reserves the right to rely upon additional prior art as discovery progresses, to the extent not addressed herein. Actavis further reserves the right to rely on all prior art cited or discussed during the prosecution of any of the patents-in-suit or any patents or patent applications to or through which the patents-in-suit claim priority, including provisional applications, as well as any related patents and applications, and any prior art identified in any other actions involving the patents-in-suit or related patents. Actavis further reserves the right to identify and rely on additional art or teachings within the art in the event that Actavis's evaluation of the prior art teachings is in any way contested, including to the extent plaintiff seeks to claim an earlier priority date for the asserted claims.

Unless otherwise stated, it should be presumed that Actavis intends to rely upon each reference in its entirety to the extent relevant and/or appropriate, including references cited in and/or referenced within the references identified below. Actavis also incorporates, in full, all prior art references cited in the patents-in-suit, their prosecution histories, and related patents and applications and their prosecution histories.

Claims 1–22 of the '393 patent are invalid as anticipated and/or obvious in view of at least the following prior art references, which are exemplary of the state of the art at the time of the filing of the '393 patent.

- U.S. Patent No. 6,765,117
- Moriarty et al., The Intramolecular Asymmetric Pauson-Khan Cyclization as a Novel and General Stereoselective Route to Benzidindene Protacyclins: Synthesis

of UT-15 (Treprostinil) J. Org. Chemistry, 2004, 69(6), 1890-1902 ("Moriarty 2004")

- Remodulin®
- Remodulin® Label
- Tyvaso® and Tyvaso® Label
- J. Olmsted III and G. M. Williams, Chemistry, The Molecular Science, Mosby-Year Book, Inc. (1994) ("Olmsted")
- Lin et al., Benzindene Prostaglandins. Synthesis of Optically Pure 15-Deoxy-U-68,215 and Its Enantiomer via a Modified Intramolecular Wadsworth-Emmons-Wittig Reaction, J. Org. Chemistry, 1987,52,5594-5601 ("Lin 1987")
- Aristoff et al., Total Synthesis of a Novel Antiulcer Agent via a Modification of the Intramolecular Wadsworth-Emmons-Wittig Reaction, J. Am. Chem. SOC. 1985, 107, 7967-7974 ("Aristoff 1985")
- McManus et al., Tetrazole Analogs of Plant Auxins, J. Org. Chemistry. 1959, 24, 1464-1467 ("McManus 1959")
- Ege, S., *Organic Chemistry Second Edition*, 543-547 (1989) ("Ege 1989")
- U.S. Patent Publication No. 2005/0085540 April 2005, Phares et al. ("Phares 2005")
- U.S. Patent Publication No. 2005/0165110 July 2005, Wade et al. ("Wade 2005")
- Japanese Patent App. No. 56-122328A, September 1981 ("Kawakami 1981")
- Arumugan et al., A New Purification Process for Pharmaceutical and Chemical Industries, Organic Process Research & Development 2005, 9, 319-320 ("Arumugan 2005")
- Yu et al., Novel Synthetic Route of a Pivotal Intermediate for the Synthesis of 1â-Methyl Carbapenem Antibiotics, Organic Process Research & Development 2006, 10, 829-832 ("Yu 2006")
- Monson, Advanced Organic Synthesis, Methods and Techniques, 178-188 (1971) ("Monson 1971")
- Harwood, Experimental organic chemistry: Principles and Practice, 127-134 (1989) ("Harwood 1989")
- Eliel, Stereochemistry of Organic Compounds, 322-325 (1994) ("Eliel 1994")

- Jones, Organic Chemistry, 153-155 (2nd ed. 2000) ("Jones 2000")
- Sorrell, Organic Chemistry, 755-758 (1999) ("Sorrell 1999")
- Pavia, Introduction to Organic Laboratory Techniques, 648 (1998) ("Pavia 1998")
- Priscinzano, Piperidine Analogues of 1-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-4-(3-phenylpropyl)piperazine (GBR 12909): High Affinity Ligands for the Dopamine Transporter, J. Med. Chem. 2002, 45, 4371-4374 ("Priscinzano 2002")
- Ohno, Development of Dual-Acting Benzofurans for Thromboxane A2 Receptor Antagonist and Prostacyclin Receptor Agonist: Synthesis, Structure-Activity Relationship, and Evaluation of Benzofuran Derivatives, J. Med. Chem. 2005, 48, 5279-5294 ("Ohno 2005")
- Burk, An Enantioselective Synthesis of (S)-(+)-3-Aminomethyl-5-methylhexanoic Acid via Asymmetric Hydrogenation, J. Org. Chem. 2003, 68, 5731-5734 ("Burk 2003")
- Wiberg, Laboratory Technique In Organic Chemistry, 112 (1960) ("Wiberg 1960")
- Schoffstall, et al., Microscale and Miniscale Organic Chemistry Laboratory Experiments, 200-202 (2d ed.) (2004) ("Schoffstall 2004")
- The 2005 Physicians' Desk Reference for Bicillin® L-A (penicillin G benzathine suspension) ("PDR 2005 Bicillin® L-A")
- The references cited or disclosed during prosecution of the '393 patent
- All references cited for the other patents-in-suit

Claims 1–3 of the '070 patent are invalid as anticipated and/or obvious in view of at least the following prior art references, which are exemplary of the state of the art at the time of the filing of the '070 patent.

- U.S. Patent No. 4,306,075
- U.S. Patent No. 4,434,164
- U.S. Patent No. 5,153,222
- U.S. Patent No. 5,466,713
- U.S. Patent No. 5,506,265

- U.S. Patent No. 5,234,953
- U.S. Patent Publication No. 2001/0056095 December 2001 ("Mylari 2001")
- 07/07/11 Correspondence enclosing new set of claims related to EP application 04776104
- Ansel et al., Pharmaceutical Dosage Forms and Drug Delivery Systems, 102-106; 116-117; 196-203 tablets; 548, eds., 7th ed. (1999)
- Beghetti et al., Aerosolized Iloprost Induces a Mild but Sustained Inhibition of Platelet Aggregation 2002, 518-524
- Chattaraj, Current Opinion Investig. Drugs, 3(4) 582-6 (Abstract) (2002)
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- Remodulin®
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- Vizza et al., Long Term Treatment of Pulmonary Arterial Hypertension with Beraprost, An Oral Prostacyclin Analogue 2001, 661-665
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- L. Yu et al., "Crystallization and Polymorphism of Conformationally Flexible Molecules: Problems, Patterns, and Strategies," Organic Process Research & Development 4, 396- 402 (2000) ("Yu 2000")

- J. Haleblian and W. McCrone, "Pharmaceutical Applications of Polymorphism," J. Pharm. Sci., 58, 911-929 (1969) ("Haleblian 1969")

- J.K. Haleblian, "Characterization of Habits and Crystalline Modification of Solids and Their Pharmaceutical Applications," J. Pharm. Sci., 64, 1269-1288 ("Haleblian 1975")

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Claims 1 and 3–5 of the '839 patent are invalid as anticipated and/or obvious in view of at least the following prior art references, which are exemplary of the state of the art at the time of the filing of the '839 patent.

- U.S. Patent No. 4,306,075
- U.S. Patent No. 4,434,164
- U.S. Patent No. 5,153,222
- U.S. Patent No. 5,466,713
- U.S. Patent No. 5,506,265
- Shekunov, B.Yu, et al., *Crystallization process in pharmaceutical technology and drug delivery design*, Journal of Crystal Growth 211 (2000) 122–36 ("Shekunov")
- U.S. Patent No. 5,234,953
- U.S. Patent Publication No. 2001/0056095 December 2001 ("Mylari 2001")
- 07/07/11 Correspondence enclosing new set of claims related to EP application 04776104
- Ansel et al., Pharmaceutical Dosage Forms and Drug Delivery Systems, 102-106; 116-117; 196-203 tablets; 548, eds., 7th ed. (1999)
- Beghetti et al., Aerosolized Iloprost Induces a Mild but Sustained Inhibition of Platelet Aggregation 2002, 518-524
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- L. Yu et al., "Crystallization and Polymorphism of Conformationally Flexible Molecules: Problems, Patterns, and Strategies," Organic Process Research & Development 4, 396- 402 (2000) ("Yu 2000")

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- The prior art for the '070 patent and other patents-in-suit

Claims 23–25 of the '713 patent are invalid as anticipated and/or obvious in view of at least the following prior art references, which are exemplary of the state of the art at the time of the filing of the '713 patent.

- U.S. Patent No. 4,306,075

- U.S. Patent No. 4,434,164

- U.S. Patent No. 5,153,222

- U.S. Patent No. 5,466,713

- U.S. Patent No. 5,506,265

- Shekunov, B.Yu, et al., *Crystallization process in pharmaceutical technology and drug delivery design*, Journal of Crystal Growth 211 (2000) 122–36 ("Shekunov")

- U.S. Patent No. 5,234,953

- U.S. Patent Publication No. 2001/0056095 December 2001 ("Mylari 2001")

- 07/07/11 Correspondence enclosing new set of claims related to EP application 04776104

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- EP 04776104 Supplementary European Search Report
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- The prior art for the '070 patent and other patents-in-suit

Claims 8–11 of the '169 patent are invalid as anticipated and/or obvious in view of at least the following prior art references, which are exemplary of the state of the art at the time of the filing of the '169 patent.

- U.S. Patent No. 4,306,075
- U.S. Patent No. 4,434,164
- U.S. Patent No. 5,153,222
- U.S. Patent No. 5,466,713
- U.S. Patent No. 5,506,265
- WO 98/18452
- U.S. Patent No. 5,234,953
- U.S. Patent Publication No. 2001/0056095 December 2001 ("Mylari 2001")
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- EP 04776104 Letter 12/20/05 enclosing a new set of claims for the purposes of examination of the European patent application

- EP 04776104 Supplementary European Search Report

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- EU Application No. EP20040776104 ("EP '104 application," filed on May 24, 2004): Reply (July 11, 2011)

- EU Application No. EP20040776104, Annex to Communication (April 29, 2014)

- EU Application No. EP20040776104, Letter (December 20, 2005)
- Fisher, United Therapeutics Receives FDA Approvable Letter for Remodulin to Treat Pulmonary Arterial Hypertension 2002

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- Keith Guillory, "Generation of Polymorphs, Hydrates, Solvates, and Amorphous Solids," Polymorphism in Pharmaceutical Sciences (H. Brittain ed. 1999) ("Guillory")

- L. Yu et al. "Physical Characterization of Polymorphic Drugs: An

Integrated Characterization Strategy" PSTT 1(3):118-127 (1998) ("Yu 1998")

- L. Yu et al., "Crystallization and Polymorphism of Conformationally Flexible Molecules: Problems, Patterns, and Strategies," Organic Process Research & Development 4, 396-402 (2000) ("Yu 2000")

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- N. Rodriguez-Hornedo and D. Murphy, "Significance of Controlling Crystallization Mechanisms and Kinetics in Pharmaceutical Systems," Journal of Pharmaceutical Sciences, 88, 651-660 (1999) ("Hornedo")

- Office Action App. No. 11/189,072 - 05/24/2011

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- Phares et al., Compounds and Methods for Delivery of Prostacyclin Analogs appl. No. 12/078,955
- Reepmeyer et al., *Characterization and Crystal Structure of Two Polymorphic Forms of Racemic Thalidomide*, J. Chem. Soc. Perkin Trans. 2, 2063-67 (1994) ("Reepmeyer")

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- Walter C. McCrone, Polymorphism, Physics and Chemistry Of The Organic Solid State 727, Fox, et al., eds., (1965) ("McCrone")
- The prior art for the '070 patent and other patents-in-suit

Claims 1–11 of the '311 patent are invalid as anticipated and/or obvious in view of at least the following prior art references, which are exemplary of the state of the art at the time of the filing of the '311 patent.

- The references for the '070 patent and other patents-in-suit
- U.S. Patent No. 5,234,953
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- U.S. Patent Application No. 13/906,585, Amendment (August 27, 2014)
- U.S. Patent Application No. 13/906,585, Amendment (November 15, 2013)
- Shekunov, B.Yu, et al., *Crystallization process in pharmaceutical technology and drug delivery design*, Journal of Crystal Growth 211 (2000) 122–36 ("Shekunov")
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- Sharp, J.T., et al., *Practical Organic Chemistry: A student handbook of techniques*, pp. 64–85 (1989)
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- Yeo, Sang-Do, et al., *Formation of Microparticulate Protein Powders Using a Supercritical Fluid Antisolvent*, Biotechnology and Bioengineering, Vol. 41, pp. 341-46 (1993) ("Yeo").
- U.S. Patent No. 4.434,464

Claims 1–60 of the '897 patent are invalid as anticipated and/or obvious in view of at least the following prior art references, which are exemplary of the state of the art at the time of the filing of the '897 patent.

- U.S. Patent No. 4,434,164
- U.S. Publication No. 2001/0056095
- U.S. Publication No. 2001/0038855
- U.S. Publication No. 2004/0170684
- WO 2005/007081
- U.S. Patent No. 5,234,953

- EP 0947196 Patent Application (Hara 1999)
- WO 98/18452
- U.S. Patent No. 6,706,283
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- Ansel et al., Pharmaceutical Dosage Forms and Drug Delivery Systems, 102-106; 116-117; 196-203 tablets; 548, eds., 7th ed. (1999)
- Berge et al., *Pharmaceutical Salts*, Journal of Pharmaceutical Sciences, 66, 1-19 (1977)
- Budavari, S., Merck Index, 218, 337, 1563-64, 11th ed. (1989)
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- D. L. Pavia et al., Introduction to Organic Laboratory Techniques, Second Edition, Saunders College Publishing (1982) ("Pavia")
- European Pharmacopoeia 5.0, 2032-2034 (2005)
- Gautam R. Desiraju, "Crystal Gazing: Structure Prediction and Polymorphism," 278 Science 404 (Oct. 17, 1997) ("Desiraju")
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- Remodulin®

- Remodulin® Label

- Tyvaso® and Tyvaso® Label

- U.S. Patent No. 6,521,212 and its file history, including 2001-7-12 Office Action

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- The prior art for the '070 patent and other patents-in-suit

Claims 1–6, 9–23, and 25–32 of the '892 patent are invalid as anticipated and/or obvious in view of at least the following prior art references, which are exemplary of the state of the art at the time of the filing of the '892 patent.

- U.S. Patent Application No. 12/775,102, Comments dated November 30, 2012
- U.S. Patent Application No. 12/775,102, Notice of Allowance September 14, 2012
- U.S. Patent Application No. 12/775,102, Office Action dated April 11, 2012
- U.S. Patent Application No. 12/775,102, Response dated July 10, 2012
- Freedom Study
- U.S. Patent Publication No. 2005/0085540 April 2005, Phares et al. ("Phares 2005")
- FDA Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics (May 1999)
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- Watson Pharmaceutical Inc. Lead Formulation Checklist
- WO 98/18452
- Webster's Ninth New Collegiate Dictionary, 718 (1989)
- U.S. Patent No. 5,234,953
- Lockhart, H., et al., *Packaging of Pharmaceuticals and Healthcare Products*, Blackie Academic & Professional, an imprint of Chapman & Hall (1996) ("Lockhart")
- *Regulatory approval received for dessicant system that allows for specific humidity targets: TricorBraun achieves FDA certification for DryKeep*, TricorBraun press release, Apr. 8, 2009.
- *Dessicant delivery systems: absorbent lined vials from CSP Technologies Inc., Auburn, AL, USA*, Pharm-Med-Packag-News, vol. 11, no. 11 (Nov. 2003), p. 70
- *Protective desiccants: product review*, Pharm-Med-Packag-News, vol. 10, no. 3 (Mar. 2002), p. 76
- The prior art for the '070 patent and other patents-in-suit

Claims 1–12 of the '901 patent are invalid as anticipated and/or obvious in view of at least the following prior art references, which are exemplary of the state of the art at the time of the filing of the '901 patent.

- The references for the '070 patent and other patents-in-suit
- U.S. Patent Application No. 11/189,072, Amendment (August 22, 2011)

- U.S. Patent Application No. 11/189,072, Office Action (May 24, 2011)
- U.S. Patent No. 4,306,075
- U.S. Patent No. 5,153,222
- U.S. Patent No. 5,466,713
- U.S. Patent No. 5,506,265
- WO 98/18452
- U.S. Publication No. 2001/0056095
- United Therapeutics, Press Release (February 11, 2002)
- U.S. Patent No. 4,434,164
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- Chattaraj, Current Opinion Investig. Drugs, 3(4) 582-6 (Abstract) (2002)
- EP 04776104 Supplementary European Search Report
- EU Application No. EP20040776104 ("EP '104 application," filed on May 24, 2004): Reply (July 11, 2011)
- EU Application No. EP20040776104, Annex to Communication (April 29, 2014)
- EU Application No.EP 04776104, Letter Dec 20, 2005
- EU Application No.EP 04776104, Reply (November 5, 2012)
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- Phares et al., Compounds and Methods for Delivery of Prostacyclin Analogs appl. No. 12/078,955 Declaration Under 37 C.F.R. §1.132 of Kenneth Phares
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- Remodulin® Label
- Tyvaso® and Tyvaso® Label
- Rowe et al., Handbook of Pharmaceutical Excipients, V-VIII; 568, 4th ed. (2003)
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- Swarbrick et al., Salt Forms of Drugs and Absorption, Encyclopedia of Pharmaceutical Technology 453-499 (1996) ("Bighley")
- Berge et al., *Pharmaceutical Salts*, Journal of Pharmaceutical Sciences, 66, 1 - 19 (1977)
- U.S. Patent No. 5,234,953

II. EXPLANATION OF ANTICIPATION AND/OR OBVIOUSNESS UNDER L. PAT. R. 3.3(b)

As reflected below, all the asserted claims of the patents-in-suit are invalid under 35 U.S.C. §§ 102 and 103 as anticipated and/or obvious over the prior art, including the specific references listed above and as further discussed below in this document and the attached Exhibits

containing claim charts discussing the prior art. A patent is anticipated under § 102 when a reference (1) discloses each and every element of the claimed invention, whether it does so explicitly or inherently; and (2) enables one of ordinary skill in the art to make the invention without undue experimentation. *In re Gleave*, 560 F.3d 1331, 1334 (Fed. Cir. 2009). A patent would have been obvious under § 103 if it claims, among other things, "the predictable use of prior art elements according to their established functions." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 401 (2007).

A. Invalidity of the '393 Patent

Actavis incorporates by reference, as if set forth verbatim herein, the invalidity defenses and supporting evidence put forth by any party in any case relating to the '393 patent.

The '393 patent contains product-by-process claims that cover making treprostinil or various salts of treprostinil. The focus of the invalidity analysis for a product-by-process claim is the product produced by the claimed process. *Amgen Inc. v. F. Hoffmann-La Roche, Ltd.*, 580 F.3d 1340, 1369-70 (Fed. Cir. 2009). The prior art does not need to teach the process limitations so long as the prior art product is the same as the claimed product. *Id.* UTC asserts that Actavis infringes claims 1-22 of the '393 patent. As explained below, Actavis hereby contends that all claims are invalid as anticipated or obvious.

1. Claims 1-22 of the '393 Patent Are Anticipated by the '117 Patent, Moriarty 2004, Remodulin®, and/or Phares 2005.

Claims 1–22 of the '393 patent are invalid as anticipated by at least the '117 patent, Moriarty 2004, UTC's own Remodulin® drug product (first approved by the FDA in May 2002 and offered for sale to the public in 2002), and Phares 2005. In the case of product-by-process claims, the focus of the anticipation analysis is the product produced by the claimed process. *See Amgen Inc.*, 580 F.3d at 1369-70. Here, as explained in further detail below, the prior art

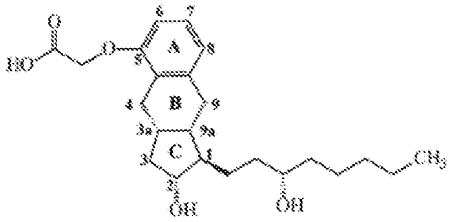
discloses the same product, treprostinil, or its pharmaceutically acceptable salt, as the claimed product and thus anticipates the claims.

a. The '117 Patent

The '117 patent issued on July 20, 2004. As such, it is prior art under at least 35 U.S.C. § 102(b). The '117 patent is titled "Process for Stereoselective Synthesis of Prostacyclin Derivatives." The face of the '117 patent indicates that it is assigned to UTC and includes one inventor in common with the '393 patent (Raju Penmasta). The '117 patent is listed in the Orange Book as covering Tyvaso® and Remodulin® (treprostinil) and claims the same compound and its salt form as the '393 patent. '117 patent at col. 20, l. 10–col. 21, l. 12, claims 1-4. Where the '117 patent discloses each of the limitations of the asserted claims is included in the corresponding chart.

b. Moriarty 2004

Moriarty 2004 is a 2004 article published in the Journal of Organic Chemistry by the named inventors of the '117 patent discussing the synthesis of UT-15 (treprostinil). As such, it is prior art under at least 35 U.S.C. § 102(b). Similar to the disclosures of the '117 patent, Moriarty 2004 discloses compound 7 (page 1892), the same compound that falls within the claimed compound for all of the claims of the '393 patent.



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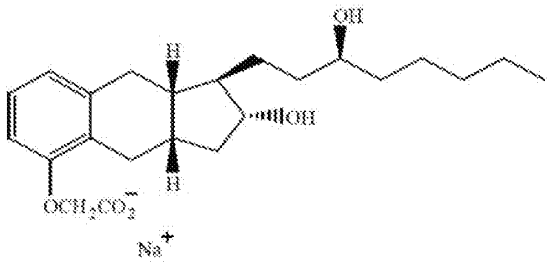
Moriarty 2004 discloses an improved "route for synthesis and subsequent manufacture of a complex drug substance on a multikilogram scale." Moriarty 2004 at Abstract. With the

exception of claims 2 and 10, there are no purity requirements in the asserted claims, and thus those claims cannot be used to distinguish the prior art. *See Cubist Pharm., Inc. v. Hospira, Inc.*, No. CA 12-367-GMS, 2014 WL 6968046, at *19-20 (D. Del. Dec. 8, 2014). Claims 2 and 10 require a purity of the product of at least 99.5%, but Moriarty 2004 discloses that the compound is produced with 99.7% purity (page 1902) and thus anticipates those claims. Where Moriarty 2004 discloses each of the limitations of the asserted claims is included in the corresponding chart.

c. Remodulin®

The treprostinil that was used in UTC's commercial embodiment Remodulin®, first approved, marketed, and sold to the public in 2002, with all its attributes and inherent qualities, also anticipates the '393 patent. Remodulin® was approved in 2002 and was publicly available at least one year prior to the application of the '393 patent. *See, e.g.*, Phares 2005 (disclosing the availability of treprostinil sodium (Remodulin®) [0004]); *see also* Wade 2005 at [0021, 0024] (disclosing treprostinil used in Remodulin® and its salt forms). As such, it is prior art under at least 35 U.S.C. § 102(b). According to its prescribing information, Remodulin® is a treprostinil sodium having the following structural formula:



Where Remodulin® discloses each of the limitations of the asserted claims is included in the corresponding chart.

d. U.S. Patent Publication No. 2005/0085540

Phares 2005 is the publication of a patent application by Ken Phares and David Mottola. It was assigned to UTC and published on April 21, 2005. As such, it is prior art under at least 35 U.S.C. § 102(b). Phares 2005 also discloses the claimed compound of the '393 patent in at least two salt forms and further discloses that the sodium salt of the compound is sold as Remodulin®. Phares 2005 para. [0051]. Where Phares 2005 discloses each of the limitations of the asserted claims is included in the corresponding chart.

e. J. Olmsted III and G. M. Williams, Chemistry, The Molecular Science, Mosby-Year Book, Inc. (1994)

Olmsted was published in 1994 and is at least § 102(b) prior art. It teaches that "[r]ecrystallization is a classic way of removing impurities from a crude solid." Olmsted at 476. For example, "[i]f a solid substance is dissolved in a minimum volume of hot solvent that is then allowed to cool, the solubility of the solid is exceeded, and it crystallizes from the solvent. In favorable cases, the impurities remain dissolved in the cold solvent, and the solid has been purified." *Id.*

f. Sharp, J.T., *Practical Organic Chemistry: A student handbook of techniques*, pp. 64–85 (1989):

Sharp is at least § 102(b) prior art. It discloses crystallization as "the most common method for purification of organic solids that are not heavily contaminated with other substances." p. 64. Sharp disclosesthe crysytallization process. *Id.* Sharp also discloses that melting point indicates purity. *Id.*

2. Claims 1-22 Would Have Been Obvious in View of the Prior Art.

Claims 1–22 are also invalid as obvious to a POSA in view of the prior art. As discussed above, claims 1–22 are product-by-process claims directed to treprostinil or its pharmaceutically acceptable salt. The claimed process involves an alkylation of triol compound to a benzindene

nitrile compound, hydrolysis of the nitrile compound, formation of a salt using "a base B," and optionally reacting the salt with an acid to form treprostinil. As noted above, in the case of a product-by-process claim, the focus of the invalidity analysis is the product produced by the claimed process. *See Amgen Inc.*, 580 F.3d at 1369-70. The prior art does not need to teach the process limitations so long as "the product in a product-by-process claim is the same as or obvious from a product of the prior art." *Id.* at 1366. Here, the prior art discloses obvious variations of the same product, treprostinil and pharmacologically acceptable salt forms of treprostinil, as well as all of the process limitations.

As discussed in the anticipation section above, treprostinil and its pharmaceutically acceptable salts as claimed in the '393 patent were well-known in the art at the time as of the '393 priority date. *See* Remodulin® product; the '117 patent, col. 20, l. 10–col. 21, l. 12; Moriarty 2004 p. 1892 compound 7, p. 1902; Phares 2005 para. [0051]. As the applicants conceded, treprostinil (the claimed product and active ingredient in Remodulin®) was well known and first described in U.S. Pat. No. 4,306,075, which issued on December 15, 1981. '393 patent, col. 1, lines 22-28. Indeed, the applicants further admitted that "[t]reprostinil, and other prostacyclin derivatives have been prepared as described in Moriarty, et al in J. Org. Chem. 2004, 69, 1890-1902 ..., 6,765,117 and 6,809,223." *Id.*

Even if the process limitations were relevant, those limitations were obvious in light of the prior art for the reasons discussed below. An improved process for making treprostinil is disclosed in U.S. Patent No. 4,668,814, which issued on May 26, 1987, and the '117 patent discloses a further improved process for making treprostinil.

The prior art shows that it would have been well known to a POSA to synthesize treprostinil via alkylation of benzindene triol followed by the hydrolysis of benzindene nitrile.

See '117 patent col. 20, l. 10–col. 21, l. 12; Moriarty 2004 p. 1892 compound 7, p. 1902. Such alkylation reactions adding $ClCH_2CN$ and then subsequent hydrolysis to the carboxylic acid would have also been well-known in the art. *See, e.g.*, Lin 1987 at p. 5595; Aristoff 1985 at p. 7971; McManus 1959 at pp. 1465-1467.

The prior art also teaches a POSA the synthesis of treprostinil using purification by column chromatography. *See* '117 Patent col. 20, l. 10–col. 21, l. 12; Moriarty 2004 p. 1892 compound 7, p. 1902. The prior art further teaches that purification by chromatography is not favored for large-scale industrial production. *See* Monson 1971 p. 185; Arumugan 2005 p. 319; Yu 2006 p. 832. The use of crystallization and recrystallization as a purification technique was well-known. *See, e.g.*, Monson 1971 pp. 181–83; Harwood 1989 pp. 127–34; Pavia 1998 p. 648. In fact, it was known since at least 1853 (from the work of Louis Pasteur) that carboxylate ammonium salts are formed from adding a carboxylic acid with an amine, and that those salts can be purified by recrystallization. *See* Eliel 1994 p. 322; *see also* Jones 2000 pp. 153–55; Sorrell, 1999 pp. 755–58. Additionally, carboxylate ammonium salts are very common and well known for use in drugs and drug targets, including diethanolamine salts. *See, e.g.*, Priscinzano 2002 pp. 4371–74; Ohno 2005 pp. 5279–94, compound 7; Burk 2003 pp. 5731–34; PDR 2005 Bicillin® L-A.

The prior art also teaches a POSA that treprostinil can be crystallized and that the diethanolamine salt of treprostinil is particularly preferred. *See* Phares 2005 para. [00051], figures 15-22; Moriarty 2004 p. 1892 compound 7, p. 1902. The prior art further discloses that other physiologically acceptable salts of treprostinil include salts derived from bases, such as ammonia, N-methyl-D-glucamine, magnesium, arginine and lysine. *See* Wade 2005 para. [0024]. It was also known in the art that salts of treprostinil could be reacted with diluted HCl to form

treprostinil. *See* '117 Patent col. 20, l. 10–col. 21, l. 12; Moriarty 2004 p. 1892 compound 7, p. 1902.

In view of the known fact that purification by chromatography is not favored for large-scale industrial production, a POSA would have been motivated to apply an obvious form of purification, salt crystallization, to form known salt forms of treprostinil.

As discussed below and further in Actavis's invalidity charts, each step of independent claims 1 and 9 was known and disclosed in the prior art, and it would have been obvious to a POSA to combine these well-known and standard steps to synthesize treprostinil. Under controlling law, of course, none of this analysis is necessary. The asserted claims are obvious if one or more of the products that results from the claimed processes is obvious. Actavis provides this analysis in the event UTC argues that it is required under applicable law.

Step (a) – Alkylation: The prior art discloses alkylation of benzindene triol with an alkylating agent to produce benzindine nitrile. *See* '117 patent col. 20, l. 10–col. 21, l. 12; Moriarty 2004 p. 1892 compound 7, p. 1902. Such alkylation reactions adding $ClCH_2CN$ for subsequent hydrolysis to the carboxylic acid were well-known in the art. *See, e.g.*, Lin 1987 p. 5595; Aristoff 1985 p. 7971; McManus 1959 pp. 1465-1467.

Step (b) – Hydrolysis: The prior art discloses the hydrolysis of benzindene nitrile. *See* '117 patent col. 20, l. 10–col. 21, l. 12; Moriarty 2004 p. 1892 compound 7, p. 1902. Such alkylation reactions adding $ClCH_2CN$ and then subsequent hydrolysis to the carboxylic acid compound were well-known in the art. *See, e.g.*, Lin 1987 p. 5595; Aristoff 1985 p. 7971; McManus 1959 pp. 1465–67.

Step (c) – formation of salt with base B: The prior art discloses the synthesis of treprostinil. As noted above, the prior art further describes the well-known technique of

purification by crystallization or recrystallization. *See, e.g.*, Monson 1971 pp. 181–83; Harwood 1989 pp. 127–34; Pavia 1998 p. 648; Eliel 1994 p. 322; *see also* Jones 2000 pp. 153–55; Sorrell 1999 pp. 755–57; Priscinzano 2002 pp. 4371–74; Ohno 2005 pp. 5279–94, compound 7; Burk 2003 pp. 5731–34; PDR 2005 Bicillin® L-A. Moreover, the prior art teaches a POSA that treprostinil can be crystallized, and that the diethanolamine salt of treprostinil is particularly preferred. *See* Phares 2005 para. [00051], figures 15–22; Moriarty 2004 p. 1892 compound 7, p. 1902. The prior art also discloses that other physiologically acceptable salts of treprostinil include salts derived from bases, such as ammonia, N-methyl-D-glucamine, magnesium, arginine and lysine. *See* Wade 2005 para. [0024].

Step (d) – optional reaction of the salt with acid to form the neutral compound: Step (d) is optional, but the prior art teaches a POSA that salts of treprostinil could be reacted with diluted HCl acid to form treprostinil. *See* '117 patent col. 20, l. 10–col. 21, l. 12; Moriarty 2004 p. 1892 compound 7, p. 1902. Therefore, it would have been obvious to react the salt formed during the crystallization step with an acid to form treprostinil.

Indeed, steps (c) and (d) of Claims 1 and 9 disclose standard well-known, organic chemistry techniques for purification of a carboxylic acid, such as treprostinil acid. The formation of a carboxylate salt, by the addition of a weak base to a neutral carboxylic acid, and the subsequent addition of a strong acid to regenerate carboxylic acid, as disclosed in steps (c) and (d), was a well-known purification technique. Such techniques were included in introductory organic chemistry textbooks, well before December 17, 2007. For example, Wiberg 1960, an organic chemistry lab textbook from 1960 states:

> A typical example is the purification of a water-insoluble solid carboxylic acid by dissolving it in sodium hydroxide solution, filtering, precipitating the compound by the addition of acid. A similar procedure may be used with amines: dissolve the compound in acid and precipitate it with a base. These procedures usually

> work quite well in that they utilize a chemical reaction to aid in separation from nonacidic or nonbasic impurities.

(Wiberg, 1960 p. 6); *see also* Schoffstall 2004 at pp. 3–40 (describing an experiment in which carboxylic acid is separated from neutral and basic organic compounds by conversion to a salt; addition of an acid, such as HCl, then regenerates the carboxylic acid, which can then be filtered or extracted into an organic solvent).

More specifically, contacting a carboxylic acid of a prostacyclin derivative, such as treprostinil, with a base to form a salt, followed by the addition of a strong acid to regenerate the carboxylic acid, was well-known in the prior art. For example, Phares 2005 discloses that the preparation of treprostinil diethanolamine includes the step of adding and dissolving diethanolamine (*i.e.*, a base) to treprostinil that is dissolved in a 1:1 molar ratio mixture of ethanol: water. (Phares 2005, Table 16). This treprostinil diethanolamine can be further precipitated and purified to form the purer and more stable crystal form called "Form B." (*id.* ¶ [0327]). *See also* Kawakami at p. 6 (disclosing the preparation and use of dicyclohexylamine (*i.e.*, a base) to form a crystalline dicyclohexylamine salt of a methanoprostacyclin derivative, in order to purify the methanoprostacyclin); Ege 1989 at p. 8 (disclosing 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.* p. 8).

Dependent claims 2 and 10 claim the product of claims 1 and 9, respectively, wherein the purity of compound is at least 99.5%. These claims are rendered obvious for the same reasons as stated above. It would have been obvious to use a pure product in a pharmaceutical product for the same reasons as stated above. Furthermore, "[p]urification by recrystallization works best when the crude solid contains a low percentage of impurities." Olmsted at 476; *see also* Sharp at 64. Therefore, it would have been obvious to obtain a more pure product in order to be able to

purify through recrystallization. Additionally, Moriarty 2004 discloses 99.7% purity for treprostinil. p. 1902.

Dependent claim 3 claims the product of claim 1, wherein the alkylating agent is $Cl(CH_2)_wCN$, $Br(CH_2)_wCN$, or $I(CH_2)_wCN$. This claim is rendered obvious for the same reasons as above. Additionally, the prior art discloses that the alkylating agent is $ClCH_2CN$. *See* '117 patent col. 20, l. 10–col. 21, l. 12; Moriarty 2004 p. 1892 compound 7, p. 1902.

Dependent claim 4 claims the product of claim 1, wherein the base in step (b) is KOH or NaOH. This claim is rendered obvious for the same reasons as above. Additionally, the prior art discloses that the base in step (b) is KOH. *See* '117 patent col. 20, l. 10–col. 21, l. 12; Moriarty 2004 p. 1892 compound 7, p. 1902.

Dependent claim 5 claims the product of claim 1, wherein the base B in step (c) is selected from the group consisting of ammonia, N-methylglucamine, procaine, tromethamine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine. This claim is rendered obvious for the same reasons as above. Also, the claim includes commonly known and utilized bases, and it would have been a matter of routine experimentation for a POSA to choose the bases included. In particular, the prior art specifically discloses that physiologically acceptable salts of treprostinil include salts derived from these bases. *See* Wade 2005 para. [0024]. Furthermore, the prior art also discloses that treprostinil can be crystallized and the diethanolamine salt of treprostinil is particularly preferred. *See* Phares 2005 para. [0051]. Thus, it would have been obvious for a POSA to choose a base that was already known to form a salt with treprostinil.

Dependent claim 6 claims the product of claim 1, wherein the acid in step (d) is HCl or H_2SO_4. This claim is rendered obvious for the same reasons as above. Additionally, the prior art

discloses salts of treprostinil could be reacted with diluted HCl to form treprostinil. *See* '117 patent col. 20, l. 10–col. 21, l. 12; Moriarty 2004 p. 1892 compound 7, p. 1902. Therefore, it would have been obvious to react the salt formed during the crystallization step with diluted HCl to form treprostinil.

Dependent claim 7 claims the product of claim 1, wherein Y_1 is —CH_2CH_2—; M_1 is α-OH:β-H or α-H:β-OH; —$C(L_1)$-R_7 taken together is —$(CH_2)_4CH_3$; and w is 1. This claim is rendered obvious for the same reasons as above.

Dependent claim 8 claims the product of claim 1, wherein the process does not include purifying the compound of formula (III) produced in step (a). This claim is rendered obvious for the same reasons as above.

Dependent claim 11 claims the product of claim 9, wherein the alkylating agent is $ClCH_2CN$. This claim is rendered obvious for the same reasons as above. Additionally, the prior art discloses that the alkylating agent is $ClCH_2CN$. *See* '117 patent col. 20, l. 10–col. 21, l. 12; Moriarty 2004 p. 1892 compound 7, p. 1902.

Dependent claim 12 claims the product of claim 9, wherein the base in step (b) is KOH. This claim is rendered obvious for the same reasons as above. Additionally, the prior art discloses that the base in step (b) is KOH. *See* '117 patent col. 20, l. 10–col. 21, l. 12; Moriarty 2004 p. 1892 compound 7, p. 1902.

Dependent claim 13 claims the product of claim 9, wherein the base B in step (c) is selected from a group consisting of ammonia, N-methylglucamine, procaine, tromethamine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine. This claim is rendered obvious for the same reasons as above. Also, the claim includes commonly known and utilized bases, and it would have been a matter of routine experimentation for a POSA to choose the

bases included. In particular, the prior art specifically teaches a POSA that physiologically acceptable salts of treprostinil include salts derived from these bases. *See* Wade 2005 para. [0024]. Furthermore, the prior art also discloses that treprostinil can be crystallized and the diethanolamine salt of treprostinil is particularly preferred. *See* Phares 2005 para. [00051]. Thus, it would have been obvious for a POSA to choose a base that was already known, like those listed in claim 13, to form a salt with treprostinil.

Claim 14 claims the product of claim 9, wherein the base B is diethanolamine. This claim is rendered obvious for the same reasons as above. The prior art also discloses that treprostinil can be crystallized and the diethanolamine salt of treprostinil is particularly preferred. *See* Phares 2005 para. [00051]. Thus, it would have been obvious for a POSA to choose a base that was already known to form a salt with treprostinil.

Claim 15 claims the product of claim 9, wherein the acid in step (d) is HCl. This claim is rendered obvious for the same reasons as above. Additionally the prior art discloses that salts of treprostinil could be reacted with diluted HCl to form treprostinil. *See* '117 patent col. 20, l. 10–col. 21, l. 12; Moriarty 2004 p. 1892 compound 7, p. 1902. Therefore, it would have been obvious for a POSA to react the salt formed during the crystallization step with diluted HCl to form treprostinil.

Dependent claim 16 claims the product of claim 9, wherein the process does not include purifying the compound of formula (VI) produced in step (a). This claim is rendered obvious for the same reasons as above.

Dependent claim 17 claims the product of claim 16, wherein the base B in step (c) is selected from a group consisting of ammonia, N-methylglucamine, procaine, tromethamine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine. This claim is rendered

obvious for the same reasons as above. Also, the claim includes commonly known and utilized bases, and it would have been a matter of routine experimentation for a POSA to choose the bases included. In particular, the prior art specifically discloses that physiologically acceptable salts of treprostinil include salts derived from these bases. *See* Wade 2005 para. [0024]. Furthermore, the prior art also discloses that treprostinil can be crystallized and the diethanolamine salt of treprostinil is particularly preferred. *See* Phares 2005 para. [00051]. Thus, it would have been obvious for a POSA to choose a base that was already known to form a salt with treprostinil.

Dependent claim 18 claims the product of claim 17, wherein the base B is diethanolamine. This claim is rendered obvious for the same reasons as above. Further, the prior art discloses that treprostinil can be crystallized, and that the diethanolamine salt of treprostinil is particularly preferred. *See* Phares 2005 para. [00051]. Thus, it would have been obvious for a POSA to choose a base that was already known to form a salt with treprostinil.

Dependent claim 19 claims the product of claim 1, wherein the base in step (b) is KOH or NaOH and wherein the base 13 in step (c) is selected from the group consisting of ammonia[,] N-methyl glucamine, procaine, tromethanine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine. This claim is rendered obvious for the same reasons as above.

Dependent claim 20 claims the product of claim 9, wherein the base in step (b) is KOH or NaOH and wherein the base B in step (c) is selected from the group consisting of ammonia, N-methylglucamine, procaine, tromethamine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine. This claim is rendered obvious for the same reasons as above.

Dependent claim 21 claims the product of claim 1, wherein step (d) is performed. This claim is rendered obvious for the same reasons as above.

Dependent claims 22 claims the product of claim 21, wherein the product comprises a pharmaceutically acceptable salt formed from the product of step (d). This claim is rendered obvious for the same reasons as above. Additionally, Moriarty 2004, on p. 1902 discloses that "[c]ompound 7 was identical in all respects to an authentic sample of UT-15" and as disclosed on p. 1890, UT-15 is Remodulin (Treprostinil Sodium). Furthermore, the '117 patent teaches a POSA the claimed compound in salt form. *See* '117 patent col. 20, l. 10–col. 21, l. 12. Phares 2005 further teaches a POSA the claimed compound in at least two salt forms and additionally discloses that the sodium salt of the compound was being commercially sold as Remodulin®, which is an FDA-approved treatment. Phares 2005 para. [0051].

3. Secondary Considerations

Plaintiffs have not set forth any evidence of secondary considerations of non-obviousness, and Actavis is not aware of any such secondary considerations that, when considered with the evidence of obviousness, would warrant a finding of non-obviousness of the claims of the '393 patent. If UTC relies on any secondary considerations of non-obviousness, Actavis reserves the right to supplement its contentions.

As explained above, the claims would have been obvious in view of a host of prior art references because the steps described in the claims were well-known procedures that would have been obvious to apply. Consequently, there are numerous different combinations of these prior art references and many exemplary references that teach each standard step. By way of example, the following combinations render the asserted claims obvious:

- Moriarty 2004 in combination with Monson 1971, Eliel 1994, Kawakami 1981, Ege 1989, and/or Phares 2005
- Moriarty 2004 in combination with Monson 1971, Jones 2000, and/or Wade 2005
- '117 patent in combination with Monson 1971, Eliel 1994, Kawakami 1981, Ege 1989, and/or Phares 2005

- '117 patent in combination with Monson 1971, Jones 2000, and/or Wade 2005
- Remodulin® in combination with Monson 1971, Eliel 1994, Kawakami 1981, Ege 1989, and/or Phares 2005
- Remodulin® in combination with Monson 1971, Eliel 1994, Jones 2000, and/or Wade 2005
- Moriarty 2004 and/or the '117 patent in combination with Phares 2005, and/or Kawakami 1981
- Moriarty 2004 and/or the '117 patent in combination with Phares 2005, and/or Kawakami 1981 and, in further view, Ege 1989

A POSA would have been motivated to combine the teachings of these references with a reasonable expectation of success in light of the fact that each of the references taught well known synthesis techniques for the synthesis of compounds such as treprostinil. In addition, Actavis's invalidity charts set forth where each prior art reference discloses the limitations of the asserted claims.

Actavis reserves the right to set forth additional such examples as discovery continues.

4. The '393 Patent Is Invalid for Obviousness-Type Double Patenting Over the '117 and '311 Patents.

The '393 patent is invalid for obviousness-type double patenting over the '117 and '311 patents. The doctrine of obviousness-type double patenting forbids obtaining more than one patent on the same invention, and is grounded in Section 101 of the Patent Act. 35 U.S.C. § 101 ("Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, . . . may obtain a patent therefor."); *see also In re Longi*, 759 F.2d 887, 892 (Fed. Cir. 1985); *Boehringer Ingelheim Int'l. GmbH v. Barr Labs., Inc.*, 592 F.3d 1340, 1346 (Fed. Cir. 2010); *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 967 (Fed. Cir. 2001). Through judicial interpretation, "this prohibition has been extended to preclude a second patent on an invention which 'would have been obvious from the subject matter of the claims in the

first patent, in light of the prior art.'" *Ortho Pharm. Corp. v. Smith*, 959 F.2d 936, 940 (Fed. Cir. 1992) (quoting *In re Longi*, 759 F.2d at 893). Accordingly, a claim in an issued patent that is not "patentably distinct" from an earlier issued claim in a separate patent is invalid for non-statutory double patenting, so long as the patents have at least one common inventor. *See, e.g.*, *Eli Lilly & Co.*, 251 F.3d at 970-71; *Geneva Pharms., Inc. v. GlaxoSmithKline PLC*, 349 F.3d 1373, 1377-78 (Fed. Cir. 2003); *see also In re Hubbell*, 709 F.3d 1140, 1145-46 (Fed. Cir. 2013) (requiring only an "overlap in the inventors," not "identity of inventors"); *In re Longi*, 759 F.2d at 892.

An obviousness-type double patenting analysis begins by comparing the invention defined by the properly construed claims of the earlier-expiring patent (the "reference claims") with the claims of the later-expiring patent in a manner analogous to an anticipation analysis under 35 U.S.C. § 102 or an obviousness analysis under 35 U.S.C. § 103, except that the reference claims rather than the patent disclosure are the subject of the comparison. *See In re Braithwaite*, 379 F.2d 594, 597 n.4 (C.C.P.A. 1967). A later-expiring claim is invalid where the alleged invention "would have been obvious to those of ordinary skill in the art at the time the invention was made, taking into account the skill of the art and prior art other than the invention claimed in the [reference] patent." *In re Longi*, 759 F.2d at 893 (quoting *In re Zickendraht*, 319 F.2d 225, 232 (C.C.P.A. 1963) (Rich, J., concurring)). The supporting patent disclosures may be relevant for interpreting the scope and meaning of the reference and rejected claims. *In re Vogel*, 422 F.2d 438, 441-42 (C.C.P.A. 1970) ("[[T]he patent disclosure] may be used as a dictionary to learn the meaning of terms in a claim"); *see also Eli Lilly & Co. v. Teva Parenteral Medicines, Inc.*, 689 F.3d 1368, 1378-79 (Fed. Cir. 2012); *In re Avery*, 518 F.2d 1228, 1232 (C.C.P.A. 1975); *In re Zickendraht*, 319 F.2d at 228.

Here, the '117 and '393 patents share at least one common inventor (Raju Penmasta) and the same owner (United Therapeutics Corporation). The '311 and '393 patents also share a common inventor (Hitesh Batra) and the same owner (United Therapeutics Corporation). The claims of the '117 and '311 patents are directed to the same subject matter, treprostinil and its pharmacologically acceptable salt form. *See* '117 patent, claims 1–4; '311 patent claims. There should be no dispute that the claims of the '393 patent, like the claims of the '117 and '311 patents, are also directed to the product treprostinil and its pharmacologically acceptable salt form. *See* '393 patent, claims 1–22. Any limitations not expressly claimed in the '117 and '311 patents would have been either inherent in the claims of the '117 or '311 patents or obvious to those of ordinary skill in the art at the time the invention was made, taking into account the skill of the POSA and the prior art. Therefore, for the reasons explained in more detail above in the anticipation and obviousness analyses, the '393 patent is invalid for obviousness type double patenting over the '117 and '311 patents.

5. Claims 1-22 of the '393 Patent Are Not Enabled or Fail to Meet the Written Description Requirement.

"The specification shall contain a written description of the invention." 35 U.S.C. § 112, first paragraph; *see also Ariad Pharm., Inc. v. Eli Lilly and Co.*, 598 F.3d 1336, 1344-45 (Fed. Cir. 2010) (en banc). "[T]he test for [written description] sufficiency is whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date. . . . [P]ossession as shown in the disclosure is a more complete formulation." *Ariad Pharm.*, 598 F.3d at 1351 (internal citations omitted). The Federal Circuit has further stated that a "definition by function" "is only a definition of a useful result rather than a definition of what achieves that result." *Regents of the Univ. of California v. Eli Lilly and Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997). Further, "[t]he

description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention." *Id.* at 1568. "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that 'the inventor invented the claimed invention.'" *Id.* at 1566 (quoting *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1572, and *In re Gosteli*, 872 F.2d 1008, 1012 (Fed. Cir. 1989)). "Thus, an applicant complies with the written description requirement 'by describing the invention, with all its claimed limitations, not that which makes it obvious,' and by using 'such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention.'" *Id.* at 1566 (quoting *Lockwood*, 107 F.3d at 1572); *see also In re Curtis*, 354 F.3d 1347, 1355 (Fed. Cir. 2004) (affirming BPAI's finding of invalidity for lack of written description where there was "unpredictability in performance of certain species or subcombinations other than those specifically enumerated [in the disclosure]" (internal quotations omitted)). "[T]he purpose of the written description requirement is to ensure that the scope of the right to exclude, as set forth in the claims, does not over-reach the scope of the inventor's contribution to the field of art as described in the patent specification") (internal quotations omitted). *Ariad Pharm.*, 598 F.3d at 1353-54.

Further, "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same." 35 U.S.C. § 112 (emphasis added). "To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation'." *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1365, (Fed. Cir. 1997) (quoting *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir.

1993)). Factors to be considered in determining whether a patent specification would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *In re Wands*, 858 F.2d 732, 737 (Fed. Cir. 1988). "[A]ll of the factors need not be reviewed when determining whether a disclosure is enabling." *Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1371 (Fed. Cir. 1999).

"The specification need not disclose what is well known in the art." *In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991). But this "is merely a rule of supplementation, not a substitute for a basic enabling disclosure." *ALZA Corp. v. Andrx Pharms., LLC*, 603 F.3d 935, 940-41 (Fed. Cir. 2010) (holding claims invalid that cover osmotic and non-osmotic dosage forms, but only teach a person of ordinary skill in the art how to make the osmotic dosage form). The patentee "cannot simply rely on the knowledge of a person of ordinary skill to serve as a substitute for the missing information in the specification." *Id.* at 941.

As discussed in the previous sections, it would have been obvious for a POSA to practice the claimed invention by applying known procedures described in the prior art. But if plaintiff contends that it would have required undue experimentation for a POSA to apply the knowledge known to a POSA from the prior art to obtain the claimed methods (for example it would have required undue experimentation to find particular bases or a particular alkylating agent), the claims would then be invalid for lack of an enabling description. To the extent that plaintiff contends that certain bases or reaction conditions, for example, are unique and that undue

experimentation would have been required to practice the claimed method, the claims of the '393 patent are not enabled or fail to meet the written description requirement.

Moreover, to the extent that plaintiff takes a broad claim construction position and asserts infringement of certain processes and resulting intermediates—such as the use of intermediates or processes that are not sufficiently disclosed, taught or claimed in the '393 patent, including the intermediates and processes that are used to make the treprostinil used in Actavis's ANDA product— the claims of the '393 patent are not enabled and/or lack written description.

6. Claims 1, 9, and Their Dependent Claims Are Indefinite

The claims of the '393 patent are invalid as indefinite because the patent does not define "step (h)." "The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention." 35 U.S.C. § 112 ¶ 2 (2003). This provision requires that "a patent's claims, viewed in light of the specification and prosecution history, inform those skilled in the art about the scope of the invention with reasonable certainty." *Nautilus, Inc. v. Biosig Instruments, Inc.*, 134 S. Ct. 2120, 2129 (2014). "[T]he certainty which the law requires in patents is not greater than is reasonable, having regard to their subject-matter." *Id.* "It cannot be sufficient that a court can ascribe some meaning to a patent's claims; the definiteness inquiry trains on the understanding of a skilled artisan at the time of the patent application." *Id.* at 2130. "One must bear in mind, moreover, that patents are 'not addressed to lawyers, or even to the public generally,' but rather to those skilled in the relevant art." *Id.* at 2128 (quoting *Carnegie Steel Co. v. Cambria Iron Co.*, 185 U. S. 403, 437 (1902)). "At the same time, a patent must be precise enough to afford clear notice of what is claimed, thereby appris[ing] the public of what is still open to them." *Id.* at 2129 (internal quotations omitted).

Claims 1 and 9 both require "contacting the product of step (h) with a base B to form a salt of formula" I_S or IV_S. Because step (h) is not defined in the patent, a person of ordinary skill would not have clear notice of what is claimed. Claims 1 and 9, and the claims dependent upon them, are indefinite because they do not provide reasonable notice of what is claimed.

B. Invalidity of the '070 Patent

1. Claims 1–3 Are Rendered Obvious by the Following References

As explained in further detail below and in the accompanying claim charts concerning the '070 patent, the prior art renders obvious the claims of the '070 patent.

a. Simonneau et al., Continous Subcutaneous Infusion of Treprostinil, a Prostacyclin Analogue, in Patients with Pulmonary Arterial Hypertension A Double-blind, Randomized, Placebo-controlled Trial 2001, 800-804

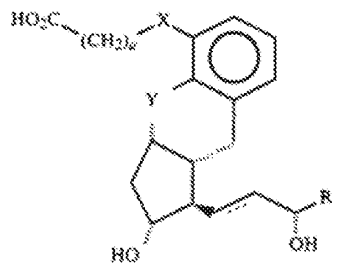
Treprostinil sodium was known to be effective in treating pulmonary arterial hypertension. Gerald Simonneau et al., Continuous Subcutaneous Infusion of Treprostinil, a Prostacyclin Analogue, in Patients with Pulmonary Arterial Hypertension, 165 Am. J. Respir. Crit. Care Med. 800 (March 15, 2002) ("Simonneau") discloses the administration of treprostinil as an alternative to epoprostenol. Simonneau qualifies as prior art to the '070 patent under at least 35 U.S.C. § 102(b). Epoprostenol had been administered by continuous intravenous infusion.[4] Simonneau at 800. Treprostinil, which Simonneau also refers to as Remodulin, "is chemically stable at room temperature and neutral pH and has a" half-life of three to four hours, permitting continuous subcutaneous infusion. It therefore avoided some of the risks associated with intravenous infusion of epoprostenol. *See id.* at 800, 801. The authors stated that "chronic

[4] At the time that Simonneau was published, the person of ordinary skill in the art would have recognized its reference to administration of treprostinil (Remodulin) to refer to administration of treprostinil sodium. *See* S.C. Chattaraj, 3 Current Opinion Investig. Drugs 582 (Abstract) (April 2002) ("Chattaraj"). Chattaraj discloses that "United Therapeutics Corp (UTC) is developing treprostinil sodium (Remodulin, UT-15), a stable structural analog of prostacyclin, for the potential treatment of primary pulmonary (arterial) hypertension (PAH)." Chattaraj qualifies as at least 35 U.S.C. § 102(b) prior art to the '070 patent. *See also* United Therapeutics, Press Release (February 11, 2002) (disclosing issuance of FDA "approvable letter for Remodulin (treprostinil sodium)").

subcutaneous infusion of treprostinil is an effective treatment with an acceptable safety profile in patients with pulmonary arterial hypertension." Nevertheless, the person of ordinary skill in the art was aware that continuous subcutaneous infusion itself presents disadvantages relative to, for example, oral administration. For example, as Simonneau discloses, infusion site pain and infusion site reaction occurred in over 80% of patients, and infusion site bleeding/bruising occurred in one-third of patients. *See* Simonneau at 803, Table 5.

b. U.S. Patent No. 5,153,222

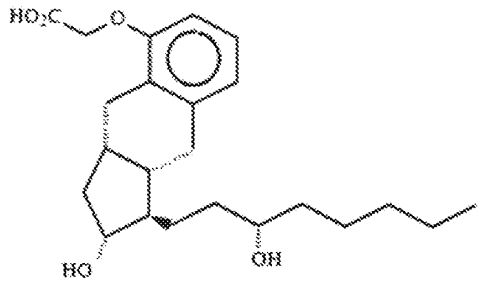
U.S. Patent No. 5,153,222 ("the '222 patent") qualifies as 35 U.S.C. § 102(b) prior art to the '070 patent because it issued on October 6, 1992, over one year before the earliest effective U.S. filing date of the '070 patent. In sum, the '222 patent discloses a genus of compounds that includes treprostinil; that ammonium salts of these compounds can be prepared; and the use of such compounds and their salts in the treatment of pulmonary hypertension. It also specifically discloses treprostinil. The '222 patent discloses the genus of compounds having the chemical structure shown below.



(I)

'222 patent at col. 2, ll. 18-43. "Further aspects of the present invention are concerned with the use of a compound of formula (I), or a pharmaceutically acceptable salt or acid derivative thereof, in the manufacture of a medicament for the treatment of pulmonary hypertension." *Id.* at col. 2, ll. 53-57. "A particularly preferred compound of formula (I) having exceptional

pulmonary anti-hypertensive properties is 9-deoxy-2',9α-methano-3-oxa-4,5,6-trinor-3,7-(1',3'-interphenylene)-13,14-dihydro-prostaglandin F1, which has the following structure:



and pharmaceutically acceptable salts and acid derivatives thereof." *Id.* at col. 3, ll. 1-20. The disclosed compound is treprostinil. *See, e.g.*, Remodulin® Label (approved by FDA May 21, 2002).

"The physiologically acceptable salts of compounds of formula (I) include salts derived from bases," including, among others, "salts with organic bases such as dicyclohexylamine and N-methyl-D-glucamine." '222 patent at col. 3, ll. 35-41.[5] The '222 patent further discloses that the physiologically acceptable salts of the compounds of formula I can be incorporated into oral formulations, among others. Such oral formulations include "capsules, cachets, lozenges, or tablets." The patent describes the preparation of tablets. *See id.* at col. 4, l. 20–col. 5, l. 2. The preparation of a formulation "typically" entails mixing a physiologically acceptable salt of a compound of formula (I), for example, with an "acceptable carrier." *See id.* at col. 4, ll. 8-19.

Regarding an effective amount to treat pulmonary hypertension, orally administrable tablets and capsules typically contain the equivalent of 1 to 50 mg of the compound of formula (I). *See id.* at col. 3, l. 49–col. 4, l. 7. "The compounds of the present invention are conveniently

[5] U.S. Patent No. 6,054,486 makes a similar disclosure. *See* '486 patent at col. 1, ll. 11-27 (referring to 9-deoxy-2',9α-methano-3-oxa-4,5,6-trinor-3,7-(1',3'-interphenylene)-13,14-dihydro-prostaglandin F1 as "UT-15" and citing the '222 patent as disclosing the compound's use to treat pulmonary hypertension) and at col. 2, ll. 28-42 (discussing salts of UT-15).

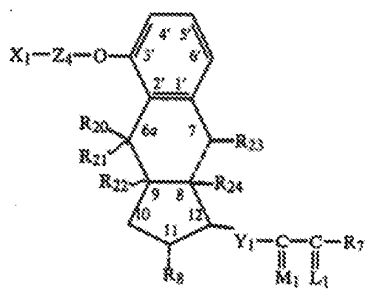
prepared by methods the same as or analogous to those described in U.S. Pat. No. 4,306,075." *Id.* at col. 5, ll. 50-52.

The '222 patent discloses an example of oral administration of treprostinil to rats. *See* '222 patent at col. 5, ll. 58-64 and col. 6, ll. 42-50. Based on results observed with "doses of 0.3 mg/kg P.O. and above," "the compound had good oral bioavailability." '222 patent at col. 6, ll. 46-50. It is not clear whether treprostinil was administered as the free acid or as a salt. The patent states that "[t]he effects of 9-deoxy-2',9α-methano-3-oxa-4,5,6-trinor-3,7-(1',3'-interphenylene)-13,14-dihydro-prostaglandin F1 monitored [sic] in experimental pulmonary hypertension models." *Id.* at col. 5, ll. 58-61. The example refers only to the "test compound" and "the compound." *Id.* at col. 6, ll. 42-50. The patent states that glycine buffer solutions of "the test compound" were administered by i.v. infusion to cats. It is not clear whether the same solution was administered orally to the rat. *Id.* at col. 5, ll. 61-63 and col. 6, ll. 3-5. The '222 patent claims a method of treating pulmonary hypertension that comprises administering an effective amount of "a pharmaceutically acceptable salt of" treprostinil. *See* '222 patent at col. 6, ll. 58-63 (claim 2).

c. U.S. Patent No. 4,306,075

U.S. Patent No. 4,306,075 ("the '075 patent") issued in 1981 and therefore qualifies as 35 U.S.C. § 102(b) prior art to the '070 patent. The '075 patent specifically discloses treprostinil, generally discloses a genus of compounds that encompasses treprostinil, and discloses that suitable salts of the compounds include the diethanolamine salt. Specifically, the '075 patent states that it provides a compound of generic formula XI (diagrammed below) and sets forth the permitted substituents of the compound. *See* '075 patent at col. 3, l. 18, col. 3, l. 21–col. 5, l. 35 and col. 74, ll. 25-37. This genus includes treprostinil.

XI



The '075 patent describes generally the synthesis of compounds of formula XI and provides a diagram of the synthesis. *See id.* at col. 26, ll. 11-58 (describing the synthesis set forth in Chart P) and col. 89, ll. 14-31 and col. 90, ll. 1-38 (diagramming Chart P). The patent further discloses generally that the compounds can be provided in salt form, including in combination with cations derived from "amines containing water solubilizing or hydrophilic groups, e.g., mono-, di-, and triethanolamine." '075 patent at col. 15, ll. 15-17; *see also id.* at col. 14, l. 56–col. 15, l. 25 (disclosing that "[p]harmacologically acceptable salts of the novel prostaglandin analogs of this invention" include salts with amine cations) and at col. 30, l. 41–col. 31, l. 5 (describing preparation of salts of "compounds of this invention," including amine salts). Example 31 of the '075 patent discloses the preparation of a compound that is identical to treprostinil except that it has a double bond instead of "13,14-dihydro." *See* '075 patent at col. 56, l. 14–col. 59, l. 33 (Example 31, disclosing preparation of 9-deoxy-2',9α-methano-3-oxa-4,5,6-trinor-3,7-(1',3'-interphenylene)-prostaglandin F1 (so identified as the "title product" at col. 59, ll. 28-30)). Example 32 discloses that the compound prepared by Example 31 can be hydrogenated to transform –CH=CH– to $-CH_2CH_2-$ as exemplified in Example 33. This hydrogenation yields treprostinil. *See id.* at col. 61, l. 62–col. 62, l. 2 (describing hydrogenation of compound of Example 31 to eliminate double bond), col. 62, ll. 3-39 (Example 33, detailing the hydrogenation procedure).

The '075 patent states that the disclosed compounds and their pharmacologically acceptable salts can be used to inhibit platelet aggregation and to reduce the adhesive character of platelets. *See id.* at col. 12, ll. 39-43 (disclosing use of compounds to inhibit platelet aggregation and to reduce the adhesive character of platelets), col. 14, ll. 56-60 (stating that pharmacologically acceptable salts of the "novel prostaglandin analogs," including those formed with amine cations, can be used "for the purposes described above"). Both of these activities were thought to be useful in treating pulmonary arterial hypertension. *See, e.g.*, M. Beghetti *et al., Aerosolized iloprost induces a mild but sustained inhibition of platelet aggregation,* 19 Eur. Respir. J. 518, 518 (March 1, 2002) ("Beghetti") (stating that the "beneficial effect" of epoprostenol infusion may be attributed to its antiproliferative and antiaggregant effects) and 522 (stating that the "antiplatelet effect observed in this study" "may explain in part the clinical improvement obtained with daily repetitive inhalations [of iloprost] in patients with primary and secondary pulmonary hypertension"), Emile R. Mohler III *et al., Trial of a novel prostacyclin analog, UT-15, in patients with severe intermittent claudication,* 5 Vascular Medicine 231, 236 (2000) ("Mohler") ("Prostanoids are believed to exert their therapeutic effect in part at the level of the microcirculation where they prevent platelet activation and facilitate repair of damage induced by activated platelets and leukocytes."). The '075 patent also discloses oral dosage in the forms of tablets and capsules as the "preferred dosage form." col. 12, ll. 64–68.

d. Lyle D. Bighley et al., Salt Forms of Drugs and Absorption, in 13 Encyclopedia of Pharmaceutical Technology 453 (James Swarbrick & James C. Boylan eds., 1995)

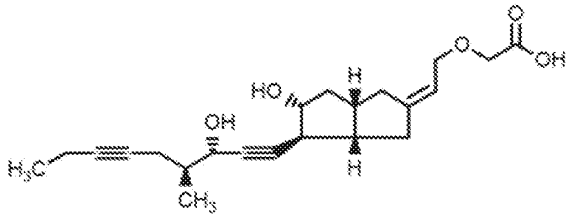
Lyle D. Bighley *et al., Salt Forms of Drugs and Absorption, in* 13 Encyclopedia of Pharmaceutical Technology 453 (James Swarbrick & James C. Boylan eds., 1995) ("Bighley") was published in 1995 and thus qualifies as prior art to the '070 patent under at least 35 U.S.C. § 102(b). Bighley discloses that "[s]alt formation is frequently performed on weak acidic or basic

drugs because it is a relatively simple chemical manipulation which may alter the physicochemical, formulation, biopharmaceutical, and therapeutic properties of a drug without modifying the basic chemical structure." *Id.* at 453. Also, "[t]he ideal characteristics of a salt are that it is chemically stable, not hygroscopic, presents no processing problems, dissolves quickly from solid dosage forms (unless it is formed with the intent to delay dissolution), and exhibits good bioavailability." *Id.* at 453. Bighley identifies 38 cationic pharmaceutical salt forms in use at the time of publication. *See id.* at 456, Table 2. One of these was the diethanolamine salt. *See id.* As of 1993, the diethanolamine salt was among the more frequently used salts, being used in 0.45% of the cationic pharmaceutical salts. Twenty-one salts were used less frequently. *See id.* Bighley points out that "[o]rganic acid salt forms of basic drugs, such as amines, frequently have higher aqueous solubilities than their corresponding inorganic salts." *Id.* at 461. "This is important in the synthesis and selection of a salt form that exhibits enhanced bioavailability and desirable formulation characteristics." *Id.* Bighley further states that "[t]o increase absorption, organic cations should be prepared, such as amino acids (lysine, arginine), glucoamines (meglumine), or hydroxyamines (diethanolamine or triethanolamine)." *Id.* at 484.

e. Diethanolamine salts of other drug compounds

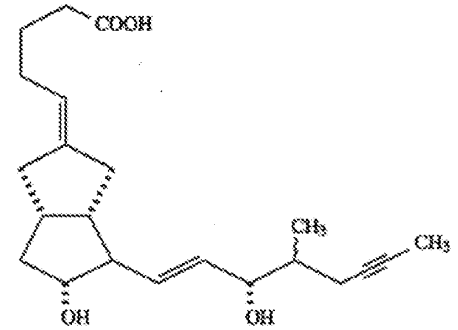
Bighley discloses generally that diethanolamine is used as a salt of various drug compounds. Examples of specific diethanolamine salts are set forth below. All of the publications cited below were published more than one year before May 22, 2003, the earliest claimed effective U.S. filing date of the '070 patent, and are at least § 102(b) prior art.

U.S. Patent No. 5,506,265 ("the '265 patent") concerns prostacyclin and carbacyclin derivatives such as cicaprost (structure shown below).



See '265 patent at col. 2, ll. 12-14, http://chem.sis.nlm.nih.gov/chemidplus. Cicaprost is one of five compounds that the patent identifies as "especially suitable." '265 patent at col. 2, ll. 11-13. Cicaprost has certain structural features in common with treprostinil, including the –O–CH_2COOH group where a salt can form with an amine such as diethanolamine. The '265 patent specifically identifies the diethanolamine salt as one of a number of suitable salts (ten salts specifically identified) of the prostacyclin and carbacyclin derivatives. '265 patent at col. 2, ll. 15-21.

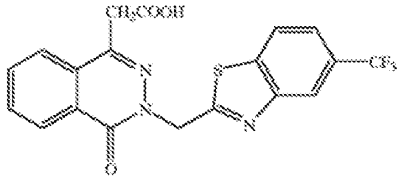
U.S. Patent No. 5,466,713 ("the '713 patent") makes a similar disclosure about iloprost, a stable prostacyclin derivative having the chemical structure shown below.



Iloprost, like cicaprost and treprostinil, is a carboxylic acid. *See* '713 patent at col. 1, ll. 15-34 (structure), col. 1, ll. 41-49 (specifically identifying diethanolamine as suitable salt of iloprost), col. 1, l. 54–col. 2, l. 6 (listing useful pharmacological properties relating to coronary function).

U.S. Publication No. 2001/0056095 states that the diethanolamine (and ethanolamine and triethanolamine) salt of zopolrestat, a carboxylic acid (diagrammed below), is "highly water-

soluble" and thus an "advantageous" salt form of zopolrestat. *See* '095 publication ¶ 0005. Zopolrestat diethanolamine has a water solubility of 100 mg/ml. In addition to high solubility, zopolrestat diethanolamine has a melting point of 163-164° C. *See id.* ¶ 0263.

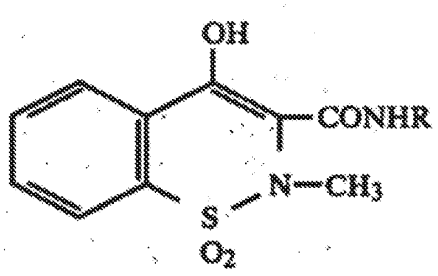


The '095 publication further discloses that: It is well known in the art that highly water-soluble medicinal preparations, when administered orally, result in efficient absorption of such preparations from the gastrointestinal tract into systemic circulation. Another hallmark of such preparations is the rapid rate at which they are absorbed into the systemic circulation resulting in a high concentration of the active agent in the blood. Also, water-soluble preparations are especially suitable for parenteral administration, for example, intravenous administration [sic]. The instant ethanolamine salt of this invention exhibits a surprising degree of water solubility. *Id.* ¶ 0003.

U.S. Patent No. 4,434,164 ("the '164 patent") specifically discloses and claims the diethanolamine salt of piroxicam, an acidic benzothiazine (diagrammed below; R is 2-pyridyl).[6] The '164 patent discloses that the diethanolamine and two other salts of the benzothiazine are "crystalline, non-hygroscopic, rapidly-dissolving solids with high water solubility" and "possess excellent chemical and physical stability properties." *See* '164 patent at col. 8, ll. 37-38 (claim 4), col. 1, ll. 37-65, col. 2, l. 43–col. 3, l. 13. These properties facilitate the salts' incorporation into pharmaceutical dosage forms. *See id.* at col. 3, ll. 13-17. Example 4 sets forth the synthesis

[6] Piroxicam itself was disclosed prior to the filing of the '164 patent. *See* '164 patent at col. 2, ll. 31-39.

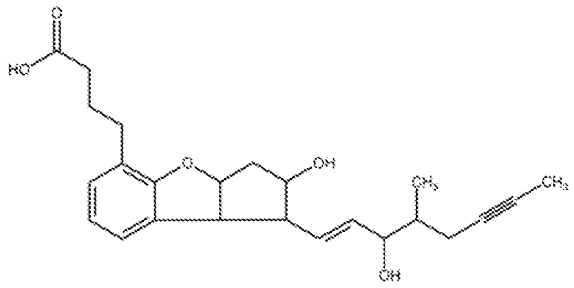
of the diethanolamine salt of piroxicam. Piroxicam diethanolamine's melting point is 143-146° C. *Id.* at col. 6, ll. 1-30.



N-(2-pyridyl)-2-methyl-4-hydroxy-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide

f. C. D. Vizza et al., 86 Heart 661 (2001)

C. D. Vizza *et al.*, *Long term treatment of pulmonary arterial hypertension with beraprost, an oral prostacyclin analogue*, 86 Heart 661 (2001) ("Vizza"), qualifies as at least 35 U.S.C. § 102(b) prior art. Vizza discloses a clinical study in which the oral prostacyclin analogue beraprost (structure shown below) was administered to 13 patients with "severe pulmonary hypertension." Vizza at 661 (Abstract: Patients).



beraprost http://chem.sis.nlm.nih.gov/chemidplus

Oral beraprost represents a solution to problems with earlier treatment of pulmonary hypertension with epoprostenol (prostacyclin) and iloprost (a prostacyclin analogue). Epoprostenol had been administered intravenously and this presented problems in chronic

treatment. *See id.* at 661. Iloprost was administered by inhalation, but this also presented problems. Iloprost has a short half-life, so up to twelve inhalations were necessary each day and each inhalation lasted up to 15 minutes. *See id.* The oral administration of beraprost avoided the problems associated with the routes of administration of the other drugs. Oral administration of beraprost was possible because of its stable structure and longer half-life (45 minutes in fasting state, 3 to 3 1/2 hours when taken after a meal). *See id.* at 663 ("Beraprost sodium is a prostacyclin analogue that is suitable for oral administration owing to its stable structure.").

Eleven patients completed the full trial of 12 months and all showed improvement. "The 11 remaining patients had persistent improvements in functional class and exercise capacity and a significant decrease in systolic pulmonary artery pressure in the period from 1–12 months. Side effects were minor." *Id.* at 661, Abstract-Results. The authors consider it "very unlikely" that the observed benefit occurred by chance. In these patients, "a decline in the six minute walk distance and a deterioration, instead of an improvement, in functional class" would have been expected in the absence of treatment.

g. U.S. Patent No. 5,234,953

The '953 patent is titled "Treatment of Congestive Heart Failure," and issued on August 10, 1993. The '953 patent is prior art under at least § 102(b). The '953 patent describes compounds for use "in the treatment of CHF [congestive heart failure] which is accompanied by pulmonary hypertension." *See* '953 patent at col. 2, ll. 8–11. In particular, the '953 patent describes a "compound A" as a preferred compound "having particularly advantageous properties in respect of the treatment of CHF." *See* '953 patent at col. 2, ll. 53–65. The "compound A" referred to in the '953 patent is treprostinil, *i.e.*, UT-15. Additionally, the '953 patent states that the treprostinil compound "was found to be a potent pulmonary vasodilator" and "markedly attenuated the pulmonary vasoconstriction induced by hypoxia." *See* '953 patent

at col. 7, ll. 19–21. The '953 patent observes that the treprostinil compound caused "substantial reductions in pulmonary vascular resistance, pulmonary arterial pressure, systemic vascular resistance and mean arterial blood pressure and increases in cardiac output and stroke volume." *See* '953 patent at col. 7, ll. 21–28.

The '953 patent also teaches that "[t]he compositions of the invention include those suitable for . . . nasal and pulmonary administration . . . ." *See* '953 patent at col. 4, ll. 32–36. The '953 patent further teaches a particle size in the range of 10-500 um for nasal administration and a particle size in the range 0.5-10 um, preferably 1–5 um, for pulmonary administration via the mouth. *See* '953 patent at col. 5, ll. 48–53.

The '953 patent discloses the use of pressurized aerosol dispensers to administer the treprostinil solution in a volume from 10 to 150 ul "to produce a fine particle spray containing the active ingredient." *See* '953 patent at col. 5, ll. 54–60. The '953 patent also discloses suitable propellants, including certain chlorofluorocarbon compounds such as dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, and mixtures thereof. *See* '953 patent at col. 5, ll. 60–64. More specifically, the '953 patent discloses the use of nebulizers for administration of treprostinil and a suitable composition for use in nebulizers consisting of "the active ingredient in a liquid carrier, the active ingredient comprising up to 40% w/w of the composition, but preferably less than 20% w/w[,]" with a carrier that "is typically water or a dilute aqueous alcoholic solution." *See* '953 patent at col. 6, ll. 8–19. The '953 patent also teaches that the compounds of the invention are suitable for administration to a mammal, such as a human. *See* '953 patent at col. 2, ll. 48–52.

h. Shekunov, B.Yu, et al., *Crystallization process in pharmaceutical technology and drug delivery design*, Journal of Crystal Growth 211 (2000) 122–36

Shekunov was published in 2000 and is at least § 102(b) prior art. Shekunov discloses that "[s]olution crystallization is widely used for manufacturing bioactive drug substances and formulation excipients during final and intermediate stages of purification and separation." at Introduction. It discloses that more than 90 percent of pharmaceutical products "contain drug in particulate, generally crystalline, form." *Id.* Shekunov also discloses that tablets are "by far the most widely used, simple and convenient solid dosage form." *Id.* at § 3.1. It teaches the importance of studying polymorphic forms of substances because "it is rare when a medicinally active substance exhibits only a single crystalline structure." *Id.* at § 3.3. Shekunov suggests selecting "the single, most stable form . . . ." *Id.* at § 3.3. Shekunov further discloses the use of antisolvents in the crystallization process. *Id.* at 4.

i. Berge et al., *Pharmaceutical Salts*, Journal of Pharmaceutical Sciences, 66, 1-19 (1977)

Berge was published in 1977 and is at least § 102(b) prior art. Berge discloses the diethanolamine salt as an FDA-approved commercially marketed salt that was "potentially useful." *See* p. 2, Table I. Berge also discloses that it was known that different salts of the same drug typically differ based on physical properties, not pharmacologically. *See* p. 5. Berge also discusses properties of various salts, including solubility and the difference between solubilities of different salt forms with the same compound as a free acid or base, the influence of pH on the solubility of pharmaceuticals, and bioavailability. pp. 4–10.

j. Reepmeyer et al., *Characterization and Crystal Structure of Two Polymorphic Forms of Racemic Thalidomide*, J. Chem. Soc. Perkin Trans. 2, 2063-67 (1994)

Reepmeyer was published in 1994 and is at least § 102(b) prior art. It discloses that "[p]olymorphism is important in pharmaceuticals because it may influence drug bioavailability." Reepmeyer at p. 2063. Reepmeyer further discloses that "[t]here are two polymorphic forms of racemic thalidomide," and discusses the discovery, preparation, and characterization of the various polymorphs of thalidomide. *Id.* at Abstract, p. 2063. In particular, Reepmeyer uses IR, differential scanning calorimetry, melting point analysis, X-ray powder diffraction, and X-ray crystallography to characterize the different thalidomide polymorphs. *Id.* at Abstract.

k. L. Yu et al. "Physical Characterization of Polymorphic Drugs: An Integrated Characterization Strategy" PSTT 1(3):118-127 (1998)

Yu was published in 1998 and is at least § 102(b) prior art. Citing to "the potential impact of changing crystal forms during late-stage drug development in terms of cost and product delay," Yu 1998 recommends "systematic and early characterization of polymorphism," to obtain a "thorough understanding of polymorph characteristics," in selecting the best form to market. Yu 1998 at Abstract, 126. Yu 1998 explains that "[a]side from its impact on drug quality, it is important to characterize polymorphism for other reasons," including expanded "[r]egulatory expectations for the characterization of new drug products . . . to include polymorph types and their purity levels." *Id.* at 118. Yu 1998 further teaches that "[p]erhaps the most important physical property for a polymorphic drug is the relative thermodynamic stability," which "for example, influences the selection of the best crystal form for development." *Id.* at 122. The relative thermodynamic stability of polymorphs is measured as the difference in free energy, ΔG, between the polymorphs. *Id.* Yu 1998 also teaches that there are several commonly used techniques to characterize crystalline materials, including x-ray diffraction and solid-state spectroscopy (NMR, IR, and Raman). *Id.* at 119-21. For example, Yu 1998 states that "DSC, TGA and HSM [hot-stage microscopy], separately or together, are often

the first steps in a comprehensive ssearch for polymorphs and the determination of their stability relationship." *Id.* at 121. Such techniques "are used in conjunction with the measurement of polymorphic conversion, solubility or intrinsic dissolution rate to provide a comprehensive determination of the stability relationship between polymorphs." *Id.*

l. L. Yu et al., "Crystallization and Polymorphism of Conformationally Flexible Molecules: Problems, Patterns, and Strategies," Organic Process Research & Development 4, 396-402 (2000)

Yu 2000 was published in 2000 and is therefore at least § 102(b) prior art. It discusses the polymorphism of conformationally flexible molecules conformational polymorphism and teaches that:

> Crystallization can be envisioned as a multistep process in which molecules first associate into pre-nucleation aggregates (molecular clusters whose structure resembles that of the mature crystal), pre-nucleation aggregates then assemble into crystal nuclei, and crystal nuclei finally grow into mature crystals. Conformational flexibility introduces two potential complications to the crystallization process. First, a greater number of structural options are available for crystallization, giving rise to polymorphs that differ not only in the mode of packing but also in molecular conformation (*conformational polymorphism*).

Yu 2000 at 396.

m. M. R. Caira, Crystalline Polymorphism of Organic Compounds, in Design of Organic Solids, E. Weber ed., Springer, New York (1998)

Caira was published in 1998 and is therefore at least § 102(b) prior art. It notes that "[c]rystal polymorphism is encountered in all areas of research involving solid substances," and that "[i]ts occurrence introduces complications during manufacturing processes." Caira at Abstract. As a result, Caira states that:

> Systematic investigation of a compound to determine whether it is prone to polymorphism, as well as the nature of the polymorphism (enantiotropic or monotropic), is routine practice in pharmaceutical

> pre-formulation studies. Identification of the different polymorphic forms of a drug substance, determination of their chemical and physical properties, thermodynamic stabilities, and temperatures and rates of interconversion are essential for ensuring drug preparations with reproducible behavior. Already, legislation requiring drug manufacturers to provide information relating to the occurrence (or apparent absence) of polymorphism in their products has been introduced.

Id. at 166.

The transformation between different polymorphic forms is driven by the difference in Gibbs Free Energy (ΔG) between the two forms. Caira at 165-167. In particular:

> Thermodynamic considerations of polymorphic crystallization include Ostwald's law of stages, according to which, at high supersaturation, the first form which crystallizes is the thermodynamically least stable (most soluble) form. This form subsequently dissolves and transforms into a more stable one. The cycle continues until only the thermodynamically stable (least soluble) polymorph remains.

Id. at 166. As a result, "[t]he practical implication is that it should be possible to isolate the different polymorphs of a given compound at different levels of supersaturation and hence exercise some control over the crystallization process." *Id.*

"At a given temperature and pressure, [however,] only one polymorphic form of a substance is thermodynamically stable, all other forms being metastable." *Id.* at 164. Even if a metastable form is desired, Caira cautions that "it can revert to the stable polymorph under suitable conditions (e.g., in suspension, via solvent-mediation, or during compression)." *Id.* at 167. Thus, "[i]t follows that to prepare a specific polymorph and be aware of its possible fate during handling, it is advantageous to know the transition temperatures and thermodynamic stabilities of all the forms that may appear in the system." *Id.*

n. N. Rodriguez-Hornedo and D. Murphy, "Significance of Controlling Crystallization Mechanisms and Kinetics in

Pharmaceutical Systems," Journal of Pharmaceutical Sciences, 88, 651-660 (1999)

Hornedo was published in 1999 and is at least § 102(b) prior art. Recognizing that "[m]etastable thermodynamic states are frequently encountered in pharmaceutical systems" and can occur "during isolation, manufacturing, storage, and dissolution," Hornedo teaches that:

> Knowledge of the propensity of a metastable solid phase to dissolve in a liquid phase from which a stable solid phase nucleates and grows is crucial in many stages of pharmaceutical development, because pharmaceutical solids are designed to be dissolved and to come in contact with solvents since the early stages of development (isolated by crystallization from solution) and during processing (wet granulation, spray-drying, freeze-drying, etc.).

Hornedo at 657. Such awareness of crystallization kinetics is especially critical because the FDA requires that "[a]ppropriate manufacturing and control procedures (including in-process testing when needed) should be established for the production of the desired solid-state form(s)." *Id.* at 651 (internal citations omitted).

o. **C.-H. Gu et al., "Polymorph Screening: Influence of Solvents on the Rate of Solvent- Mediated Polymorphic Transformation" Journal of Pharmaceutical Sciences, 90, 1878- 1890 (2001)**

Gu was published in 2001 and is at least § 102(b) prior art. Gu teaches that "[b]ecause different polymorphs exhibit significantly different pharmaceutically relevant properties, discovery, preparation, and characterization of polymorphs are essential preformulation steps in pharmaceutical research and development." Gu at 1878. Gu further explains that "[u]sually, the most stable polymorphic form is preferred in a marketed formulation, because any other polymorphs are metastable and may therefore transform to the more stable form during storage. *Id.* Gu cautions that "[s]uch a phase change may cause formulation problems, for example, precipitation from solution, physical instability of solid dosage form, and changes in

bioavailability." *Id.* Thus, "[o]verlooking the most stable polymorph may cause failure of a marketed product due to phase transformation during storage." *Id.*

p. S. R. Vippagunta et al., "Crystalline solids," Advanced Drug Delivery Reviews, 48, 3-26 (2001)

Vippagunta was published in 2001 and is at least § 102(b) prior art. It explains that "[m]any drugs exist in the crystalline solid state" and that "[b]ecause different crystalline polymoprhs and solvates differ in crystal packing, and/or molecular conformation as well as in lattice energy and entropy, there are usually significant differences in their physical properties." Vippagunta at Abstract and 4. Such differences can "have an important effect on the processing of drug substances into drug products, while differences in solubility may have implications on the absorption of the active drug from its dosage form, by affecting dissolution rate and possibly the mass transport of the molecules." *Id.* at 4-5 (internal citations omitted). Thus, "it is desirable to choose the most suitable and stable form of the drug in the initial stages of drug development." *Id.* at 3.

As a result of the concerns over polymorph interconversion that "may occur during various pharmaceutical processes, which may alter the dissolution rate and transport characteristics of the drug" (*id.* at Abstract), the FDA now requires that for approval of a new drug, "appropriate analytical procedures need to be used to detect polymporphs, hydrates and amorphous forms of the drug substance and also stresses the importance of controlling the crystal form of the drug substance during the various stages of product development." *Id.* at 5 (internal quotations and citations omitted).

Vippagunta also describes various analytical methods that are routinely used to characterize the crystalline form of the drug during various steps of processing and development

including XRPD, infrared spectroscopy, Raman spectroscopy, differential scanning calorimetry, and thermogravimetric analysis. *Id.*

q. J. Olmsted III and G. M. Williams, Chemistry, The Molecular Science, Mosby-Year Book, Inc. (1994)

Olmsted was published in 1994 and is at least § 102(b) prior art. It teaches that "[r]ecrystallization is a classic way of removing impurities from a crude solid." Olmsted at 476. For example, "[i]f a solid substance is dissolved in a minimum volume of hot solvent that is then allowed to cool, the solubility of the solid is exceeded, and it crystallizes from the solvent. In favorable cases the impurities remain dissolved in the cold solvent, and the solid has been purified." *Id.*

r. D. L. Pavia et al., Introduction to Organic Laboratory Techniques, Second Edition, Saunders College Publishing (1982)

Pavia was published in 1982 and is at least § 102(b) prior art. It teaches that "[o]rganic compounds that are solid at room temperature are usually purified by crystallization." Pavia at 481. The reference further teaches that "[a] material can be purified by crystallization when both the desired substance and the impurity have similar solubilities." *Id.* at 482. Pavia further discloses procedures for minimizing impurities by manipulating crystallization conditions. *Id.* at 482–90.

s. S. R. Byrn et al. "Pharmaceutical Solids: A Strategic Approach to Regulatory Considerations" *Pharm. Res.* 12(7):945-954 (1995)

Byrn was published in 1995 and is at least § 102(b) prior art. Byrn's paper presents a conceptual approach to the characterization of pharmaceutical solid in the development of pharmaceutical products for scientific and regulatory purposes. Byrn at Abstract. Initially, Byrn recommends screening for polymorphs of a particular substance by "crystalliz[ing] the substance

from a number of different solvents," which include "those used in the final crystallization steps and those used during formulation and processing," including "water, methanol, ethanol, propanol, isopropanol, acetone, acetonitrile, ethyl acetate, hexane and mixtures if appropriate." *Id.* at 946. Byrn further states that "[n]ew crystal forms can often be obtained by cooling hot saturated solutions or partly evaporating clear saturated solutions." *Id.*

Byrn teaches that "[i]f polymorphs exist then it is necessary to examine the physical properties of the different polymorphs that can affect dosage form performance (bioavailability and stability) or manufacturing reproducibility, including solubility profile and stability. *Id.* at 947. In the development of pharmaceutical products, Byrn states that usually the most physically stable polymorph is selected, further noting that "[s]election of the most stable form would, of course, insure it that there would be no conversion into other forms." *Id.* at 948. In characterizing the resultant polymorphs, Byrn teaches that at a minimum, x-ray diffraction should be used. *Id.* at 946-47.

t. J. Haleblian and W. McCrone, "Pharmaceutical Applications of Polymorphism," J. Pharm. Sci., 58, 911-929 (1969)

Haleblian 1969 is at least § 102(b) prior art. It states that "[i]n general, it should be possible to obtain different crystal forms of a drug and thus modify the performance properties for that compound," and that "[t]o do so requires a knowledge of the behavior of polymorphs." Haleblian 1969 at 911. Haleblian 1969 further states that "a very large number of compounds, organic and inorganic, as well as the elements themselves, have been shown to crystallize in two or more different crystalline arrangements — chemically identical, physically different." *Id.* Halenlian 1969 further states that "[i]t is now apparent that most, if not all, compounds and elements show a verity[sic] of different crystal forms." *Id.* at 912.

u. J.K. Haleblian "Characterization of Habits and Crystalline Modification of Solids and Their Pharmaceutical Applications," J. Pharm. Sci., 64, 1269-1288

Haleblian 1975 is at least § 102(b) prior art. It states that "[t]he majority of drugs marketed in various dosage forms probably can exist in different habits and crystalline modifications." Haleblian 1975 at 1270. The reference further describes the differences observed between different crystalline forms of the same substance, including solubility and bioavailablity. *Id.* at 1269-70.

v. T.L. Threlfall, "Analysis of Organic Polymorphs. A Review," *Analyst*, 120, 2435-2460

Threlfall was published in 1995 and is at least § 102(b) prior art. It estimates that "around one-third of organic substances show crystalline polymorphism under normal pressure conditions. A further third are capable of forming hydrates and other solvates." Threlfall at 2436. Threlfall explains the growing interest in polymorphism as caused by "the need to satisfy regulatory authorities in various countries as to the bioavailablity of formulations of new chemical entities." *Id.* at 2436.

w. Walter C. McCrone, Polymorphism, Physics and Chemistry Of The Organic Solid State 727, Fox, et al., eds., (1965)

McCrone was published in 1965 and is at least § 102(b) prior art. In detailing the frequency of polymorphism observed in both organic and inorganic compounds, McCrone states that "[i]t is at least this author's opinion that every compound has different polymorphic forms and that, in general, the number of forms known for a given compound is proportional to the time and money spent in research on that compound." McCrone at 727.

x. Keith Guillory, "Generation of Polymorphs, Hydrates, Solvates, and Amorphous Solids," Polymorphism in Pharmaceutical Sciences (H. Brittain ed. 1999)

Guillory was published in 1999 and is at least § 102(b) prior art. In detailing the frequency of polymorphism observed in both organic and inorganic compounds, Guillory states that:

> Those who study polymorphism are rapidly reaching the conclusion that all compounds, organic and inorganic, can crystallize in different forms or polymorphs. In fact, the more diligently any system is studied, the larger the number of polymorphs studied.

Guillory at 185. Guillory further notes that "[i]t is incumbent on the manufacturer of a new drug substance to show that due diligence has been employed to isolate and characterize the various solid-state forms of a new chemical entity." *Id.*

Guillory teaches "commonly used" crystallization techniques to crystallize new polymorphs including controlled temperature change, and explains how factors such as temperature can affect the specific crystal obtained. *Id.* at 188-202. In determining the crystallization solvent, Guillory cautions that "one should be careful to select those likely to be encountered during formulation and processing." *Id.* at 193. Guillory further teaches that certain solvents including ethyl acetate are "often used in the preparation of polymorphs." *Id.* at 189, Table 1.

y. H. Brittain (ed.), Polymorphism in Pharmaceutical Solids, Vol. 95, Marcel Dekker, New York (1999):

Brittain was published in 1999 and is at least § 102(b) prior art. It explains that "[m]any pharmaceutical solids exhibit polymorphism," and that different polymorphs "display different physical properties, including those due to packing, and various thermodynamic, spectroscopic, interfacial, and mechanical properties." Brittain at 1-2 and 5-8. Brittain further explains that "during crystallization, an unstable form is frequently obtained first that subsequently transforms into a stable form." *Id.* at 21. Citing to Ostwald's step rule, Brittain provides the following thermodynamic explanation for this observation: In all processes, it is not the most stable state

with the lowest amount of free energy that is initially formed, but the least stable state lying nearest in free energy to the original state." *Id.* at 21-22.

z. FDA Supporting Documentation Guideline

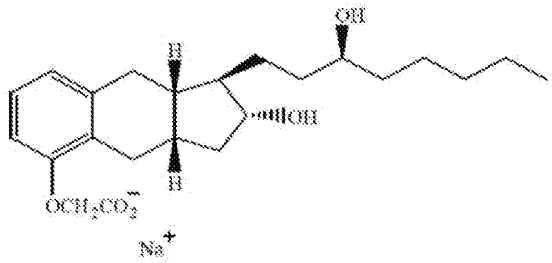
The FDA Guideline was published in 1987 and is at least § 102(b) prior art. Recognizing that certain solid-state properties of the drug substance "may profoundly affect dissolution and bioavailability from solid dosage forms," the FDA requires that "[b]y the time of an NDA submission, the applicant should have established whether (or not) the drug substance exists in multiple solid-state forms, whether these affect the dissolution and bioavailability of the drug product, and whether particle size is important for dissolution and bioavailability of the drug product. FDA Supporting Documentation Guideline at 31. In particular, the FDA requires that the drug sponsor utilize "appropriate" analytical procedures "to determine whether or not polymorphism occurs." FDA Supporting Documentation Guideline at 34. Such procedures include XRPD, infrared spectra, Raman spectroscopy, intrinsic dissolution data, differential scanning calorimetry analysis, and thermogravimetric analysis. *Id.* Recognizing the potential for changes in the solid state during development of the pharmaceutical product, the FDA further requires evidence that "no transformation is solid-state form has occurred," since "[r]outine storage conditions, as well as some conditions of product manufacture (e.g., tablet compression, or use of an organic solvent during granulation) may also cause transformations." *Id.* at 31.

aa. Gautam R. Desiraju, "Crystal Gazing: Structure Prediction and Polymorphism," 278 Science 404 (Oct. 17, 1997)

Desiraju was published in 1997 and is at least § 102(b) prior art. It teaches that "[i]n general, for any given drug molecule, one needs to know if it is likely to be polymorphic or pseudopolymorphic," noting that "an appreciation for polymorphism is fundamental to an understanding of the crystallization process itself." Desiraju at 405.

bb. Remodulin®

The treprostinil that was used in UTC's commercial embodiment Remodulin®, first approved, marketed, and sold to the public in 2002, with all its attributes and inherent qualities. Remodulin® was approved in March 2002. *See, e.g.*, Phares 2005 (disclosing the availability of treprostinil sodium (Remodulin®) [0004]); *see also* Wade 2005 at [0021, 0024] (disclosing treprostinil used in Remodulin® and its salt forms). As such, it is prior art under at least 35 U.S.C. § 102(b). According to its prescribing information, Remodulin® is a treprostinil sodium having the following structural formula:

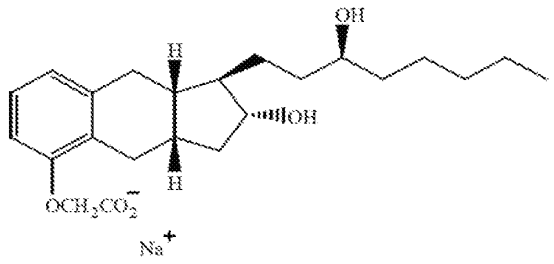


Where Remodulin® discloses each of the limitations of the asserted claims is included in the corresponding chart.

1. Claim 1 Would Have Been Obvious in View of the Prior Art.

Simonneau discloses administration of treprostinil sodium to treat pulmonary hypertension. The '075 patent discloses the chemical synthesis of treprostinil. Both the '075 and '222 patents disclose that salts of the compounds, including amine salts (which includes the diethanolamine salt), generally may also be useful. The '075 patent specifically identifies the action of diethanolamine and other compounds as useful salt counter ions of the disclosed compounds. The '075 patent points out that the diethanolamine salt, among others, may promote water-solubility. *See* '075 patent at col. 14, l. 56–col. 15, l. 25 and col. 15, ll. 15-17. According

to its prescribing information, Remodulin® is a treprostinil sodium having the following structural formula:



Bighley discloses that salt formation presents a relatively simple method to change the properties of a drug without changing its basic chemical structure. *See* Bighley at 453. Bighley discloses that the diethanolamine salt is one of 38 cationic drug salt forms in use at the time of publication. Bighley further indicates that a drug's diethanolamine salt, among others, can have useful properties such as higher aqueous solubility, enhanced bioavailability, desirable formulation characteristics, and increased absorption. *See* Bighley at 456, Table 2, 461, and 484. A drug compound's diethanolamine salt, among others, may have advantages over the corresponding inorganic salt. *See id.* at 461. With respect to certain prostacyclin derivatives, the diethanolamine salt is one of relatively few that U.S. Patent Nos. 5,506,265 and 5,466,713 specifically identify as suitable. The '095 publication discloses that the diethanolamine salt of the carboxylic acid zopolrestat possesses advantages. Simonneau discloses that continuous subcutaneous infusion of treprostinil sodium results in adverse events in a large percentage of patients.

Claim 1 of the '070 patent is invalid as obvious over the prior art. At the time of filing, the person of ordinary skill in the art would have been motivated to prepare the diethanolamine salt of treprostinil with a reasonable expectation of success. The facts here closely parallel those

of *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1371 (Fed. Cir. 2007). The '222 patent cited above specifically discloses treprostinil. Further, it generally discloses the diethanolamine salt of treprostinil and claims its use to treat pulmonary hypertension. *See* '222 patent at col. 3, ll. 1-20 and col. 6, ll. 58-63 (claim 2) (referring to a "pharmaceutically acceptable salt of treprostinil," which encompasses treprostinil diethanolamine); *cf. Pfizer*, 480 F.3d at 1353 and 1361 (noting that the prior art patent claimed a genus of amlodipine salts that encompassed amlodipine besylate, the specific salt at issue). *See* Simonneau at 800, 801, 803. The motivation to prepare the diethanolamine salt of treprostinil derives from several sources. At the time of filing, treprostinil was administered in clinical trials as the sodium salt by subcutaneous infusion. The person of ordinary skill in the art therefore would have been motivated to develop a form of treprostinil that could be administered by a less invasive and less cumbersome route. The choice of a salt form parallels the optimization of a variable within a range; the motivation to identify a superior salt form derives from the "normal desire of scientists or artisans to improve upon what is already generally known." *In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003); *see also Pfizer*, 480 F.3d at 1368 (quoting *In re Peterson* and noting the parallel between optimization of a variable and choice of salt form). A different salt form would have been recognized as a potential means of improving bioavailability and formulation characteristics relative to the sodium salt of treprostinil. *See* Bighley at 461. Consequently, in developing a formulation for oral administration, the person of ordinary skill in the art would have been motivated to test salts in addition to the sodium salt then in use. About 37 alternatives to the sodium salt were in use in drug compounds at the time. *See id.* at 456, Table 2. It was known that amine salts generally can provide higher aqueous solubility than corresponding sodium salts; high aqueous solubility in turn is important in the synthesis of the salt and can improve the drug's bioavailability and

formulation characteristics. Further, Bighley specifically identifies the diethanolamine salt, among others, as one that can provide increased absorption of the drug. *See id.* at 461, 484. Other references disclosed that diethanolamine was a suitable or advantageous salt of other prostacyclin derivatives and of piroxicam and the carboxylic acid drug zopolrestat. These considerations would have motivated the person of ordinary skill in the art to prepare and test the diethanolamine salt treprostinil. Further motivation to do so would have derived from the '222 patent, which discloses generally that organic amine salts of the disclosed compounds, including treprostinil, may be prepared, and from the '075 patent, which discloses that the diethanolamine salt of the disclosed compounds, including treprostinil, may be prepared. These circumstances are thus analogous to those of *Pfizer*, in which the court similarly relied on prior art disclosures of advantageous properties of besylate salts generally and of a specific besylate salt drug compound in determining that the person of ordinary skill in the art would have been motivated to prepare the besylate salt at issue. *See Pfizer*, 480 F.3d at 1363 (characterizing such disclosures as "highly relevant" in its analysis of motivation).

The person of ordinary skill in the art would have had a reasonable expectation of success in preparing treprostinil diethanolamine and that treprostinil diethanolamine would be therapeutically useful. Preparation of salts was routine in the pharmaceutical arts at the time of filing. *See* Bighley at 453. The '075 patent discloses general methods for preparing amine salts of the disclosed compounds, which included treprostinil (*see* '075 patent at col. 30, l. 41–col. 31, l. 5). The person of ordinary skill in the art would have recognized, from Bighley's discussion of amine salts and diethanolamine salts, that a diethanolamine salt could have useful drug properties, such as greater aqueous solubility and bioavailability than the sodium salt. *See* Bighley at 461, 484. Also, the prior art states that the diethanolamine salt of two specific

compounds, zopolrestat (a carboxylic acid, like treprostinil) and the benzothiazine compound of the '164 patent, possess advantageous properties. The '222 patent indicates that any pharmaceutically acceptable salt of treprostinil would be useful to treat pulmonary arterial hypertension by claiming such a method of treating. In view of these disclosures, treprostinil diethanolamine reasonably would have been expected to be suitable for a more conveniently administrable treprostinil dosage form. Therefore, the person of ordinary skill in the art would have been motivated to prepare treprostinil diethanolamine with a reasonable expectation of success. In sum, the person of ordinary skill in the art would have been motivated to prepare an alternative to subcutaneously administered treprostinil sodium in order to obtain a more convenient method of administration. In doing so, the person of ordinary skill in the art would have been motivated to prepare a different salt of treprostinil. The prior art would have motivated the person of ordinary skill in the art specifically to prepare the diethanolamine salt because diethanolamine generally was known to confer advantageous properties on the resulting drug salt, and because specific diethanolamine salts were known to possess certain advantageous properties. The person of ordinary skill in the art would have had a reasonable expectation of success at least because the prior art indicated that any pharmaceutically acceptable salt of treprostinil could be used to treat pulmonary arterial hypertension and because preparation of drug salts was routine in the art. *Cf. Pfizer*, 480 F.3d at 1368 ("[W]e hold that the optimization of the acid addition salt formulation for an active pharmaceutical ingredient would have been obvious whereas here the acid addition salt formulation has no effect on the therapeutic effectiveness of the active ingredient and the prior art heavily suggests the particular anion used to form the salt."). The prior art did not teach away from treprostinil diethanolamine. To the contrary, the '075 patent discloses treprostinil itself and that diethanolamine is a suitable

countering generally for the disclosed class of structurally similar compounds that includes treprostinil. The '222 patent indicates that treprostinil salts are useful to treat pulmonary hypertension and discloses that physiologically acceptable salts include salts with organic bases. The '265 and '713 patents disclose that the diethanolamine salt may be formed with other carboxylic acid prostacyclins. In view of at least these disclosures, no teaching away from treprostinil diethanolamine should be found.

2. Claims 2 and 3 Would Have Been Obvious.

Claims 2 and 3 would have been obvious to a person of skill in the art because they merely claim the most stable form of treprostinil diethanolamine.

The specification of the '070 patent refers to form B of treprostinil diethanolamine as "[a] particularly preferred embodiment of the present invention . . . ." col. 5, ll. 63–64. The specification also identifies Form B as the "thermodynamically more stable" polymorph of treprostinil diethanolamine. col. 66, ll. 42–43; col. 69, ll. 1–4. The specification further discloses that Form B, the preferred and more stable polymorph of treprostinil diethanolamine, melts at 107 degrees Celcius. col. 68, ll. 51–52.

Figure 20 shows the x-ray powder diffraction spectrum of the polymorph Form B. Figure 20 shows that Form B has a peak at about 17.2 for Form B, corresponding with the "x-ray powder diffraction pattern having a pattern peak at about 17.2 degrees 2 theta" of claim 3.

At most, claims 2 and 3 recite inherent properties of the stable polymorph of treprostinil diethanolamine. The skilled artisan would have been motivated to determine whether treprostinil diethanolamine exhibits polymorphism simply because many pharmaceutical solids exhibit polymorphism that can have different chemical and physical properties. *See* Haleblian 1969 at 911-12; Haleblian 1975 at 1669-70; Threlfall at 2436; Gu at 1878; Vippagunta; Brittain at 1-2 and 5-8; *see also* McCrone at 727 ("It is at least this author's opinion that every compound has

different polymorphic forms and that, in general, the number of forms known for a given compound is proportional to the time and money spent in research on that compound."); Guillory at 185 ("Those who study polymorphism are rapidly reaching the conclusion that all compounds, organic and inorganic, can crystallize in different forms or polymorphs. In fact, the more diligently any system is studied, the larger the number of polymorphs studied.").

Because treprostinil was intended for use as a pharmaceutical drug, a person of ordinary skill in the art would have been especially motivated to determine whether it existed in multiple polymorphic states and to determine the most stable form. Hornedo at 657; Gu at 1878; Vippagunta at 3; Byrn at 948; Bighley at 483 ("[T]he proclivity for polymorphic transformation can be assessed early before surprises are found later in the development program. A decision can be made to pursue the stable polymorphic form of the salt or to choose a completely new salt form."). Indeed, the FDA requires that the drug sponsor utilize "appropriate" analytical procedures to detect polymorphs, hydrates and amorphous forms of the drug substance and stresses the importance of controlling the crystal form of the drug substance during the various stages of product development as a prerequisite to approving a new drug. FDA Supporting Documentation Guideline at 34-35.

With the reasonable expectation that treprostinil existed in multiple polymorphic forms, one skilled in the art would have been motivated to search for the most thermodynamically stable polymorph and would have expected to identify it using simple techniques known to those skilled in the art. It is commonly known that all crystalline compounds have a most stable polymorphic form and that other metastable forms will convert to the most stable form. *See* Brittain at 21 ("[D]uring crystallization, an unstable form is frequently obtained first that subsequently transforms into a stable form."); Gu at 1878; Byrn at 948; Caira at 166. Especially

in the development of pharmaceutical products, it is often desirable to use the most thermodynamically stable polymorphic form. *See generally* Byrn, p. 948; *see also*, FDA Supporting Documentation Guideline; Gu at 1878; Vippagunta at 3; Caira at 166; Brittain at 21. The use of a less stable polymorph as a pharmaceutical risks the possibility that it will convert to a more stable form during manufacturing or storage. Gu at 1878; Caira at 167; Hornedo at 657. The use of the most stable form therefore avoids this problem and is favored for use in pharmaceutical formulations. The prior art expressly teaches that even if the most stable form was not chosen for use in a pharmaceutical formulation, it would be essential to identify it and ascertain the conditions under which less stable forms convert to the most stable form. Caira at 167; Hornedo at 657.

Accordingly, the skilled artisan wishing to develop an effective crystalline treprostinil diethanolamine product for pharmaceutical use would have been motivated to identify the most thermodynamically stable polymorph.

Additionally, the techniques for producing different polymorphs, and for isolating the most thermodynamically stable polymorph were known at the time of the alleged invention of the '070 patent. *See* Byrn at 946. One such technique that was generally known and commonly used in the art includes "ageing the crystals." *See id.* In situations where crystals of a less thermodynamically stable polymorph are initially obtained, a suspension containing this polymorph may be allowed to age so that a more thermodynamically stable polymorph can be obtained. The transformation between different polymorphic forms is driven by the difference in Gibbs Free Energy (ΔG) between the two forms. *See* Yu 1998, p. 122; *see also* Caira, p. 165-167; Brittain at 21-22. As the most thermodynamically stable polymorphic form has the lowest free energy, the unstable polymorphs will convert to the most thermodynamically stable

polymorphic form "until only the thermodynamically stable (least soluble) polymorph remains." *See* Caira, p. 166 ("Thermodynamic considerations of polymorphic crystallization include Ostwald's law of stages, according to which, at high supersaturation, the first form which crystallizes is the thermodynamically least stable (most soluble) form. This form subsequently dissolves and transforms into a more stable one. The cycle continues until only the thermodynamically stable (least soluble) polymorph remains."). Thus, obtaining the most thermodynamically stable polymorph would have been a matter of conducting simple ageing experiments using different solvents in order to obtain the most stable form, and would have been well within the ordinary skill at the relevant time.

It was also generally known that conditions allowing for slower recrystallization typically favor the formation of the most thermodynamically stable polymorphic form, whereas conditions that force crystals to form rapidly are more likely to result in less thermodynamically stable polymorphic forms. For example, use of a high initial ratio of solid to solvent will typically drive the system to form crystals and it is more likely that unstable crystalline forms may be produced. Similarly, the faster the cooling rate or evaporation rate, the greater the propensity to form crystals and the more likely that an unstable polymorphic form will be produced. *See* Guillory at 188-202. Thus, the ordinarily skilled artisan seeking to identify the most thermodynamically stable polymorph would have known how to use common crystallization techniques to do so with a reasonable expectation of success.

Because it would have been reasonable to expect that treprostinil diethanolamine is polymorphic, a person of ordinary skill in the art also would have been able to identify the Form A polymorph as a result of routine polymorphic screening. It was well-known in the art, as acknowledged by the patentee, that different polymorphic forms can have different,

advantageous properties making them more suitable for development and application in the pharmaceutical context. *See* Brittain at 6, 7-8; *see also* FDA Supporting Documentation Guideline at p. 31. Additionally, it would have been routine practice in the late 1990s and early 2000s for a person of ordinary skill in the art to conduct polymorphic screening for a new drug substance in order to discover new polymorphs and also to identify the most stable polymorph. *See* Yu 1998 at 118-27; Byrn at 945-54; Desiraju at 405. Hence, the skilled artisan would have been motivated to screen for additional, more advantageous polymorphs, resulting in identifying Form B.

3. Secondary Considerations

Plaintiffs have not set forth any evidence of secondary considerations of non-obviousness, and Actavis is not aware of any such secondary considerations that, when considered with the evidence of obviousness, would warrant a finding of non-obviousness of the claims of the '070 patent. If UTC relies on any secondary considerations of non-obviousness, Actavis reserves the right to supplement its contentions.

During prosecution of the European counterpart application, the applicants suggested that the prior art teaches away from the use of diethanolamine.[7] According to the applicants, the person of ordinary skill in the art would "likely not consider diethanolamine as a counter ion for treprostinil in view of multiple reports on toxicity of diethanolamine." EU Application No. EP20040776104 (May 24, 2004), Reply (July 11, 2011) at 3 (second full paragraph). They cited two references, an FDA cosmetics information internet page ("FDA page") that concerns diethanolamine and a journal publication (Exhibit 23). *Id.*

[7] The applicants asserted the same teaching away argument in prosecuting the '839 patent as they did in the European prosecution discussed in this section.

Neither reference teaches away from the use of the diethanolamine salt of treprostinil; that is, neither reference would have discouraged the person of ordinary skill in the art from preparing treprostinil diethanolamine. "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994). "A statement that a particular combination is not a preferred embodiment does not teach away absent clear discouragement of that combination." *Syntex (U.S.A.) LLC v. Apotex, Inc.*, 407 F.3d 1371, 1380 (Fed. Cir. 2005).

Regarding the FDA page, the document, while acknowledging an earlier study's finding of "an association between the topical application of DEA and certain DEA-related ingredients and cancer in laboratory animals," concludes that "at the present time there is no reason for consumers to be alarmed based on the use of these substances in cosmetics." FDA page (originally published December 21, 1999; updated October 27, 2006) (the applicants cited the updated version). (The applicants omitted the latter quotation from their discussion of the FDA page. *See* Reply at 3.) It is our view that the information in this page would not have "discouraged" the person of ordinary skill in the art from developing the diethanolamine salt of treprostinil. First, the FDA page relates to topical application of DEA. The person of ordinary skill in the art would have pursued a more conventionally administered treprostinil diethanolamine formulation, such as an oral formulation, and not a dermal formulation. The FDA page provides no information relating to oral or non-dermal administration of DEA. Second, the FDA page concludes that there is no reason for consumers to be alarmed about the use of DEA in cosmetics. The FDA page does not indicate that there is any reason that DEA should not be used in products intended for human use.

The journal publication, Lois D. Lehman-McKeeman et al., Diethanolamine Induces Hepatic Choline Deficiency in Mice, 67 Toxicol. Sci. 38 (2002) ("Lehman- McKeeman," Exhibit 23), notes that "the results of the present study provide evidence that 4 weeks of DEA treatment leads to a biochemical condition of hepatic choline deficiency in mice," yet concludes that "[o]verall, the results suggest that the hepatocarcinogenic effects of DEA in mice are not predictive of similar susceptibility in other laboratory animals or humans." In addition, the daily dose of DEA in this study was much higher than the daily dose that a patient would receive from treprostinil diethanolamine. Also, DEA in the study was applied dermally, which likely would not have been the route of administration pursued by the person of ordinary skill in the art developing treprostinil diethanolamine. These three considerations, taken alone or together, lead to the conclusion that the most that can be said about Lehman-McKeeman is that it is inconclusive with respect to any potential use of the diethanolamine salt of treprostinil for administration to humans or harm arising from such use. It is therefore our opinion that Lehman-McKeeman would not have discouraged the person of ordinary skill in the art from preparing treprostinil diethanolamine for human use.

No unexpected results or other secondary considerations outweigh the above considerations. The patentees did not assert unexpected results to gain allowance of the '070 patent. The patentees did, however, assert unexpected results in the European counterpart application. *See* Reply (July 7, 2011) at 3 (third full paragraph). Specifically, the applicants asserted that treprostinil diethanolamine "possesses a superior combination of the following three properties: high melting temperature, high solubility and low hygroscopicity." Id. The applicants purported to submit supporting data and asserted that the diethanolamine salt was

superior to the sodium salt in all three respects. *See id.* at 3 and *id.* Exhibit I. The data are reproduced below.

Table I: Melting temperatures, visual aqueous solubilities, and water absorption? properties of salts of treprostinil and treprostinil as the free acid.

Molecular form of treprostinil	**Melting temperature (°C)**	**Visual aqueous solubility**	**% weight change at 60% RH**	**% weight change at 95% RH**
free acid	125	<0.025	0.6	2.8
calcium	180	0.22	10	35
ethylenediamine	109	1.24	0.5	5.5
choline	153	1.38	8	55
TRIS	75	81.33	0.2	0.9
sodium	56	117.5	7	20
potassium	decomposes	167.7	15	70
diethanolamine	107	168.8	0	15
glucamine	60	92.6	4	33
benzathine	141	insoluble	3.5	6.5
procaine	182	100.6	10	55

Id.

The applicants argued that these three properties generally are "desirable in oral pharmaceutical formulations." *See* Reply at 4. They also argued that the diethanolamine salt is superior to the marketed sodium salt with respect to these three properties. *See id.* at 3–4. They further asserted that "the treprostinil diethanolamine's combination of properties is surprising/unexpected." *Id.* at 3. In support, they cited a reference that indicates that an "increase in melting point is usually accompanied by a reduction in salt solubility." Here, in contrast, the diethanolamine salt is said to have both a higher melting point and higher solubility than the sodium salt. *Id.* at 3 (citing Philip L. Gould, Salt selection for basic drugs, 33 Int. J. Pharm. 201 (1986)). Applicants further argued that treprostinil diethanolamine's possession of both higher solubility and lower hygroscopicity than treprostinil sodium is also surprising, again relying on Gould. *See id.* at 3–4.

These arguments should not be found to outweigh the considerations set forth above that weigh in favor of a finding of obviousness of treprostinil diethanolamine. It is not surprising

that, generally, different salts of a drug compound will have different properties, and that certain salts will have more preferred properties than others. *See Pfizer*, 480 F.3d at 1371 (rejecting alleged unexpected superiority of claimed amlodipine salt in part because the person of ordinary skill in the art would have expected pharmaceutically acceptable salt anions to provide amlodipine salts with a range of properties, some superior and some inferior to the prior art). It is also not surprising, in view of the prior art, that the diethanolamine salt would possess any two or all three of relatively low hygroscopicity, relatively high solubility, and relatively high melting point. Zopolrestat diethanolamine was known to have both high water solubility (at least about 100 mg/ml) and a high melting point (163-164° C). *See* '095 publication ¶¶ 0005, 0263 (hygroscopicity not reported). Piroxicam diethanolamine had all three of low hygroscopicity, high water solubility, and high melting point. *See* '164 patent at col. 1, ll. 37-63, col. 2, l. 43-col. 3, l. 13, and col. 6, ll. 28-30. The prior art thus demonstrates that these properties can be found in a single diethanolamine salt. The person of ordinary skill in the art thus would have been aware that the relationships between melting point, solubility, and hygroscopicity that Gould put forward do not always hold true. Specifically, the person of ordinary skill in the art would have known that diethanolamine salts do not necessarily conform to general rules. We therefore conclude that the water solubility, hygroscopicity, and melting point of treprostinil diethanolamine should not be found surprising or unexpected. Consequently, it is our opinion that these properties should not be found to weigh in favor of non-obviousness or to outweigh the other factors that favor a finding of obviousness, detailed above.

Even if the patentees were to succeed in establishing that the person of ordinary skill in the art would have found it surprising that treprostinil diethanolamine possesses all three of the attributes discussed above, it is our opinion that claim 1 nevertheless should be found invalid as

obvious in view of the overwhelming evidence of obviousness set forth above. "Although secondary considerations must be taken into account, they do not necessarily control the obviousness conclusion." *Pfizer*, 480 F.3d at 1372 (holding that, even if it were established that the claimed salt amlodipine besylate "exhibits unexpectedly superior results," that did not "overcome the strong showing of obviousness").

The applicants have not put forward evidence of other secondary considerations, such as skepticism of others, commercial success, failure of others, or long-felt but unmet need, that weigh in favor of a finding of nonobviousness, and we are not aware of any such other considerations.

As explained above, the claims would have been obvious in view of a host of prior art references because the steps described in the claims were well-known procedures that would have been obvious to apply. Consequently, there are numerous different combinations of these prior art references and many exemplary references that teach each standard step. By way of example, the following combinations render the asserted claims obvious:

- Simonneau, the '222 patent, Bighley or Berge, and/or the diethanolamine salts of other drug compounds,
- Simonneau, the '222 patent, the '075 patent, Bighley or Berge, and/or the diethanolamine salts of other compounds,
- The '222 patent, the '075 patent, Bighley or Berge, and/or the diethanolamine salts of other compounds.
- The '953 patent, the '222 patent, Bighley or Berge, and/or the diethanolamine salts of other compounds
- The '953 patent, Simonneau, Bighley or Berge, and/or the diethanolamine salts of other compounds
- Any of the above combinations with Byrn, Olmsted, Sharp, and Pavia
- Any of the above combinations with Remodulin and the Remodulin Label

A POSA would have been motivated to combine the teachings of these references with a reasonable expectation of success. In addition, Actavis's invalidity charts set forth where each prior art reference discloses the limitations of the asserted claims.

Actavis reserves the right to set forth additional such examples as discovery continues.

4. Claims 2 and 3 Are Also Invalid for Failure to Meet the Written Description and Enablement Requirements

Should the court not determine that claims 2 and 3 are obvious, they should alternatively be found invalid as lacking enablement and meeting the written description requirements. Claims 2 and 3 purport to cover all crystals with either a 107 degree Celcius melting point or having an x-ray powder diffraction pattering with a peak at about 17.2 degrees. There is possibly an infinite number of other treprostinil-diethanolamine crystals that meet those requirements. The specification, however, only describes one form, Form B. As described above by Guillory and McCrone, compounds have numerous different polymorphic forms and that the more time spent studying a compound, the more polymorphs are found.

As noted above, the written description requirement exists to confine the scope of the patent to the scope of the inventor's contribution to the field of art. Further, the patentee must demonstrate possession of the full scope of the claimed invention. *See LizardTech, Inc. v. Earth res. Mapping, Inc.*, 424 F.3d 1336, 1345 (Fed. Cir. 2005). Because of the breadth of claims 2 and 3, the patentee cannot demonstrate possession of the claimed invention. Further, discovering all of the polymorphs that meet the requirements of claims 2 and 3 would require undue experimentation.

C. Invalidity of the '839 Patent

1. Claims 1 and 3–5 Are Rendered Obvious by the Following References

The same references that anticipate the '070 patent also anticipate the '839 patent. These references all qualify as at least § 102(b) prior art to the '839 patent. Additional references include:

a. European Patent Application EP 0 947 196 ("the '196 Publication")

The '196 publication was filed on March 13, 1998, and was published on October 6, 1999. The '196 publication discloses a sustained-release preparation that contains a prostaglandin I ("PGI") derivative as the active ingredient and p-glycoprotein inhibitors as excipients. *See id.* at ¶ 0001. This publication specifically discloses 36 tablet compositions that contain the prostacyclin analog beraprost sodium. Beraprost is noted to be a compound similar in structure and activity to treprostinil.[8] The disclosed formulations are thus relevant to the person of ordinary skill in the art's formulation of treprostinil diethanolamine.

Eight of the exemplary tablet formulations also contain PEG-6000 at a concentration of about 35% and polyethylene oxide at a concentration of about 60%. *See id.* at 10, Table 2. One of these eight formulations, Formulation Example No. 30, was administered to six dogs and was found to be "very preferred," as it yielded sustained release of drug (beraprost) in the gastrointestinal tract, attained pH-independent release, and maintained drug in the blood for a long time. *See id.* ¶¶ 0035-0037 and Figure 39.

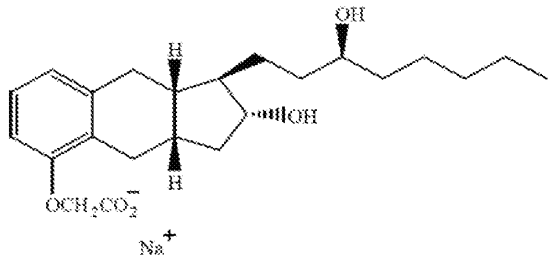
2. Claim 1 Is Obvious

Claim 1 of the '839 patent is invalid as obvious over the prior art. At the time of filing, the person of ordinary skill in the art would have been motivated to prepare a pharmaceutical formulation comprising a therapeutically effective amount of treprostinil diethanolamine and a

[8] *See also, e.g.*, Rubin M. Tuder and Ari L. Zaiman, *Prostacyclin Analogs as the Brakes for Pulmonary Artery Smooth Muscle Cell Proliferation*, 26 Am. J. Respir. Cell Mol. Biol. 171, 171 (characterizing beraprost and treprostinil ("UT-15") as "prostacyclin analogs").

pharmaceutically acceptable carrier, and would have had a reasonable expectation of success in doing so. The prior art does not teach away from such a formulation, and no secondary considerations outweigh the teachings of the prior art.

At the time of filing, the person of ordinary skill in the art would have been motivated to prepare a composition that contains a therapeutically effective amount of a salt of treprostinil and a pharmaceutically acceptable carrier with a reasonable expectation of success. According to its prescribing information, Remodulin® is a treprostinil sodium having the following structural formula:



The '222 patent discloses the preparation of oral tablets that contain a compound of formula (I), and that formulations, including tablets, typically contain a carrier. The '222 patent further discloses that an oral tablet effective amount of a compound of formula (I) for treating pulmonary hypertension is typically in the relatively narrow range of 1 to 50 mg. The '222 patent discloses that treprostinil and pharmaceutically acceptable salts of treprostinil are a "particularly preferred compound of formula (I)." In view of this disclosure, the person of ordinary skill in the art would have been motivated to prepare, for example, a tablet that contains an effective amount of a treprostinil salt and a pharmaceutically acceptable carrier, and would have had a reasonable expectation of success in doing so.

For the reasons set forth with respect to claim 1 of the '070 patent, the person of ordinary skill in the art would have been motivated to prepare treprostinil diethanolamine with a reasonable expectation of success. The primary reason for preparing treprostinil diethanolamine is to use it to treat a condition such as pulmonary hypertension. A common method of administering a drug is by incorporating it into a formulation that can be administered to a patient. For these reasons and in view of the disclosure of the '222 patent summarized above, a person of ordinary skill in the art would have been motivated to prepare, for example, an oral tablet that contains an effective amount of treprostinil diethanolamine and a pharmaceutically acceptable carrier.

Further, the person of ordinary skill in the art would have had a reasonable expectation that an oral tablet that contained treprostinil diethanolamine as the active ingredient would be effective in treating pulmonary hypertension.

Motivation to orally administer derives from the fact that the person of ordinary skill in the art knew that subcutaneous administration of treprostinil sodium was effective in treating pulmonary hypertension, but that this route of administration presented disadvantages. The person of ordinary skill in the art thus would have been motivated to administer treprostinil by an alternative route. Also, oral administration of a drug is typically more convenient than subcutaneous administration. "Compared with alternative routes, the oral route is considered the most natural, uncomplicated, convenient, and safe means of administering drugs." Ansel 1999 at 122.

The person of ordinary skill in the art would have known (or at the very least could have determined through simple, routine experimentation), from the fact that treprostinil sodium, the only form to receive an approvable letter from the FDA, was administered subcutaneously, that

treprostinil sodium was not amenable to oral formulation and/or administration. Thus, the person of ordinary skill in the art would have been motivated to prepare an alternative form of treprostinil that could be administered orally.

The person of ordinary skill in the art would have been motivated to vary the treprostinil salt form in order to obtain a treprostinil salt amenable to oral formulation and administration because such a change was a well-known, "relatively simple chemical manipulation which may alter the physicochemical, formulation, biopharmaceutical, and therapeutic properties of a drug without modifying the basic chemical structure." Bighley at 453. Thus, changing the salt of treprostinil was a simple way to obtain a form of treprostinil amenable to formulating for oral administration.

The person of ordinary skill in the art would have been motivated to prepare specifically the diethanolamine salt of treprostinil for the reasons set forth above with respect to claim 1 of the '070 patent. In sum, the prior art discloses amines generally as useful in forming salts with carboxylic acid drugs. At least two references that specifically disclose treprostinil mention either amine counterions generally or the diethanolamine counter ion specifically as potentially useful in conjunction with the subject compounds of the references. The prior art Bighley reference discloses that diethanolamine as a salt counter ion could promote solubility and absorption generally. Also, the prior art discloses specific diethanolamine salts that had properties useful in pharmaceutical compounds, including high solubility and high melting point (zopolrestat diethanolamine) and low hygroscopicity (piroxicam diethanolamine possesses all three properties).

In sum, the person of ordinary skill in the art would have been motivated to prepare treprostinil diethanolamine and to administer it orally to treat pulmonary hypertension.

The person of ordinary skill in the art also would have had a reasonable expectation that treprostinil diethanolamine would work for its intended purpose for the reasons set forth with respect to claim 1 of the '070 patent. The person of ordinary skill in the art further would have had a reasonable expectation of success in orally administering treprostinil diethanolamine to treat a subject in need thereof. Generally, this is so in view of the advanced state of the art in formulating drugs for oral administration and the variety of oral formulation options (tablet, capsule, solution, for example) available at the time of filing. *See, e.g.*, Ansel 1999 at 120-23 (discussing oral route of administration) and 196-203 (describing types of tablets).

Additional expectation of success can be found in the disclosure that another prostacyclin analogue, beraprost, had been effective in treating pulmonary hypertension when administered orally. Treprostinil is similar to beraprost in a number of ways. They are structurally similar to each other: both have three fused rings, one of which is phenyl; both have a hydroxyl group and a hydroxyalkyl group at the same positions of the five-member ring; both have a carboxyl group. As mentioned, they are both in the same functional class of prostacyclin analogues. Both are relatively stable and have relatively long half-lives. Vizza notes that it is beraprost's stability that makes it suitable for oral administration.

In view of the similarities between beraprost and treprostinil and that beraprost was therapeutically effective when administered orally to treat pulmonary hypertension, and in view of the advanced state of the art, the person of ordinary skill in the art would have had a reasonable expectation of success that treprostinil diethanolamine could be successfully administered orally to treat pulmonary hypertension. "Obviousness does not require absolute predictability. Only a reasonable expectation that the beneficial result will be achieved is necessary to show obviousness." *In re Merck & Co., Inc.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986)

(internal citations omitted) (affirming obviousness of claims reciting method of treating depression with known compound in view of its structural similarity with a known anti-depressant).

3. Claim 3 Is Obvious

Claim 3 of the '839 patent should be found invalid as obvious for the same reasons as those set forth with respect to claim 1. In addition to the limitations of claim 1, claim 3 only further requires that the recited formulation be in the form of a capsule, tablet, liquid, or suspension. The analysis of claim 1 specifically relates to a treprostinil diethanolamine-containing tablet and thus applies equally to claim 3.

4. Claim 4 Is Obvious

Claim 4 of the '839 patent should be found invalid as obvious for the same reasons as those set forth with respect to claim 1. In addition to the limitations of claim 1, claim 4 only further requires that the treprostinil diethanolamine comprise "a diethanolamine salt of (+)-treprostinil." The analysis above specifically relates to a pharmaceutical formulation that contains the commercial form of treprostinil diethanolamine—"diethanolamine salt of (+)-treprostinil." Remodulin discloses the use of (+) as the commercial form of treprostinil. The specification of the '839 patent also defines (+)-Treporostinil as the "commercial drug." col. 34, l. 10. A person of skill in the art would have found it obvious to create a pharmaceutical formulation containing the diethanolamine salt of treprostinil for the reasons described above.

5. Claim 5 Is Obvious

Claim 5 of the '839 patent would have been obvious for the same reasons as claims 2 and 3 of the '070 patent.

6. Secondary Considerations

Plaintiffs have not set forth any evidence of secondary considerations of non-obviousness, and Actavis is not aware of any such secondary considerations that, when considered with the evidence of obviousness, would warrant a finding of non-obviousness of the claims of the '839 patent. If UTC relies on any secondary considerations of non-obviousness, Actavis reserves the right to supplement its contentions.

As explained above, the claims would have been obvious in view of a host of prior art references because the claimed invention was well known and would have been obvious to apply. Consequently, there are numerous different combinations of these prior art references and many exemplary references that teach each standard step. By way of example, the following combinations render the asserted claims obvious:

- Simonneau, the '222 patent, Bighley, the '196 publication, and/or the diethanolamine salts of other drug compounds,
- Simonneau, the '222 patent, the '075 patent, Bighley, the '196 publication, and/or the diethanolamine salts of other compounds,
- The '222 patent, the '075 patent, Bighley, the '196 publication, and/or the diethanolamine salts of other compounds.
- Simonneau, the '222 patent, Bighley or Berge, and/or the diethanolamine salts of other drug compounds,
- Simonneau, the '222 patent, the '075 patent, Bighley or Berge, and/or the diethanolamine salts of other compounds,
- The '222 patent, the '075 patent, Bighley or Berge, and/or the diethanolamine salts of other compounds.
- The '953 patent, the '222 patent, Bighley or Berge, and/or the diethanolamine salts of other compounds
- The '953 patent, Simonneau, Bighley or Berge, and/or the diethanolamine salts of other compounds
- Any of the above combinations with Byrn, Olmsted, Sharp, and Pavia
- Any of the above combinations with Remodulin and the Remodulin Label

A POSA would have been motivated to combine the teachings of these references with a reasonable expectation of success. In addition, Actavis's invalidity charts set forth where each prior art reference discloses the limitations of the asserted claims.

Actavis reserves the right to set forth additional such examples as discovery continues.

D. Invalidity of the '713 Patent

1. Claim 23 Is Rendered Obvious by the Following References

The same prior art references set forth above in the analysis of claim 1 of the '070 patent apply here.

2. Claim 23 Is Obvious

Claim 23 should be found invalid as obvious for the same reason as claim 1 of the '839 patent. At the time of filing, the person of ordinary skill in the art would have been motivated to treat pulmonary hypertension by orally administering an effective amount of treprostinil diethanolamine, and would have had a reasonable expectation of success in doing so. The prior art did not teach away from such a treatment, and no secondary considerations outweigh the teachings of the prior art.

3. Claims 24 and 25 Are Invalid As Obvious

Claims 24 and 25 are obvious for the reasons described with respect to claims 2 and 3 of the '070 patent.

4. Secondary Considerations

Plaintiffs have not set forth any evidence of secondary considerations of non-obviousness, and Actavis is not aware of any such secondary considerations that, when considered with the evidence of obviousness, would warrant a finding of non-obviousness of the claims of the '713 patent. If UTC relies on any secondary considerations of non-obviousness, Actavis reserves the right to supplement its contentions.

As explained above, the claims would have been obvious in view of a host of prior art references because the steps described in the claims were well-known procedures that would have been obvious to apply. Consequently, there are numerous different combinations of these prior art references and many exemplary references that teach each standard step. By way of example, the following combinations render the asserted claims obvious:

- Simonneau, the '222 patent and/or Vizza, Bighley, and/or the diethanolamine salts of other drug compounds,
- Simonneau, the '222 patent and/or Vizza, the '075 patent, Bighley, and/or the diethanolamine salts of other compounds,
- The '222 patent, the '075 patent, Bighley, and/or the diethanolamine salts of other compounds.
- The '222 patent, the '075 patent, Bighley, the '196 publication, and/or the diethanolamine salts of other compounds.
- Simonneau, the '222 patent, Bighley or Berge, and/or the diethanolamine salts of other drug compounds,
- Simonneau, the '222 patent, the '075 patent, Bighley or Berge, and/or the diethanolamine salts of other compounds,
- The '222 patent, the '075 patent, Bighley or Berge, and/or the diethanolamine salts of other compounds.
- The '953 patent, the '222 patent, Bighley or Berge, and/or the diethanolamine salts of other compounds
- The '953 patent, Simonneau, Bighley or Berge, and/or the diethanolamine salts of other compounds
- Any of the above combinations with Byrn, Olmsted, Sharp, and Pavia
- Any of the above combinations with Remodulin and the Remodulin Label

A POSA would have been motivated to combine the teachings of these references with a reasonable expectation of success. In addition, Actavis's invalidity charts set forth where each prior art reference discloses the limitations of the asserted claims.

Actavis reserves the right to set forth additional such examples as discovery continues.

E. Invalidity of the '169 Patent

1. Claims 8–11 Are Rendered Obvious by the Following Prior Art

The same prior art references set forth above in the analysis of claim 1 of the '070 patent apply here. Additional prior art includes:

i. WO 98/18452

WO 98/18452 ("the '452 publication") was published in 1998 and therefore is at least 35 U.S.C. § 102(b) prior art to the '169 patent. The '452 publication provides extended release compositions and points out their advantages:

> In arriving at the present invention it has been discovered that it is possible to efficiently deliver therapeutically effective doses, at controlled rates and for extended times, of a broad variety of drugs without the need for polymers that swell or expand within the tablet wall so as to physically force the medicament particles out into their intended environment of use.

'452 publication at 2. *See also id.* at 9 ("The delivery system of the invention can be used to provide controlled release of any of a broad variety of therapeutically active agents."). The advantages of extended release at a controlled rate would have been particularly attractive for a drug like treprostinil, which has a relatively short half-life and is administered in low doses for a chronic condition. Specifically, treprostinil is indicated for the treatment of pulmonary arterial hypertension, a chronic condition, has "a terminal half-life of approximately 2-4 hours," and is administered at doses ranging, for a 70 kg person, from an initial dose of about 0.13 mg/day to not more than about 4 mg/day. *See* REMODULIN™ Prescribing Information (2002) at 5, 9-10; *see also* Ansel (2005) at 263 (drugs best suited for extended release have certain characteristics, including having a low dosage and being administered to treat chronic conditions).

As noted above, the disclosed delivery system "can be used to provide controlled release of any of a broad variety of therapeutically active agents." *Id.* at 9. Among various examples, the

'452 publication identifies specifically a number of substantially water-soluble salts of active agents that the system can be used to deliver (without referring to the solubility of each active). These include chlorpheniramine maleate (water solubility 160 mg/ml), brompheniramine maleate ("sol in water"), verapamil hydrochloride (water solubility 70 mg/ml),[9] metoprolol succinate (freely soluble in water), and metoprolol tartrate (very soluble in water).[10] *See* '452 publication at 9 (listing examples of actives); for solubilities, *see Merck Index* 337, 218, 1563-64 (Susan Budavari ed., 11th ed. 1989) and *European Pharmacopoeia* 2032 and 2034 (2005), respectively. Other specifically listed actives that the disclosed delivery system can deliver are water-insoluble salts (e.g., dextromethorphan hydrobromide, enalapril maleate, diclofenac sodium) and water-insoluble non-salts (e.g., carbamazepine, acyclovir). *See* '452 publication at 9. Thus, although the '452 publication elsewhere states that, "[i]n accordance with the preferred invention, there is provided an osmotic delivery system, preferably in the form of a tablet, which dispenses a therapeutic agent having a limited solubility in water or physiological environments," '452 publication at 2,[11] it is not limited to such therapeutic agents, as it also explicitly discloses that the disclosed composition is suitable for delivery of water-soluble salts of therapeutic agents, including salts of anti-hypertensive agents. This class includes treprostinil diethanolamine. In sum, the disclosed system is useful for both water-soluble salts of active ingredients and for active ingredients with relatively lower water solubility.

The '452 publication further discusses the other components of the disclosed composition. "Preferred non-swelling osmotic agents include" fructose, lactose, xylitol and

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[9] The '452 publication does not refer specifically to verapamil hydrochloride, but rather to "antihypertensives such as nifedipine, verapamil, enalapril and salts thereof." *See* '452 publication at 9.

[10] The '897 patent also lists metoprolol succinate as a "therapeutic agent[ ] that will benefit from this invention." '897 patent at col. 7, ll. 8-16.

[11] *See also* '452 publication at 9 ("The system of the present invention is particularly applicable to therapeutic agents which are insoluble or poorly soluble in water or aqueous environments at physiological pH.").

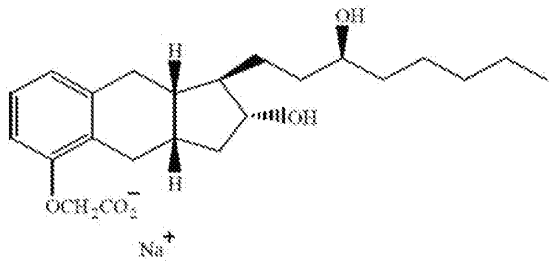
sorbitol. *Id.* at 3. Triethyl citrate ("TEC") is a suitable plasticizer for use with a semipermeable, polymeric coating material such as cellulose acetate. *See id.* at 6.

The '452 publication further discloses a general method for preparing such a composition as coated tablets. *See id.* at 10-13, Example 1.

2. Claims 8–11 Would Have Been Obvious in View of the Prior Art.

a. Treprostinil diethanolamine is obvious

The '222 patent cited above specifically discloses treprostinil. Further, it generally discloses the diethanolamine salt of treprostinil and claims its use to treat pulmonary hypertension. *See* '222 patent at col. 3, ll. 1-20 and col. 6, ll. 58-63 (claim 2) (referring to a "pharmaceutically acceptable salt of treprostinil," which encompasses treprostinil diethanolamine); *cf. Pfizer*, 480 F.3d at 1353 and 1361 (noting that the prior art patent claimed a genus of amlodipine salts that encompassed amlodipine besylate, the specific salt at issue). *See* Simonneau at 800, 801, 803. According to its prescribing information, Remodulin® is a treprostinil sodium having the following structural formula:



The motivation to prepare the diethanolamine salt of treprostinil derives from several sources. At the time of filing, treprostinil was administered in clinical trials as the sodium salt by subcutaneous infusion. The person of ordinary skill in the art therefore would have been motivated to develop a form of treprostinil that could be administered by a less invasive and less

cumbersome route. The choice of a salt form parallels the optimization of a variable within a range; the motivation to identify a superior salt form derives from the "normal desire of scientists or artisans to improve upon what is already generally known." *In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003); *see also Pfizer*, 480 F.3d at 1368 (quoting *In re Peterson* and noting the parallel between optimization of a variable and choice of salt form).

A different salt form would have been recognized as a potential means of improving bioavailability and formulation characteristics relative to the sodium salt of treprostinil. *See* Bighley at 461. Consequently, in developing a formulation for oral administration, the person of ordinary skill in the art would have been motivated to test salts in addition to the sodium salt then in use. About 37 alternatives to the sodium salt were in use in drug compounds at the time. *See id.* at 456, Table 2. It was known that amine salts generally can provide higher aqueous solubility than corresponding sodium salts; high aqueous solubility in turn is important in the synthesis of the salt and can improve the drug's bioavailability and formulation characteristics. Further, Bighley specifically identifies the diethanolamine salt, among others, as one that can provide increased absorption of the drug. *See id.* at 461, 484. Other references disclosed that diethanolamine was a suitable or advantageous salt of other prostacyclin derivatives and of piroxicam and the carboxylic acid drug zopolrestat. These considerations would have motivated the person of ordinary skill in the art to prepare and test the diethanolamine salt treprostinil.

Further motivation to do so would have derived from the '222 patent, which discloses generally that organic amine salts of the disclosed compounds, including treprostinil, may be prepared, and from the '075 patent, which discloses that the diethanolamine salt of the disclosed compounds, including treprostinil, may be prepared. These circumstances are thus analogous to those of *Pfizer*, in which the court similarly relied on prior art disclosures of advantageous

properties of besylate salts generally and of a specific besylate salt drug compound in determining that the person of ordinary skill in the art would have been motivated to prepare the besylate salt at issue. *See Pfizer*, 480 F.3d at 1363 (characterizing such disclosures as "highly relevant" in its analysis of motivation).

The person of ordinary skill in the art would have had a reasonable expectation of success in preparing treprostinil diethanolamine and that treprostinil diethanolamine would be therapeutically useful. Preparation of salts was routine in the pharmaceutical arts at the time of filing. *See* Bighley at 453. The '075 patent discloses general methods for preparing amine salts of the disclosed compounds, which included treprostinil (*see* '075 patent at col. 30, l. 41–col. 31, l. 5). The person of ordinary skill in the art would have recognized, from Bighley's discussion of amine salts and diethanolamine salts, that a diethanolamine salt could have useful drug properties, such as greater aqueous solubility and bioavailability than the sodium salt. *See* Bighley at 461, 484. Also, the prior art states that the diethanolamine salt of two specific compounds, zopolrestat (a carboxylic acid, like treprostinil) and the benzothiazine compound of the '164 patent, possess advantageous properties. The '222 patent indicates that any pharmaceutically acceptable salt of treprostinil would be useful to treat pulmonary arterial hypertension by claiming such a method of treating. In view of these disclosures, treprostinil diethanolamine reasonably would have been expected to be suitable for a more conveniently administrable treprostinil dosage form. Therefore, the person of ordinary skill in the art would have been motivated to prepare treprostinil diethanolamine with a reasonable expectation of success.

In sum, the person of ordinary skill in the art would have been motivated to prepare an alternative to subcutaneously administered treprostinil sodium in order to obtain a more

convenient method of administration. In doing so, the person of ordinary skill in the art would have been motivated to prepare a different salt of treprostinil. The prior art would have motivated the person of ordinary skill in the art specifically to prepare the diethanolamine salt because diethanolamine generally was known to confer advantageous properties on the resulting drug salt, and because specific diethanolamine salts were known to possess certain advantageous properties. The person of ordinary skill in the art would have had a reasonable expectation of success at least because the prior art indicated that any pharmaceutically acceptable salt of treprostinil could be used to treat pulmonary arterial hypertension and because preparation of drug salts was routine in the art. *Cf. Pfizer*, 480 F.3d at 1368 ("[W]e hold that the optimization of the acid addition salt formulation for an active pharmaceutical ingredient would have been obvious whereas here the acid addition salt formulation has no effect on the therapeutic effectiveness of the active ingredient and the prior art heavily suggests the particular anion used to form the salt.").

The prior art did not teach away from treprostinil diethanolamine. To the contrary, the '075 patent discloses treprostinil itself and that diethanolamine is a suitable counter ion generally for the disclosed class of structurally similar compounds that includes treprostinil. The '222 patent indicates that treprostinil salts are useful to treat pulmonary hypertension and discloses that physiologically acceptable salts include salts with organic bases. The '265 and '713 patents disclose that the diethanolamine salt may be formed with other carboxylic acid prostacyclins. In view of at least these disclosures, no teaching away from treprostinil diethanolamine should be found.

During prosecution of the '169 patent (and during prosecution of the European counterpart application), the applicants suggested that the prior art teaches away from the use of

diethanolamine. According to the applicants, the person of ordinary skill in the art would "likely not consider diethanolamine as a counter ion for treprostinil in view of multiple reports on toxicity of diethanolamine." *See* Amendment (August 22, 2011) at 6; *see also* EU Application No. EP20040776104 ("EP '104 application," filed on May 24, 2004): Reply (July 11, 2011) at 3 (second full paragraph). The applicants cited two references, an FDA cosmetics information internet page ("FDA page") that concerns diethanolamine and a journal publication. *Id.*

Neither reference teaches away from the use of the diethanolamine salt of treprostinil; that is, neither reference would have discouraged the person of ordinary skill in the art from preparing treprostinil diethanolamine. "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994). "A statement that a particular combination is not a preferred embodiment does not teach away absent clear discouragement of that combination." *Syntex (U.S.A.) LLC v. Apotex, Inc.*, 407 F.3d 1371, 1380 (Fed. Cir. 2005).

Regarding the FDA page, the document, while acknowledging an earlier study's finding of "an association between the topical application of DEA and certain DEA-related ingredients and cancer in laboratory animals," concludes that "at the present time there is no reason for consumers to be alarmed based on the use of these substances in cosmetics." FDA page (originally published December 21, 1999; updated October 27, 2006) (the applicants cited the updated version).[12,13] (The applicants omitted the latter quotation from their discussion of the FDA page. *See* Amendment at 6.) The information in this page would not have "discouraged"

[12] The FDA page can be found at http://www.fda.gov/Cosmetics/ProductsIngredients/Ingredients/ucm109655.htm (last checked December 10, 2014).

[13] Because cosmetics provide the greatest exposure to diethanolamine, the cited study examined dermal application of diethanolamine.

the person of ordinary skill in the art from developing the diethanolamine salt of treprostinil. First, the FDA page relates to topical application of DEA. The person of ordinary skill in the art would have pursued a more conventionally administered treprostinil diethanolamine formulation, such as an oral formulation, and not a dermal formulation. The FDA page provides no information relating to oral or non-dermal administration of DEA. Second, the FDA page concludes that there is no reason for consumers to be alarmed about the use of DEA in cosmetics. The FDA page does not indicate that there is any reason that DEA should not be used in products intended for human use.

The journal publication Lehman-McKeeman notes that "the results of the present study provide evidence that 4 weeks of DEA treatment leads to a biochemical condition of hepatic choline deficiency in mice," yet concludes that "[o]verall, the results suggest that the hepatocarcinogenic effects of DEA in mice are not predictive of similar susceptibility in other laboratory animals or humans." In addition, the daily dose of DEA in this study was much higher than the daily dose that a patient would receive from treprostinil diethanolamine.[14] Also, DEA in the study was applied dermally, which likely would not have been the route of administration pursued by the person of ordinary skill in the art developing treprostinil diethanolamine. These three considerations, taken alone or together, lead to the conclusion that the most that can be said about Lehman-McKeeman is that it is inconclusive with respect to any potential use of the diethanolamine salt of treprostinil for administration to humans or harm arising from such use.

[14] The lowest dermally applied dosage was 10 mg/kg/day, five days a week for four weeks. *See* Lehman-McKeeman at 39 (last full paragraph). For comparison, using Remoudlin® (treprostinil sodium) subcutaneous dosages as an approximation for treprostinil diethanolamine dosages. The average daily dosage of Orenitram® turned out to be 6.8 mg/day. *See* Orenitram® prescribing information at 5. In a 50 kg (110 pound) patient, this is about 0.14 mg/kg/day of treprostinil diethanolamine.)

Lehman-McKeeman would not have discouraged the person of ordinary skill in the art from preparing treprostinil diethanolamine for human use.[15]

No unexpected results or other secondary considerations outweigh the above considerations. The patentees asserted unexpected results to gain allowance of the '169 patent. *See* Amendment at 6–8. Specifically, the applicants asserted that treprostinil diethanolamine "possesses an unexpected combination of properties," which they listed as "a relatively high melting temperature, a relatively high aqueous solubility and a relatively low hygroscopicity" and further asserted that this "combination is superior to other salts of treprostinil." *Id.* at 6. The applicants purported to submit supporting data and asserted that the diethanolamine salt was superior to the sodium salt in all three respects. *See id.* at 7 and accompanying Declaration of Kenneth Phares ("Phares Declaration"). The data are reproduced below.

Table I: Melting temperatures, visual aqueous solubilities, and water sorption properties of salts of treprostinil and treprostinil as the free acid.

Molecular form of treprostinil	**Melting temperature (°C)**	**Visual aqueous solubility (mg/mL)**	**% weight change at 60% RH sorption**	**% weight change at 95% RH sorption**
free acid	125	<0.025	0.6	2.8
calcium	180	0.22	10	35
ethylenediamine	109	1.24	0.5	5.5
choline	153	1.38	8	55
TRIS	75	81.33	0.2	0.9
sodium	56	117.5	7	20
Potassium	decomposes	167.7	15	70
Diethanolamine	107	168.8	0	15
Glucamine	60	92.6	4	33
Benzathine	141	insoluble	3.5	6.5
procaine	182	100.6	10	55

[15] The person of ordinary skill in the art would have found Lehman-McKeeman to indicate that the low amounts of DEA in an oral formulation of treprostinil diethanolamine would in fact be safe. When a DEA dose of 10 mg/kg/day was dermally administered to mice, Lehman-McKeeman found no statistically significant effects in any of the eight parameters measured. *See* Lehman-McKeeman at 41, Table 2 and at 43 (right-hand column, first full paragraph) (stating that "[t]he present work has determined the NOEL [no-observed-effect level] for DEA-induced choline deficiency in mice" to be 10 mg/kg/day). Also, doses of both 10 and 20 mg/kg/day were not considered "carcinogenic." *See id.* at 42 (right-hand column, first full paragraph).

Phares Declaration at 3.

The applicants argued that these three properties generally are "desirable in oral pharmaceutical formulations." *See* Amendment at 7. They asserted that high melting temperature can reduce degradation from high temperatures encountered during processing, high solubility improves absorption in vivo, and low hygroscopicity can reduce "undesirable effects of moisture." *See id.* at 7. They also argued that the diethanolamine salt is superior to the marketed sodium salt with respect to these three properties. *See id.* at 7. They further asserted that "the treprostinil diethanolamine's combination of properties is unexpected." *Id.* at 7. In support, they cited a reference that indicates that an "increase in melting point is usually accompanied by a reduction in salt solubility." *Id.* at 7-8 (citing Philip L. Gould, *Salt selection for basic drugs*, 33 Int. J. Pharm. 201 (1986) ("Gould")). Here, in contrast, the diethanolamine salt is said to have both a higher melting point and higher solubility than the sodium salt. *Id.* at 8. Applicants further argued that treprostinil diethanolamine's possession of both higher solubility and lower hygroscopicity than treprostinil sodium is also surprising, again relying on Gould. *See id.* at 8.

These arguments should not be found to outweigh the considerations set forth above that weigh in favor of a finding of obviousness of treprostinil diethanolamine. It is not surprising that, generally, different salts of a drug compound will have different properties, and that certain salts will have more preferred properties than others. *See Pfizer*, 480 F.3d at 1371 (rejecting alleged unexpected superiority of claimed amlodipine salt in part because the person of ordinary skill in the art would have expected pharmaceutically acceptable salt anions to provide amlodipine salts with a range of properties, some superior and some inferior to the prior art). It is also not surprising, in view of the prior art, that the diethanolamine salt would possess any two or all three of relatively low hygroscopicity, relatively high solubility, and relatively high melting

point. Zopolrestat diethanolamine was known to have both high water solubility (at least about 100 mg/ml) and a high melting point (163-164° C). *See* '095 publication ¶¶ 0005, 0263 (hygroscopicity not reported). Piroxicam diethanolamine had all three of low hygroscopicity, high water solubility, and high melting point. *See* '164 patent at col. 1, ll. 37-63, col. 2, l. 43–col. 3, l. 13, and col. 6, ll. 28-30. The prior art thus demonstrates that these properties can be found in a single diethanolamine salt. The person of ordinary skill in the art thus would have been aware that the relationships between melting point, solubility, and hygroscopicity that Gould put forward do not always hold true. Specifically, the person of ordinary skill in the art would have known that diethanolamine salts do not necessarily conform to general rules. We therefore conclude that the water solubility, hygroscopicity, and melting point of treprostinil diethanolamine should not be found surprising or unexpected. Consequently, these properties should not be found to weigh in favor of non-obviousness or to outweigh the other factors that favor a finding of obviousness, detailed above.

Even if the patentees were to succeed in establishing that the person of ordinary skill in the art would have found it surprising that treprostinil diethanolamine possesses all three of the attributes discussed above, treprostinil diethanolamine nevertheless should be found obvious in view of the overwhelming evidence of obviousness set forth above. "Although secondary considerations must be taken into account, they do not necessarily control the obviousness conclusion." *Pfizer*, 480 F.3d at 1372 (holding that, even if it were established that the claimed salt amlodipine besylate "exhibits unexpectedly superior results," that did not "overcome the strong showing of obviousness").

Treprostinil diethanolamine would have been obvious to the person of ordinary skill in the art at the time of filing for at least these reasons.

b. A pharmaceutical composition for oral administration comprising a therapeutically effective amount of treprostinil diethanolamine is obvious

The person of ordinary skill in the art would have been motivated to prepare a composition that contains a therapeutically effective amount of a salt of treprostinil with a reasonable expectation of success. The '222 patent discloses the preparation of oral tablets that contain a compound of formula (I). The '222 patent further discloses the oral tablet effective amount of a compound of formula (I) for treating pulmonary hypertension is typically in the relatively narrow range of 1 to 50 mg. The '222 patent discloses that treprostinil and pharmaceutically acceptable salts of treprostinil are a "particularly preferred compound of formula (I)." In view of this disclosure, the person of ordinary skill in the art would have been motivated to prepare, for example, a tablet that contains an effective amount of a treprostinil salt and a pharmaceutically acceptable carrier, and would have had a reasonable expectation of success in doing so.

For the reasons set forth above, the person of ordinary skill in the art would have been motivated to prepare treprostinil diethanolamine with a reasonable expectation of success. The primary reason for preparing treprostinil diethanolamine is to use it to treat a condition such as pulmonary hypertension. A common method of administering a drug is by incorporating it into a formulation that can be administered to a patient. For these reasons and in view of the disclosure of the '222 patent summarized above, the person of ordinary skill in the art would have been motivated to prepare, for example, an oral tablet that contains an effective amount of treprostinil diethanolamine and a pharmaceutically acceptable carrier.

c. Claims 8 and 9 are further invalid because the bioavailability of the diethanolamine salt would be determined through routine testing

Claim 8 claims a composition for oral administration with an effective amount of a salt or ester of treprostinil in which the composition "provides an oral bioavailability of treprostinil at least 50% greater than the oral bioavailability of a composition with treprostinil as a free acid." Claim 9 depends on claim 8 in which the composition has "an oral biavailability of treprostinil at least 100% greater than the oral availability of a composition with treporstinil as a free acid."

First, it would have been understood by a person of skill in the art that the salt of treprostnil would have a high bioavailability. The Remodulin Label discloses that "Remodulin is relatively rapidly and completely absorbed after subcutaneous infusion, with an absolute bioavailability approximating 100%." p. 1. The '452 publication would give the person of skill in the art confidence that treprostinil could be administered orally.

Further, the bioavailability of the treprostinil is an inherent property that a person of skill in the art could determine through clinical testing and routine experimentation. Nevertheless, it would have been obvious to a person of skill in the art that a salt form, particularly the ioinc organic diethanolamine salt, would be more bioavailable than the free acid of treprostinil. A person of skill in the art would know that the organic diethanolamine salt would be more lipid like than other salts and therefore more able to dissolve in cells.

Bighley discloses that ideal salts exhibit good bioavailability. p. 453. It further discloses that organic acid salt forms of drugs, such as amines, "frequently have higher acqueous solubilities than their corresponding inorganic salts. *Id.* at 461. The dissolution rate often indicates biavailability. The "salt form frequently exhibits a higher dissolution rate than the corresponding conjugate acid or base at the same pH." *Id.* at 463–64. Bighley discloses that high water solubility is usually associated with higher dissolution and absorption. *Id.* at 486; *see also* Berge at 5–6 ("In many cases . . . [dissolution] best refelects the bioavailability of the

compound."). Salt formation also "generally increases the dissolution rate." *Id.* at 464. For example, "[a]lthough no direct comparisons of the [salt and acid forms of benzoic acid] were made, inspection of the data shows that the deaggregation of the salt was considerably more rapid than that of the free acid in equivalent dosage forms. Therefore, if absorption is dependent on the dissolution rate, which in turn is dependent on the deaggregation rate, the salt should produce the highest and earliest blood levels." *Id.* at 464. In another example, bioavailability in rates of magnesium and calcium salts of indomethacin was "significantly higher" as compared to indomethacin free acid after an oral dose of the salts as measured by plasma levels. *Id.* at 474. As explained above regarding lipids, "[t]he increased absorption was attributed to enhanced lipid solubility and increased solubility in bile and intestinal juice." *Id.* Bighley discloses that "[t]o increase absorption, organic cations should be prepared, such as amino acids . . . or hydroxyamines (diethanolamine or triethanolamine)." *Id.* at 484. The '095 publication also discloses that the diethanolamine salt of zopolrestat is highly water-soluble and, therefore, "advantageous." at ¶ [0005]. The '164 patent also discloses that the diethanolamine salt is water-soluble. Abstract. Bighley teaches that "[s]alts are also employed to increase the absorption rate and hence speed of action . . . ." p. 484. In short, absorption can be increased by selecting a salt with higher solubility, as in the diethanolamine salt. *See id.* at 486. Berge also disclosed experiments in which "[i]n all cases, the sodium salt dissolved more rapidly than the free acid." p. 6.

Therefore, it would have been obvious to a person of skill in the art that the oral bioavailability of treprostinil as a diethanolamine salt would be significantly higher than that of the free acid. The precise difference in bioavailability between a particular salt, such as the

diethanolamine salt, and the free acid could be determined by a person of skill in the art, rendering claims 8 and 9 obvious.

3. Secondary Considerations

Plaintiffs have not set forth any evidence of secondary considerations of non-obviousness, and Actavis is not aware of any such secondary considerations that, when considered with the evidence of obviousness, would warrant a finding of non-obviousness of the claims of the '169 patent. If UTC relies on any secondary considerations of non-obviousness, Actavis reserves the right to supplement its contentions.

As explained above, the claims would have been obvious in view of a host of prior art references because the steps described in the claims were well-known procedures that would have been obvious to apply. Consequently, there are numerous different combinations of these prior art references and many exemplary references that teach each standard step. By way of example, the following combinations render the asserted claims obvious:

- Simonneau, the '222 patent and/or Vizza, Bighley, and/or the diethanolamine salts of other drug compounds,
- Simonneau, the '222 patent and/or Vizza, the '075 patent, Bighley, and/or the diethanolamine salts of other compounds,
- The '222 patent, the '075 patent, Bighley, and/or the diethanolamine salts of other compounds.
- The '222 patent, the '075 patent, Bighley, the '196 publication, and/or the diethanolamine salts of other compounds.
- Simonneau, the '222 patent, Bighley or Berge, and/or the diethanolamine salts of other drug compounds,
- Simonneau, the '222 patent, the '075 patent, Bighley or Berge, and/or the diethanolamine salts of other compounds,
- The '222 patent, the '075 patent, Bighley or Berge, and/or the diethanolamine salts of other compounds.

- The '953 patent, the '222 patent, Bighley or Berge, and/or the diethanolamine salts of other compounds
- The '953 patent, Simonneau, Bighley or Berge, and/or the diethanolamine salts of other compounds
- Any of the above combinations with the '452 publication
- Any of the above combinations with Byrn, Olmsted, Sharp, and Pavia
- Any of the above combinations with Remodulin and the Remodulin Label

A POSA would have been motivated to combine the teachings of these references with a reasonable expectation of success. In addition, Actavis's invalidity charts set forth where each prior art reference discloses the limitations of the asserted claims.

Actavis reserves the right to set forth additional such examples as discovery continues.

4. Claims 8–11 Are Invalid for Lack of Written Description

In the alternative, should the Court find that the asserted claims are not invalid as obvious, Claims 8–11 are invalid for failure to satisfy the written description requirement. "The specification shall contain a written description of the invention." 35 U.S.C. § 112, first paragraph; *see also Ariad Pharm., Inc. v. Eli Lilly and Co.*, 598 F.3d 1336, 1344-45 (Fed. Cir. 2010) (en banc). "[T]he test for [written description] sufficiency is whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date. . . . [P]ossession as shown in the disclosure is a more complete formulation." *Ariad Pharm.*, 598 F.3d at 1351 (internal citations omitted). The Federal Circuit has further stated that a "definition by function" "is only a definition of a useful result rather than a definition of what achieves that result." *Regents of the Univ. of California v. Eli Lilly and Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997). Further, "[t]he description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention." *Id.* at 1568. "To fulfill

the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that 'the inventor invented the claimed invention.'" *Id.* at 1566 (quoting *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, and *In re Gosteli*, 872 F.2d 1008, 1012 (Fed. Cir. 1989)). "Thus, an applicant complies with the written description requirement 'by describing the invention, with all its claimed limitations, not that which makes it obvious,' and by using 'such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention.'" *Id.* at 1566 (quoting *Lockwood*, 107 F.3d at 1572); *see also In re Curtis*, 354 F.3d 1347, 1355 (Fed. Cir. 2004) (affirming BPAI's finding of invalidity for lack of written description where there was "unpredictability in performance of certain species or subcombinations other than those specifically enumerated [in the disclosure]" (internal quotations omitted)). "[T]he purpose of the written description requirement is to ensure that the scope of the right to exclude, as set forth in the claims, does not over-reach the scope of the inventor's contribution to the field of art as described in the patent specification") (internal quotations omitted). *Ariad Pharm.*, 598 F.3d at 1353-54. The specification does not demonstrate that any treprostinil diethanolamine-containing composition, oral or otherwise, provides bioavailability, oral or otherwise, of treprostinil at least 50% greater than a composition with treprostinil as a free acid.

Claim 8 encompasses (but is not limited to) a genus of oral compositions that contain a treprostinil salt. The claimed composition "provides an oral bioavailability of treprostinil" that is "at least 50% greater than the oral bioavailability of a composition" that contains treprostinil as a free acid. Yet the specification provides no relevant, supporting data. That is, the specification provides no data relating to the oral bioavailability of treprostinil from oral compositions that

contain treprostinil salts relative to the oral bioavailability of treprostinil from compositions that contain treprostinil free acid.

The specification purports to provide "compounds described herein [that] have enhanced oral bioavailability compared to the oral bioavailability of treprostinil, either in free acid or salt form." '070 patent at col. 8, ll. 33-35. Specific compounds for which the specification provides data are discussed below. Although the specification discusses treprostinil diethanolamine, it does not make any claims about its oral bioavailability relative to that of treprostinil free acid.

In view of the lack of support in the specification for the claimed treprostinil salt compositions, claim 8 should be found invalid for lack of written description. The specification does not demonstrate that any treprostinil diethanolamine-containing composition, oral or otherwise, provides bioavailability, oral or otherwise, of treprostinil at least 50% greater than a composition with treprostinil as a free acid. In fact, in the '169 patent's only bioavailability comparisons, treprostinil diethanolamine compositions serve as the reference against which the treprostinil bioavailability of compositions that contain treprostinil esters and other covalent derivatives is measured. In Example 1, treprostinil diethanolamine compositions were prepared and administered by different routes to rats, including by the intravenous and oral routes. *See* '169 patent at col. 46, l. 14–col. 48, l. 45 and Table 1. Treprostinil plasma concentration was measured as a function of time and corresponding graphs were prepared. The area under the curves ("AUC") was determined and bioavailability of each route were calculated by dividing each AUC by the average AUC of the intravenous administrations. *See id.* at col. 48, l. 46–col. 50, l. 44 and Tables 3 (plasma concentrations), 4 (average bioavailability's (of two or three rats for each administration route), and 5 (individual bioavailability's). This established the baseline against which treprostinil derivatives were measured in Example 2.

In Example 2, solutions of treprostinil derivatives (not salts) were prepared and orally administered to rats. *See id.* at col. 50, l. 45–col. 52, l. 44. Again, treprostinil plasma concentrations were determined as a function of time and the same data analysis as in Example 1 was performed. *See id.* at col. 52, l. 44–col. 53, l. 36. The data were compared to the oral and intravenous data of Example 1. *See id.* at col. 7, ll. 55-67, *and see id.* at col. 55, Table 10 (providing relative and absolute bioavailability's) and ll. 15-35 (explaining that certain treprostinil "prodrugs" "had Treprostinil average AUCs greater than that after dosing of the active compound").

None of the remaining examples entail comparing the bioavailability of a treprostinil salt composition to that of a treprostinil free acid composition. Example 3 concerns the pharmacokinetics of compositions that contain treprostinil monophosphate (ring), treprostinil monovaline (ring), treprostinil monoalinine (ring), and treprostinil monoalinine (chain) relative to a composition that contained treprostinil. *See, e.g., id.* at col. 55, l. 43–col. 56, l. 27 and table of compounds (showing that the tested compounds are treprostinil covalently modified to contain the recited additions (monophosphate, monovaline, monoalinine) as substituents) and at col. 59, ll. 12-37.

Prophetic Example 4 also concerns the pharmacokinetics of covalent derivatives of treprostinil compared to that of "treprostinil [and] treprostinil sodium." *See id.* at col. 60, l. 35–col. 63, l. 37. No bioavailability data are provided in Example 4. Example 5 concerns clinical studies with treprostinil diethanolamine. In these studies, treprostinil diethanolamine was administered orally as a solution and in tablets and capsules. The study did not include the administration of corresponding compositions that contained treprostinil free acid. The only bioavailability values disclosed in this study were those of the oral solutions compared to

"historical intravenous treprostinil sodium data." *See id.* at col. 63, l. 38–col. 65, l. 10. Further, the patent does not disclose the composition of the administered solutions, tablets, and capsules (ingredients and amounts of each) except the amount of treprostinil diethanolamine that each contained.

The person of ordinary skill in the art reading the '169 patent would not have recognized the patentees to have had in their possession, at the time of filing, any oral treprostinil salt compositions that provide an oral bioavailability at least 50% greater than the oral bioavailability of a composition that contains treprostinil as a free acid. Yet, claim 8 encompasses the entire genus of such oral treprostinil salt compositions. Claim 8 therefore amounts to no more than a description or "indication" of a desired result of which the specification provides no examples or other relevant data. The specification further provides no "definition of what achieves that result." *See Regents of the Univ. of California v. Eli Lilly and Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997).

The '169 patent does not provide any information that establishes that compositions such as those covered by claim 8 have greater bioavailability than compositions that contain treprostinil free acid. Thus, the person of ordinary skill in the art could not have recognized, from the specification's disclosure, that the patentees had possession of the claimed invention. *See Ariad Pharm.*, 598 F.3d at 1351 ("[P]ossession as shown in the disclosure is a more complete formulation."). Further, even if, for example, the treprostinil diethanolamine tablets of Example 5 provide the required bioavailability, this constitutes only a single composition, whereas the claim encompasses all treprostinil salt compositions that satisfy the bioavailability limitation. Also, the patent does not disclose structural features common to those compositions that satisfy the claim's bioavailability limitation, further supporting a conclusion of lack of written

description. *See Abbvie Deutschland GmbH & Co. v. Janssen Biotech, Inc.*, 2014 U.S. App. LEXIS 12372, at *31, 32 (Fed. Cir. July 1, 2014) (quoted above). Claim 8 thus appears to represent the patentees' attempt to claim compositions that have desirable properties, but that the patentees did not possess or disclose. *Cf. Univ. of Rochester v. G.D. Searle & Co., Inc.*, 358 F.3d 916, 927, 930 (Fed. Cir. 2004) (affirming summary judgment of invalidity for lack of written description, noting, among other things, that "the '850 patent does not disclose any compounds that can be used in its claimed methods" and that "an adequate written description of a DNA . . . requires a precise definition, such as by structure, formula, chemical name, or physical properties, not a mere wish or plan for obtaining the claimed chemical invention" (internal quotations omitted) (quoting *Regents of the Univ. of Cal. v. Eli Lilly & Co., Inc.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997))). Claim 8 should be found invalid for lack of written description.

Claims 9–11, which depend from claim 8, should be found invalid for the same reasons as those set forth with respect to claim 8. Claim 9 depends from claim 8 and differs only in requiring that the difference in bioavailability's of the two compositions be at least 100%. The claim 8 range "at least 50% greater" encompasses the claim 9 range "at least 100% greater." Thus, because the specification does not provide written description support for "at least 50% greater," for the reasons set forth with respect to claim 8, it necessarily does not provide written description support for "at least 100% greater." Therefore, claim 9 should be found invalid for lack of written description support for the same reasons as those set forth with respect to claim 8.

Both claims 10 and 11 recite that "the ester is selected from" a recited group of esters. Claims 10 and 11 do not, however, require that the claimed composition comprise a treprostinil ester and not a treprostinil salt. Rather, these claims indicate only that, if the claimed composition comprises a treprostinil ester, then that ester must be selected from the claim-recited

group. If the claimed composition comprises a treprostinil salt, then it can be any salt, since neither claim 8 nor the dependent claims limit the salt. Therefore, claims 10 and 11 encompass the same genus of treprostinil salt-containing compositions as claim 8. The written description analysis of claim 8 set forth above therefore applies equally to claims 10 and 11. Therefore, claims 10 and 11 should also be found invalid for lack of written description. *See LizardTech, Inc. v. Earth Res. Mapping, Inc.*, 424 F.3d 1336, 1345 (Fed. Cir. 2005) (patentee must demonstrate possession of full scope of the claimed invention).

5. Claims 8–11 Are Invalid for Lack of Enablement

Should the Court find that the asserted claims are not invalid as obvious, Claims 8–11 are also invalid because they do not meet the enablement requirement. "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same." 35 U.S.C. § 112 (emphasis added). "To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation'." *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1365, (Fed. Cir. 1997) (quoting *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993)). Factors to be considered in determining whether a patent specification would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *In re Wands*, 858 F.2d 732, 737 (Fed. Cir. 1988). "[A]ll of the factors need not be reviewed when determining whether a disclosure is enabling." *Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1371 (Fed. Cir. 1999).

"The specification need not disclose what is well known in the art." *In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991). But this "is merely a rule of supplementation, not a substitute for a basic enabling disclosure." *ALZA Corp. v. Andrx Pharms., LLC*, 603 F.3d 935, 940-41 (Fed. Cir. 2010) (holding claims invalid that cover osmotic and non-osmotic dosage forms, but only teach a person of ordinary skill in the art how to make the osmotic dosage form). The patentee "cannot simply rely on the knowledge of a person of ordinary skill to serve as a substitute for the missing information in the specification." *Id.* at 941.

Claim 8 encompasses all pharmaceutical compositions that contain a treprostinil salt and that meet the recited bioavailability limitation. In view of the *Wands* factors and the applicable case law, claim 8 should be found not enabled. In short, the patent provides no guidance or working examples relating to treprostinil salt compositions that meet the required bioavailability limitation, the claim is broad, and bioavailability is unpredictable. The person of ordinary skill in the art therefore would have to engage in undue experimentation in order to make and use the full scope of the claimed subject matter.

Independent claim 8 encompasses any type of oral composition that contains any treprostinil salt and that also meets the recited bioavailability limitation. The claim therefore encompasses at least oral solutions, capsules, and tablets, of which there are a great variety. *See, e.g.*, Ansel 1999, *supra*, at 196-203 (listing and discussing over ten different tablet types). Tablets and other oral dosage forms can contain virtually an infinite number of different combinations of composition ingredients and amounts. *See, e.g.*, Ansel 1999 at 197-98 (listing types of ingredients that compressed tablets contain), *Handbook of Pharmaceutical Ingredients* (Raymond C. Rowe *et al.* eds., 4th ed. 2003) (listing over 150 ingredients suitable for use in pharmaceutical compositions in combination with various other such ingredients). There are also

more than 40 potential cationic species that can serve as a counter ion to treprostinil. *See* Lyle D. Bighley *et al.*, *Salt Forms of Drugs and Absorption, in 13 Encyclopedia of Pharmaceutical Technology* 453, 456 Table 2 (James Swarbrick & James C. Boylan eds., 1996). The claimed composition therefore could contain any of a variety of treprostinil salts. The claim is therefore potentially very broad.

The specification provides no working examples and no guidance concerning which treprostinil salt compositions meet the limitations of the claim, for the reasons stated above in connection with the written description defense. Although the specification discusses certain oral compositions that contain treprostinil diethanolamine, it does not disclose the inactive ingredients of the compositions or their amounts or how the compositions were prepared. Thus, the specification provides no information that would enable the person of ordinary skill in the art to prepare those compositions. It also does not provide any evidence that any of the mentioned compositions in fact satisfy the bioavailability limitation of claim 8.

Although there is a large amount of literature available concerning pharmaceutical compositions and the person of ordinary skill in the art was experienced in preparing such compositions, bioavailability is unpredictable and varies from organism to organism. For example, the '169 patent discloses that the oral bioavailability of treprostinil from a solution of treprostinil diethanolamine was experimentally determined to be about 9% in rats and around 20-25% in humans, depending on the amount of treprostinil diethanolamine in the dose. In view of the complete absence of working examples and guidance from the patent, the person of ordinary skill in the art would have to prepare and test each treprostinil salt composition to determine whether it is within the scope of the claim. Further, such testing would have to be done in different organisms until one was identified in which the required bioavailability was observed

or until enough negative results were obtained that the person of ordinary skill in the art could reasonably conclude that the composition is outside the scope of the claim. In other words, the person of ordinary skill in the art would have to invent the claimed invention.

In sum, if the court does not find that the '169 patent is obvious, at least because the specification essentially leaves it to the person of ordinary skill in the art to devise, prepare, and test numerous different oral treprostinil salt compositions in order to "practic[e] the full scope of the claim," and claim 8 is broad, the art unpredictable, and the specification provides no guidance or working examples, should the Court find that this claim is not obvious, it should find that the claim requires undue experimentation to practice the full scope of claim 8. Therefore, claim 8 is not enabled by the specification and should be found invalid. *See Wyeth & Cordis Corp. v. Abbott Labs.*, 720 F.3d 1380, 1386 (Fed. Cir. 2013) (affirming finding of lack of enablement where the specification "discloses only a starting point for further iterative research in an unpredictable and poorly understood field" and there was a "need to engage in a systematic screening process" in view of the "specification offer[ing] no guidance or predictions" about which potential drug candidates would be effective).

Claims 9–11, which depend from claim 8, should be found invalid for lack of enablement for the same reasons as those set forth with respect to claim 8. The analysis parallels that set forth with respect to written description so we provide it in summary form and incorporate the above discussion concerning written description. Claim 9 differs from claim 8 only in requiring a greater difference in bioavailability between the two recited compositions. The specification does not provide any more support for claim 9 than for claim 8. The non-enablement analysis that applies to claim 8 therefore applies equally to claim 9. As discussed above, claims 10 and 11 encompass the same treprostinil salt compositions as claim 8. The non-enablement analysis that

applies to claim 8 therefore also applies equally to claims 10 and 11. Therefore, dependent claims 9–11 should be found invalid for lack of enablement.

F. Invalidity of the '901 Patent

1. Claims 1–12 Are Invalid for Indefiniteness

Claims 1–12 are invalid because they are indefinite.

a. Lack of reasonable certainty with respect to "absolute bioavailability" recited by claims 1–12

All of the '901 patent's claims 1–12 should be found invalid as indefinite. All claims recite the phrase "which has an absolute bioavailability of at least 15%." The person of ordinary skill in the art cannot determine the meaning of this phrase for two distinct reasons. Consequently, the claims, "viewed in light of the specification and prosecution history," fail to "inform those skilled in the art about the scope of the invention with reasonable certainty." *Nautilus, Inc. v. Biosig Instruments, Inc.*, 134 S. Ct. 2120, 2129 (2014).

First, as discussed above, the claim-recited "absolute bioavailability" can be understood to refer to, for example, an average absolute bioavailability for the treprostinil salt or ester in the claim-recited composition, determined prior to the claim-recited administering of the composition, a single measurement of that absolute bioavailability made prior to the administering, or the absolute bioavailability in the claim-recited subject subsequent to the administering. The person of ordinary skill in the art could not determine which of these is the correct interpretation. As noted above, the claim does not recite the term "average" and does not indicate how the recited absolute bioavailability is determined.

The '901 patent does not resolve the ambiguity because it discloses both absolute bioavailability values obtained from individual administrations as well as average absolute bioavailability values. For example, the patent discusses individual measurements when it

instructs that "[t]ypically, bioavailability is assessed by measuring the drug concentration in the blood at various points of time after administration of the drug and then integrating the values obtained over time to yield the total amount of drug circulating in the blood." *See* '901 patent at col. 40, ll. 26-30. The '901 patent also reports both average and individual measurements of absolute bioavailability. *See id.* at cols. 49-50, Tables 4 (average bioavailability) and 5 (individual bioavailability).

The prosecution history does not clarify the issue. When the applicants introduced into the claims the phrase referring to absolute bioavailability, they did not discuss its meaning other than to state that support for the amendment could be found in the penultimate paragraph of page 13 of the specification as filed. That paragraph states, in part, that "[g]enerally, the compounds described herein have enhanced oral bioavailability compared to the oral bioavailability of treprostinil, either in free acid or salt form. . . . The absolute oral bioavailability of these compounds can range between 10%, 15%, 20%, 25%, 30% and 40%, 45%, 50%, 55%, 60% or more when administered orally." *See* '694 application at 13. This statement does not clearly support any of the above possible interpretations of "absolute bioavailability" as recited in the claims.

These facts parallel those in *Teva Pharms. USA, Inc. v. Sandoz, Inc.*, 789 F.3d 1335, 1345 (Fed. Cir. 2015), in which the court held the claim at issue indefinite. In that case, the claim at issue required "molecular weight" range of the claim-recited polymer without specifying which one of three possible, distinct measures of molecular weights was required. *See Teva*, 789 F.3d at 1338, 1341 (identifying the three different measures as "peak average molecular weight (*M*p), number average molecular weight (*M*n), and weight average molecular weight (*M*w)").

Analogous to the present facts, the claim in that case "offers no guidance on which measure of 'molecular weight' the claims cover." *Id.* at 1341.

In *Teva*, the specification did not expressly specify which measure of molecular weight to use. *Id.* at 1341. Here, as discussed above, the specification discloses both individual and average absolute bioavailability values but states no preference as to which measure is used when referring to a treprostinil salt or ester in a composition.

In *Teva*, during prosecution, the applicants argued, on one occasion, that the claim-recited molecular weight referred to *M*w but, on another occasion, argued that it referred to *M*p. *See Teva*, 789 F.3d at 1342-45. In prosecuting the '694 application, the applicants did not define the term "absolute bioavailability." In *Teva*, the court concluded that "molecular weight" could have any one of three different meanings and that the claim language, specification, and prosecution "the patentee has failed to inform with reasonable certainty those skilled in the art about the scope of the invention" because "there is not reasonable certainty that molecular weight should be measured using *M*p." Here, similarly, all of claims 1-12 of the '901 patent should be found invalid as indefinite because "there is not reasonable certainty" that the claim term "absolute bioavailability" refers to an average value or single value measured prior to the claimed administration or to the absolute bioavailability of the subject after the claim-recited administration.

Even though dependent claims 2 and 8 narrow the range of the recited absolute bioavailability, they do not clarify how this value is determined. The indefiniteness analysis set forth above thus applies equally to these two claims.

Second, the claims recite "has an absolute bioavailability of at least 15%" without indicating the species in which absolute bioavailability should be determined. The claim does not

indicate whether, for example, the absolute bioavailability limitation must be satisfied in the same species as the subject to whom the formulation is administered, or in any one species, or in all species.

The facts here are similar to those in *Geneva Pharm., Inc. v. GlaxoSmithKline PLC*, 349 F.3d 1373 (Fed. Cir. 2003), in which the court held indefinite a claim that recited a functional limitation because infringement would depend on the circumstances in which it was used. Specifically, the claims at issue recited a pharmaceutical formulation that contained a "synergistically effective amount" of two antibiotic ingredients. But the claims did not specify the bacteria to be used to determine whether any formulation exhibited the required synergy. Thus, a composition "might infringe or not depending on its usage in changing circumstances. In other words, a given embodiment would simultaneously infringe and not infringe the claims, depending on the particular bacteria chosen for analysis." Applying the standard that "[a] claim is indefinite if its legal scope is not clear enough that a person of ordinary skill in the art could determine whether a particular composition infringes or not," the court held that the claims represented "the epitome of indefiniteness." *See Geneva*, 349 F.3d at 1382-84.

Similarly, here, a given composition could "simultaneously infringe and not infringe the claims, depending on" the organism chosen for analysis. For example, in rats, an oral solution of treprostinil diethanolamine had an absolute bioavailability of about 9%, below the claim-recited 15%. *See* '901 patent, Example 1, col. 46, ll. 39-45 and col. 49, Tables 4 and 5. In humans, an oral solution of treprostinil diethanolamine had an absolute bioavailability of at least 21%, within the scope of the claims. *See id.* at col. 63, l. 37–col. 64, l. 20. Thus, the '901 patent's oral treprostinil diethanolamine solution has the claim-required absolute bioavailability in humans but not in rats. Claims 1–12 should be found invalid as indefinite in view of this ambiguity.

b. Lack of reasonable certainty with respect to "Cmax in a plasma of the subject increases in a linear fashion" recited by claims 1–6

Claims 1–6 recite a method that entails administration to a subject of a treprostinil salt or ester formulation "wherein a Cmax in a plasma of the subject increases in a linear fashion with a dose of at least 0.05 mg administered to the subject." The language of the claim requires the increase "in a linear fashion" to take place in the subject to whom the composition is administered by the claimed method because the limiting phrase twice refers to "the subject." The use of the definite article "the" indicates that the phrase is referring to a subject already referred to earlier in the claim. The claim's only earlier reference to a subject is "a subject in need thereof" to whom the formulation is administered according to the claimed method. Further, the increase results from the administration of "a dose," that is, of only one dose. As discussed above, according to the definition of "Cmax," the administration of a single dose will result in only a single Cmax, not a Cmax that increases. In sum, taken as a whole, the Cmax limitation, read in the context of the claim, can only mean that the Cmax increases in the subject after the administration of a formulation to the subject.

The person of ordinary skill in the art understands that Cmax varies as a function of dosage, among other things, and thus would expect a claim to state that the administered composition is characterized in that varying the amount of treprostinil ester or salt in the administered formulation, but holding everything else constant, would result in different Cmax values that vary linearly with dosage. The claim could have been worded to clearly convey the linear proportionality of Cmax to dose. But this is not how the claim was drafted. Also, the specification and prosecution history do not suggest that this is what the claim means.

The '901 patent specification does not use the claim's Cmax limitation phrasing or explain how to interpret it. Its only discussion of linear variation is the disclosure that, in a

human clinical study in which different subjects received different doses of treprostinil diethanolamine (where each dose was divided into four equal parts administered two hours apart), "[b]oth AUC_{inf} and C_{max} increased in a linear fashion with dose for each of the four dose aliquots." *See* '901 patent, col. 63, l. 63–col. 64, l. 14. In other words, where different subjects received different doses of treprostinil diethanolamine, the different C_{max} values (one for each patient) varied linearly as a function of the dose administered. The specification does not indicate that different Cmax values are observed upon the administration of a single dose of a composition.

The meaning of this phrase was not discussed during prosecution. Because the claim specifically requires that "a Cmax in a plasma of the subject increases in a linear fashion with a dose of at least 0.05 mg administered to the subject," (emphases added) but any single dose can only yield a single, constant Cmax, not one that increases, the person of ordinary skill in the art would not be able to determine with reasonable certainty the scope of the claim as defined by the Cmax limitation. *See Nautilus, Inc. v. Biosig Instruments, Inc.*, 134 S. Ct. 2120, 2129 (2014). For this additional reason, claims 1–6 should be found invalid as indefinite.

Claims 1–6 should be found invalid for lack of utility and lack of enablement because they embody an "impossible limitation." As discussed in the text, claims 1–6 require a Cmax "in a plasma" that increases linearly "with a dose of at least 0.05 mg," whereas "a dose" "administered to the subject" can only yield a single, invariant Cmax value, not a value that increases. Claims 1–6 are therefore inoperable and should be found invalid for lack of utility and lack of enablement under 35 U.S.C. §§ 101 and 112, respectively. *See Process Control Corp. v. Hydre-Claim Corp.*, 190 F.3d 1350, 1358-59 (Fed. Cir. 1999) (holding claims invalid for lack of utility and lack of enablement because they embodied "an impossible limitation"). Further,

because of the clear and unambiguous language used to limit the claim with respect to Cmax, the claims should not be rewritten or construed contrary to that language in order to preserve their validity. *See Chef Am., Inc. v. Lamb-Weston, Inc.*, 358 F.3d 1371, 1374 (Fed. Cir. 2004) (endorsing and implementing the view that "where as here, claims are susceptible to only one reasonable interpretation and that interpretation results in a nonsensical construction of the claim as a whole, the claim must be invalidated" (internal quotations omitted) (quoting *Process Control*, 190 F.3d at 1357)).

c. Lack of reasonable certainty with respect to "AUCinf in a plasma of the subject increases in a linear fashion" recited by claims 7–12

The arguments set forth above with respect to the Cmax limitation in claims 1–6 apply equally to the AUCinf limitation in claims 7–12. The two limitations are identical except for the substitution of "AUCinf" for "Cmax." Like Cmax, a single AUCinf results from a single administration of a composition to a subject. AUCinf, like Cmax, does not increase. Therefore, claims 7–12 should be found invalid as indefinite for the same reasons as those set forth above with respect to claims 1–6.[16]

2. Claims 1–12 Are Obvious

To the extent that the claims are defeinite, it would have been obvious to the person of ordinary skill in the art at the time of filing to prepare and administer, to treat pulmonary hypertension, a pharmaceutical composition for oral administration that comprises a therapeutically effective amount of treprostinil diethanolamine. Further, no secondary considerations should be found to outweigh the obviousness of such administration. Therefore, any claim from the group consisting of independent claims 1 and 7 and dependent claims 2–6

[16] Similarly, the invalidity for lack of utility and lack of enablement analysis set forth with respect to claims 1–6 also applies to claims 7–12.

and 8–12 of the '901 patent that is construed to encompass such administration should be found invalid as obvious. *See In re Cuozzo Speed Techs., LLC*, 793 F.3d 1268, 1281 (Fed. Cir. 2015) (reciting the "long-established rule that claims which are broad enough to read on obvious subject matter are unpatentable even though they also read on nonobvious subject matter" (internal quotations omitted)). That is, if an oral treprostinil diethanolamine composition necessarily meets all of the pharmacokinetic and bioavailability limitations of any claim of the '901 patent, that claim should be found invalid as obvious.

a. The following prior art renders Claims 1–12 obvious

The same prior art references set forth above in the analysis of claim 1 of the '070 patent apply here. Additional prior art includes:

i. WO 98/18452

WO 98/18452 ("the '452 publication") was published in 1998 and therefore is at least 35 U.S.C. § 102(b) prior art to the '901 patent. This application (or related applications and patents) was not before the Examiner during prosecution of the '100 application. The '452 publication provides extended release compositions and points out their advantages:

> In arriving at the present invention it has been discovered that it is possible to efficiently deliver therapeutically effective doses, at controlled rates and for extended times, of a broad variety of drugs without the need for polymers that swell or expand within the tablet wall so as to physically force the medicament particles out into their intended environment of use.

'452 publication at 2. *See also id.* at 9 ("The delivery system of the invention can be used to provide controlled release of any of a broad variety of therapeutically active agents."). The advantages of extended release at a controlled rate would have been particularly attractive for a drug like treprostinil, which has a relatively short half-life and is administered in low doses for a chronic condition. Specifically, treprostinil is indicated for the treatment of pulmonary arterial hypertension, a chronic condition, has "a terminal half-life of approximately 2-4 hours," and is

administered at doses ranging, for a 70 kg person, from an initial dose of about 0.13 mg/day to not more than about 4 mg/day. *See* Remodulin® Label (2002) at 5, 9-10; *see also* Ansel (2005) at 263 (drugs best-suited for extended release have certain characteristics, including having a low dosage and being administered to treat chronic conditions).

As noted above, the disclosed delivery system "can be used to provide controlled release of any of a broad variety of therapeutically active agents." *Id.* at 9. Among various examples, the '452 publication identifies specifically a number of substantially water-soluble salts of active agents that the system can be used to deliver (without referring to the solubility of each active). These include chlorpheniramine maleate (water solubility 160 mg/ml), brompheniramine maleate ("sol in water"), verapamil hydrochloride (water solubility 70 mg/ml),[17] metoprolol succinate (freely soluble in water), and metoprolol tartrate (very soluble in water).[18] *See* '452 publication at 9 (listing examples of actives); for solubilities, *see Merck Index* 337, 218, 1563-64 (Susan Budavari ed., 11th ed. 1989) and *European Pharmacopoeia* 2032 and 2034 (2005), respectively. Other specifically listed actives that the disclosed delivery system can deliver are water-insoluble salts (e.g., dextromethorphan hydrobromide, enalapril maleate, diclofenac sodium) and water-insoluble non-salts (e.g., carbamazepine, acyclovir). *See* '452 publication at 9. Thus, although the '452 publication elsewhere states that, "[i]n accordance with the preferred invention, there is provided an osmotic delivery system, preferably in the form of a tablet, which dispenses a therapeutic agent having a limited solubility in water or physiological environments," '452 publication at 2,[19] it is not limited to such therapeutic agents, as it also explicitly discloses that

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[17] The '452 publication does not refer specifically to verapamil hydrochloride, but rather to "antihypertensives such as nifedipine, verapamil, enalapril and salts thereof." *See* '452 publication at 9.
[18] The '897 patent also lists metoprolol succinate as a "therapeutic agent[ ] that will benefit from this invention." '897 patent at col. 7, ll. 8-16.
[19] *See also* '452 publication at 9 ("The system of the present invention is particularly applicable to therapeutic agents which are insoluble or poorly soluble in water or aqueous environments at physiological pH.").

the disclosed composition is suitable for delivery of water-soluble salts of therapeutic agents, including salts of anti-hypertensive agents. This class includes treprostinil diethanolamine. In sum, the disclosed system is useful for both water-soluble salts of active ingredients and for active ingredients with relatively lower water solubility.

The publication further discusses the other components of the disclosed composition. "Preferred non-swelling osmotic agents include" fructose, lactose, xylitol and sorbitol. *Id.* at 3. Triethyl citrate ("TEC") is a suitable plasticizer for use with a semipermeable, polymeric coating material such as cellulose acetate. *See id.* at 6.

The '452 publication further discloses a general method for preparing such a composition as coated tablets. *See id.* at 10-13, Example 1.

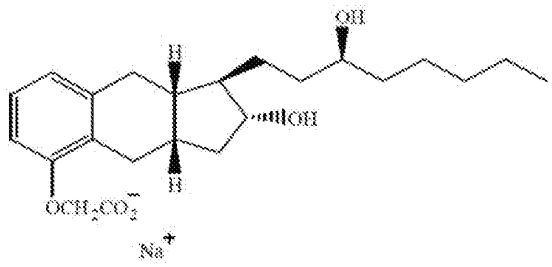
b. Claims 1–12 are obvious if construed to encompass a treprostinil diethanolamine composition

Any claim from the group consisting of independent claims 1 and 7 and dependent claims 2-6 and 8-12 of the '901 patent that is construed to encompass a composition that contains treprostinil diethanolamine should be found invalid as obvious. For the reasons detailed below, at the time of filing, the person of ordinary skill in the art would have been motivated to prepare the diethanolamine salt of treprostinil with a reasonable expectation of success. The prior art does not teach away from this salt. There are no unexpected results or other considerations that weigh in favor of finding treprostinil diethanolamine non-obvious. The facts here closely parallel those of *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1371 (Fed. Cir. 2007). Further, for the reasons detailed below, at the time of filing, the person of ordinary skill in the art would have been motivated to prepare an oral pharmaceutical formulation comprising a therapeutically effective amount of treprostinil diethanolamine, and would have had a reasonable expectation of success

in doing so. The prior art does not teach away from such a formulation, and no secondary considerations outweigh the teachings of the prior art.

i. Treprostinil diethanolamine is obvious

The '222 patent cited above specifically discloses treprostinil. Further, it generally discloses the diethanolamine salt of treprostinil and claims its use to treat pulmonary hypertension. *See* '222 patent at col. 3, ll. 1-20 and col. 6, ll. 58-63 (claim 2) (referring to a "pharmaceutically acceptable salt of treprostinil," which encompasses treprostinil diethanolamine); *cf. Pfizer*, 480 F.3d at 1353 and 1361 (noting that the prior art patent claimed a genus of amlodipine salts that encompassed amlodipine besylate, the specific salt at issue). *See* Simonneau at 800, 801, 803. According to its prescribing information, Remodulin® is a treprostinil sodium having the following structural formula:



The motivation to prepare the diethanolamine salt of treprostinil derives from several sources. At the time of filing, treprostinil was administered in clinical trials as the sodium salt by subcutaneous infusion. The person of ordinary skill in the art therefore would have been motivated to develop a form of treprostinil that could be administered by a less invasive and less cumbersome route. The choice of a salt form parallels the optimization of a variable within a range; the motivation to identify a superior salt form derives from the "normal desire of scientists or artisans to improve upon what is already generally known." *In re Peterson*, 315 F.3d 1325,

1329 (Fed. Cir. 2003); *see also Pfizer*, 480 F.3d at 1368 (quoting *In re Peterson* and noting the parallel between optimization of a variable and choice of salt form).

A different salt form would have been recognized as a potential means of improving bioavailability and formulation characteristics relative to the sodium salt of treprostinil. *See* Bighley at 461. Consequently, in developing a formulation for oral administration, the person of ordinary skill in the art would have been motivated to test salts in addition to the sodium salt then in use. About 37 alternatives to the sodium salt were in use in drug compounds at the time. *See id.* at 456, Table 2. It was known that amine salts generally can provide higher aqueous solubility than corresponding sodium salts; high aqueous solubility in turn is important in the synthesis of the salt and can improve the drug's bioavailability and formulation characteristics. Further, Bighley specifically identifies the diethanolamine salt, among others, as one that can provide increased absorption of the drug. *See id.* at 461, 484. Other references disclosed that diethanolamine was a suitable or advantageous salt of other prostacyclin derivatives and of piroxicam and the carboxylic acid drug zopolrestat. These considerations would have motivated the person of ordinary skill in the art to prepare and test the diethanolamine salt treprostinil. Further motivation to do so would have derived from the '222 patent, which discloses generally that organic amine salts of the disclosed compounds, including treprostinil, may be prepared, and from the '075 patent, which discloses that the diethanolamine salt of the disclosed compounds, including treprostinil, may be prepared. These circumstances are thus analogous to those of *Pfizer*, in which the court similarly relied on prior art disclosures of advantageous properties of besylate salts generally and of a specific besylate salt drug compound in determining that the person of ordinary skill in the art would have been motivated to prepare the besylate salt at issue.

See Pfizer, 480 F.3d at 1363 (characterizing such disclosures as "highly relevant" in its analysis of motivation).

The person of ordinary skill in the art would have had a reasonable expectation of success in preparing treprostinil diethanolamine and that treprostinil diethanolamine would be therapeutically useful. Preparation of salts was routine in the pharmaceutical arts at the time of filing. *See* Bighley at 453. The '075 patent discloses general methods for preparing amine salts of the disclosed compounds, which included treprostinil (*see* '075 patent at col. 30, l. 41–col. 31, l. 5). The person of ordinary skill in the art would have recognized, from Bighley's discussion of amine salts and diethanolamine salts, that a diethanolamine salt could have useful drug properties, such as greater aqueous solubility and bioavailability than the sodium salt. *See* Bighley at 461, 484. Also, the prior art states that the diethanolamine salt of two specific compounds, zopolrestat (a carboxylic acid, like treprostinil) and the benzothiazine compound of the '164 patent, possess advantageous properties. The '222 patent indicates that any pharmaceutically acceptable salt of treprostinil would be useful to treat pulmonary arterial hypertension by claiming such a method of treating. In view of these disclosures, treprostinil diethanolamine reasonably would have been expected to be suitable for a more conveniently administrable treprostinil dosage form. The person of ordinary skill in the art would have been motivated to prepare treprostinil diethanolamine with a reasonable expectation of success.

The person of ordinary skill in the art also would have been motivated to prepare an alternative to subcutaneously administered treprostinil sodium in order to obtain a more convenient method of administration. In doing so, the person of ordinary skill in the art would have been motivated to prepare a different salt of treprostinil. The prior art would have motivated the person of ordinary skill in the art specifically to prepare the diethanolamine salt because

diethanolamine generally was known to confer advantageous properties on the resulting drug salt, and because specific diethanolamine salts were known to possess certain advantageous properties. The person of ordinary skill in the art would have had a reasonable expectation of success at least because the prior art indicated that any pharmaceutically acceptable salt of treprostinil could be used to treat pulmonary arterial hypertension and because preparation of drug salts was routine in the art. *Cf. Pfizer*, 480 F.3d at 1368 ("[W]e hold that the optimization of the acid addition salt formulation for an active pharmaceutical ingredient would have been obvious whereas here the acid addition salt formulation has no effect on the therapeutic effectiveness of the active ingredient and the prior art heavily suggests the particular anion used to form the salt.").

(i) Secondary Considerations

The prior art did not teach away from treprostinil diethanolamine. To the contrary, the '075 patent discloses treprostinil itself and that diethanolamine is a suitable counter ion generally for the disclosed class of structurally similar compounds that includes treprostinil. The '222 patent indicates that treprostinil salts are useful to treat pulmonary hypertension and discloses that physiologically acceptable salts include salts with organic bases. The '265 and '713 patents disclose that the diethanolamine salt may be formed with other carboxylic acid prostacyclins. In view of at least these disclosures, no teaching away from treprostinil diethanolamine should be found.

During prosecution of a predecessor of the '901 patent, U.S. Patent No. 8,410,169 (and during prosecution of the '169 patent's European counterpart application), the applicants suggested that the prior art teaches away from the use of diethanolamine. According to the applicants, the person of ordinary skill in the art would "likely not consider diethanolamine as a counter ion for treprostinil in view of multiple reports on toxicity of diethanolamine." *See* U.S.

Patent Application No. 11/189,072, Amendment (August 22, 2011) at 6; *see also* EU Application No. EP20040776104 ("EP '104 application," filed on May 24, 2004): Reply (July 11, 2011) at 3 (second full paragraph). The applicants cited two references, an FDA cosmetics information internet page ("FDA page") that concerns diethanolamine and a journal publication. *Id.*

Neither reference teaches away from the use of the diethanolamine salt of treprostinil; that is, neither reference would have discouraged the person of ordinary skill in the art from preparing treprostinil diethanolamine. "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994). "A statement that a particular combination is not a preferred embodiment does not teach away absent clear discouragement of that combination." *Syntex (U.S.A.) LLC v. Apotex, Inc.*, 407 F.3d 1371, 1380 (Fed. Cir. 2005).

Regarding the FDA page, the document, while acknowledging an earlier study's finding of "an association between the topical application of DEA and certain DEA-related ingredients and cancer in laboratory animals," concludes that "at the present time there is no reason for consumers to be alarmed based on the use of these substances in cosmetics." FDA page (originally published December 21, 1999; updated October 27, 2006) (the applicants cited the updated version).[20,21](The applicants omitted the latter quotation from their discussion of the FDA page. *See* Amendment at 6.) The information in this page would not have "discouraged" the person of ordinary skill in the art from developing the diethanolamine salt of treprostinil. First, the FDA page relates to topical application of DEA. The person of ordinary skill in the art

[20] The FDA page can be found at http://www.fda.gov/Cosmetics/ProductsIngredients/Ingredients/ucm109655.htm (last checked December 10, 2014).
[21] Because cosmetics provide the greatest exposure to diethanolamine, the cited study examined dermal application of diethanolamine.

would have pursued a more conventionally administered treprostinil diethanolamine formulation, such as an oral formulation, and not a dermal formulation. The FDA page provides no information relating to oral or non-dermal administration of DEA. Second, the FDA page concludes that there is no reason for consumers to be alarmed about the use of DEA in cosmetics. The FDA page does not indicate that there is any reason that DEA should not be used in products intended for human use.

The journal publication Lehman-McKeeman notes that "the results of the present study provide evidence that 4 weeks of DEA treatment leads to a biochemical condition of hepatic choline deficiency in mice," yet concludes that "[o]verall, the results suggest that the hepatocarcinogenic effects of DEA in mice are not predictive of similar susceptibility in other laboratory animals or humans." In addition, the daily dose of DEA in this study was much higher than the daily dose that a patient would receive from treprostinil diethanolamine. Also, DEA in the study was applied dermally, which likely would not have been the route of administration pursued by the person of ordinary skill in the art developing treprostinil diethanolamine. These three considerations, taken alone or together, lead to the conclusion that the most that can be said about Lehman-McKeeman is that it is inconclusive with respect to any potential use of the diethanolamine salt of treprostinil for administration to humans or harm arising from such use. Therefore, Lehman-McKeeman would not have discouraged the person of ordinary skill in the art from preparing treprostinil diethanolamine for human use.[22]

[22] The person of ordinary skill in the art might even have found Lehman-McKeeman to indicate that the low amounts of DEA in an oral formulation of treprostinil diethanolamine would in fact be safe. When a DEA dose of 10 mg/kg/day was dermally administered to mice, Lehman-McKeeman found no statistically significant effects in any of the eight parameters measured. *See* Lehman-McKeeman at 41, Table 2 and at 43 (right-hand column, first full paragraph) (stating that "[t]he present work has determined the NOEL [no-observed-effect level] for DEA-induced choline deficiency in mice" to be 10 mg/kg/day). Also, doses of both 10 and 20 mg/kg/day were not considered "carcinogenic." *See id.* at 42 (right-hand column, first full paragraph).

No unexpected results or other secondary considerations outweigh the above considerations. The patentees asserted unexpected results to gain allowance of the '169 patent. *See* U.S. Pat. App. No. 11/189,072, Amendment at 6-8. Specifically, the applicants asserted that treprostinil diethanolamine "possesses an unexpected combination of properties," which they listed as "a relatively high melting temperature, a relatively high aqueous solubility and a relatively low hygroscopicity" and further asserted that this "combination is superior to other salts of treprostinil." *Id.* at 6. The applicants purported to submit supporting data and asserted that the diethanolamine salt was superior to the sodium salt in all three respects. *See id.* at 7 and accompanying Declaration of Kenneth Phares ("Phares Declaration"). The data are reproduced below.

Table I: Melting temperatures, visual aqueous solubilities, and water sorption properties of salts of treprostinil and treprostinil as the free acid.

Molecular form of treprostinil	Melting temperature (°C)	Visual aqueous solubility (mg/mL)	% weight change at 60% RH sorption	% weight change at 95% RH sorption
free acid	125	<0.025	0.6	2.8
calcium	180	0.22	10	35
ethylenediamine	109	1.24	0.5	5.5
choline	153	1.38	8	55
TRIS	75	81.33	0.2	0.9
sodium	56	117.5	7	20
potassium	decomposes	167.7	15	70
diethanolamine	107	168.8	0	15
glucamine	60	92.6	4	33
benzathine	141	insoluble	3.5	6.5
procaine	182	100.6	10	55

Phares Declaration at 3.

The applicants argued that these three properties generally are "desirable in oral pharmaceutical formulations." *See* Amendment at 7. They asserted that high melting temperature can reduce degradation from high temperatures encountered during processing, high solubility improves absorption in vivo, and low hygroscopicity can reduce "undesirable effects of moisture." *See id.* at 7. They also argued that the diethanolamine salt is superior to the marketed

sodium salt with respect to these three properties. *See id.* at 7. They further asserted that "the treprostinil diethanolamine's combination of properties is unexpected." *Id.* at 7. In support, they cited a reference that indicates that an "increase in melting point is usually accompanied by a reduction in salt solubility." *Id.* at 7-8 (citing Philip L. Gould, *Salt selection for basic drugs*, 33 Int. J. Pharm. 201 (1986) ("Gould"). Here, in contrast, the diethanolamine salt is said to have both a higher melting point and higher solubility than the sodium salt. *Id.* at 8. Applicants further argued that treprostinil diethanolamine's possession of both higher solubility and lower hygroscopicity than treprostinil sodium is also surprising, again relying on Gould. *See id.* at 8.

These arguments should not be found to outweigh the considerations set forth above that weigh in favor of a finding of obviousness of treprostinil diethanolamine. It is not surprising that, generally, different salts of a drug compound will have different properties, and that certain salts will have more preferred properties than others. *See Pfizer*, 480 F.3d at 1371 (rejecting alleged unexpected superiority of claimed amlodipine salt in part because the person of ordinary skill in the art would have expected pharmaceutically acceptable salt anions to provide amlodipine salts with a range of properties, some superior and some inferior to the prior art). It is also not surprising, in view of the prior art, that the diethanolamine salt would possess any two or all three of relatively low hygroscopicity, relatively high solubility, and relatively high melting point. Zopolrestat diethanolamine was known to have both high water solubility (at least about 100 mg/ml) and a high melting point (163-164° C). *See* '095 publication ¶¶ 0005, 0263 (hygroscopicity not reported). Piroxicam diethanolamine had all three of low hygroscopicity, high water solubility, and high melting point. *See* '164 patent at col. 1, ll. 37-63, col. 2, l. 43–col. 3, l. 13, and col. 6, ll. 28-30. The prior art thus demonstrates that these properties can be found in a single diethanolamine salt. The person of ordinary skill in the art thus would have been aware

that the relationships between melting point, solubility, and hygroscopicity that Gould put forward do not always hold true. Specifically, the person of ordinary skill in the art would have known that diethanolamine salts do not necessarily conform to general rules. Therefore, the water solubility, hygroscopicity, and melting point of treprostinil diethanolamine should not be found surprising or unexpected. Consequently, these properties should not be found to weigh in favor of non-obviousness or to outweigh the other factors that favor a finding of obviousness, detailed above.

Even if the patentees were to succeed in establishing that the person of ordinary skill in the art would have found it surprising that treprostinil diethanolamine possesses all three of the attributes discussed above, treprostinil diethanolamine nevertheless should be found obvious in view of the overwhelming evidence of obviousness set forth above. "Although secondary considerations must be taken into account, they do not necessarily control the obviousness conclusion." *Pfizer*, 480 F.3d at 1372 (holding that, even if it were established that the claimed salt amlodipine besylate "exhibits unexpectedly superior results," that did not "overcome the strong showing of obviousness").

The applicants have not put forward evidence of other secondary considerations, such as skepticism of others, commercial success, failure of others, or long-felt but unmet need, that weigh in favor of a finding of nonobviousness, and we are not aware of any such other considerations.

Treprostinil diethanolamine would have been obvious to the person of ordinary skill in the art at the time of filing.

ii. A pharmaceutical composition for oral administration comprising a therapeutically effective amount of treprostinil diethanolamine is obvious

At the time of filing, the person of ordinary skill in the art would have been motivated to prepare and administer, to treat pulmonary hypertension, a composition that contains a therapeutically effective amount of a salt of treprostinil with a reasonable expectation of success. The '222 patent discloses the preparation of oral tablets that contain a compound of formula (I). The '222 patent further discloses that an oral tablet effective amount of a compound of formula (I) for treating pulmonary hypertension is typically in the relatively narrow range of 1 to 50 mg. The '222 patent discloses that treprostinil and pharmaceutically acceptable salts of treprostinil are a "particularly preferred compound of formula (I)." In view of this disclosure, the person of ordinary skill in the art would have been motivated to prepare and administer, for example, a tablet that contains an effective amount of a treprostinil salt and a pharmaceutically acceptable carrier, and would have had a reasonable expectation of success in doing so.

For the reasons set forth above, the person of ordinary skill in the art would have been motivated to prepare treprostinil diethanolamine with a reasonable expectation of success. The primary reason for preparing treprostinil diethanolamine is to use it to treat a condition such as pulmonary hypertension. A common method of administering a drug is by incorporating it into a formulation that can be administered to a patient. For these reasons and in view of the disclosure of the '222 patent summarized above, the person of ordinary skill in the art would have been motivated to prepare, for example, an oral tablet that contains an effective amount of treprostinil diethanolamine and a pharmaceutically acceptable carrier.

(i) Secondary Considerations

There was no teaching away from preparing or administering such a composition. For the reasons set forth above, the USFDA document and Lehman-McKeeman publication would not

have discouraged the person of ordinary skill in the art from preparing treprostinil diethanolamine and thus would not have discouraged the person of ordinary skill in the art from incorporating an effective amount of treprostinil diethanolamine into a composition for oral administration.

There are no unexpected results that weigh in favor of finding such a composition nonobvious. We are not aware of any unexpected results that the applicants put forward other than those addressed above. Those alleged results should not be found persuasive for reasons set forth above. Also, the alleged results should not be found persuasive because they are not commensurate in scope with claims 1–12. Claims 1–12 recite a method of treating pulmonary hypertension that entails administering a treprostinil salt or ester-containing oral pharmaceutical formulation (dependent claims 5 and 11 are limited to administering treprostinil diethanolamine formulations). The results, however, relate only to treprostinil diethanolamine itself, not to a method of treating by administering an oral pharmaceutical formulation, and therefore establish nothing with respect to such a method of treating. To support claims 1–12 of the '901 patent, unexpected results would relate to the method of treating, not merely to the active ingredient.

iii. Claims 1–12 are invalid because a person of skill in the art would have known that the diethanolamine salt would have a high bioavailability in comparison to the free acid.

The claims of the '901 patent are also similar to claims 8 and 9 of the '169 patent and are invalid for the same reasons. Exemplary claims directed toward bioavailability are as follows: Claim 1 is directed toward a pharmaceutically acceptable salt or ester of treprostinil with an absolute bioavailablity of at least 15%. Claim 2 depends on claim 1, but adds that the absolute bioavailability is 21 to 25%. Claim 3 depends on claim 1, but adds that the oral availability is at least 50% greater than that of treprostinil as a free acid. Claim 7 claims a method of treating

pulmonary hypertension through administration of an oral formulation of the salt or ester of treprostinil with an absolute bioavailability of at least 15%. Claims 8–12 are similar to claims 2–6.

First, it would have been understood by a person of skill in the art that the salt of treprostnil would have a high bioavailability. The Remodulin Label discloses that "Remodulin is relatively rapidly and completely absorbed after subcutaneous infusion, with an absolute bioavailability approximating 100%." p. 1. The '452 publication would give the person of skill in the art confidence that treprostinil could be administered orally.

Further, the bioavailability of the treprostinil is an inherent property that a person of skill in the art could determine through clinical testing and routine experimentation. Nevertheless, it would have been obvious to a person of skill in the art that a salt form, particularly the ioinc organic diethanolamine salt, would be more bioavailable than the free acid of treprostinil. A person of skill in the art would know that the organic diethanolamine salt would be more lipid like than other salts and therefore more able to dissolve in cells.

Bighley discloses that ideal salts exhibit good bioavailability. p. 453. It further discloses that organic acid salt forms of drugs, such as amines, "frequently have higher acqueous solubilities than their corresponding inorganic salts. *Id.* at 461. The dissolution rate often indicates biavailability. The "salt form frequently exhibits a higher dissolution rate than the corresponding conjugate acid or base at the same pH." *Id.* at 463–64. Bighley discloses that high water solubility is usually associated with higher dissolution and absorption. *Id.* at 486; *see also* Berge at 5–6 ("In many cases . . . [dissolution] best refelects the bioavailability of the compound."). Salt formation also "generally increases the dissolution rate." *Id.* at 464. For example, "[a]lthough no direct comparisons of the [salt and acid forms of benzoic acid] were

made, inspection of the data shows that the deaggregation of the salt was considerably more rapid than that of the free acid in equiOvalent dosage forms. Therefore, if absorption is dependent on the dissolution rate, which in turn is dependent on the deaggregation rate, the salt should produce the highest and earliest blood levels." *Id.* at 464. In another example, bioavailability in rates of magnesium and calcium salts of indomethacin was "significantly higher" as compared to indomethacin free acid after an oral dose of the salts as measured by plasma levels. *Id.* at 474. As explained above regarding lipids, "[t]he increased absorption was attributed to enhanced lipid solubility and increased solubility in bile and intestinal juice." *Id.* Bighley discloses that "[t]o increase absorption, organic cations should be prepared, such as amino acids . . . or hydroxyamines (diethanolamine or triethanolamine)." *Id.* at 484. The '095 publication also discloses that the diethanolamine salt of zopolrestat is highly water-soluble and, therefore, "advantageous." at ¶ [0005]. The '164 patent also discloses that the diethanolamine salt is water-soluble. Abstract. Bighley teaches that "[s]alts are also employed to increase the absorption rate and hence speed of action . . . ." p. 484. In short, absorption can be increased by selecting a salt with higher solubility, as in the diethanolamine salt. *See id.* at 486. Berge also disclosed experiments in which "[i]n all cases, the sodium salt dissolved more rapidly than the free acid." p. 6.

Therefore, it would have been obvious to a person of skill in the art that the oral bioavailability of treprostinil as a diethanolamine salt would be significantly higher than that of the free acid. The precise difference in bioavailability between a particular salt, such as the diethanolamine salt, and the free acid could be determined by a person of skill in the art, rendering claims 1–12 obvious for that additional reason.

Plaintiffs have not set forth any evidence of secondary considerations of non-obviousness, and Actavis is not aware of any such secondary considerations that, when considered with the evidence of obviousness, would warrant a finding of non-obviousness of the claims of the '901 patent. If UTC relies on any secondary considerations of non-obviousness, Actavis reserves the right to supplement its contentions.

As explained above, the claims would have been obvious in view of a host of prior art references because the steps described in the claims were well-known procedures that would have been obvious to apply. Consequently, there are numerous different combinations of these prior art references and many exemplary references that teach each standard step. By way of example, the following combinations render the asserted claims obvious:

- Simonneau, the '222 patent and/or Vizza, Bighley, and/or the diethanolamine salts of other drug compounds,
- Simonneau, the '222 patent and/or Vizza, the '075 patent, Bighley, and/or the diethanolamine salts of other compounds,
- The '222 patent, the '075 patent, Bighley, and/or the diethanolamine salts of other compounds.
- The '222 patent, the '075 patent, Bighley, the '196 publication, and/or the diethanolamine salts of other compounds.
- Simonneau, the '222 patent, Bighley or Berge, and/or the diethanolamine salts of other drug compounds,
- Simonneau, the '222 patent, the '075 patent, Bighley or Berge, and/or the diethanolamine salts of other compounds,
- The '222 patent, the '075 patent, Bighley or Berge, and/or the diethanolamine salts of other compounds.
- The '953 patent, the '222 patent, Bighley or Berge, and/or the diethanolamine salts of other compounds
- The '953 patent, Simonneau, Bighley or Berge, and/or the diethanolamine salts of other compounds

- Any of the above combinations with the '452 publication
- Any of the above combinations with Byrn, Olmsted, Sharp, and Pavia
- Any of the above combinations with Remodulin and the Remodulin Label

A POSA would have been motivated to combine the teachings of these references with a reasonable expectation of success. In addition, Actavis's invalidity charts set forth where each prior art reference discloses the limitations of the asserted claims.

Actavis reserves the right to set forth additional such examples as discovery continues.

3. Claims 1–12 Are Invalid for Lack of Enablement and Failure to Meet the Written Description Requirement

In the alternative, should the court not find that the asserted claims are obvious, they are invalid for lack of enablement and written description.

a. Claims 1 and 7 Are Not Enabled

i. Overbroad scope of formulations and treprostinil salts and esters within the claims

If the claims are not found to be obvious, independent claim 1 should be found invalid as not enabled at least in view of the breadth of formulations and treprostinil salts and esters within the claim's scope. The claim encompasses the administration of any oral pharmaceutical formulation that meets the other claim limitations. The claim therefore encompasses at least oral solutions, capsules, and tablets, of which there are a great variety. *See, e.g.*, Ansel 1999, at 196-203 (listing and discussing over ten different tablet types). Tablets and other oral dosage forms can contain virtually an infinite number of different combinations of composition ingredients and amounts. *See, e.g.*, Ansel 1999 at 197-98 (listing types of ingredients that compressed tablets contain), *Handbook of Pharmaceutical Ingredients* (Raymond C. Rowe et al. eds., 4th ed. 2003) (listing over 150 ingredients suitable for use in pharmaceutical compositions in combination with various other such ingredients).

Further, the formulation can contain any pharmaceutically acceptable treprostinil salt or ester. There are over forty potential cationic species that can serve as a counter ion to treprostinil. *See* Lyle D. Bighley *et al.*, *Salt Forms of Drugs and Absorption, in 13 Encyclopedia of Pharmaceutical Technology* 453, 456 Table 2 (James Swarbrick & James C. Boylan eds., 1996). There are also a large number of treprostinil esters that can be conceived, since any organic group can substitute for the acidic-H of the carboxyl group to form an ester. As detailed below, the specification provides data on only a few of these species. Not all of them (if any) meet all of the claim-recited pharmacokinetic limitations.

As detailed further in the next section, the specification provides little or no working examples and no guidance concerning which treprostinil salt compositions meet the pharmacokinetic limitations of the claim. Although the specification discusses certain oral compositions that contain treprostinil diethanolamine, it does not disclose the inactive ingredients of the compositions or their amounts or how the compositions were prepared. Although there is a large amount of literature available concerning pharmaceutical compositions and the person of ordinary skill in the art was experienced in preparing such compositions, pharmacokinetics is unpredictable and varies from organism to organism. For example, the '901 patent discloses that the oral bioavailability of treprostinil from a solution of treprostinil diethanolamine was experimentally determined to be about 9% in rats and around 20-25% in humans, depending on the amount of treprostinil diethanolamine in the dose. In view of the paucity of working examples and guidance from the patent, the person of ordinary skill in the art would have to prepare and test each treprostinil salt or ester composition to determine whether it is within the scope of the claim. In other words, the person of ordinary skill in the art would have to invent the claimed invention.

In sum, at least because the specification essentially leaves it to the person of ordinary skill in the art to devise, prepare, and test numerous different oral treprostinil salt and ester compositions in order to "practic[e] the full scope of the claim," and claim 1 is broad, the art unpredictable, and the specification provides little or no guidance or working examples, it would require undue experimentation to practice the full scope of claim 1. Therefore, claim 1 is not enabled by the '901 patent specification and should be found invalid. *See Wyeth & Cordis Corp. v. Abbott Labs.*, 720 F.3d 1380, 1386 (Fed. Cir. 2013) (affirming finding of lack of enablement where the specification "discloses only a starting point for further iterative research in an unpredictable and poorly understood field" and there was a "need to engage in a systematic screening process" in view of the "specification offer[ing] no guidance or predictions" about which potential drug candidates would be effective).

The same analysis applies to claim 7, which differs from claim 1 only by reciting "AUCinf" instead of "Cmax." This does not affect those aspects of claim breadth addressed above. Claim 7 should be found invalid for the same reasons as claim 1.

ii. Overbroad unbounded ranges within the claims

A second, independent basis for finding claim 1 invalid for lack of enablement derives from its breadth deriving from its three open-ended "at least" value range limitations. As discussed above, claim 1 recites a method that entails administering a treprostinil salt or ester composition that "has an absolute bioavailability of at least 15%."[23] The claimed method thus encompasses the administering of any composition that provides an absolute bioavailability that falls within the open-ended range of 15% or greater, such as 40%, 60%, or 80%. At the same time, claim 1 also requires Cmax linearity for doses of "at least 0.05 mg," thus requiring linearity

[23] Solely for the purpose of this analysis, we assume that this limitation is properly understood to mean that the treprostinil salt or ester, as formulated in the recited composition, has an absolute bioavailability of at least 15%. Whether the absolute bioavailability is an average value or something else is not material to the analysis.

for doses up to, for example, 30 mg. Also at the same time, claim 1 requires that treprostinil concentration in the subject's plasma "is at least 50 pg/ml for at least 8 hours." Thus, the claim encompasses methods that achieve minimum concentrations of greater than 50 pg/ml over eight hours, such as 100 pg/ml.

The '901 patent does not enable the universe of methods that claim 1 encompasses at least because it does not enable the universe of treprostinil salt or ester formulations that meet all three recited "at least" conditions. The '901 patent provides little guidance regarding the treprostinil salt or ester composition that will meet these conditions. The guidance that the '901 patent provides that relates to the alleged inventive compensations amounts to no more than general instruction in preparing pharmaceutical formulations generally. No guidance is provided relating to any quantity of any specific ingredients that will provide the claim-required bioavailability and pharmacokinetic properties. Despite the general discussion of the use of p-glycoprotein inhibitors to promote bioavailability, the '901 patent also does not provide any working examples that illustrate this effect and no specific guidance relating to how much or in what proportions p-glycoprotein inhibitors should be included in a formulation of the alleged invention.

The '901 patent does not provide working examples sufficient to compensate for the omission of general guidance. Notably, the patent does not disclose the formulation of any composition other than the oral solution provided to rats in Example 1. *See* '901 patent at col. 46, ll. 40-45. The patent does not provide a description of the solution that was administered to humans. *See id.* at col. 63, ll. 44-47 and at col. 63, l. 62–col. 64, l. 12 (discussing administration to human volunteers of an oral solution of treprostinil diethanolamine but not disclosing the solution's composition). In addition, the formulations in the examples did not satisfy all of the

limitations of the claims. In the rats used in Example 1, the treprostinil diethanolamine solutions did not yield the required absolute bioavailability. *See id.* at col. 49, Tables 4 and 5 (reporting average and individual oral bioavailability's relative to intravenous administration). The highest individual oral absolute bioavailability was 10.7%. *See id.* Table 5. Example 2 examined two treprostinil esters administered to rats by oral solution. Only one of the esters, the benzyl ester, met the claim-recited 15% absolute oral bioavailability limitation. Because only one dose was used in Examples 1 and 2 (expressed only in mg/kg), the data cannot be used to support the Cmax linearity limitation. Example 3 provides no support for the claim because it only examined intraduodenal administration. Also, although the patent states that pharmacokinetic data are provided in Table 14, in fact that table only repeats the description of Figures 8-12 set forth in Table 13. *See* '901 patent at col. 55, ll. 39-43 (describing Example 3 study of "single duodenal dose of treprostinil and various prodrugs"), col. 58, ll. 32-39 (discussing intraduodenal administration of treprostinil prodrugs), col. 59, ll. 33-43 and Tables 13 and 14.[24] Example 4 provides no support for claim 1 because it is prophetic. It provides no data to indicate that the claim limitations were satisfied. *See id.* at col. 60, l. 42–col. 63, l. 36.

Example 5 is the only remaining example. In the first part of the example, four treprostinil diethanolamine doses (0.2, 0.5, 1.0, and 2.0 mg) divided into four equal parts were administered at two-hour intervals to healthy adult humans in an oral solution. As mentioned above, the composition of the solution is not disclosed. The solutions yielded absolute oral bioavailability of 21%, 23%, 24%, and 25%, respectively. For at least two of the dosages, it appears that the claim's minimum treprostinil plasma concentration is not met because the

[24] The statement in Example 3 that the "plasma concentrations of Treprostinil following oral administration of each prodrug were evaluated in" male rats thus appears to misstate the route of administration. Shortly after that statement, the patent states that the animals "were dosed via an indwelling duodenal cannula." *See* '901 patent at col. 57, ll. 14-16 and col. 57, l. 54.

concentration appears to fall to, or very close to, zero ng/ml every two hours. *See* '901 patent at col. 63, l. 37–col. 64, l. 21 and Figures 13A-13D (showing, at least in Figures 13A and 13B (reporting data for 0.2 mg and 0.5 mg doses) periodic plasma concentrations at or near zero ng/ml).

Further, these solutions do not meet claim 1's Cmax limitation. Plotting the Cmax values obtained from Figure 13 against dosage shows that the oral solution of treprostinil diethanolamine does not fall within the scope of claim 1 because it does not satisfy the Cmax linearity requirement for doses within the recited range of at least 0.05 mg.[25]

In the second part of Example 5, a 1 mg dose of treprostinil diethanolamine was administered to fed and fasted patients in sustained-release capsules and tablets. The patent does not disclose the composition of the capsules and tablets. The '901 patent provides a plot of average concentration versus time. The patent does not provide the corresponding numeric values or the calculated AUCs, but these might be approximated from the chart. *See* '901 patent at col. 64, l. 35–col. 65, l. 10. The patent provides no information regarding Cmax at other doses for this formulation, so this part of the example fails to support claim 1 at least with respect to the Cmax linearity requirement.

In sum, the patent provides no general guidance relating to the composition of formulations that meet all of the limitations of claim 1, and it provides no specific examples of any compositions that meet all of the limitations of claim 1.

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[25] Further support for the conclusion that some, if not all, treprostinil salt and ester formulations fail to satisfy the Cmax and AUCinf limitations of the claims derives from the Orenitram® NDA. United Therapeutics Corporation, which is both the '901 patent assignee and the Orenitram® NDA applicant, provided data in its NDA that the Center for Drug Evaluation and Research understood to establish that the "[p]harmacokinetics of treprostinil in PAH patients is linear with a dose-proportional increase for AUC_{0t} and less than dose-proportional increase for C_{max} in the dose range of 0.5-15 mg." Center for Drug Evaluation and Research, NDA 203496-Treprostinil diethanolamine, Clinical Pharmacology and Biopharmaceutics Review(s) at 16, § 2.4.1 (emphasis added). This suggests that, at least for the Orenitram® formulation, AUCinf and Cmax linearity does not extend throughout the claim-recited dose range of "at least 0.05 mg."

For a given composition that contains a specific treprostinil salt or ester, it cannot be predicted that the composition will meet all three limitations discussed above in any specific animal. While the person of ordinary skill in the art generally knew how to prepare pharmaceutical formulations, including sustained-release formulations, and might be able to predict generally what effect a certain ingredient was likely to have on the bioavailability of the active ingredient, the person of ordinary skill in the art could not have predicted what formulations would meet all three of the absolute bioavailability, Cmax, and plasma concentration limitations. This is evidenced by the fact that, for each treprostinil derivative, the patentees determined by experiment the corresponding pharmacokinetics relative to a corresponding treprostinil diethanolamine composition. *See Ariad Pharm.*, 598 F.3d at 1351 (citing predictability as a factor to consider in assessing written description support). Further, it is apparent from the '901 patent's data that not all compositions that contain a treprostinil salt or ester will meet all of the limitations of the claim. For example, the data for the methyl ester administered orally to rats showed insufficient oral bioavailability. The treprostinil diethanolamine oral solution administered to humans failed to exhibit Cmax linearity at doses within the scope of the claim.

In view of the broad scope of the claims, the unpredictability of formulation pharmacokinetics, and the lack of guidance and working examples, claim 1 of the '901 patent should be found invalid for lack of enablement. Undue experimentation would be required to develop formulations for use in the claimed method because the person of ordinary skill in the art would have to devise and test every potentially infringing treprostinil salt or ester formulation to determine its pharmacokinetic properties, and the specification provides almost no guidance as to which compositions satisfy the claim-recited pharmacokinetic properties.

The enablement issue here is comparable to that presented in *MagSil Corp. v. Hitachi Global Storage Techs.*, 687 F.3d 1377 (Fed. Cir. 2012), where the court found the claim at issue invalid for lack of enablement. There, as here, the claim at issue contained an open-ended range. The claimed device was recited as forming a junction comprising two electrodes separated by an insulator, "wherein applying a small magnitude of electromagnetic energy to the junction reverses at least one of the magnetization directions and causes a change in the resistance by at least 10% at room temperature." *MagSil*, 687 F.3d at 1379. In the prior art, a change in resistance of only 2.7% had been achieved. The patent at issue disclosed a device that exhibited up to an 11.8% change. *See id.* at 1379-80. Yet the claim, properly construed, encompassed a change in resistance from 10% to infinity because the claim recited a minimum value but no maximum value for the recited range. Advances in the art after the patent's filing date had yielded much greater changes in resistance, and these were encompassed by the claim. *See id.* at 1381, 1382. In affirming that the claim was invalid for lack of enablement, the court noted that, despite the claim's breadth, "[t]he '922 patent specification does not disclose working examples of tunnel junctions with resistive changes of 20%, 120%, 604%, or 1000%." *See id.* at 1382. Rather, the specification only "enabled a marginal advance over the prior art." Similarly, here, claim 1 of the '901 patent encompasses treprostinil salt and ester oral formulations that provide an absolute oral bioavailability of anything greater than 15% (a range with no upper limit), so long as the Cmax and minimum plasma concentration limitations are met. Yet the specification, at best, describes a composition that yields a 25% absolute oral bioavailability (and it is not clear that that composition satisfies the other limitations of the claim). Conceivably, an oral formulation could be devised that provides an 80% absolute bioavailability and otherwise meets the limitations of claim 1. Such a formulation would be within the scope of claim 1 even though the '901 patent

does not disclose such a composition or provide guidance in preparing one. The court's holding in *MagSil* thus reinforces the conclusion that claim 1 should be found invalid for lack of enablement. *See also In re Fisher*, 427 F.2d 833, 838-40 (C.C.P.A. 1970) (finding lack of enablement of a claim reciting an open-ended potency limitation of "at least 1" unit where the "appellant has not enabled the preparation of ACTHs having potencies much greater than 2.3").

The lack of enablement analysis set forth above with respect to claim 1 applies equally to claim 7. Claim 7 is identical to claim 1 except it recites "AUCinf" instead of "Cmax." Even if the data in Example 5 supported an AUFinf that varies linearly with dose in the low dose range, the specification would still fall far short of the enabling disclosure required by law. Those data relate only to an oral solution. The specification does not disclose the composition of the solution.

Further, there are no other data that provide guidance for all of the other formulations within the scope of claim 7, including tablets. The open-ended ranges thus also defeat enablement of claim 7. As with claim 1, claim 7 encompasses the administration of compositions that provide an absolute oral bioavailability of 15% or greater, so long as they satisfy the other pharmacokinetic limitations. But the specification provides no guidance or examples to support that range, for the reasons set forth with respect to claim 1. Claim 7 should be found invalid for lack of enablement.

b. Invalidity of dependent claims 2 and 8 for lack of enablement

Dependent claims 2 and 8 should be found invalid for lack of enablement even though their scope is narrower with respect to the absolute bioavailability "of said salt or ester."[26] Despite this narrowing, the claims still encompass the administration of <u>any</u> oral composition

[26] All of the issues raised by the claims' uninterpretable reference to absolute bioavailability apply here, as discussed in the text above.

containing any treprostinil salt or ester if such a composition satisfies all of the claims' limitations, as discussed with respect to claims 1 and 7. Yet the specification, as discussed with respect to claims 1 and 7, discloses few if any such formulations as working examples. Further, it provides no guidance in preparing such formulations. Only the oral solution administered in the first part of Example 5 is said to meet the narrowed absolute bioavailability limitation of claims 2 and 8. As discussed above, that solution appears not to meet the Cmax linearity limitation that claims 2 and 8 incorporate by reference to claims 1 and 7.

Further, based on the graphs presented in Figures 14A-D, it appears that all of the absolute bioavailability's in Ex. 5 were below 20% and thus outside the scope of claims 2 and 8. The specification does not disclose the composition of the administered tablets and capsules, so the person of ordinary skill in the art would not be able to prepare this formulation except through trial and error.

An argument that any 1 mg treprostinil diethanolamine sustained-release tablet or capsule would be within the scope of the claim should fail. The actual marketed product Orenitram®, for example, has an absolute oral bioavailability of about 17%, and thus its administration falls outside the scope of claims 2 and 8. *See* Center for Drug Evaluation and Research, NDA 203496-Treprostinil diethanolamine, Clinical Pharmacology and Biopharmaceutics Review(s) at 5, § 1.3 ("The absolute bioavailability of treprostinil oral ER tablet is 17%.") and at 16, § 2.4.1 ("The absolute bioavailability of treprostinil following oral administration of treprostinil ER tablet is 17.6%.").

In view of the limited disclosure of the '901 patent, the unpredictability of pharmacokinetics, and the breadth of claims 2 and 8 with respect to treprostinil salts and esters

and with respect to pharmaceutical formulations, which is the same as claims 1 and 7, discussed above, dependent claims 2 and 8 should be found invalid for lack of enablement.

c. Invalidity of dependent claims 3, 4, 9, and 10 for lack of enablement

Dependent claims 3, 4, 9, and 10 should be found invalid for lack of enablement for the same reasons set forth with respect to independent claims 1 and 7. The additional limitations of claims 3, 4, 9, and 10 relate to the treprostinil salt or ester's oral bioavailability relative to the oral bioavailability of treprostinil free acid. Thus, all of the limitations of the independent claims from which they depend are incorporated into these dependent claims with the same breadth. That breadth is not enabled by the specification for the reasons set forth with respect to claims 1 and 7.[27]

Claims 3, 4, 9, and 10 are further unsupported because they contain open-ended relative oral bioavailability limitations that the specification does not support. In short, the specification does not provide guidance or working examples sufficient to support the breadth of treprostinil salts and esters or the breadth of oral pharmaceutical compositions encompassed by the claims. Of two esters tested in the specification, only one had a mean relative oral bioavailability that would satisfy either of the relative oral bioavailability limitations of these claims. That data is unreliable because of the large standard deviations attached to it. Also, those experiments were performed in rats. It is unclear whether the same results would be obtained in other organisms, such as humans. It is also unclear whether the administered formulations met the Cmax linearity limitation of the claims. It appears that that information was not obtained, since only one dose of each ester, 0.5 mg/kg (measured on a treprostinil basis), was administered. *See* '901 patent at col. 52, Table 6.

[27] The claims also fail to provide the person of ordinary skill in the art with reasonable certainty regarding in what organism the recited absolute and relative bioavailability limitations must be satisfied.

Therefore, dependent claims 3, 4, 9, and 10 should be found invalid for lack of enablement.

d. Invalidity of dependent claims 5 and 11 for lack of enablement

Dependent claims 5 and 11 should be found invalid for lack of enablement. Claims 5 and 11 are limited relative to claims 1 and 7 only by requiring that the treprostinil salt or ester is treprostinil diethanolamine. The analysis of claims 1 and 7 therefore applies to claims 5 and 11.

The breadth of oral compositions remains the same. The specification does not provide the composition of any oral formulation except an oral composition provided to rats. The oral tablets and capsules administered to humans are characterized only in being sustained release. This narrow disclosure does not enable the broad spectrum of oral compositions that claims 5 and 11 encompass.

Claims 5 and 11 retain the unbounded ranges of independent claims 1 and 7, which the specification does not enable for the reasons set forth above. Even though claims 5 and 11 encompass only treprostinil diethanolamine compositions, they nevertheless encompass all oral pharmaceutical formulations that provide a treprostinil diethanolamine absolute oral bioavailability of at least 15%. The specification discusses (without disclosing) compositions that provide at most 25% absolute oral bioavailability. The claims nevertheless encompass compositions that provide much higher absolute oral bioavailability. Also, as noted above, some formulations have this absolute bioavailability in some species but not others. The specification does not provide guidance regarding how to prepare compositions that have this absolute bioavailability in all species or in any specific species or in at least one species. The specification is further largely silent with respect to linearity of Cmax for parts of the claim-recited range. The '901 patent thus essentially leaves it to the person of ordinary skill in the art to invent

compositions that are within the scope of the claim. At least for these reasons, dependent claims 5 and 11 should be found invalid for lack of enablement.

e. Invalidity of dependent claims 6 and 12 for lack of enablement

Dependent claims 6 and 12 should be found invalid for lack of enablement. Claims 6 and 12 are limited relative to claims 1 and 7 only by requiring that the subject is human. The nonenablement analysis set forth with respect to claims 1 and 7 therefore applies equally to claims 6 and 12.

In sum, even though the '901 patent discusses two working examples in humans, this remains a tiny subset of what is claimed. As stated with respect to claims 1 and 7, there are many treprostinil salts and esters and many oral pharmaceutical formulations within the scope of claims 6 and 12. The specification does not disclose the composition of even a single composition administered to humans. Also, claims 6 and 12 still retain the open-ended ranges of claims 1 and 7. The examples do not come close to supporting the full extent of those ranges, or even a large part of those ranges. The highest absolute oral bioavailability in humans that the specification discusses is 25%, whereas the claims encompass values up to or approaching 100%. Therefore, claims 6 and 12 should be found invalid for lack of enablement.

4. Claims 1–12 Are Invalid for Lack of Written Description

a. Independent claims 1 and 7 are invalid for lack of written description

Claims 1 and 7 claim a genus of methods that entail administering an oral treprostinil salt or ester pharmaceutical formulation that is defined functionally with respect to absolute bioavailability, Cmax or AUCinf, and treprostinil plasma concentration. For the reasons set forth above with respect to enablement, the scope of the claims is very broad in view of the treprostinil salt and ester species, oral pharmaceutical formulations, and open-ended ranges that the claims

recite. Pharmacokinetic and bioavailability properties such as those recited in the claims are unpredictable. Although the drug formulation field was somewhat developed at the time of filing, that degree of development did not permit the person of ordinary skill in the art to predict the pharmacokinetic and bioavailability properties of any specific drug formulation. Those properties were ascertained by making formulations and measuring their properties experimentally. The prior art does not disclose the properties of treprostinil salt or ester compositions other than treprostinil sodium. The '901 patent provides no formulation species that clearly fall within the scope of the claims' limitations. The '901 patent does not provide any formulation species with properties that span the full recited ranges, such as oral treprostinil salt or ester formulations that provide absolute oral bioavailability of 80% or Cmax linearity at doses below 0.2 mg and doses above 2 mg. The '901 patent discloses bioavailability and pharmacokinetic information for formulations that contain only a very small, and therefore non-representative, subset of the species of treprostinil salts and esters within the scope of independent claims 1 and 7.

The '901 patent does not disclose "structural features common to" the recited formulations that enable "one of skill in the art [to] visualize or recognize the members of the genus" of administered formulations. *See Abbvie*, 759 F.3d at 1299. For example, in humans, four different treprostinil diethanolamine doses were administered by oral solution and a single dose of treprostinil diethanolamine was administered by sustained-release tablets and capsules. As noted above, the '901 patent does not disclose or "describe" the composition of the administered formulations. Further, even if the '901 patent had fully described these formulations, they nevertheless would not be representative of the full range of oral formulations

within the scope of the claim, the full range of treprostinil salts and esters within the scope of the claim, or the full range of dose amounts within the scope of claims 1 and 7.

In sum, the '901 patent fails to "demonstrate that the applicant has made a generic invention that achieves the claimed result." *See AbbVie*, 759 F.3d at 1299. Claims 1 and 7 amount to no more than a description or "indication" of a desired result of which the specification provides, at most, very few examples. The specification further provides no "definition of what achieves that result." *See Regents of the Univ. of California v. Eli Lilly and Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997). Because of the breadth of claims 1 and 7 with respect to treprostinil salts and esters, oral pharmaceutical formulations, and the breadth and unpredictability of the absolute oral bioavailability, Cmax, and plasma treprostinil concentration that the claims require of the administered composition, the person of ordinary skill in the art could not have recognized, from the specification's disclosure, that the patentees had possession of the claimed invention. *See Ariad Pharm.*, 598 F.3d at 1351 ("[P]ossession as shown in the disclosure is a more complete formulation."). Claims 1 and 7 thus appear to represent the patentees' attempt to claim compositions that have desirable properties but that the patentees did not possess or disclose. *Cf. Univ. of Rochester v. G.D. Searle & Co., Inc.*, 358 F.3d 916, 927, 930 (Fed. Cir. 2004) (affirming summary judgment of invalidity for lack of written description, noting, among other things, that "the '850 patent does not disclose any compounds that can be used in its claimed methods" and that "an adequate written description of a DNA . . . requires a precise definition, such as by structure, formula, chemical name, or physical properties, not a mere wish or plan for obtaining the claimed chemical invention" (internal quotations omitted) (quoting *Regents of the Univ. of Cal. v. Eli Lilly & Co., Inc.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997))). Claims 1 and 7 should be found invalid for lack of written description.

b. Invalidity of dependent claims 2 and 8 for lack of written description

Dependent claims 2 and 8 should be found invalid for lack of written description even though their scope is narrower with respect to the absolute bioavailability "of said salt or ester."[28] Despite this narrowing, the claims have a very broad scope because they encompass the administration of any oral composition containing any treprostinil salt or ester if such a composition satisfies all of the claims' limitations, as discussed with respect to claims 1 and 7. As for claims 1 and 7, the claim-required characteristics of the administered formulations are unpredictable.

As detailed in the enablement analysis above, the '901 patent's narrow disclosure omits formulation information and other information that would permit the person of ordinary skill in the art to judge whether the formulations discussed in Example 5 and the other examples are within the scope of the claims. Further, in view of the breadth of claims 2 and 8, the '901 patent does not provide representative species or a description of the invention that would permit "one of skill in the art [to] visualize or recognize the members of the genus" of claims 2 and 8. Therefore, claims 2 and 8 should be found invalid for lack of written description.

c. Invalidity of dependent claims 3, 4, 9, and 10 for lack of written description

Dependent claims 3, 4, 9, and 10 should be found invalid for lack of written description for the same reasons set forth with respect to independent claims 1 and 7. The additional limitations of claims 3, 4, 9, and 10 relate to the treprostinil salt or ester's oral bioavailability relative to the oral bioavailability of treprostinil free acid. Thus, all of the limitations of the independent claims from which they depend are incorporated into these dependent claims with

[28] All of the issues raised by the claims' uninterpretable reference to absolute bioavailability apply here, as discussed in the text above.

the same breadth. Such broad claims lack written description support and therefore should be found invalid for the reasons set forth with respect to claims 1 and 7.

Claims 3, 4, 9, and 10 are further unsupported because they contain open-ended relative oral bioavailability limitations that the specification does not support. As stated in the enablement section, the specification provides few, if any, examples that meet the additional limitations in addition to the limitations of the independent claims from which they depend. These fail to serve as representative examples from which the person of ordinary skill in the art could visualize or recognize other members of the genus. Dependent claims 3, 4, 9, and 10 should be found invalid for lack of written description.

d. Invalidity of dependent claims 5 and 11 for lack of written description

Dependent claims 5 and 11 should be found invalid for lack of written description. Claims 5 and 11 are limited relative to claims 1 and 7 only by requiring that the treprostinil salt or ester is treprostinil diethanolamine. The analysis of claims 1 and 7 therefore applies in large part to claims 5 and 11.

The breadth of oral compositions remains the same. The specification does not provide the composition of any oral formulation except an oral composition provided to rats. The oral tablets and capsules administered to humans are characterized only in being sustained release.

Claims 5 and 11 retain the unbounded ranges of independent claims 1 and 7. Thus, while the formulations administered to humans provide at most 25% absolute oral bioavailability, the claims nevertheless encompass compositions that provide much higher absolute oral bioavailability. The specification is further largely silent with respect to the discussed formulations' linearity of Cmax for parts of the claim-recited range.

At the same time, the required pharmacokinetic and bioavailability formulation characteristics are unpredictable. In view of the breadth of claims 5 and 11, the '901 patent's narrow disclosure, and the unpredictability of the art, the specification does not demonstrate that the '901 patentees have "made a generic invention that achieves the claimed result" by showing that they "invented species sufficient to support" the broad genus of compositions that are administered in the claimed method of treating. *See Abbvie*, 759 F.3d at 1299. Dependent claims 5 and 11 should be found invalid for lack of written description.

e. Invalidity of dependent claims 6 and 12 for lack of written description

Dependent claims 6 and 12 should be found invalid for lack of written description. Claims 6 and 12 are limited relative to claims 1 and 7 only by requiring that the subject is human. The lack of written description analysis set forth with respect to claims 1 and 7 therefore applies equally to claims 6 and 12.

In sum, even though the '901 patent discusses two working examples in humans, this remains a tiny subset of what is claimed. As stated with respect to claims 1 and 7, there are many treprostinil salts and esters and many oral pharmaceutical formulations within the scope claims 6 and 12. The specification does not disclose the composition of even a single formulation administered to humans. Also, claims 6 and 12 still retain the open-ended ranges of claims 1 and 7. The examples do not support the full extent of those ranges, or even a large part of those ranges. The highest absolute oral bioavailability in humans that the specification discusses is 25%, whereas the claims encompass values up to or approaching 100%. In view of the broad claim scope, narrow disclosure, and unpredictability of the claimed subject matter, claims 6 and 12 should be found invalid for lack of written description.

G. Invalidity of the '311 Patent

As explained in further detail below and in the accompanying claim charts concerning the '070 patent, the prior art renders obvious the claims of the '311 patent.

1. Claims 1–11 Are Obvious Based on the Following Prior Art

a. Berge et al., *Pharmaceutical Salts,* Journal of Pharmaceutical Sciences, 66, 1-19 (1977)

Berge was published in 1977 and is at least § 102(b) prior art. Berge discloses the diethanolamine salt as an FDA-approved commercially marketed salt that was "potentially useful." *See* p. 2, Table I. Berge also discloses that it was known that different salts of the same drug typically differ based on physical properties, not pharmacologically. *See* p. 5. Berge also discusses properties of various salts, including solubility and the difference between solubilities of different salt forms with the same compound as a free acid or base, the influence of pH on the solubility of pharmaceuticals, and bioavailability. pp. 4–10.

a. J. Olmsted III and G. M. Williams, Chemistry, The Molecular Science, Mosby-Year Book, Inc. (1994)

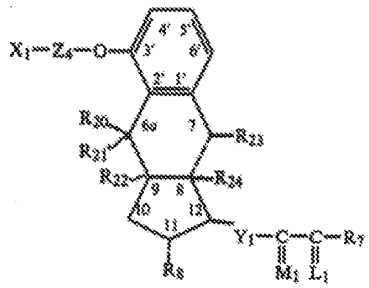
Olmsted was published in 1994 and is at least § 102(b) prior art. Olmsted teaches that "[r]ecrystallization is a classic way of removing impurities from a crude solid." p. 476. For example, "[i]f a solid substance is dissolved in a minimum volume of hot solvent that is then allowed to cool, the solubility of the solid is exceeded, and it crystallizes from the solvent. In favorable cases the impurities remain dissolved in the cold solvent, and the solid has been purified." *Id.*

b. U.S. Patent No. 4,306,075

U.S. Patent No. 4,306,075 ("the '075 patent") issued in 1981 and therefore qualifies as 35 U.S.C. § 102(b) prior art to the '070 patent. The '075 patent specifically discloses treprostinil, generally discloses a genus of compounds that encompasses treprostinil, and discloses that

suitable salts of the compounds include the diethanolamine salt. Specifically, the '075 patent states that it provides a compound of generic formula XI (diagrammed below) and sets forth the permitted substituents of the compound. *See* '075 patent at col. 3, l. 18, col. 3, l. 21–col. 5, l. 35 and col. 74, ll. 25-37. This genus includes treprostinil.

XI



The '075 patent describes generally the synthesis of compounds of formula XI and provides a diagram of the synthesis. *See id.* at col. 26, ll. 11-58 (describing the synthesis set forth in Chart P) and col. 89, ll. 14-31 and col. 90, ll. 1-38 (diagramming Chart P). The patent further discloses generally that the compounds can be provided in salt form, including in combination with cations derived from "amines containing water solubilizing or hydrophilic groups, e.g., mono-, di-, and triethanolamine." '075 patent at col. 15, ll. 15-17; *see also id.* at col. 14, l. 56–col. 15, l. 25 (disclosing that "[p]harmacologically acceptable salts of the novel prostaglandin analogs of this invention" include salts with amine cations) and at col. 30, l. 41–col. 31, l. 5 (describing preparation of salts of "compounds of this invention," including amine salts). Example 31 of the '075 patent discloses the preparation of a compound that is identical to treprostinil except that it has a double bond instead of "13,14-dihydro." *See* '075 patent at col. 56, l. 14–col. 59, l. 33 (Example 31, disclosing preparation of 9-deoxy-2',9α-methano-3-oxa-4,5,6-trinor-3,7-(1',3'-interphenylene)-prostaglandin F1 (so identified as the "title product" at col. 59, ll. 28-30)). Example 32 discloses that the compound prepared by Example 31 can be

hydrogenated to transform –CH=CH– to –CH_2CH_2– as exemplified in Example 33. This hydrogenation yields treprostinil. *See id.* at col. 61, l. 62–col. 62, l. 2 (describing hydrogenation of compound of Example 31 to eliminate double bond), col. 62, ll. 3-39 (Example 33, detailing the hydrogenation procedure).

The '075 patent states that the disclosed compounds and their pharmacologically acceptable salts can be used to inhibit platelet aggregation and to reduce the adhesive character of platelets. *See id.* at col. 12, ll. 39-43 (disclosing use of compounds to inhibit platelet aggregation and to reduce the adhesive character of platelets), col. 14, ll. 56-60 (stating that pharmacologically acceptable salts of the "novel prostaglandin analogs," including those formed with amine cations, can be used "for the purposes described above"). Both of these activities were thought to be useful in treating pulmonary arterial hypertension. *See, e.g.*, M. Beghetti *et al.*, *Aerosolized iloprost induces a mild but sustained inhibition of platelet aggregation*, 19 Eur. Respir. J. 518, 518 (March 1, 2002) ("Beghetti") (stating that the "beneficial effect" of epoprostenol infusion may be attributed to its antiproliferative and antiaggregant effects) and 522 (stating that the "antiplatelet effect observed in this study" "may explain in part the clinical improvement obtained with daily repetitive inhalations [of iloprost] in patients with primary and secondary pulmonary hypertension"), Emile R. Mohler III *et al.*, *Trial of a novel prostacyclin analog, UT-15, in patients with severe intermittent claudication*, 5 Vascular Medicine 231, 236 (2000) ("Mohler") ("Prostanoids are believed to exert their therapeutic effect in part at the level of the microcirculation where they prevent platelet activation and facilitate repair of damage induced by activated platelets and leukocytes."). The '075 patent also discloses oral dosage in the forms of tablets and capsules as the "preferred dosage form." col. 12, ll. 64–68.

c. Lyle D. Bighley *et al.*, *Salt Forms of Drugs and Absorption, in* 13 Encyclopedia of Pharmaceutical Technology 453 (James Swarbrick & James C. Boylan eds., 1995)

Lyle D. Bighley *et al.*, *Salt Forms of Drugs and Absorption, in* 13 Encyclopedia of Pharmaceutical Technology 453 (James Swarbrick & James C. Boylan eds., 1995) was published in 1995 and thus qualifies as prior art to the '070 patent under at least 35 U.S.C. § 102(b). Bighley discloses that "[s]alt formation is frequently performed on weak acidic or basic drugs because it is a relatively simple chemical manipulation which may alter the physicochemical, formulation, biopharmaceutical, and therapeutic properties of a drug without modifying the basic chemical structure." *Id.* at 453. Also, "[t]he ideal characteristics of a salt are that it is chemically stable, not hygroscopic, presents no processing problems, dissolves quickly from solid dosage forms (unless it is formed with the intent to delay dissolution), and exhibits good bioavailability." *Id.* at 453. Bighley identifies 38 cationic pharmaceutical salt forms in use at the time of publication. *See id.* at 456, Table 2. One of these was the diethanolamine salt. *See id.* As of 1993, the diethanolamine salt was among the more frequently used salts, being used in 0.45% of the cationic pharmaceutical salts. Twenty-one salts were used less frequently. *See id.* Bighley points out that "[o]rganic acid salt forms of basic drugs, such as amines, frequently have higher aqueous solubilities than their corresponding inorganic salts." *Id.* at 461. "This is important in the synthesis and selection of a salt form that exhibits enhanced bioavailability and desirable formulation characteristics." *Id.* Bighley further states that "[t]o increase absorption, organic cations should be prepared, such as amino acids (lysine, arginine), glucoamines (meglumine), or hydroxyamines (diethanolamine or triethanolamine)." *Id.* at 484.

d. S. R. Byrn et al. "Pharmaceutical Solids: A Strategic Approach to Regulatory Considerations" *Pharm. Res.* 12(7):945-954 (1995)

Byrn was published in 1995 and is at least § 102(b) prior art. Byrn presents a conceptual approach to the characterization of pharmaceutical solids in the development of pharmaceutical products for scientific and regulatory purposes. Byrn at Abstract. Initially, Byrn recommends screening for polymorphs of a particular substance by "crystalliz[ing] the substance from a number of different solvents" which include "those used in the final crystallization steps and those used during formulation and processing," including "water, methanol, ethanol, propanol, isopropanol, acetone, acetonitrile, ethyl acetate, hexane and mixtures if appropriate." *Id.* at 946. Byrn further states that "[n]ew crystal forms can often be obtained by cooling hot saturated solutions or partly evaporating clear saturated solutions." *Id.*

Byrn teaches that "[i]f polymorphs exist then it is necessary to examine the physical properties of the different polymorphs that can affect dosage form performance (bioavailability and stability) or manufacturing reproducibility, including solubility profile and stability. *Id.* at 947. In the development of pharmaceutical products, Byrn states that usually the most physically stable polymorph is selected, further noting that "[s]election of the most stable form would, of course, insure it that there would be no conversion into other forms." *Id.* at 948. In characterizing the resultant polymorphs, Byrn teaches that at a minimum, x-ray diffraction should be used. *Id.* at 946-47.

e. D. L. Pavia et al., Introduction to Organic Laboratory Techniques, Second Edition, Saunders College Publishing (1982)

Pavia was published in 1982 and is at least § 102(b) prior art. It teaches that "[o]rganic compounds that are solid at room temperature are usually purified by crystallization." Pavia at 481. The reference further teaches that "[a] material can be purified by crystallization when both

the desired substance and the impurity have similar solubilities." *Id.* at 482. Pavia further discloses procedures for minimizing impurities by manipulating crystallization conditions. *Id.* at 482–90.

f. Sharp, J.T., *Practical Organic Chemistry: A student handbook of techniques*, pp. 64–85 (1989)

Sharp is at least § 102(b) prior art. It discloses crystallization as "the most common method for purification of organic solids that are not heavily contaminated with other substances." p. 64. Sharp discloses using a hot solution of the compound, allowing it to cool, and become super saturated. The compound will then separate out as crystals. *Id.* at 65. The impurity will then remain in the solution, while the primary compound crystallizes. *Id.* Sharp discloses the steps of this process. *Id.* Sharp also discloses that melting point indicates purity. *Id.*

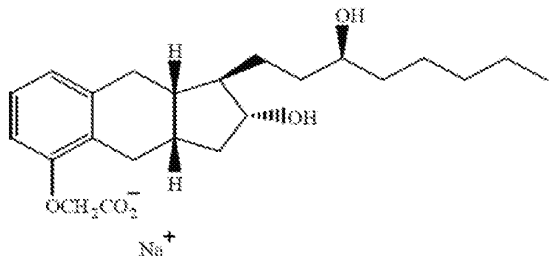
g. FDA Supporting Documentation Guideline:

The FDA Guideline was published in 1987 and is at least § 102(b) prior art. Recognizing that certain solid-state properties of the drug substance "may profoundly affect dissolution and bioavailability from solid dosage forms," the FDA requires that "[b]y the time of an NDA submission, the applicant should have established whether (or not) the drug substance exists in multiple solid-state forms, whether these affect the dissolution and bioavailability of the drug product, and whether particle size is important for dissolution and bioavailability of the drug product. FDA Supporting Documentation Guideline at 31. In particular, the FDA requires that the drug sponsor utilize "appropriate" analytical procedures "to determine whether or not polymorphism occurs." FDA Supporting Documentation Guideline at 34. Such procedures include XRPD, infrared spectra, Raman spectroscopy, intrinsic dissolution data, differential scanning calorimetry analysis, and thermogravimetric analysis. *Id.* Recognizing the potential for changes in the solid state during development of the pharmaceutical product, the FDA further

requires evidence that "no transformation is solid-state form has occurred," since "[r]outine storage conditions, as well as some conditions of product manufacture (e.g., tablet compression, or use of an organic solvent during granulation) may also cause transformations." *Id.* at 31.

h. Remodulin®

The treprostinil that was used in UTC's commercial embodiment Remodulin®, first approved, marketed, and sold to the public in 2002, with all its attributes and inherent qualities, also anticipates the '393 patent. Remodulin® was approved in 2002 and was publicly available at least one year prior to the application of the '393 patent. *See, e.g.*, Phares 2005 (disclosing the availability of treprostinil sodium (Remodulin®) [0004]); *see also* Wade 2005 at [0021, 0024] (disclosing treprostinil used in Remodulin® and its salt forms). As such, it is prior art under at least 35 U.S.C. § 102(b). According to its prescribing information, Remodulin® is a treprostinil sodium having the following structural formula:



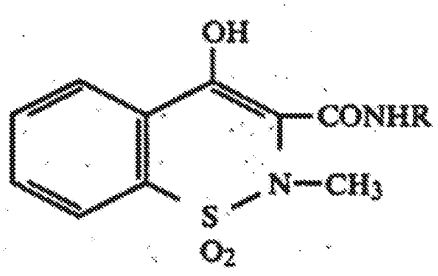
i. Shekunov, B.Yu, et al., *Crystallization process in pharmaceutical technology and drug delivery design*, Journal of Crystal Growth 211 (2000) 122–36

Shekunov was published in 2000 and is at least § 102(b) prior art. Shekunov discloses that "[s]olution crystallization is widely used for manufacturing bioactive drug substances and formulation excipients during final and intermediate stages of purification and separation." *See* Introduction. It discloses that more than 90 percent of pharmaceutical products "contain drug in

particulate, generally crystalline, form." *Id.* Shekunov also discloses that tablets are "by far the most widely used, simple and convenient solid dosage form." *Id.* at § 3.1. It teaches the importance of studying polymorphic forms of substances because "it is rare when a medicinally active substance exhibits only a single crystalline structure." *Id.* at § 3.3. Shekunov suggests selecting "the single, most stable form . . . ." *Id.* at § 3.3. Shekunov further discloses the use of antisolvents in the crystallization process. *Id.* at 4.

j. U.S. Patent No. 4,434,164

The '164 patent specifically discloses and claims the diethanolamine salt of piroxicam, an acidic benzothiazine (diagrammed below; R is 2-pyridyl).[29] The '164 patent discloses that the diethanolamine and two other salts of the benzothiazine are "crystalline, non-hygroscopic, rapidly-dissolving solids with high water solubility" and "possess excellent chemical and physical stability properties." *See* '164 patent at col. 8, ll. 37-38 (claim 4), col. 1, ll. 37-65, col. 2, l. 43–col. 3, l. 13. These properties facilitate the salts' incorporation into pharmaceutical dosage forms. *See id.* at col. 3, ll. 13-17. Example 4 sets forth the synthesis of the diethanolamine salt of piroxicam. Piroxicam diethanolamine's melting point is 143-146° C. *Id.* at col. 6, ll. 1-30. Specifically, the '164 patent discloses adding diethanolamine to a solution of water and piroxicam and then warming the solution. After cooling under a dry nitrogen atmosphere, the processes yielded pure diethanolamine salt of piroxicam. col. 6, ll. 1–34.



[29] Piroxicam itself was disclosed prior to the filing of the '164 patent. *See* 164 patent at col. 2, ll. 31-39.

N-(2-pyridyl)-2-methyl-4-hydroxy-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide

k. Yeo, Sang-Do, et al., Formation *of Microparticulate Protein Powders Using a Supercritical Fluid Antisolvent*, Biotechnology and Bioengineering, Vol. 41, pp. 341-46 (1993)

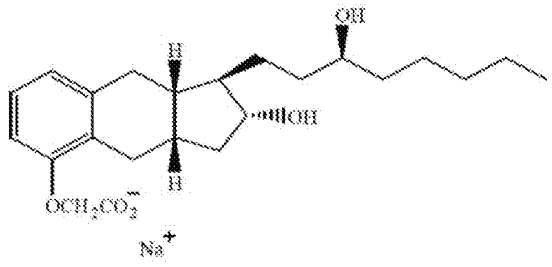
Yeo was published in 1993 and is at least § 102(b) prior art. Yeo discloses ethanol and acetone as antisolvents. p. 1.

2. Claims 1–11 Are Invalid Because They Are Obvious

Claims 1–11 are invalid because they are obvious in view of the prior art. The person of skill in the art would have understood the basic crystal and salt formation processes described in the claims of the '311 patent.

Claim 1 describes a "method of producing a pharmaceutically acceptable salt of treprostinil comprising dissolving treprostinil in a solvent, adding a base, heating, and cooling in an antisolvent to form a pharmaceutically acceptable salt of treprostinil as a crystalline solid."

First, it would have been obvious to produce a salt of treprostinil, particularly the diethanolamine salt, for the reasons described above regarding the '070 patent and other patents in this family. Those discussions are incorporated herein by reference. *See also* Remodulin's® prescribing information, which discloses treprostinil sodium having the following structural formula:



Second, it would have been obvious to make the crystal form of the claimed salt, as claimed for the reasons described regarding invalidity of the '393 patent (crystallization works bet when there is not an overabundance of impurities). *See, e.g.*, Olmsted at 476 (crystallization is a classic way to remove impurities"); Sharp at 64 (disclosing crystallization as a common method to purify organic solids).

Third, the claim's steps for making the claimed salt, including the crystalline version of that salt, are also obvious. For instance, dissolving the drug of choice and adding a base to make a salt is disclosed in a number of references and was a common way to make salts as of the time of the alleged invention. *See, e.g.*, '075 patent at col. 30, l. 41–col. 31, l. 5 (disclosing treprostinil and describing the process of dissolving a substance in its free acid form in a solvent and adding a base to the solvent). The '311 patent claims do not suggest that there is anything inventive about the steps taken to make the claimed salt.

Fourth, the process of heating and then cooling to make a crystalline version of the salt from a superstatured solution was also obvious. *See, e.g.*, Olmsted at p. 476 (disclosing the crystallization and recrystallization process); Pavia 481–82; Sharp at p. 65 (describing forming a crystalline solid); '164 patent col. 6, ll. 1–34 (describing synthesis of the crystalline diethanolamine salt of prioxicam, another prostaglandin); Byrn at p. 946 (disclosing forming crystal forms and the importance of screening for crystal forms (polymorphs) of a particular substance by "crystalliz[ing] the substance from a number of different solvents" which include "those used in the final crystallization steps and those used during formulation and processing." These solvents include "water, methanol, ethanol, propanol, isopropanol, acetone, acetonitrile, ethyl acetate, hexane and mixtures if appropriate.").

Finally, using an antisolvent was obvious as part of the crystallization process. Shekunov discloses the use of antisolvents in the crystallization process. *Id.* at 4. Sharp also discloses the use of a "poor" solvent, which functions as an antisolvent. Sharp at 83–84.

Claim 2 depends on claim 1 and adds that the base is an inorganic base. The '075 patent discloses the use of an inorganic base and provides examples, including sodium hydroxide. col. 30, ll. 41–62. Claim 3 depends on claim 2, but also claims that the base is an alkali metal.[30] Claim 4 depends on claim 3, but adds that the alkali metal is sodium or potassium. The '075 patent discloses metal salts, and specifically, sodium salt. *Id.* It further discloses metal cations that are "[e]specially preferred," including sodium and potassium. col. 14, ll. 56–66. Bighley discloses metallic cations, including potassium and sodium, for use in pharmaceutical salts. p. 456, Table 2, 482 (sodium salts), 483 (metal salts, including sodium and potassium).

Claim 5 depends on claim 1, but adds that the base is an organic base. Claim 6 depends on claim 5 and adds that the organic base is diethanolamine. The '075 patent teaches the use of an organic base, including amine salts. Col. 30, ll. 41–col. 31, ll. 5. It also specifically discloses the diethanolamine salt. Col. 15, ll. 1–25. Further, as described above, it would have been obvious to use the DEA salt, which was well known. *See, e.g.*, Bighley.

Claim 7 depends on claim 3, but also claims that the solvent comprises ethanol and water. Sharp discloses the use of ethanol and water as solvents, as well as considerations relating to the choice of solvents. pp. 81–82; '075 patent col. 30, ll. 41–66; *see also* Sharp at pp. 83–84 (describing mixed solvents); Olmsted at 458 (disclosing water as a solvent), 476 (disclosing ethanol as a solvent); Byrn at 946. Pavia discloses a solvent mixture containing ethanol and

[30] Claims 3 and 4 are unclear, and therefore may be indefinite, because the language is ambiguous. It is unclear whether the claim is directed to an alkali metal, like metallic sodium or potassium, which would be highly reactive and therefore unusual, or an alkali metal ion containing a basic salt, such as sodium hydroxide, which would be more common.

water. Claim 8 depends on claim 5, and also claims that the solvent comprises ethanol and water. The '075 patent describes the use of ethanol and water as potential solvents. col. 30, ll. 41–66; Olmsted at 458 (disclosing water as a solvent), 476 (disclosing ethanol as a solvent); Byrn at 946; Pavia at 489. Ethanol and water are extremely common solvents and their use is a part of everyday laboratory work in this field. Pavia also discloses that finding the proper solvent is done by trial and error. *Id.* at 483, 490.

Claim 9 depends on claim 1, but adds that the antisolvent comprises acetone. Olmsted describes the use of acetone in solvents. pp. 455, 458; *see also* Sharp at 81–82; Byrn at 946. Acetone is an extremely common organic solvent in daily use in chemistry labs worldwide. It is well known that it has a polarity less than that of ethanol and water, and hence, for drug substances that are salts known to be soluble in highly polar solvents, acetone is an obvious choice as an antisolvent. Yeo discloses ethanol and acetone as antisolvents. p. 1.

Claim 10 claims the crystalline salt of treprostinil produced by the method of claim 1. Because claim 10 is a product-by-process claim, it is anticipated by Remodulin®, which contains as its active ingredient a salt of treprostinil that was crystalline before dissolved in the product formulation. Furthermore, it would have been obvious to use the method in claim 1, which itself was obvious for the reasons described above, to create the obvious crystal of claims 2 and 3 of the '070 patent. Claim 11 is also a product-by-process claim that claims the "pharmaceutical composition prepared by combining a pharmaceutically acceptable salt of treprostinil produced according to the method of claim 1 and a pharmaceutically acceptable carrier." For the reasons described for claim 10, claim 11 is rendered obvious by Remodulin® and the other art discussed above. The '222 patent also discloses a salt of treprostinil in a carrier. The patent describes the preparation of tablets. *See id.* at col. 4, ll. 20–col. 5, ll. 2. The preparation of a formulation

"typically" entails mixing a physiologically acceptable salt of a compound of formula (I), for example, with an "acceptable carrier." *See id.* at col. 4, ll. 8-19. The '953 patent discloses the use of nebulizers for administration of treprostinil and a suitable composition for use in nebulizers consisting of "the active ingredient in a liquid carrier, the active ingredient comprising up to 40% w/w of the composition, but preferably less than 20% w/w[,]" with a carrier that "is typically water or a dilute aqueous alcoholic solution." *See* '953 patent at col. 6, ll. 8–19. The '953 patent also teaches that the compounds of the invention are suitable for administration to a mammal, such as a human. *See* '953 patent at col. 2, ll. 48–52.

Plaintiffs have not set forth any evidence of secondary considerations of non-obviousness, and Actavis is not aware of any such secondary considerations that, when considered with the evidence of obviousness, would warrant a finding of non-obviousness of the claims of the '839 patent. If UTC relies on any secondary considerations of non-obviousness, Actavis reserves the right to supplement its contentions.

As explained above, the claims would have been obvious in view of a host of prior art references because the claimed invention was well known and would have been obvious to apply. Consequently, there are numerous different combinations of these prior art references and many exemplary references that teach each standard step. By way of example, the following combinations render the asserted claims obvious:

- Simonneau, the '222 patent, Bighley, the '196 publication, and/or the diethanolamine salts of other drug compounds,
- Simonneau, the '222 patent, the '075 patent, Bighley, the '196 publication, and/or the diethanolamine salts of other compounds,
- The '222 patent, the '075 patent, Bighley, the '196 publication, and/or the diethanolamine salts of other compounds.
- Simonneau, the '222 patent, Bighley or Berge, and/or the diethanolamine salts of other drug compounds,

- Simonneau, the '222 patent, the '075 patent, Bighley or Berge, and/or the diethanolamine salts of other compounds,
- The '222 patent, the '075 patent, Bighley or Berge, and/or the diethanolamine salts of other compounds.
- The '953 patent, the '222 patent, Bighley or Berge, and/or the diethanolamine salts of other compounds
- The '953 patent, Simonneau, Bighley or Berge, and/or the diethanolamine salts of other compounds
- Any of the above combinations with Byrn, Olmsted, Sharp, Shekunov, the '164 patent, and Pavia
- Any of the above combinations with Remodulin and the Remodulin Label

A POSA would have been motivated to combine the teachings of these references with a reasonable expectation of success. In addition, Actavis's invalidity charts set forth where each prior art reference discloses the limitations of the asserted claims.

Actavis reserves the right to set forth additional such examples as discovery continues.

3. Claims 1–11 Are Invalid for Lack of Written Description and Enablement

In the alternative, should the court not find that the asserted claims are obvious, they would fail to meet the written description or enablement requirements. One of skill in the art would not have recognized the applicants to have had, at the time of filing, possession of the full genus of methods and the related treprostinil salt and treprostinil salt composition that the claims recite. *See Ariad Pharm., Inc. v Eli Lilly and Co.*, 598 F.3d 1336, 1353-54 (Fed. Cir. 2010) (en banc) (stating that "the purpose of the written description requirement is to ensure that the scope of the right to exclude, as set forth in the claims, does not over-reach the scope of the inventor's contribution to the field of art as described in the patent specification") (internal quotations omitted).

While it would be obvious to create the diethanolamine salt of treprostinil, the scope of claims 1–11 is not enabled. Further, claims 1–11 do not meet the written description requirement. Claims 1–11 attempts to claim any salt of treprostinil, using any base, any heating, any cooling, and any antisolvent.

Additionally, to the extent that the Court finds that creating the diethanolamine salt of treprostinil was not obvious, it is less likely that the specification of the '311 patent meets the requirements of § 112.

a. Claim 1 does not meet the written description requirement

First, the specification of the '311 patent does not provide written description support for claim 1. At least the following terms of claim 1 encompass a sizeable genus: "pharmaceutically acceptable salt," "solvent," "base," "heating," "cooling," and "antisolvent." The term "pharmaceutically acceptable salt" encompasses at least twenty-seven organic cations and eleven metallic cations. *See* Lyle D. Bighley *et al.*, *Salt Forms of Drugs and Absorption*, *in* 13 *Encyclopedia of Pharmaceutical Technology* (James Swarbrick and James C. Boylan eds., 1996) 453, 456 (providing a table of "Cationic Pharmaceutical Salt Forms Currently in Use"). Both the terms "solvent" and "antisolvent" encompass at least a large number of liquids. The claim encompasses the use of any solvent and any antisolvent, and thus further encompasses the use of any combination of solvent and antisolvent. Further, it encompasses the use of any amount of solvent and antisolvent. The person of ordinary skill in the art would understand the term "base" to encompass at least any base in solid or liquid form, including aqueous solutions of base. It further encompasses the use of any amount of base. The claim does not require that base be added in any specific molar ratio of base to treprostinil. The terms "heating" and "cooling" encompass at least heating to any temperature and cooling to any temperature. Further, the heating and cooling may take place at any rate. In sum, claim 1 encompasses a vast number of

different methods, each of which uses a different combination of materials, quantities, and other parameters.

Claim 1 encompasses not only a broad genus of methods, as discussed above, but also requires a very narrow result in that the treprostinil salt that the recited method yields must be "a crystalline solid."

The specification provides at most only a single example of a preparation of a treprostinil salt.[31] That example reads in full as follows:

> Synthesis of Treprostinil Diethanolamine (UT-15C)
>
> Treprostinil acid is dissolved in a 1:1 molar ratio mixture of ethanol:water and diethanolamine is added and dissolved. The solution is heated and acetone is added as an antisolvent during cooling.

'311 patent at col. 15, ll. 36-41. The specification does not explicitly indicate that a solid is obtained after cooling. Thus, there is no indication that the "synthesis" yields a crystalline solid.[32]

Claim 1 lacks the required written description support. First, the treprostinil diethanolamine synthesis discussed above uses a mixture of water and ethanol as solvent. This indicates that mixtures of solvents, as well as individual solvents, are within the scope of "solvent." Such mixtures could extend to mixtures of more than two solvents, as well as encompassing many two-solvent mixtures in many different ratios. Thus, the example broadens

[31] In contrast, the specification purports to provide numerous examples of syntheses of treprostinil esters. *See* '311 patent at col. 13, l. 51-col. 34, l. 19 (purporting to describe the synthesis of over thirty esters of treprostinil).

[32] As discussed above, the specification discusses at length two crystalline forms of treprostinil diethanolamine and their preparation. *See* '311 patent, col. 64, Tables 15 and 16 and accompanying text. The methods discussed appear to entail mixing treprostinil diethanolamine with a solvent, evaporating the solvent, and collecting the treprostinil diethanolamine. They do not appear to entail the method of claim 1. For example, this discussion does not disclose or mention the use of any antisolvent in general or in particular. Thus, these methods are recrystallizations and do not represent the preparation of treprostinil diethanolamine by dissolving treprostinil in a solvent, adding a base, heating, and adding an antisolvent.

the scope of "solvent" beyond what may be immediately apparent from the claim language itself, and therefore also broadens the scope of claim 1.

Second, this example and the absence of any other examples indicate that, at most, the applicants had in their possession only a single method of making only one salt, treprostinil diethanolamine. As noted above, the claim encompasses all methods of making all pharmaceutically acceptable treprostinil salts by the recited steps, using any solvent (which may be a mixture of solvents), base, and antisolvent. In view of this minimal disclosure and the breadth of claim 1, the person of ordinary skill in the art would not have recognized the patentees as possessing, at the time of filing, all of the methods within the scope of the claim or even methods that are representative of the full scope of the claim. This is because conditions for dissolution and choice of solvent and antisolvent, for example, are empirically determined and not generalizable from a single experiment. Thus, the '311 patent leaves it to the person of ordinary skill in the art to invent additional methods of preparing pharmaceutically acceptable salts of treprostinil using the sequence of steps set forth in the claim. In doing so, the person of ordinary skill in the art would have to determine which solvents or solvent combinations can be used to prepare any particular treprostinil salt, the quantities of treprostinil and each reagent to use, and the heating and cooling parameters. "One needs to show that one has truly invented the genus, *i.e.*, that one has conceived and described sufficient representative species encompassing the breadth of the genus. Otherwise, one has only a research plan, leaving it to others to explore the unknown contours of the claimed genus." *Abbvie Deutschland GmbH & Co. v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1300 (Fed. Cir. 2014); *and see id.* at 1302 (affirming jury verdict of invalidity for lack of written description of the claimed genus and the district court's denial of JMOL on that issue).

Claim 1 should be found to lack written description for the additional reason that the specification does not support the claim's functional requirement that the product of the method be crystalline. The synthesis set forth in the patent, quoted above, does not indicate whether the product is crystalline.

Thus, the specification does not describe the preparation of a crystalline material by the recited method. Even if the sole example in the specification were considered to describe preparation of a crystalline material despite not describing the product as crystalline, that example does not extend beyond the single set of conditions stated. The preparation of a crystalline salt is unpredictable, as the patentees themselves argued during prosecution in order to overcome the asserted prior art. *See* Amendment (August 27, 2014) at 5-10 ("[I]t is unpredictable whether a particular solid form will be a crystalline one or an amorphous one"). In sum, the specification discloses no examples of the preparation of a crystalline treprostinil salt by the claim-recited method. Claim 1 requires that the method yield a crystalline treprostinil salt. Preparing a crystalline treprostinil salt is unpredictable. In view of the lack of disclosure and the unpredictability in preparing a crystalline treprostinil salt, the person of ordinary skill in the art would not have considered the patentees to be in possession of the genus of claim 1-recited methods that yield a crystalline treprostinil salt.

b. Claims 2–9 do not meet the written description requirement

Dependent claims 2–9 should also be found invalid for lack of written description. Dependent claim 2 requires that the base be an inorganic base. The '311 patent's only discussion of preparation of a treprostinil salt uses diethanolamine, an organic base. Thus, the specification provides no discussion at all of the preparation of a treprostinil salt with an inorganic base. In view of the scant disclosure, the breadth of claim 2 in respects other than the base, as set forth with respect to claim 1, and the absence of an example that uses an inorganic base, and,

independently, claim 2's unsupported requirement for a crystalline product, as discussed with respect to claim 1, dependent claim 2 should be found invalid for lack of written description.

The analysis of claim 2 applies equally to claims 3 and 4, which depend from claim 2 and further require that the base is an alkali metal (claim 3) that is either sodium or potassium (claim 4). As for claim 2, the specification provides no example of the preparation of an alkali metal salt of treprostinil, and all of the other elements (including selection of and amounts of solvent and antisolvent, and heating and cooling parameters) remain as broad as for claim 1. Claims 3 and 4, like claim 2, also require that the claimed method yield a crystalline product. Dependent claims 3–4 should be found invalid for lack of written description.

The analysis of claim 1 applies to claim 5, which requires that the base be an organic base. First, the breadth of claim 5 remains nearly as great as the breadth of claim 1, because there are a substantial number of organic bases and because all of the other conditions of the claimed method remain as broad for claim 5 as they are for claim 1. Second, claim 5 requires that the product of the claimed method be crystalline. In view of the claim's breadth and requirement for a crystalline product, and the dearth of disclosure in the '311 patent, as detailed above, claim 5 should be found invalid for lack of written description.

The analysis of claim 5 applies to claim 6, which depends from claim 5 and requires that the organic base be diethanolamine. First, the claim remains much broader than the synthesis set forth in the specification. The claim-recited method and the specification's synthesis both use the same base, but all of the other conditions of the claimed method remain exceedingly broad, as discussed in detail above with respect to claim 1. Further, claim 6 requires that the product of the recited method be crystalline. The specification provides no support for this requirement. For

these two independent reasons—overbreadth and crystalline limitation—claim 5 should be found invalid for lack of written description.

The analysis of claim 3 applies equally to claim 7, which depends from claim 3 and thus requires that the base is an alkali metal and further requires that the solvent "comprises ethanol and water." The specification does not describe any syntheses within the scope of the claim that use an alkali metal salt as the base. Even though the synthesis mentioned in the specification entails dissolving treprostinil in a mixture of ethanol and water, that synthesis yielded an organic salt of treprostinil, not an alkali metal salt of treprostinil, as required by claim 7. There is no indication or basis for believing that the same solvent would succeed in producing an alkali metal salt of treprostinil. Further, the other conditions of the method, such as the antisolvent and heating and cooling parameters, remain as broad as for claim 1. Also, for the reasons set forth above with respect to claim 1, the specification provides no description of a method as recited by claim 7 that yields a crystalline solid, as the claim requires. The person of ordinary skill in the art would not have recognized the patentees as having been in possession, at the time of filing, of the claim-recited genus of methods for producing a crystalline alkali metal salt of treprostinil.

Claim 8 depends from claim 5 and requires that the solvent comprise ethanol and water as well as that the base is an organic base. The reasoning set forth with respect to claim 5 applies to claim 8 in spite of the additional limitation. First, claim 8 lacks written description support at least because it encompasses the use of any organic base, and the specification provides at most a synthesis that uses only one organic base, diethanolamine, and further uses only one antisolvent. The person of ordinary skill in the art would not have recognized the applicants, at the time of filing, to have been in possession of a method of using any organic base to obtain the corresponding organic salt of treprostinil. Each organic base has different properties, including

solubility, which may determine which solvents and antisolvents will be effective, and the ability to form salts with other compounds, such as treprostinil. Second, and independently, as with the preceding claims, the specification does not describe the preparation of a crystalline treprostinil salt using other organic bases within the scope of the claim. Even if the sole example in the specification were considered to describe preparation of a crystalline material despite not describing the product as crystalline, that example does not extend beyond the single set of conditions stated. Thus, there is no written description support for the preparation of other crystalline organic salts of treprostinil.

Claim 9 depends directly from claim 1 and requires that the antisolvent comprise acetone. The '311 patent's only discussion of preparation of a treprostinil salt also uses acetone as an antisolvent. The analysis of claim 1 set forth above applies to claim 9 because claim 9 remains as broad as claim 1 in all other respects, such as encompassing the use of any solvent and any base. As detailed above, the minimal discussion of the corresponding method in the specification does not, for example, describe the full genus of methods of preparing pharmaceutically acceptable treprostinil salts, organic or inorganic, that are within the scope of the claim, or a number of such methods that are sufficient to represent the full genus of methods within the scope of the claim. Also, the specification is deficient with respect to the description of methods that yield crystalline treprostinil salts, as detailed above. Dependent claim 9 should be found invalid for lack of written description.

In sum, because claims 1-9 recite methods that are much broader than the single synthetic method the specification purports to disclose, and because claims 1-9 require that the recited methods' product be crystalline, yet the specification does not even indicate whether that single synthetic method yields a crystalline product, the person of ordinary skill in the art would not

have considered the patentees to be in possession of the full genus of claimed methods. Claims 1–9 should therefore be found invalid for lack of written description.

c. Claims 10–11 do not meet the written description requirement

Independent claims 10–11 should be found invalid for lack of written description for the same reasons as set forth with respect to claim 1. Claims 10 and 11 both claim products that are made by the process of claim 1. They therefore have the same breadth as claim 1 and encompass the same genus of methods. The analysis of claim 1 therefore applies equally to claims 10 and 11. Claims 10 and 11, like claim 1, should be found invalid for lack of written description.

d. Claim 1 is not enabled

Claim 1 should be found invalid for lack of enablement. As detailed above in the written description analysis, claim 1 is very broad. The specification provides, at most, only a single working example for a single species of treprostinil salt, as discussed above. That example does not provide adequate guidance with respect to treprostinil diethanolamine specifically and for treprostinil salts generally. It omits many experimental details, including at least: the quantity of treprostinil acid and the quantity of solvent, either in absolute terms or relative to each other; the quantity of diethanolamine, either in absolute terms or relative to the quantity of treprostinil acid; the temperature to which the mixture is heated; the rate of heating; the quantity of acetone used, in absolute terms or relative to the quantity of solvent, for example; the rate of cooling; the rate at which the acetone is added; whether the mixture is permitted to cool prior to the addition of the acetone; the temperature to which the mixture is cooled. As noted above, the example does not state whether the salt obtained is crystalline. The person of ordinary skill in the art would therefore need to determine all of the experimental details necessary to perform the claimed method at least for those methods within the scope of the claim that do not entail preparing treprostinil diethanolamine. Such methods encompass at least methods for preparing treprostinil

salts other than the diethanolamine salt. And even for the preparation of crystalline treprostinil diethanolamine, the person of ordinary skill in the art would have to determine at least those experimental details that the patent omits.

In addition, the state of the art at least with respect to methods for preparing treprostinil salts was not advanced. As the applicants argued during prosecution, the prior art provided no examples of preparation of a solid treprostinil salt. The applicants argued further that whether any compound even can exist in solid form "cannot be predicted" from knowledge of the compound's existence in solution. *See* Amendment (November 15, 2013) at 6–7. Further, as noted above, the preparation of crystalline treprostinil salts, as required by the claim, is unpredictable.

In sum, in view of claim 1's breadth, the specification's provision of little guidance with respect to performing the method and, at most, a single, incomplete example, the primitive state of the art of preparing treprostinil salts, and the unpredictability of preparing crystalline treprostinil salts, the '311 patent specification would not have enabled the person of ordinary skill in the art, at the time of filing, to perform the full scope of the method of claim 1 to obtain the required crystalline product. Therefore, claim 1 should be found invalid for lack of enablement.

e. Claims 2-9 are not enabled

Dependent claims 2-9 should also be found invalid for lack of enablement. Dependent claim 2 requires that the base be an inorganic base. The analysis of independent claim 1 applies to claim 2. Even though the breadth of claim 2 is narrower than that of claim 1 with respect to the base, the specification does not provide enabling support. The '311 patent's only discussion of preparation of a treprostinil salt uses diethanolamine, an organic base. Thus, the specification provides no example or guidance at all for the preparation of a treprostinil salt with an inorganic

base. At least in view of the scant disclosure, including the absence of an example that uses an inorganic base, the breadth of claim 2 in respects other than the base, as set forth with respect to claim 1, the unpredictability of preparing a crystalline salt, and the primitive state of the art, dependent claim 2 should be found invalid for lack of enablement.

The analysis of claim 2 applies equally to claims 3 and 4, which depend from claim 2 and further require that the base is an alkali metal (claim 3) that is either sodium or potassium (claim 4). As for claim 2, the specification provides no example of the preparation of an alkali metal salt of treprostinil, and all of the other elements (including selection of and amounts of solvent and antisolvent, and heating and cooling parameters) remain as broad as for claim 1. Claims 3 and 4, like claim 2, also require that the claimed method yield a crystalline product. Dependent claims 3–4 should be found invalid for lack of enablement.

The analysis of claim 1 applies to claim 5, which requires that the base be an organic base. First, the breadth of claim 5 remains nearly as great as the breadth of claim 1, because there are a substantial number of organic bases and because all of the other conditions of the claimed method remain as broad for claim 5 as they are for claim 1. Second, claim 5 requires that the product of the claimed method be crystalline. In view of the claim's breadth and unpredictability with respect to preparing a crystalline product, and the dearth of guidance and examples in the '311 patent, and the primitive state of the art, as detailed above, claim 5 should be found invalid for lack of enablement.

The analysis of claim 5 applies to claim 6, which depends from claim 5 and requires that the organic base be diethanolamine. First, the claim remains much broader than the synthesis set forth in the specification. The claim-recited method and the specification's synthesis both use the same base, but all of the other conditions of the claimed method remain exceedingly broad, as

discussed in detail above with respect to claim 1. For example, the claim purports to encompass methods that use solvents other than a mixture of ethanol and water and antisolvents other than acetone, but, for any such method, the person of ordinary skill in the art would have to determine all of the experimental details. The person of ordinary skill in the art essentially would have to invent the method that the patentees claim if Plaintiffs are correct that the claims are not obvious. Further, claim 6 requires that the product of the recited method be crystalline. The specification does not enable this requirement at least because it provides no examples or guidance for obtaining crystalline treprostinil diethanolamine for methods that use solvents other than a mixture of ethanol and water and antisolvents other than acetone, which are within the scope of the claim. Claim 6 should be found invalid for lack of enablement.

The analysis of claim 3 applies equally to claim 7, which depends from claim 3 and thus requires that the base is an alkali metal and further requires that the solvent "comprises ethanol and water." The specification provides no discussion or examples of any syntheses within the scope of the claim that use an alkali metal salt as the base. Even though the synthesis mentioned in the specification entails dissolving treprostinil in a mixture of ethanol and water, that synthesis yielded an organic salt of treprostinil, not an alkali metal salt of treprostinil, as required by claim 7. There is no indication or basis for believing that the same solvent would succeed in producing an alkali metal salt of treprostinil, or that such a salt would be crystalline. Further, the other conditions of the method, such as the antisolvent and heating and cooling parameters, remain as broad as for claim 1. The specification does not enable the genus of methods that claim 7 encompasses.

Claim 8 depends from claim 5 and requires that the solvent comprise ethanol and water as well as that the base is an organic base. The reasoning set forth with respect to claim 5 applies

to claim 8 in spite of the additional limitation. Claim 8 is not enabled at least because it encompasses the use of any organic base, and the specification provides at most a synthesis that uses only one organic base, diethanolamine, and further uses only one antisolvent. The specification does not provide examples or guidance at least for methods of using other organic bases to obtain other organic salts of treprostinil. Each organic base has different properties, such as solubility, which may determine which solvents and antisolvents will be effective, and such as the ability to form salts with other compounds, like treprostinil. Further, the specification does not provide examples or guidance with respect to the preparation of other crystalline treprostinil salts within the scope of the claim. Even if the sole example in the specification were considered to enable preparation of a crystalline material despite not describing the product as crystalline, that example does not extend beyond the single set of conditions stated. This does not amount to enabling guidance in an unpredictable art, which is how the applicants characterized it during prosecution.

Claim 9 depends directly from claim 1 and requires that the antisolvent comprise acetone. The '311 patent's only discussion of preparation of a treprostinil salt also uses acetone as an antisolvent. The analysis of claim 1 set forth above applies to claim 9 because claim 9 remains as broad as claim 1 in all other respects, such as encompassing the use of any solvent and any base. As detailed above, the minimal discussion of the corresponding method in the specification does not, for example, enable the full genus of methods of preparing pharmaceutically acceptable treprostinil salts, organic or inorganic, that are within the scope of the claim. Also, the specification is deficient with respect to the description of methods that yield crystalline treprostinil salts, as detailed above. Dependent claim 9 should be found invalid for lack of enablement.

f. Claims 10–11 are not enabled

Independent claims 10–11 are invalid for lack of enablement for the same reasons as set forth with respect to claim 1. Claims 10 and 11 both claim products that are made by the process of claim 1. They therefore have the same breadth as claim 1 and encompass the same genus of methods. The analysis of claim 1 therefore applies equally to claims 10 and 11. Claims 10 and 11, like claim 1, are invalid for lack of enablement.

H. Invalidity of the '897 Patent

1. Claims 1–60 of the '897 Patent Are Obvious Based on the Following Prior Art.

a. WO 2005/007081

WO 2005/007081 ("the '081 publication") was published on January 27, 2005, and thus qualifies as prior art to the '897 patent under at least 35 U.S.C. § 102(b). The '081 publication names United Therapeutics Corporation as the applicant. *See* '081 publication, cover page. In brief, as detailed below, the '081 publication discloses treprostinil diethanolamine, that treprostinil diethanolamine is a preferred embodiment of the disclosed subject matter, treprostinil diethanolamine's utility as an antihypertensive agent, and the delivery of treprostinil diethanolamine to human patients in a sustained-release, oral, 1 mg tablet.

The '081 publication specifically discloses and describes the preparation of treprostinil diethanolamine. *See* '081 publication at 9 ("A preferred embodiment of the present invention is the diethanolamine salt of treprostinil."), 22.

The '081 publication indicates that, at the time, there was clinical interest in developing an orally administered treprostinil formulation. The available treprostinil formulation, marketed as the Remodulin® product, was administered subcutaneously, which has various disadvantages, including patient discomfort. *See id.* at 2.

The '081 publication discloses results from clinical studies with different oral formulations of treprostinil diethanolamine. One study compared the administration of four oral "immediate release" solutions containing 0.05, 0.125, 0.25, or 0.5 mg treprostinil diethanolamine (presumably the dosages were the amount of treprostinil diethanolamine that is equivalent to 0.05, 0.125, 0.25, or 0.5 mg treprostinil).[33] Four doses were administered, one every two hours. The plasma concentration of treprostinil was measured and appears as a series of four peaks spaced at two-hour intervals. *See* '081 publication at 82-84 and Figures 13A-13D.

A second study entailed administration of a solid, oral, sustained-release tablet formulation that contained treprostinil diethanolamine in the amount either of 1 mg or that amount that is equivalent to 1 mg treprostinil, and a comparable capsule formulation that contained microparticulate beads. *See id.* at 84-85. The tablet and the capsule were designed to release treprostinil diethanolamine over approximately eight hours. One tablet or capsule was administered to each subject. Administration to fed subjects was compared to administration to fasted subjects. *See id.* at 84. All four study sections (tablet/fed, tablet/fasted, capsule/fed, capsule/fasted) showed sustained elevated serum concentrations of treprostinil. *See id.* at Figure 14. "These results demonstrate that detectable and potentially therapeutic drug concentrations can be obtained from a solid dosage form of UT-15C [treprostinil diethanolamine] and that these concentrations can be maintained over an extended period of time through sustained release formulation technology." *Id.* at 85; *see also id.* at 82 (indicating that "UT-15C" refers to

[33] In the '081 publication, referral to an integral amount of drug or to an amount of drug evenly divisible by 5, such as 1.0 or 0.5 mg, usually refers to the amount of treprostinil. For example, in Example 1, an amount of treprostinil diethanolamine was used that is equivalent to 12.0 mg treprostinil, in Example 2, the listed amounts of treprostinil esters are those that are equivalent to 0.5 mg/kg of treprostinil, and in Example 3, the concentrations of treprostinil derivatives that were used were equivalent to 0.5 mg/ml treprostinil. *See* '081 publication at 58, at 67, Table 6, and at 73-74. We assume this to be the practice even where not stated explicitly.

treprostinil diethanolamine).[34] The '081 publication does not disclose the formulation ingredients.

During prosecution of the application that issued as the '897 patent, the Applicants mischaracterized the '081 publication by stating, with respect to the disclosed tablets, that the disclosure "only recite[s] that there is a tablet prototype and a capsule prototype containing microparticulate beads (*see* page 84) without any further characterization of the tablet or capsule anywhere in the disclosure of Phares [WO2005/007081]." Amendment (January 10, 2014) at 14-15; *see also id.* at 11, Office Action (September 10, 2013) at 3 (indicating that "Phares" refers to the '081 publication). "[N]othing in the generic disclosure, which is also admitted by the Office Action, points to an oral osmotic delivery system." Amendment at 15.

In fact, as noted above, the '081 publication indicates that the tablet was of the sustained-release variety, was orally administered, and contained 1 mg treprostinil diethanolamine. It also discloses that the tablets were administered to humans in a clinical study and provides significant pharmacokinetic information relating to that administration.

b. WO 98/18452

WO 98/18452 ("the '452 publication") was published in 1998 and therefore is at least 35 U.S.C. § 102(b) prior art to the '897 patent. This application (or related applications and patents)

[34] The person of ordinary skill in the art would have understood "sustained release" as used in the '081 publication to be interchangeable with "extended release" and thus to refer to a class of dosage forms that encompasses osmotic dosage forms. Here, the "sustained release" tablets were administered once and provided treprostinil diethanolamine for eight hours, whereas the "immediate release" formulations had to be administered four times to provide treprostinil diethanolamine for eight hours. The sustained-release dosage form thus permitted a reduction in dosing frequency relative to the immediate release dosage form. *See, e.g.*, Loyd V. Allen, Jr. *et al.*, *Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems* 262 (8th ed. 2005) (hereinafter "Ansel (2005)") (stating that "sustained release," "extended release," and other terms are often used interchangeably and that, according to U.S. FDA definitions, extended release forms permit a reduction in dosing frequency from that required by a conventional dosage form); *see also id.* at 263, 267-68 (listing osmotic pump delivery systems as within the class of extended-release oral dosage forms).

was not before the Examiner during prosecution of the '100 application.[35] The '452 publication provides extended release compositions and points out their advantages:

> In arriving at the present invention it has been discovered that it is possible to efficiently deliver therapeutically effective doses, at controlled rates and for extended times, of a broad variety of drugs without the need for polymers that swell or expand within the tablet wall so as to physically force the medicament particles out into their intended environment of use.

'452 publication at 2. *See also id.* at 9 ("The delivery system of the invention can be used to provide controlled release of any of a broad variety of therapeutically active agents."). The advantages of extended release at a controlled rate would have been particularly attractive for a drug like treprostinil, which has a relatively short half-life and is administered in low doses for a chronic condition. Specifically, treprostinil is indicated for the treatment of pulmonary arterial hypertension, a chronic condition, has "a terminal half-life of approximately 2-4 hours," and is administered at doses ranging, for a 70 kg person, from an initial dose of about 0.13 mg/day to not more than about 4 mg/day. *See* Remodulin® Label (2002) at 5, 9-10; *see also* Ansel (2005) at 263 (drugs best-suited for extended release have certain characteristics, including having a low dosage and being administered to treat chronic conditions).

The '452 publication discloses a generic osmotic formulation that comprises, among other things, a pharmaceutically active agent, a non-swelling solubilizing agent, and a non-swelling wicking agent.

> [I]n one aspect, the invention provides an osmotic pharmaceutical delivery system comprising (a) a semipermeable wall that maintains its integrity during pharmaceutical delivery and which has at least one passage therethrough; (b) a single, homogeneous composition within said wall, which composition contains (i) a pharmaceutically active agent, (ii) at least one non-swelling solubilizing agent which enhances the solubility of the pharmaceutically active agent; (iii) at

[35] The '897 patent mentions certain Rudnic patents related to the '452 publication but characterizes the disclosure as limited to compositions for enhancing the solubility of glipizide, a poorly soluble drug. *See* '897 patent at col. 1, l. 63-col. 2, l. 11. The applicants did not list these references in any of their information disclosure statements and they are not listed on the face of the '897 patent.

> least one non-swelling osmotic agent and (iv) a non-swelling wicking agent dispersed throughout the composition which enhances the surface area contact of the pharmaceutical agent with the incoming aqueous fluid. The pharmaceutical agent is thus released in a predominantly soluble form.

'452 publication at 3. The disclosed system is preferably in the form of a tablet. *See id.* at 2.

As noted above, the disclosed delivery system "can be used to provide controlled release of any of a broad variety of therapeutically active agents." *Id.* at 9. Among various examples, the '452 publication identifies specifically a number of substantially water-soluble salts of active agents that the system can be used to deliver (without referring to the solubility of each active). These include chlorpheniramine maleate (water solubility 160 mg/ml), brompheniramine maleate ("sol in water"), verapamil hydrochloride (water solubility 70 mg/ml), metoprolol succinate (freely soluble in water), and metoprolol tartrate (very soluble in water). *See* '452 publication at 9 (listing examples of actives); for solubilities, *see Merck Index* 337, 218, 1563-64 (Susan Budavari ed., 11th ed. 1989) and *European Pharmacopoeia* 2032 and 2034 (2005), respectively. Other specifically listed actives that the disclosed delivery system can deliver are water-insoluble salts (e.g., dextromethorphan hydrobromide, enalapril maleate, diclofenac sodium) and water-insoluble non-salts (e.g., carbamazepine, acyclovir). *See* '452 publication at 9. Thus, although the '452 publication elsewhere states that, "[i]n accordance with the preferred invention, there is provided an osmotic delivery system, preferably in the form of a tablet, which dispenses a therapeutic agent having a limited solubility in water or physiological environments," '452 publication at 2,[36] it is not limited to such therapeutic agents, as it also explicitly discloses that the disclosed composition is suitable for delivery of water-soluble salts of therapeutic agents, including salts of anti-hypertensive agents. This class includes treprostinil diethanolamine. In

[36] *See also* '452 publication at 9 ("The system of the present invention is particularly applicable to therapeutic agents which are insoluble or poorly soluble in water or aqueous environments at physiological pH.").

sum, the disclosed system is useful for both water-soluble salts of active ingredients and for active ingredients with relatively lower water solubility.

The '452 publication would be relevant prior art even if it were found to be limited to actives "having a limited solubility in water or physiological environments" or "which are insoluble or poorly soluble in water or aqueous environments at physiological pH." '452 publication at 2, 9. Treprostinil diethanolamine is a salt of a carboxylic acid. *See* '081 publication at 8. Carboxylic acids are weak acids. *See, e.g.*, Andrew Streitwieser, Jr. and Clayton H. Heathcock, *Introduction to Organic Chemistry* 501 (2d ed. 1981) ("Streitwieser") (stating that "compounds containing the functional group [–C(O)OH] are weakly acidic"), 502 (characterizing carboxylic acids as "relatively weak acids"). The person of ordinary skill in the art would have expected treprostinil diethanolamine, the salt of a weak acid, to have low solubility at low (acidic) pH, such as is found in the stomach. *See* Ansel (2005) at 103 ("a soluble salt of a weak acid will precipitate as the free acid in the bulk phase of an acidic solution, such as gastric fluid").[37] The '897 patent acknowledges that known extended release osmotic tablets "function by allowing water from gastric or intestinal fluid, to flow through the semi-permeable membrane and dissolve the active ingredient." The '897 patent at col. 1, ll. 19-23. Thus, the '452 publication is "particularly applicable" to treprostinil diethanolamine.[38]

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[37] Gastric fluid has a pH of about 1. *See* Howard C. Ansel et al., Pharmaceutical Dosage Forms and Drug Delivery Systems 105 (7th ed. 1999) (hereinafter "Ansel (1999)"). At such a pH, treprostinil diethanolamine would be expected to have very low solubility because the treprostinil acid would be in its un-ionized form. Specifically, when the salt of a weak acid dissolves to yield the acid and salt ions, the ionization state of the acid will depend on the pH of the surrounding solvent. In a relatively acidic environment (pH=1), the acid will be almost entirely in the un-ionized state (that is, it will retain its proton). In the un-ionized form, the acid will precipitate. *See* Ansel (1999) at 104-105.

[38] The Examiner thus should not have been persuaded by the patentees' assertion during prosecution that the person of ordinary skill in the art would not consider enhancing the solubility of treprostinil diethanolamine by including, for example, SLS in a treprostinil diethanolamine formulation, because, for example, the prior art did not teach or suggest that treprostinil diethanolamine needed solubility enhancement (*see* Reply at 18-19 (January 10, 2014)). Rather, prior art disclosures relating to improving solubility of low-solubility drugs are in fact relevant to treprostinil diethanolamine. As discussed above, the person of ordinary skill in the art would have expected treprostinil

The '452 publication specifically identifies sodium lauryl sulfate as a suitable solubilizing agent and as a suitable wicking agent. Regarding solubilizing agents, "[p]referred non-swelling solubilizing agents include" "long chain anionic surfactants, particularly sodium lauryl sulfate." *Id.* at 8. Regarding the wicking agent, "[t]he function of the wicking agent is to carry water to surfaces inside the core of the tablet, thereby creating channels or a network of increased surface area." Sodium lauryl sulfate is "particularly suitable for the purpose of this invention." *Id.* at 7-8.

The publication further discusses the other components of the disclosed composition. "Preferred non-swelling osmotic agents include" fructose, lactose, xylitol, and sorbitol. *Id.* at 3. Triethyl citrate ("TEC") is a suitable plasticizer for use with a semipermeable, polymeric coating material such as cellulose acetate. *See id.* at 6.

The '452 publication further discloses a general method for preparing such a composition as coated tablets. *See id.* at 10-13, Example 1.

As examples of the disclosed composition, the '452 publication sets forth 45 specific formulations, all of which contained nifedipine as the active ingredient. *See id.* at 14-19, Tables 1–6. The dissolution profiles of 12 of these were measured in simulated gastric fluid over a period of twenty to twenty-four hours and compared to the marketed nifedipine product Procardia XL 30 mg or 60 mg. *See id.* at 20-21 and Figures 3-8. Procardia XL consistently released over 90% of nifedipine after 24 hours. Of the test compositions, at least compositions 2C and 2D had endpoints comparable to that of Procardia XL (releasing about 110% and about 90% of the drug, respectively). *See id.* at Figure 4. Both of these test compositions contained 5% sodium lauryl sulfate. *See id.* at 15, Table 2.

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diethanolamine, by virtue of its chemical structure, to have low solubility under physiological conditions, such as in the low-pH environment of the stomach.

c. U.S. Publication No. 2001/0038855

U.S. Publication No. 2001/0038855 ("the '855 publication") was published in 2001 and therefore is at least 35 U.S.C. § 102(b) prior art to the '897 patent. The '855 publication recognizes the problem of incomplete release of drug from prior art sustained/extended release dose forms, and that this may arise from stickiness of an excipient in the presence of fluid that enters the dosage form, or failure to hydrate of an excipient intended to transport the drug. *See* '855 publication ¶¶ 0003–04 (discussing prior art dosage forms for "delivering a drug to aqueous environment including biological fluids over time" and "controlled release" dosage forms), ¶ 0005. The '855 publication therefore discloses including in a "sustained-release dosage form" a drug and a means for aiding delivery of the maximum dose of the drug or for reducing the amount of drug retained in the dosage form. *See id.* ¶¶ 0009–10. The inclusion of a surfactant and a salt provides a means to improve drug delivery and reduce the amount of residual drug in the composition:

> Another object of the invention is to provide a therapeutic composition for delivering a beneficial drug to be administered as the composition, or for incorporating the composition into a dosage form, which composition in either application comprises a drug, a pharmaceutically acceptable salt, and a pharmaceutically acceptable surfactant which pharmaceutically acceptable salt and the pharmaceutically acceptable surfactant improves the amount of drug delivered by reducing the residual drug remaining in the composition and in the dosage form after twenty-four hours of drug delivery.

Id. ¶ 0014.

> The surfactant functions to increase the water solubility of constituents in the therapeutic composition, the surfactant reduces interfacial tension between constituents, the surfactants enhances the free-flow and delivery of constituents, and the surfactant lessens the incidence of constituent retention in a dosage form. The surfactants useful for the purpose of this invention comprise amphoteric surfactants, anionic surfactants, cationic surfactants and nonionic surfactants.

Id. ¶ 0027.

"The concentration of surfactant in a therapeutic composition is 0.01 mg to 25 mg, in operation 0.01 mg to 5 mg, or 1 wt % to 7.5 wt %." *Id.*

The composition is an osmotic composition. *See, e.g.*, *id.* ¶ 0018 ("Another object of the invention is to provide a dosage form manufactured as a pharmaceutically acceptable controlled-release oral tablet comprising a single composition possessing osmotic properties and can be manufactured by conventional compression and coating techniques."), ¶ 0035 ("The exit means comprises at least one passageway" "that provides for the osmotic controlled release of oxybutynin."), ¶ 0060 ("The therapeutic composition in the dosage form develops osmotic energy that causes the therapeutic composition to be administered through the exit (D) from the dosage form over a prolonged period of time up to 24 hours").

The active drug may be selected from a variety of different therapeutic classes of drug, including cardiovascular drugs. *See id.* ¶ 0021. The '855 publication focuses on oxybutynin and its salts, and specifically the hydrochloride salt. *See id.* ¶ 0022. Oxybutynin hydrochloride has a water-solubility of at least 50 mg/ml. *See, e.g.*, Sigma-Aldrich, Oxybutynin hydrochloride information sheet at 1 (50 mg/ml), U.S. Publication No. 2004/0170684 at ¶ 0026 (stating that oxybutynin (understood to refer to oxybutynin hydrochloride[39]) is a "highly soluble drug"), ¶ 0049 (defining "highly soluble" as having an aqueous solubility of more than about 100 grams per liter). The '855 publication thus recognizes and discloses that a water-soluble salt of a drug might not be fully released from a sustained-release composition, and recommends generally

[39] The '684 publication is directed to solving a problem associated with highly soluble drugs, and all of the exemplary oxybutynin compositions contain oxybutynin hydrochloride. *See* '684 publication ¶¶ 0011, 0027, and, *e.g.*, ¶¶ 0226-0227 (Tables 36-37), 0233-0234 (Tables 40-41) We therefore understand the '684 publication to refer to oxybutynin hydrochloride, and not free oxybutynin, when it characterizes oxybutynin hydrochloride as highly soluble. This is consistent with salts of organic drug compounds typically being more soluble than the free form of the drug compound.

incorporating a surfactant into drug-containing, sustained-release compositions to optimize delivery of the drug.

Example 2 discloses the preparation of a composition that contains oxybutynin hydrochloride and, as surfactant, 1% by weight of polyoxyethylene sorbitan monooleate comprising 20 moles of ethylene oxide (marketed under the name Tween™ 80) "for administering oxybutynin over twenty four hours." *See id.* ¶ 0048; *see also id.* ¶ 0027 (listing as surfactants various Tween™s and their chemical descriptions). Example 5 discloses preparation of a "medical device with a sustained-release profile" using the composition of Example 2. The device includes a semipermeable wall with a 0.51 mm orifice. *See id.* ¶¶ 0051-0053. The device had a shorter start-up delivery time (1.57 hours) and delivered more drug (91.6%) than a device lacking surfactant (1.86 hours, 89.8%). *See id.* ¶ 0054. Examples 6-8 disclose similar exemplary oxybutynin hydrochloride dosage forms. Example 8 specifically identifies the device as "an oral dosage form tablet." *See id.* ¶¶ 0055-0057. The compositions can be administered to a human patient in need of oxybutynin therapy. *See id.* ¶ 0060.

d. U.S. Patent No. 6,706,283

U.S. Patent No. 6,706,283 ("the '283 patent") issued in 2004 and is therefore at least 35 U.S.C. § 102(b) prior art to the '897 patent. The '283 patent discloses an osmotic composition that comprises a drug- and osmotic-agent-containing core, and a coating. *See* '283 patent at col. 3, ll. 57-61. The core can further contain a solubility-enhancing agent, which can be a surfactant. *See id.* at col. 3, ll. 61-62, col. 12, ll. 20-23.

The drug of the composition "is a 'low-solubility drug,' meaning that the drug has a minimum aqueous solubility of about 40 mg/mL or less at a physiologically relevant pH (e.g., pH 1-8)." '283 patent at col. 6, ll. 5-7. "In general, it may be said that the drug has a dose-to-aqueous solubility ratio greater than about 5 mL, where the drug solubility is the minimum value

observed in any physiologically relevant aqueous solution, including unbuffered water and USP simulated gastric and intestinal buffered solutions." *Id.* at col. 6, ll. 14-19 (emphasis added). (A drug that has a dosage of 10 mg and a solubility of 2 mg/ml, for example, has a dose-to-aqueous solubility ratio of 5 ml.) The solubility to be considered in determining whether a drug is "low-solubility" is the minimum solubility observed in relevant solutions. In the case of treprostinil diethanolamine to be administered orally, one relevant solution would be gastric juice, which has a pH of about 1. *See* Ansel (1999) at 105. As discussed above, at such a pH, treprostinil diethanolamine would be expected to have very low solubility because the treprostinil acid would be in its un-ionized form. The '283 patent's disclosure of formulations for low solubility drugs is therefore relevant to treprostinil diethanolamine.

The drug may be an antihypertensive agent. *See id.* at col. 6, ll. 34-35. Specific examples of the drug that may be present in the composition include alprostadil (prostaglandin E_1) (a vasodilator), prostacyclin (a platelet inhibitor), also known as epoprostenol, and enalaprilic acid (an antihypertensive agent like treprostinil; enalaprilic acid is "slightly soluble in water"[40]). Alprostadil, prostacyclin and enalaprilic acid, like treprostinil, are carboxylic acid compounds. *See id.* at col. 7, ll. 31-34, http://chem.sis.nlm.nih.gov/chemidplus. Treprostinil is a chemically stable analog of prostacyclin. '081 publication at 2. Further, the drug may be used in the form of a pharmaceutically acceptable salt. *See id.* at col. 6, ll. 30-31.

"The core may also include solubility-enhancing agents that promote the water solubility of the drug, present in an amount ranging from about 5 to about 50 wt %. Examples of suitable solubility-enhancing agents include surfactants." '283 patent at col. 12, ll. 20-23.

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[40] *See* USP Medicines Compendium, Enalaprilat: Final Authorized Version 1.0 (posted September 27, 2013) (*see* https://mc.usp.org/monographs/enalaprilat-1-0 (last visited February 4, 2015)). U.S. Patent No. 4,374,829 (issued February 22, 1983) discloses enalaprilic acid (*see* Examples 24 and 25, col. 17, l. 25-col. 18, l. 2).

> In some cases, it is also desirable to enhance the solubility of the drug within the dosage form to increase the rate of release from the dosage form or to improve the absorption of drug in the colon. In such cases, the invention may be applied to drugs with solubility as high as 20 to 40 mg/mL.

Id. at col. 6, ll. 20-24. The '283 patent specifically identifies sodium lauryl sulfate as an example of an additive or excipient that the core may contain. *See id.* at col. 11, ll. 66-67 and col. 12, l. 14. At the time of filing, the person of ordinary skill in the art recognized SLS as a surfactant. *See Handbook of Pharmaceutical Excipients* 568 (Raymond C. Rowe *et al.* eds., 4th ed. 2003).

e. Ansel (2005)

Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems was published in 2005 and is § 102(b) or § 102(a) prior art to the '897 patent. As described above, Ansel (2005) describes the benefits of extended-release dosage systems. Ansel 1999 is at least § 102(b) prior art to the '897 patent.

f. Berge et al., *Pharmaceutical Salts,* Journal of Pharmaceutical Sciences, 66, 1-19 (1977)

Berge was published in 1977 and is at least § 102(b) prior art. Berge discloses the diethanolamine salt as an FDA-approved commercially marketed salt that was "potentially useful." *See* p. 2, Table I. Berge also discloses that it was known that different salts of the same drug typically differ based on physical properties, not pharmacologically. *See* p. 5. Berge also discusses properties of various salts, including solubility and the difference between solubilities of different salt forms with the same compound as a free acid or base, the influence of pH on the solubility of pharmaceuticals, and bioavailability. pp. 4–10.

g. U.S. Patent No. 6,521,212

U.S. Patent 6,521,212 ("the '212 patent"), titled "Method for Treating Peripheral Vascular Disease by Administering Benzindene Prostaglandins by Inhalation," is dated February 18, 2003. It is at least § 102(b) art to the '897 patent. The '212 patent discloses a method of

delivering such prostaglandins, including treprostinil, identified as UT-15, via inhalation. Abstract. The '212 patent discloses sustained-release formulations of UT-15. col. 4, l. 54. During prosecution, the patent examiner even remarked during the prosecution of the '212 patent that "[s]ustained or pulse-released forms of prostaglandins are not novel, absent evidence to the contrary." Office Action dated July 12, 2001 at p.2.

2. Claims 1–19, 40–43, and 48–60 Are Obvious

a. Claim 1 Is Obvious Over the Combination of the '452 and '081 Publications

Claim 1 of the '897 patent should be found invalid as obvious over the combination of the '452 and '081 publications. Consideration of the '283 patent and '855 publication reinforces this conclusion. The claim elements and exemplary prior art disclosures are set forth in the table below.

Elements of Claim 1	Prior Art Disclosure
oral osmotic pharmaceutical dosage form	**'452 publication:** • osmotic pharmaceutical delivery system (at 3) • the "present invention relates" to dose delivery systems, "particularly preparations which can be administered orally" (at 1) • tablet is the preferred form of the disclosed osmotic delivery system (at 2) **'283 patent:** • an osmotic composition that comprises a drug- and osmotic-agent-containing core (col. 3, ll. 57-61) **'081 publication:** • solid, oral, sustained-release tablet formulation (at 82, 84-85) **'855 publication:** • osmotic oral tablet composition (¶¶ 0018, 0035, 0060)
osmotically active drug core	**'452 publication:** the osmotic pharmaceutical delivery system comprises a single, homogeneous composition within a semipermeable wall (at 3) **'283 patent:** • an osmotic composition that comprises a drug- and osmotic-agent-containing core (col. 3, ll. 57-61)

Elements of Claim 1	Prior Art Disclosure
surrounded by a semi-permeable membrane	**'452 publication:** single, homogeneous composition within a semipermeable wall (at 3) **'283 patent:** the osmotic composition also comprises a coating that is water permeable and does not dissolve or erode in the environment of use that comprises a drug- and osmotic-agent-containing core (col. 3, ll. 57-58 & 62-65) **'855 publication:** • composition is surrounded by a semi-permeable wall (¶ 0031)
drug core comprises at least one release enhancing agent selected from a group that includes SLS	**'452 publication:** • the composition within the wall contains a solubilizing that "enhances the solubility of the pharmaceutically active agent" (at 3) • the composition contains a wicking agent that "enhances the surface area contact of the pharmaceutical agent with the incoming aqueous fluid" to release the agent "in a predominantly soluble form" (at 3) • The non-swelling osmotic agent can be fructose, lactose, xylitol, or sorbitol. Wicking agents may be colloidal silicon dioxide and polyvinyl pyrrolidone in addition to SLS (3–4, 7–8) • the solubilizing agent can be SLS. Numerous other potential agents are listed. (at 8) **'283 patent:** • the core can further contain a solubility-enhancing agent, which can be a surfactant (col. 3, ll. 61-62, col. 12, ll. 20-23) • the core can contain SLS or a variety of other listed components (col. 12, ll. 2–34) **'855 publication:** • composition comprises an anionic surfactant (¶ 0027)

Elements of Claim 1	Prior Art Disclosure
drug core comprises treprostinil diethanolamine	**'452 publication:** • the composition within the wall contains a pharmaceutically active agent (at 3) • the active can be "any of a broad variety of therapeutically active agents," including "antihypertensives" (at 9) • exemplary actives include water-soluble salts such as chlorpheniramine maleate, brompheniramine maleate, verapamil hydrochloride, metoprolol succinate, and metoprolol tartrate (at 9) (*see supra*, discussion of '452 publication, for solubility references) • the system can be used to deliver actives that "are insoluble or poorly soluble in water or aqueous environments at physiological pH" (at 9) **'283 patent:** • the drug of the composition may be an antihypertensive agent (col. 6, ll. 34-35) • the drug of the composition may be alprostadil (prostaglandin E1) (a vasodilator), prostacyclin (a platelet inhibitor), also known as epoprostenol, and enalaprilic acid (an antihypertensive agent) (col. 7, ll. 31-34) • the drug may be used in the form of a pharmaceutically acceptable salt. (col. 6, ll. 30-31) **'081 publication:** • the sustained-release tablet formulation contained treprostinil diethanolamine (at 82, 84-85) • treprostinil diethanolamine is a "particularly preferred" antihypertensive agent: • a "particularly preferred" compound for use in treating pulmonary hypertension is the diethanolamine salt of treprostinil (*see* '081 publication at 4, 9) • treprostinil is a carboxylic acid ('081 publication at 8), which is a weak acid[41] **'855 publication:** • composition comprises an active ingredient that can be a cardiovascular drug (¶ 0021)

[41] *See, e.g.*, Andrew Streitwieser, Jr. and Clayton H. Heathcock, Introduction to Organic Chemistry 501 (2d ed. 1981) (stating that "compounds containing the functional group [–C(O)OH] are weakly acidic"), 502 (characterizing carboxylic acids as "relatively weak acids").

Elements of Claim 1	Prior Art Disclosure
semi-permeable membrane includes at least one opening suitable for providing the osmotic delivery of the treprostinil from the drug core	**'452 publication:** the semipermeable wall maintains its integrity during pharmaceutical delivery and has at least one passage therethrough (at 3) **'283 patent:** • the coating "has at least one delivery port therein" (col. 3, ll. 62-64) **'855 publication:** • In an embodiment, "[t]he wall comprises an exit passageway to provide for the continuous release of drug." (¶ 0021); *see also* ¶¶ 0037

At the time of filing, the person of ordinary skill in the art would have been motivated to include treprostinil diethanolamine in the generic composition of the '452 publication or to modify one of its disclosed SLS-containing exemplary compositions by substituting the '081 publication's treprostinil diethanolamine for nifedipine. In both cases, the resulting composition would have been within the scope of claim 1. That is, it would have been an oral osmotic pharmaceutical dosage form that contains treprostinil diethanolamine and comprises an osmotically active drug core surrounded by a semi-permeable membrane, wherein the core contains SLS and the membrane has at least one opening suitable for osmotic delivery of the drug from the core.

In both cases, the motivation derives from several sources. The '452 publication discloses that the generic composition can be used to deliver "any of a broad variety of therapeutically active agents." '452 publication at 9. These include antihypertensives, a class that encompasses treprostinil diethanolamine. *See id.* The disclosed composition is suitable for actives that have low solubility in a physiological environment. Such actives include treprostinil diethanolamine, which, being a salt of a carboxylic acid, the person of ordinary skill in the art would have recognized as having low solubility in the low-pH environment of the stomach. *See* '081 publication at 8, '452 publication at 2, 9, Streitwieser at 501, 502, Ansel (2005) at 103.

The '081 publication states that "there is clinical interest in providing treprostinil orally" instead of by the then-available subcutaneous route. *See* '081 publication at 2. The '081 publication discloses the existence of a sustained-release oral treprostinil diethanolamine tablet, but not its composition. *See id.* at 82. The tablet produced "detectable and potentially therapeutic drug concentrations" when administered to humans. *Id.* at 85. These concentrations were "maintained over an extended period of time through sustained release formulation technology." *Id.* "All adverse events were mild to moderate in severity." *Id.*

In view of the disclosures of the '452 and '081 publications, the person of ordinary skill in the art would have been motivated to prepare a sustained-release treprostinil diethanolamine composition by modifying the sustained-release, SLS-containing osmotic formulation of the '452 publication by incorporating into it treprostinil diethanolamine, a preferred antihypertensive agent disclosed and described by the '081 publication.

The '283 patent provides additional motivation to prepare an osmotic composition that contains treprostinil diethanolamine and SLS. The '283 patent discloses an osmotic composition that comprises a drug- and osmotic-agent-containing core and a coating, and that may further contain a solubility-enhancing agent such as a surfactant. *See* '283 patent at col. 3, ll. 57-62 and col. 12, ll. 20-23. The '283 patent further identifies SLS specifically as an additive or excipient that may be included in the composition. *See id.* at col. 11, ll. 66-67 and col. 12, l. 14. Drugs to be included in the composition include those that have low solubility at a "physiologically relevant pH (e.g., pH 1-8)." '283 patent at col. 6, ll. 5-7. As explained above, the person of ordinary skill in the art would have recognized that this class encompasses treprostinil diethanolamine. As detailed above, specific suitable drugs further resemble treprostinil diethanolamine in that they may be in the same chemical (carboxylic acid) and functional

(antihypertensive) classes. Specific suitable drugs are prostaglandins (prostacyclin, alprostadil), thereby suggesting treprostinil diethanolamine, a prostaglandin analog. As set forth in the table above, the '283 patent discloses the other elements of the claim, such as a semi-permeable membrane that includes an opening for drug delivery.

The '855 publication also provides additional motivation to prepare an osmotic composition that contains treprostinil diethanolamine and SLS. The '855 publication discloses an osmotic composition. *See* '855 publication ¶¶ 0018, 0035, 0060. To increase the proportion of a drug that the composition releases, the composition contains a surfactant and a salt. *See id.* ¶ 0014. The surfactant can serve several purposes in addition to promoting the solubility of the composition's constituents. *See id.* ¶ 0027. The drug of the composition can be a cardiovascular drug, a class that encompasses treprostinil diethanolamine. The '855 publication does not specify the water-solubility of the active ingredient, indicating that an active ingredient's inclusion in the disclosed composition does not depend on its solubility. As set forth in the table above, the '855 publication discloses the other elements of the claim, such as a semi-permeable membrane that includes an opening for drug delivery.

Reasonable expectation of success derives from the fact that the delivery system of the '452 publication can be used to deliver a wide range of compounds, including (but not limited to) salts of active ingredients that are freely soluble in water and/or of limited solubility in physiologic environments. Thus, the person of ordinary skill in the art would have recognized treprostinil diethanolamine as likely to be compatible with the SLS-containing compositions of the '452 publication, as the person of ordinary skill in the art would have expected treprostinil diethanolamine to have limited solubility in the stomach. Also, at least some of the formulations of the '452 publication exhibited dissolution profiles in vitro that were comparable to that of the

corresponding marketed drug, indicating the compositions' effectiveness. *See* '452 publication at 15, Table 2 and Figure 4. Reasonable expectation of success further derives from the fact that a sustained-release, oral, treprostinil diethanolamine tablet had already been prepared and administered to humans and had yielded favorable and promising results.

The '855 publication reinforces the reasonable expectation of success by disclosing that an osmotic device of the invention provided improved drug release relative to a comparable device that lacked surfactant. *See* '855 publication ¶ 0054.

i. Obviousness as routine optimization of the extended release treprostinil diethanolamine composition of the '081 publication

Claim 1 should also be found invalid as obvious as mere routine optimization of the prior art. *See In re Aller*, 220 F.2d 454, 456 (C.C.P.A. 1955) (stating that "where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation"). The '897 patent acknowledges that "[e]xtended release tablets that have an osmotically active drug core surrounded by a semi-permeable membrane are known in the art." '897 patent at col. 1, ll. 17-19. The '897 patent acknowledges that at least one osmotic delivery system included "sodium lauryl sulfate and other solubilizers to enhance the solubility" of a poorly soluble drug. *Id.* at col. 1, ll. 63-67. Such disclosures include those of the '452 publication, discussed above. Further, the '081 publication disclosed the existence and clinical promise of a sustained-release, oral, 1 mg treprostinil diethanolamine tablet without further details on the tablet's composition. Also, the person of ordinary skill in the art knew at the time of filing that treprostinil is administered over a long period of time and its concentration in the blood must be maintained at a therapeutic level. The Remodulin® product, for example, was administered continuously. *See* Remodulin® Label (2002).

At least in light of these disclosures, the person of ordinary skill in the art would have been motivated to prepare an osmotic sustained-release composition that contained treprostinil diethanolamine within the scope of claim 1 with a reasonable expectation of success. The '081 publication would have motivated the person of ordinary skill in the art to prepare a sustained-release treprostinil diethanolamine tablet. The '212 patent discloses sustained-release formulations of UT-15. col. 4, l. 54. During prosecution, the patent examiner even remarked during the prosecution of the '212 patent that "[s]ustained or pulse-released forms of prostaglandins are not novel, absent evidence to the contrary." Office Action dated July 12, 2001 at p.2. At the time of filing the '897 patent, osmotic dosage forms represented one of the known methods of achieving sustained drug release. Thus, the person of ordinary skill in the art would have been motivated to prepare an osmotic treprostinil diethanolamine tablet.

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.

KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 421 (2007). Routine optimization of the osmotic tablet to maximize drug release would have led to inclusion of SLS, a well-known surfactant that had been used in other osmotic dosage forms to increase the amount of drug released by the tablet. *See* '855 publication ¶¶ 0014, 0027, '452 publication at 2–4. The other aspects of the composition of claim 1 are routinely included in osmotic dosage forms. *See, e.g.*, Table *supra*, '452 publication disclosures. In sum, the claimed composition is a routine osmotic dosage form modified to contain the prior-art-disclosed antihypertensive agent treprostinil diethanolamine and an agent known to promote drug release from osmotic dosage forms. Such compositions containing other drugs had been successfully prepared previously. *See, e.g.*, '452 publication at 15, Table 2 and Figure 4, '855 publication ¶ 0054. The person of ordinary skill in the art would

have been motivated to prepare such a composition with a reasonable expectation of success, and that this would have represented no more than routine optimization of prior art formulations. Furthermore, the '196 publication discloses a sustained-release preparation that contains a prostaglandin derivative as the active ingredient and excipients. ¶ 0001.

No teaching away from such preparation should be found for the same reasons as those set forth with respect to the combination of the '452 and '081 publications. There is nothing in the art relied on in this obviousness analysis that would have discouraged the person of ordinary skill in the art from preparing the claimed dosage form according to the reasoning set forth herein.

b. Claims 2–19, 40–43, and 48–60 Are Obvious

Dependent claims 2-19, 40-43, and 48-60 of the '897 patent, all of which recite a composition, should be found invalid as obvious. The obviousness analysis of claim 1 also applies to each of its dependent claims. Additional reasoning is set forth below.

Claim 2 depends from claim 1 and further requires that the treprostinil diethanolamine have "water solubility of at least about 30 mg/ml." Claim 2 thus merely recites an intrinsic and necessary property of treprostinil diethanolamine.[42] Further, there is no assertion that a water solubility of at least 30 mg/ml is unique or inventive. The '095 publication discloses that zopolrestat (a carboxylic acid, like treprostinil) diethanolamine has a water solubility of 100 mg/ml. ¶¶ [0005], [0019]; *see also* '164 patent at col. 1, ll. 59–61 (disclosing high water

[42] Claim 2 and other claims that recite intrinsic properties are left over from earlier claim sets that did not survive prosecution. The original claim 1 encompassed compositions that contained a group of drugs and was not limited to treprostinil diethanolamine. Thus, the applicants appear to have drafted these claims to further limit the drug of the composition. Neither the applicants nor the Examiner recognized that these claims no longer made sense once claim 1 was limited to treprostinil diethanolamine, and therefore these claims were not cancelled prior to issuance. To the extent that these claims do not further limit the claim from which they derive, they should be found invalid on the additional basis that they are improper dependent claims. *See Pfizer Inc. v. Ranbaxy Labs. Ltd.*, 457 F.3d 1284, 1291-92 (Fed. Cir. 2006) (holding a claim invalid under 35 U.S.C. § 112, ¶ 4 for failing to "'specify a further limitation of the subject matter' of the claim to which it refers").

solubility of diethanolamine salts). As noted above, it would have been obvious to a person of skill in the art that treprostinil diethanolamine would be highly soluble. The Remodulin Label discloses that "Remodulin is relatively rapidly and completely absorbed after subcutaneous infusion, with an absolute bioavailability approximating 100%." p. 1.

Furthermore, the '684 publication discloses a long, non-exclusive list of "highly soluble" drugs that can be incorporated into a sustained-release solid oral dosage form. ¶¶ [0023], [0026], [0119]. The publication defines "highly soluble" as more than 100 g/l. ¶¶ [0043], [0049]. It would have been obvious to combine the highly soluble salt treprostinil diethanolamine with the delivery system of the '684 combination to achieve a water solubility of 30 mg/ml; *see also* '283 patent, col. 7, l. 31 (disclosing use of a prostacyclin in the invention).

Claim 3 depends from claim 1 and further requires that the dosage form exhibit "an in-vivo release profile that may be predicted from an in-vitro release profile." This is also an intrinsic property of the composition of claim 1. The dosage form of the invention "provides in vivo release profiles that can be predicted based on in vitro release profiles." *See* '897 patent at col. 6, ll. 21-24. Sustained-release in vivo release profies were well understood in the prior art. '081 publication at 83; '452 publication at 11; '855 publication at ¶ [0051]; '684 publication at ¶¶ [0016], [0017], [0023]. Also, this claim feature merely recites the ordinary purpose of performing an in vitro release study: to predict the in vivo release profile. There is nothing novel or non-obvious in this feature.

Claim 4 depends from claim 1 and requires that the dosage form be "a sustained-release dosage form." The patent does not define "sustained-release dosage form" or "sustained-release." The patent indicates that "sustained-release" refers to the provision of a therapeutic level of drug in the blood for at least about two hours. For example, the patent states that

> the present invention provides an orally administered sustained release formulation of Treprostinil effective to produce plasma concentrations varying between a Cmin of 0.1 to 0.2 ng/ml to a maximum plasma concentration of treprostinil of about 0.5 ng/ml to about 2 ng/ml for a time of about 2 hours to 8 hours. The formulation may be designed to provide desired steady-state blood levels of the drug in a twice-a-day regimen.

'897 patent at col. 6, ll. 47-54. The '081 publication, '452 publication, and '283 patent all disclose sustained-release dosage forms. The '081 publication explicitly describes sustained-release treprostinil diethanolamine tablets that provided elevated blood drug levels for more than two hours and indicated that this was desirable. *See, e.g.*, '081 publication at 82—5 and Figure 14. The '452 publication discloses osmotic nifedipine formulations that released drug over a prolonged period of time in *in vitro* dissolution tests. *See, e.g.*, '452 publication at 6–9 (describing the composition of the "osmotic delivery system" that "can be used to provide controlled release" of a variety of actives), Figures 3–9 and accompanying text. From the description and properties, the person of ordinary skill in the art would have recognized these as sustained-release dosage forms. Similarly, the '283 patent describes and discloses exemplary sustained-release compositions. *See, e.g.*, '283 patent at col. 14, ll. 60-65 (describing "sustained release osmotic dosage forms"), col. 17, ll. 57–61 (same), Figures 5, 6, and 7 and accompanying text.

The person of ordinary skill in the art also would have been motivated to prepare a sustained-release formulation in order to provide a reduced dosing schedule that improves patient compliance. *See, e.g.*, Ansel (2005) at 262 and Table 9.1 (listing advantages of extended-release dosage forms).

Claim 5 depends from claim 4 and further recites that "the treprostinil diethanolamine has a short half-life." Treprostinil diethanolamine's half-life is an intrinsic property of treprostinil diethanolamine and was well known in the art. *See* '081 publication at 63 ("Treprostinil has a

terminal plasma half-life of 94 minutes." The distribution phase of treprostinil has a half-life of 10.3 minutes and over 90% of the distribution and elimination of the compound occurs by 60 minutes post-dosing."). The same obviousness analysis that applies to the treprostinil diethanolamine composition of claim 4 therefore applies equally to claim 5.

Claim 6 depends from claim 5 and further requires that the "half-life ranges from several minutes to three hours." The same analysis that applies to claim 5 applies equally to claim 6, which purports to limit an intrinsic property of treprostinil diethanolamine.

Claim 7 depends from claim 1 and further requires that "the amount of treprostinil diethanolamine is sufficient to produce a therapeutically effective plasma concentration of treprostinil." The additional feature adds nothing because it was routine in the art to provide an effective dose amount of any administered drug.

A reasonable expectation of success derives from the advanced state of the art of pharmaceutical formulation at the time of filing and from the guidance provided by the '081 publication and the Remodulin® Label relating to treprostinil therapy and treprostinil diethanolamine compositions.

The '081 publication discloses the amount of treprostinil diethanolamine used in four different oral treprostinil diethanolamine solutions and the resulting treprostinil blood concentrations and pharmacokinetics. *See* '081 publication at 83 and Figures 13A-D. These amounts provide a useful starting point in determining the amount of treprostinil diethanolamine to include in an oral sustained-release tablet. The '081 publication further discloses that an oral sustained-release treprostinil diethanolamine (1 mg) tablet can provide potentially therapeutic drug concentrations over an extended period. *See id.* at 84, 85. Also, the oral, sustained-release

tablets yielded peak blood concentrations of over 600 pg/ml (0.6 µg/liter) in humans. *See id.* at 82, 84-85 and Figure 14.

The Remodulin® Label provides further relevant guidance, indicating that a therapeutic steady-state treprostinil blood concentration is about 2 µg/liter (which equals 2 ng/ml). *See* Remodulin® Label (2002) at 4. In view of the disclosed dosage amounts and serum treprostinil concentrations, the person of ordinary skill in the art would have been motivated to meet the additional limitation of claim 7 with a reasonable expectation of success.

Claim 8 depends from claim 7 and further recites that "the therapeutically effective plasma concentration of treprostinil in a human has a C_{min} of 0.1 ng/ml to 0.2 ng/ml." We understand claim 8 to require a concentration of at least 0.1 ng/ml. The analysis of claim 7 applies to claim 8. In view of the prior art guidance relating to treprostinil effective concentration set forth in the analysis of claim 7, the person of ordinary skill in the art would have been motivated to prepare the dosage form of claim 7 in such a way that it would provide this minimum plasma concentration. Further, for the reasons set forth with respect to claim 7, the person of ordinary skill in the art would have had a reasonable expectation of success in doing so. This is reinforced by the fact that the '081 publication sustained-release treprostinil diethanolamine tablets met the claim-recited C_{min} in both the fed and fasted administration states. *See* '081 publication Figure 14.

Claim 9 depends from claim 7 and further recites that "the therapeutically effective plasma concentration of treprostinil in a human has a C_{max} of 0.5 ng/ml to 2 ng/ml." The analysis of claim 9 parallels that of claim 8. We understand the claim to require that the dosage form of claim 7 provide a maximum treprostinil plasma concentration of 2 ng/ml, which is about the same as the steady-state concentration achieved by Remodulin®. In view of this fact and further

in view of the additional prior art guidance relating to treprostinil effective concentration set forth in the analysis of claim 7, the person of ordinary skill in the art would have been motivated to prepare the dosage form of claim 7 in such a way that it would provide the required maximum plasma concentration. Further, for the reasons set forth with respect to claim 7, the person of ordinary skill in the art would have had a reasonable expectation of success in doing so. A reasonable expectation of success is further supported by the fact that both sustained-release treprostinil diethanolamine tablets of the '081 publication had a C_{max} within the claim-recited range (about 0.65 ng/ml for fed administration and about 0.8 ng/ml for fasted administration). *See* '081 publication Figure 14.

Claim 10 depends from claim 9 and further recites that "the therapeutically effective plasma concentration of treprostinil in a human has a T_{max} (time to reach C_{max}) of 2 hours to 8 hours." The analysis of claim 9 applies to claim 10. Further, the person of ordinary skill in the art would have been motivated to prepare the composition of claim 9 with a T_{max} within the range recited in claim 10 with a reasonable expectation of success in view of the prior art guidance set forth with respect to claim 7. Specifically, the '081 publication tablet administered in the fed state reached a maximum concentration at a time of about 4 1/2 hours. Of the four sustained-release dosage forms, this tablet administered in the fed state gave the highest area under the curve, or total exposure to treprostinil diethanolamine. *See* '081 publication at 84 and Figure 14; *see also* '684 publication at ¶ [0018]. The person of ordinary skill in the art therefore would have been motivated to prepare a treprostinil diethanolamine sustained-release osmotic dosage form that had pharmacokinetics similar to this tablet, and thus would have prepared a dosage form with a T_{max} in the recited range.

Claim 11 depends from claim 7 and requires that "the therapeutically effective plasma concentration of treprostinil is maintained to allow for a twice-a-day or once-a-day administration." The analysis of claim 7 applies to claim 11. Further, the person of ordinary skill in the art would have been motivated to prepare the composition of claim 7 to allow for the dosing frequency of claim 11 with a reasonable expectation of success. Motivation to provide low-frequency dosing derives from the fact that the simpler it is to adhere to a dosing regimen, the more likely it is that a patient will do so. Low-frequency dosing is one of the advantages of sustained-release formulations recognized in the prior art. *See* Ansel (2005) at 262 and Table 9.1. "Extended release tablets and capsules are commonly taken only once or twice daily." *Id.* at 261. In view of these disclosures, the person of ordinary skill in the art would have been motivated to provide a sustained-release osmotic treprostinil diethanolamine dosage form that is administered once or twice a day.

The person of ordinary skill in the art would have had a reasonable expectation of success in doing so. The art of drug formulation was sufficiently advanced at the time of filing that the person of ordinary skill in the art could reasonably expect to provide such a formulation, particularly in view of the '081 publication's disclosure that an 8-hour sustained-release treprostinil diethanolamine formulation had already been prepared that provided potentially therapeutic drug concentrations. *See* '081 publication at 82, 84-85 and Figure 14. This conclusion is reinforced by the '452 publication's statement that "it may be desirable to modify the solubility characteristics of the osmagents, solubilizers, granulation or other ingredient to achieve a desired release profile." '452 publication at 11. This indicates that the state of the art was sufficiently advanced that it would have been mere routine to modify the disclosed formulation's release profile by manipulation of its composition.

Claim 12 depends from claim 7 and further requires that "the therapeutically effective plasma concentration of treprostinil results in reduced side effects." The claim does not indicate from what level the side effects are reduced. The specification indicates that the "controlled delivery of the medicinal agent will result in an essentially flat pharmacokinetic profile that reduces side effects associated with spikes in blood concentration of the medicinal agent." '897 patent at col. 6, ll. 29-32. The spikes are those that would occur from frequent dosing of a non-extended release dosage form, such as the oral immediate release formulations of the '081 publication. *See* '081 publication Figures 13A-D. The analysis of claim 7 applies to claim 12. Further, the '897 patent and the prior art acknowledge that reduced side effects are a property of a sustained-release formulation. *See* col. 6: 29–32; '081 publication at 62, 79–80 (describing plasma spikes with treprostinil); Ansel (2005) at 262 (describing advantages of extended-release dosage forms, including less fluctuation in drug blood levels); '684 publication at ¶ [0046] (describing "therapeutically beneficial blood levels" obtained through sustained release); '283 patent at col. 1, ll. 61–col. 2, ll. 10. For the reasons set forth with respect to claim 4, the composition of claim 7 is a sustained-release formulation (because the composition of claim 1, from which claim 7 depends, is a sustained-release formulation). Thus, the composition of claim 7 will necessarily exhibit the reduced side effects required by claim 12.

Claim 13 depends from claim 1 and further requires that the "at least one release enhancing agent is present in the dosage form in a concentration of 0.5% to 90% by weight." A number of the specific nifedipine formulations disclosed by the '452 publication contained SLS in this range; SLS is a release enhancing agent. *See* '452 publication Tables 1-6 (disclosing formulations that contain, among others, 3% SLS, 5% SLS, and 10% SLS), '897 patent at col. 4, l. 65–col. 5, l. 2. The person of ordinary skill in the art therefore would have been motivated to

incorporate a similar concentration of SLS in a treprostinil diethanolamine osmotic sustained-release tablet, thereby meeting the additional limitation of claim 13. The person of ordinary skill in the art would have had a reasonable expectation of success in doing so at least in view of the dissolution data of a subset of the disclosed SLS-containing formulations. *See* '452 publication Figures 3–9.

Claim 14 depends from claim 1 and further requires that "said release-enhancing agent is selected from the group consisting of wicking agents and micelle-forming agents." Because the patentees acknowledge that SLS is both a wicking agent and a micelle-forming agent (*see* '897 patent at col. 4, l. 65–col. 2, l. 9), the analysis of claim 13 necessarily applies equally to claim 14. Further, the prior art discloses that SLS is a wicking agent and a micelle-forming agent. *See* '452 publication at 3–4, 7-8. Thus, the person of ordinary skill in the art would have been motivated to incorporate a wicking and/or micelle-forming agent into the composition with a reasonable expectation of success.

Claim 15 depends from claim 1 and further requires that "at least one release enhancing agent is a wicking agent selected from the group consisting of ionic surfactants, and non-swelling hydrophilic polymers." The '897 patent acknowledges, and the prior art discloses, that SLS is an ionic surfactant. *See* '897 patent at col. 5, ll.1-2, '452 publication at 8. Thus, for reasons that parallel those set forth with respect to claim 14, the analysis of claim 13 applies equally to claim 15.

Claim 16 depends from claim 1 and further requires that "said at least one release enhancing agent is a non-swelling hydrophilic polymer selected from the group consisting of polyethylene oxide-polypropylene oxide block copolymers, cellulose ethers, and polyethylene glycols." The prior art discloses this additional feature. Specifically, the generic composition

disclosed by the '452 publication includes a solubilizing agent which can be polyethylene glycol. *See* '452 publication at 3 and 8. The '452 publication further discloses specific osmotic compositions that contain a polyethylene glycol and related dissolution data. *See, e.g.*, '452 publication at 14-15, Tables 1 and 2 (disclosing thirteen compositions that contain PEG8000) and Figures 3 and 4.

Claim 17 depends from claim 1 and further requires that "said at least one release enhancing agent is a complexing agent selected from the group consisting of polyvinyl pyrrolidone, and non-ionic surface active agents." The prior art discloses the additional feature. Specifically, the composition disclosed by the '452 publication includes a solubilizing agent which can be polyvinyl pyrrolidone. The wicking agent of the disclosed composition also can be polyvinyl pyrrolidone. *See* '452 publication at 3, 7-8, 16-17, Tables 3 and 4 (disclosing specific osmotic compositions that contain PVPK25 and Figures 5 and 6 (disclosing dissolution data for four of the disclosed compositions).

Claim 18 depends from claim 1 and further requires that "said at least one release enhancing agent is a micelle-forming agent selected from the group consisting of poly(ethylene oxide) modified sorbitan monoesters, fatty acid sorbitan esters, and sodium lauryl sulfate." As noted with respect to claim 13, the person of ordinary skill in the art would have been motivated to prepare a composition of claim 1 that contains SLS.

Claim 19 depends from claim 1 and further requires that "said dosage form is selected from the group consisting of tablets, capsules, and pellets." The prior art discloses this additional feature. Specifically, the '081 publication discloses the existence of sustained-release treprostinil diethanolamine tablets and related, promising in vivo data, and the '452 publication discloses a

general method for preparing an osmotic tablet and formulations and dissolution data for sustained-release, osmotic nifedipine tablets.

Claim 40 depends from claim 1 and further requires that the dosage form "is a tablet comprising treprostinil diethanolamine in an amount equivalent to about 1 mg treprostinil." The prior art discloses this additional feature. Specifically, the '081 publication discloses that 1 mg sustained-release formulations provided, in humans, "potentially therapeutic drug concentrations." *See* '081 publication at 84 (stating that the sustained-release dosage forms were designed to release 1 mg treprostinil diethanolamine (which, as discussed above, we understand to mean that the tablets released the equivalent of 1 mg treprostinil)), 85 ("These results demonstrate that detectable and potentially therapeutic drug concentrations can be obtained from a solid dosage form of UT-15C and that these concentrations can be maintained over an extended period of time through sustained release formulation technology.").

Further, Remodulin® was ordinarily administered at a rate ranging from 1.25 ng/kg/min to 40 ng/kg/min. *See* Remodulin® Label (2002) at 9-10. A rate of 10 ng/kg/min administered to a 70 kg person would total about 1 mg/day.[43] Thus, the person of ordinary skill in the art would have been motivated to prepare the composition of claim 1 containing the equivalent of about 1 mg treprostinil as a replacement for a 70 kg patient currently receiving the Remodulin® product at 10 ng/kg/min, assuming a once-a-day formulation and that 1 mg provided by the oral tablet is equivalent to 1 mg by continuous infusion. If these assumptions are not accurate, a 1 mg tablet would still be useful for a heavier or lighter patient and/or a patient receiving more or less than 10 ng/kg/min, depending on how the assumptions vary. In sum, a 1 mg tablet is well within the range of total daily dosage of treprostinil prescribed by the Remodulin® Label. *Cf. Iron Grip Barbell Co., Inc. v. USA Sports, Inc.*, 392 F.3d 1317, 3121-25 (Fed. Cir. 2004) (affirming

[43] The calculation is: 10 ng/kg/min x (24 x 60 minutes/day) x 70 kg = 1.008 x 106 ng/day, or 1.008 mg/day.

obviousness of claim because claim-recited specific value fell within prior art range and secondary considerations did not demonstrate non-obviousness).

Claim 41 depends from claim 1 and further requires that the dosage form is "a tablet comprising treprostinil diethanolamine in an amount equivalent to about 1 mg to 5 mg of treprostinil." Similarly, claim 42 depends from claim 1 and further requires that the dosage form is "a tablet comprising treprostinil diethanolamine in an amount equivalent to about 1 mg to 10 mg of treprostinil." The same prior art that applies to claim 40 applies equally to claims 41 and 42, since all three claims encompass a 1 mg treprostinil composition.

Claim 43 depends from claim 7 and further requires that "the therapeutically effective plasma concentration of treprostinil in a human has a C_{min} of 0.1 ng/ml to 0.2 ng/ml, and a C_{max} of 0.5 ng/ml to 2 ng/ml, and a T_{max} (time to reach C_{max}) of 2 hours to 8 hours." The analysis of claim 7 applies to claim 43. The three additional limitations are the same as the additional limitations of claims 8, 9, and 10, respectively. The analysis that applies to claims 8, 9, and 10 applies in combination to claim 43. These three limitations work together to provide a dosage form that provides a therapeutically effective amount of treprostinil for a prolonged period of time.

Claim 48 depends from claim 1 and further requires that "the semi-permeable membrane comprises cellulose acetate and at least one component select [sic] from the group consisting of triethyl citrate (TEC), propylene glycol(PG), mixtures in ratios of TEC to PG ranging from 25:75 to 75:25, Tween 80, polyethylene glycol (PEG); a polyoxyethylene sorbitan ester, triacetin, diethyl phthalate, mineral oil, tributyl sebacate, and glycerol." The prior art discloses the additional feature. Specifically, the '452 publication's tablet's coating comprises cellulose acetate and triethyl citrate. *See* '452 publication at 10-11 (instructing that tablets be coated with an acetone solution of cellulose acetate and a plasticizer such as triethyl citrate).

Claim 49 depends from claim 48 and requires that the "the semi-permeable membrane comprises triethyl citrate." As discussed above, the '452 publication discloses this feature and it would have been obvious to a person of ordinary skill in the art to include it in a treprostinil diethanolamine formulation for the reasons stated above.

Claim 50 depends from claim 1 and further requires that the dosage form contain "an effective amount of treprostinil diethanolamine up to about 1 mg of treprostinil as treprostinil diethanolamine." Similarly, claims 51 and 52 depend from claim 1 and require up to about 5 mg treprostinil and up to about 10 mg treprostinil, respectively, as treprostinil diethanolamine. All of these claims encompass a composition that contains treprostinil diethanolamine in an amount equivalent to about 1 mg treprostinil. This is the composition of claim 40 (which likewise depends from claim 1). The discussion of claim 40 thus also applies to claims 50-52.

Claim 53 depends from claim 1 and further recites that "the semi-permeable membrane comprises 3% to 10% by weight of the oral osmotic pharmaceutical dosage form." The prior art discloses this additional feature. Specifically, the '452 publication discloses that the semipermeable wall should be present at 2-15% of the tablet weight, which fully encompasses the recited range. *See* '452 publication at 6. *Cf. In re Peterson*, 315 F.3d 1325, 1330-32 (Fed. Cir. 2003) (finding claim obvious where prior art range encompassed claim-recited range and there were no unexpected results associated with the entire, narrower claimed range).

Claim 54 depends from claim 1 and further recites that "the semi-permeable membrane includes one opening suitable for providing for the osmotic delivery of the treprostinil diethanolamine from the osmotically active drug core." The prior art discloses this additional feature. Specifically, for example, the '452 publication states that the "semi-permeable wall of the tablet can contain at least one passageway communicating the contents of the core with the

exterior of the device, delivering the beneficial drug through the passageways from the elementary osmotic device." '452 publication at 6. It goes on to describe further details of the passageway. *See id.* at 6-7. It was routine at the time to make such a hole. *See, e.g.*, '855 publication ¶ [0037] ("A passageway is drilled, by laser or mechanically through the wall to contact the therapeutic composition for releasing the drug from the dosage form. The dosage form is optically oriented automatically by the drilling equipment for forming an exit passageway on the preselected drug surface.").

Claim 55 depends from claim 13 and further requires that "at least one release enhancing agent is present in the dosage form in a concentration of 1% to 20% by weight." Claim 55 is ambiguous, and potentially indefinite, because, for compositions that contain more than one release enhancing agent, it is unclear whether each release enhancing agent is present in the recited concentration range, or the sum of the concentrations of the release enhancing agents is within the recited range. We construe this term to require that the sum is within the recited range because the specification states that "[m]ost preferably, release-enhancing agents constitute from 1% to 20% by weight of the formulation." '897 patent at col. 5, ll. 12-14.

The analysis of claim 13 applies to claim 55. Further, the prior art discloses this additional feature. Specifically, the '452 publication discloses compositions, such as compositions 6A-6H, that contain a total concentration of release-enhancing agents of from 10% (6G) to 20% (6A, 6B). *See* '452 publication at 19, Table 6. All of these values are within the claim-recited range.

Claim 56 depends from claim 1 and further requires that "the osmotically active drug core further comprises at least one osmotic agent." It is not clear that claim 56 further limits the subject matter of claim 1 because claim 1 requires an "osmotic" dosage form that comprises "an

osmotically active drug core." It is not clear how a drug core could be osmotically active without containing an osmotic agent. "The osmotic agent(s) in the core tablet draws water into the core tablet creating an osmotic gradient across the semi-permeable membrane. The osmotic gradient pushes the drug in the solution out through the laser-drilled hole." '897 patent at col. 5, l. 66–col. 6, l. 3. Osmotic agents include xylitol.

Assuming, for the purposes of this analysis, that this constitutes a limitation, the prior art discloses this additional feature. Specifically, the '452 publication discloses a composition of claim 1 that comprises an osmotic agent. *See* '452 publication at 3.

Claim 57 depends from claim 56 and further requires that the "at least one osmotic agent" be selected from a group that includes xylitol. The analysis of claim 56 applies to claim 57. Further, the prior art discloses this additional feature. Specifically, xylitol was a well-known osmotic agent at the time of filing (as the patentees concede) and the '452 publication discloses osmotic compositions that contain it. *See, e.g.*, '897 patent at col. 5, ll. 27-29 (stating that "[o]smotic agents are well known to those skilled in the art" and include xylitol), '452 publication at 15, Table 2 and at 19, Table 6.

Claim 58 depends from claim 57 and further requires that the "at least one osmotic agent is present in the dosage form in a concentration of 1% by weight to 90% by weight." The claim construction discussion of claim 55 applies equally to claim 58. The '897 patent states that "[o]smotic agents can be incorporated in the formulation of this invention in the amount of from 1% by weight to 90% by weight."

The discussion of claim 57 applies to claim 58. Further, the prior art discloses claim 58's additional feature. The '452 publication discloses a number of compositions each of which contains a total concentration of osmotic agent within the claimed range. *See, e.g.*, '452

publication at 19, Table 6 (e.g., composition: 6A and 6B: 27.5% xylitol and 25% sorbitol; 6C and 6H: 25.5% xylitol and 26% sorbitol; 6E: 28.5% xylitol and 29% sorbitol; 6F: 32.5% xylitol and 30% sorbitol).

Claim 59 depends from claim 1 and requires that "the at least one release enhancing agent is sodium lauryl sulfate." The prior art discloses this additional feature. Specifically, the '452 publication discloses that SLS generally can be used as a solubilizing agent (citing as an example "particularly sodium lauryl sulfate") and further discloses a number of specific osmotic formulations that contain SLS. *See* '452 publication at 8 and at 14-19, Tables 1-6.

Claim 60 depends from claim 59 and further requires that "the at least one osmotic agent is comprises [sic] xylitol." The analysis of claim 59 applies to claim 60. Further, the prior art discloses claim 60's additional feature. Specifically, xylitol was a known osmotic agent at the time of filing (*see* above discussion of claim 57) and further because a number of the osmotic compositions of the '452 publication contain both xylitol and SLS. *See, e.g.*, '452 publication at 15, Table 2 (showing that compositions 2A through 2E contain xylitol and SLS).

In light of the above prior art disclosures, the person of ordinary skill in the art would have been motivated to incorporate the additional features of the dependent claims into the obvious composition of claim 1 with a reasonable expectation of success.

No secondary considerations that relate to the additional features militate in favor of finding these dependent claims nonobvious. To the extent UTC suggests there are any such considerations, Actavis reserves the right to supplement these contentions to address them.

Therefore, all of dependent claims 2-19, 40-43, and 48-60 should be found invalid as obvious.

c. Claims 20–39 and 44–47 are obvious

Claims 20–39 and 44–47 should also be found invalid as obvious. Independent method claim 20 should be found invalid as obvious at least because the person of ordinary skill in the art would have been motivated to administer the oral osmotic pharmaceutical dosage form of claim 1 to a patient in need thereof with a reasonable expectation of success. Motivation has the same derivation as the motivation to prepare the dosage form of claim 1, detailed above with respect to claim 1. For example, the person of ordinary skill in the art would have been motivated to prepare the composition of claim 20 because there was clinical interest in providing treprostinil orally. *See* '081 publication at 2. Once the person of ordinary skill in the art had prepared the composition, the person of ordinary skill in the art would have been motivated to administer it to a person in need thereof to provide clinical therapeutic benefit. The person of ordinary skill in the art further would have had a reasonable expectation of success in view of the promising results previously obtained with the treprostinil diethanolamine sustained-release formulation of the '081 publication and in view of the dissolution properties of the osmotic compositions disclosed by the '452 publication detailed above. The route of administration would have been oral because the obvious composition is an oral dosage form. There are no secondary considerations that relate to the administration of the obvious dosage form of claim 1.

Claims 21–32 depend from claim 20 and further recite the same additional limitations that are found in claims 14–18 and 5–11, respectively. The analysis of claim 20 applies in kind to dependent claims 21–32. In short, the compositions of claims 14–18 and 5–11 would have been obvious for the reasons detailed above. The person of ordinary skill in the art would have been motivated to prepare those compositions because of their anticipated beneficial therapeutic effect. It follows that the person of ordinary skill in the art would have been motivated to administer the obvious compositions to a person in need thereof. The person of ordinary skill in

the art would have had a reasonable expectation of success for the reasons set forth with respect to claims 20, 14–18, and 5–11. There are no secondary considerations that relate to the administration of the obvious dosage forms of claims 14–18 and 5–11. Therefore, dependent claims 21–32 should be found invalid as obvious.

Claims 44–47 depend directly from claim 20 and recite the same additional dosage form limitations as claims 40–43. The same analysis that applies to claim 20 applies to claims 40–43. Further, the person of ordinary skill in the art would have been motivated to administer a composition having the additional qualities recited by claims 44–47 with a reasonable expectation of success for the same reasons as those set forth with respect to claims 40–43. There are no secondary considerations that relate to the administration of the obvious dosage forms of claims 40–43. Therefore, dependent claims 40–47 should be found invalid as obvious.

Independent method claim 33 should be found invalid as obvious at least because the person of ordinary skill in the art would have been motivated to treat pulmonary arterial hypertension by administering a dosage form of claim 1 to a patient in need thereof with a reasonable expectation of success. The analysis of claim 20 applies equally to method claim 33. Further, at the time of filing, the person of ordinary skill in the art would have known that the treprostinil drug product Remodulin® was indicated for "the treatment of pulmonary arterial hypertension in patients with NYHA [New York Heart Association] Class II-IV symptoms." Remodulin® Label (2002) at 6. The person of ordinary skill in the art would have been motivated to treat pulmonary hypertension by administering a treprostinil diethanolamine dosage form of claim 1 with a reasonable expectation of success. There are no secondary considerations that relate to the administration of the obvious dosage form of claim 1 to treat pulmonary arterial hypertension.

The analysis that applies to independent claim 33 applies equally to its dependent claims 34–38, which merely add the same qualifications to the composition to be administered as claims 14–18. The person of ordinary skill in the art would have been motivated to treat pulmonary hypertension by administering a dosage form of claims 34–38 with a reasonable expectation of success. There are no secondary considerations that relate to the administration of the obvious dosage forms of claims 14–18 to treat pulmonary arterial hypertension. Therefore, claims 34–38 should be found invalid as obvious.

Claim 39 depends from claim 33 and requires that the disease be pulmonary hypertension. The obviousness of treating pulmonary hypertension by administering a composition of claim 1 was set forth above with respect to claim 33 and applies equally to claim 39. Claim 39 should be found invalid as obvious.

d. Secondary Considerations

Plaintiffs have not set forth any evidence of secondary considerations of non-obviousness, and Actavis is not aware of any such secondary considerations that, when considered with the evidence of obviousness, would warrant a finding of non-obviousness of the claims of the '897 patent. If UTC relies on any secondary considerations of non-obviousness, Actavis reserves the right to supplement its contentions.

As explained above, the claims would have been obvious in view of a host of prior art references because the steps described in the claims were well-known procedures that would have been obvious to apply. Consequently, there are numerous different combinations of these prior art references and many exemplary references that teach each standard step. By way of example, the following combinations render the asserted claims obvious:

- The '452 publication and the '081 publication,

- The '452 publication, the '081 publication, the '283 patent, and the '855 publication.
- Remodulin and the Remodulin Label in addition to any of the above combinations

A POSA would have been motivated to combine the teachings of these references with a reasonable expectation of success in light of the fact that each of the references taught well known synthesis techniques for the synthesis of compounds such as treprostinil. In addition, Actavis's invalidity charts set forth where each prior art reference discloses the limitations of the asserted claims.

Actavis reserves the right to set forth additional such examples as discovery continues.

I. Invalidity of the '892 Patent

1. The Asserted Claims Are Invalid as Obvious

The asserted claims of the '892 patent are also invalid as obvious.

a. The Asserted Claims Are Invalid as Obvious Based on the Following Prior Art

i. WO 98/18452

WO 98/18452 ("the '452 publication") was published in 1998 and therefore is at least 35 U.S.C. § 102(b) prior art to the '169 patent. This application (or related applications and patents) was not before the Examiner during prosecution of the '100 application. The '452 publication provides extended release compositions and points out their advantages:

> In arriving at the present invention it has been discovered that it is possible to efficiently deliver therapeutically effective doses, at controlled rates and for extended times, of a broad variety of drugs without the need for polymers that swell or expand within the tablet wall so as to physically force the medicament particles out into their intended environment of use.

'452 publication at 2. *See also id.* at 9 ("The delivery system of the invention can be used to provide controlled release of any of a broad variety of therapeutically active agents."). The advantages of extended release at a controlled rate would have been particularly attractive for a

drug like treprostinil, which has a relatively short half-life and is administered in low doses for a chronic condition. Specifically, treprostinil is indicated for the treatment of pulmonary arterial hypertension, a chronic condition, has "a terminal half-life of approximately 2-4 hours," and is administered at doses ranging, for a 70 kg person, from an initial dose of about 0.13 mg/day to not more than about 4 mg/day. *See* Remodulin® Label (2002) at 5, 9-10; *see also* Ansel (2005) at 263 (drugs best suited for extended release have certain characteristics, including having a low dosage and being administered to treat chronic conditions).

As noted above, the disclosed delivery system "can be used to provide controlled release of any of a broad variety of therapeutically active agents." *Id.* at 9. Among various examples, the '452 publication identifies specifically a number of substantially water-soluble salts of active agents that the system can be used to deliver (without referring to the solubility of each active). These include chlorpheniramine maleate (water solubility 160 mg/ml), brompheniramine maleate ("sol in water"), verapamil hydrochloride (water solubility 70 mg/ml),[44] metoprolol succinate (freely soluble in water), and metoprolol tartrate (very soluble in water).[45] *See* '452 publication at 9 (listing examples of actives); for solubilities, *see Merck Index* 337, 218, 1563-64 (Susan Budavari ed., 11th ed. 1989) and *European Pharmacopoeia* 2032 and 2034 (2005), respectively. Other specifically listed actives that the disclosed delivery system can deliver are water-insoluble salts (e.g., dextromethorphan hydrobromide, enalapril maleate, diclofenac sodium) and water-insoluble non-salts (e.g., carbamazepine, acyclovir). *See* '452 publication at 9. Thus, although the '452 publication elsewhere states that, "[i]n accordance with the preferred invention, there is provided an osmotic delivery system, preferably in the form of a tablet, which dispenses a

[44] The '452 publication does not refer specifically to verapamil hydrochloride, but rather to "antihypertensives such as nifedipine, verapamil, enalapril and salts thereof." *See* '452 publication at 9.
[45] The '897 patent also lists metoprolol succinate as a "therapeutic agent[ ] that will benefit from this invention." '897 patent at col. 7, ll. 8-16.

therapeutic agent having a limited solubility in water or physiological environments," '452 publication at 2,[46] it is not limited to such therapeutic agents, as it also explicitly discloses that the disclosed composition is suitable for delivery of water-soluble salts of therapeutic agents, including salts of anti-hypertensive agents. This class includes treprostinil diethanolamine. In sum, the disclosed system is useful for both water-soluble salts of active ingredients and for active ingredients with relatively lower water solubility.

The publication further discusses the other components of the disclosed composition. "Preferred non-swelling osmotic agents include" fructose, lactose, xylitol, and sorbitol. *Id.* at 3. Triethyl citrate ("TEC") is a suitable plasticizer for use with a semipermeable, polymeric coating material such as cellulose acetate. *See id.* at 6.

The '452 publication further discloses a general method for preparing such a composition as coated tablets. *See id.* at 10-13, Example 1.

ii. Phares

United States Patent Application Publication US 2005/0085540, titled "Compounds and Methods for Delivery of Prostacyclin Analogs," was published April 21, 2005, and therefore qualifies as at least § 102(b) prior art. Prior to the earliest priority date of the '892 patent, a person skilled in the art would have been aware of Phares, which describes various treprostinil derivatives including treprostinil diethanolamine. Phares teaches the preparation of treprostinil diethanolamine. Phares at [0105]–[0107]. Phares also describes a safety, tolerability, and pharmacokinetic study comparing a sustained-release treprostinil diethanolamine tablet and a sustained-release treprostinil diethanolamine capsule administered to healthy human volunteers. *See* Phares at [0321]-[0326].

[46] *See also* '452 publication at 9 ("The system of the present invention is particularly applicable to therapeutic agents which are insoluble or poorly soluble in water or aqueous environments at physiological pH.").

Phares also provides data from a polymorphic study conducted on treprostinil diethanolamine that reports that two crystalline polymorphic forms are possible and both readily absorb moisture. *See* Phares at [0327]–[0349].

Phares further teaches that the treprostinil derivatives can be formulated into various dosage forms such as tablets, capsules, powders, granules, etc. using known pharmaceutical methods and excipients. *See* Phares at [0175]–[0184].

iii. Safdar, Phase 2 and 3 Clinical Trials in Pulmonary Arterial Hypertension, Advances in Pulmonary Hypertension, 7(1):228-234 (2008)

Safdar was published in March 2008 and is at least § 102(b) prior art. A person skilled in the art also would have known of the teachings of Safdar prior to the earliest priority date of the '892 patent. Safdar reports on phase 2 and phase 3 clinical trials for the treatment of pulmonary arterial hypertension. *Id.* at 228–29, Table 1. One of the studies described in Safdar is the FREEDOM study that was evaluating the efficacy of an oral sustained-release osmotic tablet containing treprostinil diethanolamine administered to patients for 12 or 16 weeks. *Id.* at 228–29.

iv. FDA Container Guidance

A person skilled in the art also would have known of the FDA container requirements prior to the earliest priority date of the '892 patent and is at least § 102(b) prior art. The FDA Container Guidance provides an overview of what information the FDA requires from an applicant regarding the packaging of a drug product in order to obtain approval to sell the drug product in the United States.

> The FDA Container Guidance provides the following table outlining the information that should be submitted for a solid oral drug product:

Table 7
Information That Typically Should Be Submitted for Solid Oral Drug Products and Powders

Description	Overall general description of container closure system, plus: For Each Packaging Component: • Name, product code, manufacturer • Materials of construction • Description of any additional treatments
Suitability	Protection: (by each component and/or the container closure system, as appropriate) • Light exposure • Moisture permeation • Seal integrity or leak tests for unit-dose packaging Safety: (for each material of construction, as appropriate) • Chemical composition of all plastics, elastomers, adhesives, etc.[a] • For tablets, capsules, and powders, appropriate reference to the indirect food additive regulation may be submitted, but may not be appropriate for Powders for Reconstitution. • For rayon and cotton fillers, data from USP monographs. For non-USP materials, data and acceptance criteria should be provided. • For desiccants and other absorbent materials: the size and shape should differ from that of the dosage form. Compatibility: (on each component or the packaging system) • For glass and plastic containers, data from USP Containers' testing. Performance: (on each component or the packaging system, as appropriate) • Functionality and/or drug delivery, as appropriate
Quality Control	For Each Packaging Component Received by the Applicant: • Applicant's tests and acceptance criteria[c] • Dimensional (drawing) and performance criteria • Method to monitor consistency in composition, as appropriate For Each Packaging Component Provided by the Supplier: • Manufacturer's acceptance criteria for release, as appropriate • Description of manufacturing process, as appropriate
Stability	• See section III.C.4

[a] Including any additives used in the manufacture of a packaging component.
[b] Testing of plastics should be performed on the packaging component, not on the unformed resin.
[c] Note that applicant's acceptance tests may include, among others, test parameters indicated under the description, suitability, and quality control sections of this table.

FDA Container Guidance at 36.

Section III.C.4 of the FDA Container Guidance referenced in the preceding table reads as follows:

> 4. Stability Data (Packaging Concerns)
>
> Stability testing of the drug product should be conducted using the container closure systems proposed in the application. The packaging system used in each stability study should be clearly identified.

> The contained closure system should be monitored for signs of instability. When appropriate, an evaluation of the packaging system should be included in the stability protocol. ...
>
> For general guidance on conducting stability studies, refer to the FDA *Guidelines for Submitting Documentation for the Stability of Human* Drugs *and Biologics* (February 1987). The stability guideline is undergoing revision and will be superseded by the FDA's draft guidance for industry *Stability Testing of Drug Substance and Drug Products* (June 1998), once it is issued in final form.

FDA Container Guidance at pp. 20-21.

The FDA Container Guidance also states the following with respect to solid dosage forms:

> G. Solid Oral Dosage Forms and Powders for Reconstitution
>
> The most common solid oral dosage forms are capsules and tablets. For purpose of this guidance, oral powders and granules for reconstitution are also included in this group.
>
> The risk of interaction between packaging components and a solid oral dosage form is generally recognized to be small. ...
>
> A typical container closure system is a plastic (usually HDPE) bottle with a screw-on cap or snap-off closure and a flexible packaging system, such as a pouch or blister package. A typical closure consists of a cap, often with a liner, and frequently with an inner seal. If used, fillers, desiccants, and other absorbent materials are considered primary packaging components.
>
> The most common forms of flexible packaging are the blister package and pouch. A blister package usually consists of a lidding material and a forming film. The lidding material is usually a laminate which includes a barrier layer (e.g. aluminum foil) with a print primer on one side and a sealing agent (e.g., a heat-sealing lacquer) on the other side. The sealing agent contacts the dosage form and the forming film. The forming film may be a single film, a coated film, or a laminate. A pouch typically consists of film or laminate which is sealed at the edges by heat or adhesive. Leak testing is usually performed on flexible packages as part of the in-process controls.
>
> Solid oral dosage forms generally need to be protected from the potential adverse effects [sic] of water vapor. Protection from light and reactive gases may also be needed. For example the presence of moisture may affect the decomposition rate of the active drug substance or dissolution rate of the dosage form. The container

> should have an intrinsically low rate of vapor permeation, and the container closure system should establish a seal to protect the drug product. Three standard tests for water vapor permeation have been established by the USP for use with solid oral dosage forms.

FDA Container Guidance at p. 33.

v. Freedom

According to the Freedom Study, which is at least § 102(b) prior art, patients received samples of oral treprostinil to be self-administered twice a day at home. *See* FREEDOM — M: Oral Treprostinil as Monotherapy for the Treatment of Pulmonary Arterial Hypertension (PAH or pulmonary hypertension), available at https://clinicaltrials.gov/ct2/show/NCT00325403?term=treprostinil+diethanolamine&rank=17clinical. The drug product would have been packaged in some form to provide to the patients and should have been stable. *See* FDA Guidance for Industry, E6 Good Clinical Practice: Consolidated Guidance (April 1996) § 5.13 "Manufacturing, Packaging, Labeling and Coding of Investigational Product(s)." We additionally do not believe that the study should qualify as an experimental use with respect to the packaging of the drug product because the only purpose of the study was to determine efficacy for a specific condition, and the packaging and stability profile should have already been known by the time the study was conducted.

vi. Lockhart, H., et al., *Packaging of Pharmaceuticals and Healthcare Products*, Blackie Academic & Professional, an imprint of Chapman & Hall (1996)

Lockhart was published in 1996 and is at least § 102(b) prior art. Lockhart contains a thorough discussion of pharmaceutical packaging, including the effects of moisture on oral tablets. pp. 13–15. It further discloses the importance of moisture protection of solid oral preparations. *Id.* at 28–29. It further discloses factors involving the selection of containers and the use of desiccants. *Id.* at 30, 93.

vii. ***Regulatory approval received for dessicant system that allows for specific humidity targets: TricorBraun achieves FDA certification for DryKeep*, TricorBraun press release, Apr. 8, 2009. ("Desiccant press release")**

This news release was published in April 2009 and is at least § 102(a) prior art to the '892 patent. It discloses FDA approval for TricorBraun's DryKeep desiccant polymer, which absorbs 100% of its weight in water. The press release discloses that "DryKeep has a controllable moisture uptake allowing internal humidity to be maintained and can be moulded into any polymer container."

viii. ***Dessicant delivery systems: absorbent lined vials from CSP Technologies Inc., Auburn, AL, USA*, Pharm-Med-Packag-News, vol. 11, no. 11 (Nov. 2003), p. 70 ("Desiccant delivery systems")**

Desiccant delivery systems was published in 2003 and is at least § 102(b) prior art. This article discloses various containers and vials for drugs "with airtight and leak proof coinjected desiccant linings." It further discloses desiccant sheets and desiccant film.

ix. ***Protective desiccants: product review*, Pharm-Med-Packag-News, vol. 10, no. 3 (Mar. 2002), p. 76 ("Protective desiccants")**

Protective desiccants was published in 2002 and is at least § 102(b) prior art. This article discloses a cartridge containing DryGuard desiccants that "are highly effective static adsorbents desgined to protect moisture sensitive products from corrosion, mildew and other humidity related problems during shipping."

b. The Asserted Claims of the '892 Patent Are Obvious

There are no patentable differences between the claims of the '892 patent and the prior art. As discussed above, both Phares and Safdar describe solid sustained-release treprostinil diethanolamine tablets that are administered to humans. To obtain FDA permission to administer

the tablets to humans, the sponsor of the drug product would have had to determine appropriate packaging for the tablets and conduct stability testing. *See* FDA Guidance for Industry, E6 Good Clinical Practice: Consolidated Guidance (April 1996) § 5.13 "Manufacturing, Packaging, Labeling and Coding of Investigational Product(s)." *See also* FDA Guidance at 36, 20-21.

Neither Phares nor Safdar specifically describe the type of packaging for the tablet, the use of a desiccant, the moisture level of the tablets, or the humidity within the packaging. These deficiencies would necessarily be resolved by a person of ordinary skill in the art based on the teachings of the FDA Container Guidance. Specifically, the FDA Container Guidance teaches that to be packaged, the drug product must be stable; a common packaging for solid dosage forms, such as a tablet, is either a bottle or a blister pack; a desiccant may be included in the packaging if desired; and the effects of water vapor transmission should be evaluated.

Furthermore, Lockhart contains a thorough discussion of pharmaceutical packaging, including the effects of moisture on oral tablets. pp. 13–15. It further discloses the importance of moisture protection of solid oral preparations. *Id.* at 28–29. It discloses factors involving the selection of containers and the use of desiccants. *Id.* at 30, 93.

The TricorBraun press release, Desiccant delivery systems article, and the protective desiccants article all disclose the advanced state of desiccant development and the use of desiccants in containers and regulation of the amount of moisture in the container. Furthermore, the '452 publication further discusses the other components of the disclosed composition and renders claims 3, 11, and 17 obvious. The '452 publication discloses, "Preferred non-swelling osmotic agents include" fructose, lactose, xylitol and sorbitol. *Id.* at 3. Triethyl citrate ("TEC") is a suitable plasticizer for use with a semipermeable, polymeric coating material such as cellulose acetate. *See id.* at 6.

Determining the amount of desiccant and moisture level of a solid treprostinil diethanolamine formulation are matters of routine product development within the ordinary ability of a skilled artisan. A skilled artisan would be motivated to optimize these features based upon a desire to obtain FDA approval to sell a treprostinil diethanolamine product. A skilled artisan would be motivated to combine Phares or Safdar with the FDA Container Guidance based again on the skilled artisan's desire to obtain FDA approval to sell a treprostinil diethanolamine product.[47] Therefore, the asserted claims are invalid as obvious.

c. Secondary Considerations

Plaintiffs have not set forth any evidence of secondary considerations of non-obviousness, and Actavis is not aware of any such secondary considerations that, when considered with the evidence of obviousness, would warrant a finding of non-obviousness of the claims of the '892 patent. If UTC relies on any secondary considerations of non-obviousness, Actavis reserves the right to supplement its contentions.

As explained above, the claims would have been obvious in view of a host of prior art references because the steps described in the claims were well-known procedures that would have been obvious to apply. Consequently, there are numerous different combinations of these prior art references and many exemplary references that teach each standard step. By way of example, the following combinations render the asserted claims obvious:

- Phares and the FDA Container Guidance,
- Phares, the FDA Container Guidance, Safdar, and the Freedom Study.
- Phares, the FDA Container Guidance, and Lockhart

[47] If the patent owner were to argue that a skilled artisan could not obtain the claimed invention based upon the teachings of Phares or Safdar combined with the FDA Container Guidance due to a lack of details and/or guidance, then the claims of the '892 patent are invalid on the same basis for lack of an enabling disclosure, as discussed previously.

- Phares, the FDA Container Guidance, and Desiccant press release, desiccant delivery systems, and protective desiccants

A POSA would have been motivated to combine the teachings of these references with a reasonable expectation of success in light of the fact that each of the references taught well-known synthesis techniques for the synthesis of compounds such as treprostinil. In addition, Actavis's invalidity charts set forth where each prior art reference discloses the limitations of the asserted claims.

Actavis reserves the right to set forth additional such examples as discovery continues.

2. Claims 1–6, 9–23, and 25–32 of the '892 Patent Are Invalid for Lack of Enablement

In the alternative, if the court does not find that the asserted claims of the '892 patent are obvious, they should be found invalid because they do not satisfy the enablement requirement.

a. Claims 1–6 and 15–23

Independent claim 1 requires a packaging that "maintains" the moisture level in a solid treprostinil diethanolamine formulation at a level greater than 3% but less than 7%. Claims 2–6 depend from claim 1 and further limit the packaging to a bottle, blister packaging or a packaging without a desiccant; require that the solid treprostinil diethanolamine formulation comprise an excipient such as maltodextrin or xylitol; and limit the moisture level range to 3.5% to 6.0% or 3.5% to 4.5%.

Independent claim 15 requires a method for storing a solid treprostinil diethanolamine formulation in a packaging so after storage the moisture level in the treprostinil diethanolamine formulation is greater than 3% but less than 7%. Claims 16–23 depend from claim 15 and further limit the packaging to a bottle, blister packaging or a packaging with less than an effective amount of a desiccant; require that the solid treprostinil diethanolamine formulation comprise an

excipient such as maltodextrin or xylitol; limit the moisture level range after storage to 3.5% to 6.0% or 3.5% to 4.5%; and require storage time of at least 12 months or at least 24 months.

The specification of the '892 patent fails to describe how the claimed moisture levels are to be maintained or obtained. More specifically, the specification of the '892 patent contains a section entitled "Example" that briefly describes and provides data from a number of stability studies. The data are reported in four tables. The information provided in the "Example" portion of the '892 patent specification fails to provide critical information necessary to practice the invention recited in claims 1-8 and 15-24. The following is a summary of the information provided, and not provided, in the "Example" portion of the '892 patent specification:

Table 1 data (40°C/75% RH)

	Information provided	Information NOT provided
Formulation	1 mg tablets of treprostinil diethanolamine	• Total weight of the tablet • Excipients present in tablet • How tablet is prepared
Packaging	45 cc HDPE bottle with desiccant	• Type of desiccant • Amount of desiccant • Thickness of bottle wall
		• Closure/sealing • Number of tablets in bottle
	Blister using a ACLAR® UltRx 3000	• Covering/lidding material
Moisture level		
Bottles	Initial: 2.80% 3 months: 3.10% 6 months: 3.10%	
Blister	Initial: 2.80% 3 months: 4.10% 6 months: 4.30%	

Table 2 data (40°C/75% RH)

	Information provided	Information NOT provided
Formulation	1 mg tablets of treprostinil diethanolamine	• Total weight of the tablet • Excipients present in tablet • How tablet is prepared
Packaging	45 cc HDPE bottle with desiccant	• Type of desiccant • Amount of desiccant • Closure/sealing • Thickness of bottle wall • Number of tablets in bottle
	45 cc HDPE bottle without desiccant	• Type of desiccant • Closure/sealing • Thickness of bottle wall • Number of tablets in bottle
	Blister using a ACLAR® UltRx 3000	• Covering/lidding material
Moisture level		
Bottles with Desiccant	Initial: 3.2% 3 months: 2.2%	
Bottles without Desiccant	Initial: 2.9%	
	3 months: 2.7%	
Blister	Initial: 3.1% 3 months: 3.5%	

Table 3 data (40°C/75% RH)

	Information provided	Information NOT provided
Formulation	1 mg tablets of treprostinil diethanolamine; biconex, round film-coated, white, with a hole only on one side and may have imprinting on one side	• Total weight of the tablet • Excipients present in tablet • Composition of film-coating • How tablet is prepared

Packaging	1 gram desiccant	• Type of packaging • Type of desiccant • Number of tablets in packaging • Volume of packaging • Closure system for packaging
Moisture level		
Lot0702406	Initial: 3.2% 1 month: 3.1% 3 months: 2.2% 6 months: 2.3%	
Lot0702407	Initial: 3.1% 1 month: 2.8% 3 months: 3.0% 6 months: 2.7%	
Lot0702406	Initial: 3.5% 1 month: 2.5% 3 months: 2.5% 6 months: 2.8%	

Table 4 data (40°C/75%RH)

	Information provided	**Information NOT provided**
Formulation	1 mg tablets of treprostinil diethanolamine; biconex, round film-coated, white, with a hole only on one side and may have imprinting on one side	• Total weight of the tablet • Excipients present in Tablet • Composition of film-coating • How tablet is prepared
Packaging	no desiccant	• Type of packaging • Number of tablets in packaging • Volume of packaging • Closure system for packaging
Lot 0803176	Initial: 2.9% 3 months: 2.7% 6 months: 2.9%	

	Information provided	Information NOT provided
Lot 0805724	Initial: 2.5% 3 months: 2.8% 6 months: 3.4%	

The data in the tables above demonstrate that storing some type of solid treprostinil diethanolamine formulation, with or without some type of desiccant, may or may not result in a product that meets the features of claims 1–6 and 15–23 of the '892 patent. The examples do not provide sufficient information for a skilled artisan to determine which formulation, manufacturing and packaging criteria are necessary to obtain a dosage form that meets the limitations of claims 1–6 and 15–23 of the '892 patent. For example, assuming (for purposes of argument only) the data presented in Tables 1 and 2 are for the same formulation (the composition and manufacturing method are not provided) and further assuming (for purposes of argument only) the data presented in Tables 1 and 2 are packaged in the same bottle with the same amount and type of desiccant, the data would inform the skilled artisan that sometimes a moisture level of greater than 3% is obtained and/or maintained (Table 1) but other times it is not (Table 2). The information provided in the "Example" portion of the '892 patent does not provide any information sufficient to enable a skilled artisan to determine how to obtain and/or maintain the moisture levels recited in claims 1–6 and 15–23 of the '892 patent.

The remaining portions of the specification of the '892 patent also fail to provide the necessary information that would enable a skilled artisan to determine how to predictably obtain and/or maintain the moisture levels recited in claims 1–6 and 15–23 of the '892 patent. Specifically, the specification of the '892 patent merely provides a listing of possible or desirable moisture values without providing guidance on how to obtain them. For example, the specification of the '892 patent at 4:65–6:16 merely provides very general concepts and potentially desirable values that invite experimentation, but does not provide any definitive

information that would enable a skilled artisan to prepare and package the broad range of possible solid formulations containing treprostinil diethanolamine within the possible scope of claims 1–6 and 15–23 of the '892 patent without undue experimentation.

b. Claims 9–14 and 25–32

Independent claim 9 requires a packaging that contains a desiccant in an amount that is less than the amount necessary to maintain the humidity inside the packaging below 40% during storage. Claims 10–14 depend from claim 9 and further limit the packaging to a bottle; require that the solid treprostinil diethanolamine formulation comprise an excipient such as maltodextrin or xylitol; and require that the storage time is 24 months.

Independent claim 25 requires a method for storing a solid treprostinil diethanolamine formulation in a packaging with a desiccant in an amount that is less than the amount necessary to maintain the humidity inside the packaging below 40% during storage. Claims 26–32 depend on claim 25 and further limit the packaging to a bottle or blister packaging and require that the solid treprostinil diethanolamine formulation comprise an excipient such as maltodextrin or xylitol; limit the moisture level range to 3.5% to 6.0% or 3.5% to 4.5%; and require that the storage time is 12 or 24 months.

Claim 22, which depends from claim 15, also recites that the packaging contains a desiccant in an amount that is less than the amount necessary to maintain the humidity inside the packaging below 40% during storage similar to independent claims 9 and 25.

The specification of the '892 patent fails to describe a single embodiment that is packaged with "less than an effective amount of desiccant" because the specification of the '892 patent never reports a measurement of a humidity level inside the packaging. Therefore, there is no enabling disclosure of an embodiment meeting the elements of claims 9–14, 22 and 25–32 of the '892 patent. The only disclosure in the '892 patent specification relating to the "effective

amount of desiccant" feature recited in claims 9–14, 22 and 25–32 can be found in the patent at 3:31–60, 5:21–29, and 5:60–6:16.

Although the foregoing passages provide potential amounts of desiccant that could be used to practice the invention, this disclosure is merely an invitation to experiment because it does not provide any specific guidance on how to measure the humidity inside a packaging, especially in view of the broad range of possible storage and packaging conditions encompassed by the claims. The humidity inside a packaging will depend upon a number of factors, including but not limited to, the external conditions, the type of packaging, and the contents of the container. Specifically, storage at a high humidity and high temperature will result in greater water permeation through the packaging than storage in low humidity and low temperature. Similarly, the type of packaging material will result in different water permeation through the packaging. For example, a glass bottle will exhibit lower water permeation than a plastic bottle. In addition, the contents of the container, such as the amount of pharmaceutical product within the container and its initial moisture content, could also contribute to a higher humidity level inside the packaging. *See generally* Lachman et al., The Theory and Practice of Industrial Pharmacy (1976) ("Lachman") at pp. 680-699; Modern Pharmaceutics, 4th ed. (2002) ("Modern Pharmaceutics") at pp. 587-605; Remington, The Science and Practice of Pharmacy, 21st ed. (2006) ("Remington") at pp. 1034-1035, 1047-1057. A determination of undue experimentation relies on an analysis of the *Wands* factors: (1) the quantity of experimentation necessary; (2) the amount of direction or guidance disclosed in the patent; (3) the presence or absence of working examples in the patent; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability of the art; and (8) the breadth of the claims. *In re Wands*, 858 F.2d at 737. *See also Alza Corp. v. Andrx Pharm., LLC*, 607 F. Supp. 2d 614

(D. Del. 2009), *aff'd*, 603 F.3d 935 (Fed. Cir. 2010). The following is an application of the *Wands* factors to the claims of the '892 patent.

c. Quantity Experimentation Necessary

A person of ordinary skill in the art would be required to engage in a level of experimentation exceeding routine experimentation to prepare and package a treprostinil diethanolamine solid formulation meeting the features of claims 1–14 and the methods of claims 15–33 of the '892 patent.

Pharmaceutical packaging is highly variable and depends upon a number of potential factors such as the physical and chemical properties of the product being packaged and stored as well as the physical and chemical properties of the packaging. *See generally* Lachman at p. 680 ("In the pharmaceutical industry it is vital that the package selected adequately preserve the integrity of the product. The selection of a package therefore begins with a determination of the product's physical and chemical characteristics, its protective needs and its marketing requirements. . . . Owing to the broad scope of the subject, a detailed treatment of the science of packaging as related to pharmaceuticals cannot be adequately covered in this chapter."); Modern Pharmaceutics at 604 ("Package design must address the finished product's needs, including: Physical and chemical properties of the product[;] Deteriorating factors in the environment[;] Process requirements[;] Packaging machine operation[;] Storage and distribution requirements[;] Distribution flow and timing[;] Methods of distribution. Successful packaging can be achieved when all factors in the system are addressed adequately."); Remington at p. 1035, 1047-1057 ("The choice of containers and closures can have a profound effect on the stability of many pharmaceuticals. Now that a large variety of glass, plastic . . . etc are available, the possibilities for interaction between the packaging components and the formulation ingredients are

immense."); FDA Container Guidance at p. 5 ("A packaging system found acceptable for one drug product is not automatically assumed appropriate for another.").

The asserted claims broadly recite "a packaging" and "a treprostinil diethanolamine solid formulation." These very broad features can include a wide variety of packaging types and materials as well as a wide variety of solid formulations with hundreds of possible excipients. The specification of the '892 patent provides virtually no information on the chemical and physical properties of the solid treprostinil diethanolamine formulation on which to begin the investigation into an appropriate packaging, with or without a desiccant. As evidenced by Lachman, Modem Pharmaceutics, Remington and the FDA Container Guidance, without knowing the chemical and physical properties of the solid dosage form, an investigation into the appropriate packaging on which to begin the necessary experimentation is futile.

The data provided in the "Example" portion of the '892 patent as well as the general knowledge in the art supports the view that the chemical and physical properties of the pharmaceutical composition to be packaged and stored is necessary in order to even begin the required experimentation. Specifically, the "Example" portion of the '892 patent reports data on the levels of various impurities that form during storage of the treprostinil diethanolamine tablet. One of the impurities reported is the xylitol ester of treprostinil. *See* '892 patent at 10:31-40. The formation ofxylitol esters of treprostinil could be avoided by not employing xylitol in the manufacture of treprostinil diethanolamine tablets. Therefore, this factor favors a finding of undue experimentation.

d. The Amount of Direction or Guidance Disclosed in the Patent I / The Presence or Absence of Working Examples in the Patent

The '892 patent provides piecemeal direction and guidance to prepare products within the scope of claims 1–6 and 9–14 and practice the methods of claims 15–23 and 25–32. This

piecemeal direction and guidance fails to provide critical information, such as the composition of a solid formulation, the closure type of the packaging and the type of desiccant, that would allow a skilled artisan to determine how to consistently practice the alleged invention. More importantly, the information that is provided by way of the working embodiments strongly suggests that even under similar packaging conditions, such as a 45 cc HDPE bottle with a desiccant, there is no predictability in maintaining the claimed moisture levels. This unpredictability is demonstrated by comparing the water content data reported in Tables 1–2 for the 1 mg tablet stored in a 45 cc HDPE bottle with the water content data reported in Tables 3 and 4, which is summarized below:

	Initial	1 month	3 months	6 months
Table 1 (with desiccant)	2.8%		3.1%	3.1%
Table 2 (with desiccant)	3.2%		2.9%	
Table 2 (without desiccant)	2.2%		2.7%	
Table 3 (with desiccant) Lot 0702406 Lot 0702407 Lot 0703802	3.2% 3.1% 3.5%	3.1% 2.8% 2.5%	2.2% 3.0% 2.5%	2.8% 2.7% 2.8%
Table 4 (without desiccant) Lot 0802503 Lot 0805724	2.9% 2.5%		2.7% 2.8%	2.9% 3.4%

The above summary demonstrates that the moisture level is highly variable and unpredictable even under similar storage conditions of 40°C and 75% relative humidity.

Therefore, this factor favors a finding of undue experimentation.

e. The Nature of the Invention / The Predictability of the Art

There is a wide variety of possible packaging options for pharmaceutical products. For example, the container may be a bottle, bag, box, drum, tube, or blister pack and can be made of glass, plastic, metal, or paper/board material. Each of these container materials also contains a

number of different submaterials, *e.g.*, plastic type, in addition to possible additives to vary the barrier properties of the container. The containers also have a wide variety of possible closures such as stoppers, twist ties, heat seals, screw caps, etc. *See generally* Lachman at 680-699; Modern Pharmaceutics at 587-605; Remington at 1034–1035, 1047–1057. There are also many possible treprostinil diethanolamine solid formulation compositions. Thus, the nature of the alleged claimed invention is very broad.

The moisture data provided in the '892 patent and summarized above show that there is no predictability in obtaining and maintaining the moisture levels in a packaged solid treprostinil diethanolamine formulation. In addition, the FDA has recognized that there is little predictability in the pharmaceutical packaging arts. *See, e.g.*, FDA Container Guidance at 5 ("A packaging system found acceptable for one drug product is not automatically assumed appropriate for another.").

Therefore, this factor favors a finding of undue experimentation.

f. The Relative Skill of Those in the Art

The level of skill in the art is relatively high with practitioners possessing, in addition to a degree in a relevant field, several years of practical experience related to solid dosage form development, including evaluation of stability and packaging. Although the relative level of skill in the art is high, this factor does not weigh against a finding of undue experimentation because the specification of the '892 patent provides practically no guidance for preparing and packaging all of the possible treprostinil diethanolamine solid formulations meeting the features of claims 1–14 and the methods of claims 15–33.

Therefore, this factor favors a finding of undue experimentation.

g. The State of the Prior Art

Prior to the filing of the '892 patent, it was well known that solid pharmaceutical formulations could be packaged and stored in a wide variety of options and it was well known that the various packaging options would need to be tested with the specific solid formulation to ensure that the acceptable storage stability was present.

Prior to the filing date of the '892 patent, solid treprostinil diethanolamine formulations were known and it was known that these formulations were being used in clinical studies. *See generally* Phares; Safdar. However, the exact packaging to provide desired storage stability was not described in the art.

Therefore, due to the wide variety of possible packaging options, this factor favors a finding of undue experimentation.

h. The Breadth of the Claims

The asserted claims of the '892 patent are very broad. The claims cover a broad range of packaging options, a broad range of solid treprostinil diethanolamine formulations, a broad range of storage conditions, and an unlimited possibility of stability profiles.

In view of the large breadth of the claims of the '892 patent, this factor favors a finding of undue experimentation.

The *Wands* factors weigh in favor of a finding that a person of ordinary skill in the art would have to engage in undue experimentation to prepare and package a treprostinil diethanolamine solid formulation meeting the features of claims 1–6 and 9–14 and the methods of claims 15–23 and 25–32 of the '892 patent. *Alza Corp. v. Andrx Pharm., LLC*, 607 F. Supp. 2d 614 (D. Del. 2009), *aff'd*, 603 F.3d 935 (Fed. Cir. 2010).

3. Claims 15, 16, and 18–21 Are Invalid Under 35 U.S.C. § 101

Claims 15, 16, and 18–21 are invalid under 35 U.S.C. § 101 as being drawn to patent-ineligible subject matter.

To determine if a patent claim meets the requirements of patent-eligible subject matter, a court must first determine if the claim is directed to one of the patent-ineligible concepts, *i.e.*, a law of nature, natural phenomena or abstract idea. If the claim is directed to a patent-ineligible concept, the court must determine if the claim contains additional elements that transform the nature of the claim into patent-eligible subject matter, *i.e.*, additional elements to "ensure that the patent in practice amounts to significantly more than a patent upon the [ineligible concept] itself." *Alice*, 134 S. Ct. at 2355 (internal citations omitted). *See also Ariosa*, 788 F.3d at 1375. The courts have held that "simply appending conventional steps, specified at a high level of generality to laws of nature, natural phenomena and abstract ideas cannot make those laws, natural phenomena and ideas patentable." *Mayo*, 132 S. Ct. at 1300; *Alice*, 134 S. Ct. at 2357; *Ariosa*, 788 F.3d at 1378.

The Supreme Court in *Alice* described "abstract ideas" as follows:

> The "abstract ideas" category embodies "the longstanding rule that '[a]n idea of itself is not patentable.'" In *Benson*, for example, this Court rejected as ineligible patent claims involving an algorithm for converting binary-coded decimal numerals into pure binary form, holding that the claimed patent was "in practical effect ... a patent on the algorithm itself." ...
>
> On their face, the claims before us are drawn to the concept of intermediated settlement, *i.e.*, the use of a third party to mitigate settlement risk. Like the risk hedging in *Bilski*, the concept of intermediated settlement is "'a fundamental economic practice long prevalent in our system of commerce.'" Thus, intermediated settlement, like hedging, is an "abstract idea" beyond the scope of § 101.

Alice, 134 S. Ct. at 2355-56 (internal citations omitted).

Claims 15, 16, and 18–21 of the '892 patent recite the abstract idea of simply storing a solid treprostinil diethanolamine formulation in a packaging. Therefore, claims 15, 16, and 18–21 recite patent-ineligible subject matter. The additional recited features of moisture content after storage and storing for 12 or 24 months are conventional steps known in the pharmaceutical arts

and are recited at such a high level of generality that they do not transform claims 15, 16, and 18–21 of the '892 patent into patent-eligible subject matter. For example, claim 15 places no limits on the packaging, the storage time, the storage conditions or formulation. Moreover, it is known that treprostinil diethanolamine is hygroscopic. *See* Phares at [0332], [0336]. Thus, the patent owner could obtain a sample of a treprostinil diethanolamine or a formulation containing treprostinil diethanolamine from an alleged infringer, open the packaging to allow the sample to absorb moisture, and periodically test the sample until a moisture level of greater than 3% but less than 7% is observed.

Claims 17, 22–23, and 25–32 similarly recite the abstract idea of simply storing a solid treprostinil diethanolamine formulation in a packaging. Claims 17 and 22–23 simply add additional features such as specific excipients, *i.e.*, maltodextrin or xylitol, general packaging types, *i.e.*, bottle or blister, and the addition of a desiccant. The inclusion of these conventional pharmaceutical materials in such a broad general manner into the claim reciting the abstract idea of storing a solid treprostinil diethanolamine formulation in a packaging does not transform the claims into patent-eligible subject matter.

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CERTIFICATION OF SERVICE

I, Bryce A. Cooper, hereby certify that on August 30, 2016, I caused a true and correct copy of the foregoing Defendant Actavis Laboratories FL, Inc.'s Invalidity Contentions to be served upon the following counsel for Plaintiffs United Therapeutics Corporation and Supernus Pharmaceuticals, Inc. by e-mail:

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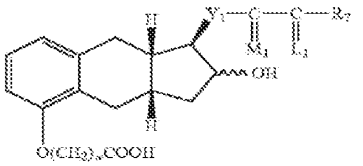
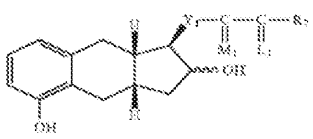
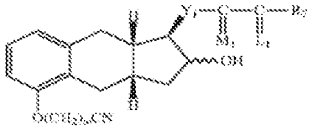
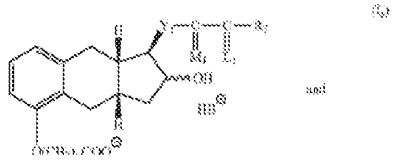
EXHIBIT A

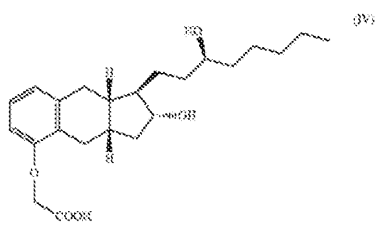
The '393 Patent

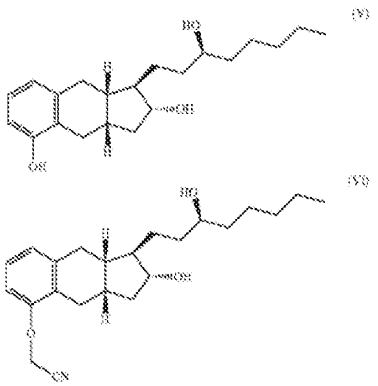
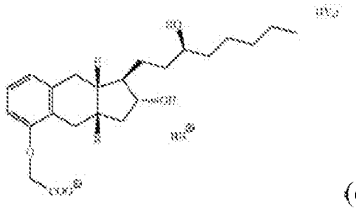
	Claim Term	Prior Art Where Limitation Is Found
1	A product comprising a compound of formula I  or a pharmaceutically acceptable salt thereof, wherein said product is prepared by a process comprising (a) alkylating a compound of structure II with an alkylating agent to produce a compound of formula III,  (II)  (III) wherein w=1, 2, or 3; Y_1 is trans-CH=CH—, cis-CH=CH—, —$CH_2(CH_2)_m$—, or —C≡C—; m is 1,	• The **'117 patent** claims treprostinil, the same compound and its salt form as the '393 patent. It also discloses a way to synthesize treprostinil via alkylation of benzindene trial followed by the hydrolysis of benzindene nitrile. Col. 20, l. 10-col. 21, l. 12, claims 1-4 • **Phares 2005** discloses the compound claimed by the '393 patent in at least two salt forms and further discloses that the sodium salt of the compound is sold as Remodulin®. It further discloses that treprostinil can be crystallized and that the diethanolamine salt of treprostinil is particularly preferred. It discloses that the preparation of treprostinil diethanolamine includes a step of adding and dissolving the diethanolamine base to treprostinil that can be further purified to form the purer and more stable crystal form called "form B." pp. [0004], [0024], [0041-42], [0051], [0085-93], [99], [0327], Figures 15-22, Table 16, claim 49 • **Remodulin®** and the **Remodulin® Label** disclose treprostinil sodium and the product claimed by the '393 patent. • **Moriarty 2004** discloses compound 7, the compound that falls within the claimed compound for all claims of the '393 patent. Moriarty 2004 discloses an improved "route for synthesis and subsequent manufacture of a complex drug substance on a multikilogram scale." It further discloses that treprostinil can be crystallized and that

	Claim Term	Prior Art Where Limitation Is Found
	2, or 3; R_7 is (1) —C_pH_{2p}—CH_3, wherein p is an integer from 1 to 5, inclusive, (2) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3) alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl, with the proviso that R_7 is phenoxy or substituted phenoxy, only when R_3 and R_4 are hydrogen or methyl, being the same or different, (3) phenyl, benzyl, phenylethyl, or phenylpropyl optionally substituted on the aromatic ring by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3)alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl, (4) cis-CH=CH—CH_2—CH_3, (5) —$(CH_2)_2$—CH(OH)—CH_3, or (6) —$(CH_2)_3$—CH=$C(CH_3)_2$; —C(L_1)—R_7 taken together is (1) (C_4-C_7)cycloalkyl optionally substituted by 1 to 3 (C_1-C_5)alkyl; (2) 2-(2-furyl)ethyl, (3) 2-(3-thienyl)ethoxy, or (4) 3-thienyloxymethyl; M_1 is α-OH:β-R_5 or α-R_5β-OH or α-OR_1:β-R_5 or α-R_5:β-OR_2, wherein R_5 is hydrogen or methyl, R_2 is an	the diethanolamine salt of treprostinil is particularly preferred and that the salts of treprostinil can be reacted with diluted HCl to form treprostinil. Moriarty 2004 also discloses that the compound is produced with 99.7% purity. Abstract, pp. 1892, 1895, compound 7, p. 1902 • The **'075 patent** discloses treprostinil and discloses a genus of compounds that encompasses treprostinil. It further discloses that suitable salts of the compounds include the diethanolamine salt. The '075 patent also discloses the synthesis of treprostinil. col. 14, ll. 5-43, Example 33 • **Wade 2005** discloses treprostinil and its salt forms. ¶¶ [0021], [0024] • **Kawakami 1981** discloses purification through the preparation and use of a base to form a crystalline salt. p. 6 • **Monson 1971** discloses that purification by chromatography is not favored for large-scale industrial production and the use of crystallization and recrystallization as a purification technique. pp. 181-183, 185 • **Eliel 1994** discloses that carboxylate ammonium salts are formed from adding a carboxylic acid with an amine, and that those salts can be purified by recrystallization. p. 322 • **Jones 2000** discloses that carboxylate ammonium salts are formed from adding a carboxylic acid with an amine, and that those salts can be purified by recrystallization. pp. 153-155

	Claim Term	Prior Art Where Limitation Is Found
	alcohol protecting group, and L_1 is α-R_3:β-R_4, α-R_4:β-R_3, or a mixture of α-R_3:β-R_4 and α-R_4:β-R_3, wherein R_3 and R_4 are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R_3 and R_4 is fluoro only when the other is hydrogen or fluoro, (b) hydrolyzing the product of formula III of step (a) with a base, (c) contacting the product of step (h) with a base B to form a salt of formula I_s.  (d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula I.	• **Lin 1987** discloses alkylation reactions adding $ClCH_2CN$ followed by hydrolysis to the carboxylic acid. p. 5595 • **Aristoff 1985** discloses alkylation reactions adding $ClCH_2CN$ followed by hydrolysis to the carboxylic acid. p. 7971 • **McManus 1959** discloses alkylation reactions adding $ClCH_2CN$ followed by hydrolysis to the carboxylic acid. pp. 1465-1467 • **Ege 1989** discloses that a carboxylate salt can be converted back to a carboxylic acid by treatment with the acid HCl. p. 8 • **Arumugan 2005** discloses that purification by chromatography is not favored for large-scale industrial production. p. 319 • **Yu 2006** discloses that purification by chromatography is not favored for large-scale industrial production. p. 832 • **Harwood 1989** discloses the use of crystallization and recrystallization as a purification technique. pp. 127-134 • **Pavia 1998** discloses that purification by chromatography is not favored for large-scale industrial production. p. 648 • **Sorrell 1999** discloses that purification by chromatography is not favored for large-scale industrial production. pp. 755-758 • **Priscinzano 2002** discloses the well-known technique of purification by crystallization or recrystallization and the use of salts in drug treatment. pp. 4371-4374

	Claim Term	Prior Art Where Limitation Is Found
		• **Ohno 2005** discloses that carboxylate ammonium salts, including diethanolamine salts, are common and well known for use in drugs and drug targets. It further discloses the technique of purification by crystallization or recrystallization and the use of salts in drug treatment. pp. 5279-5294, compound 7. • **Burk 2003** discloses the technique of purification by crystallization or recrystallization and the use of salts in drug treatment. pp. 5731-5734 • **Wiberg 1960** discloses purification of a water-insoluble solid carboxylic acid by dissolving it in sodium hydroxide, filtering, and then adding an acid. It further discloses that the procedure for use in amines. p. 6 • **Schoffstall 2004** discloses converting carboxylic acid to a salt, adding an acid, which regenerates the carboxylic acid and can then be filtered or extracted into an organic solvent. pp. 3-40 • **PDR 2005 Bicillin® L-A** • **Olmsted** discloses that purification by recrystallization. p. 476 • **Sharp** discloses purification by recrystallization. p. 64
2	The product of claim 1, wherein the purity of compound of formula I in said product is at least 99.5%.	• *See* prior art cited above with respect to claim 1. • **Olmsted at 476 and Sharp at 64 disclose that** purification by crystallization is most effective when the solid contains a low

	Claim Term	Prior Art Where Limitation Is Found
		percentage of impurities.
3	The product of claim 1, wherein the alkylating agent is $Cl(CH_2)_wCN$, $Br(CH_2)_wCN$, or $I(CH_2)_wCN$.	• *See* prior art cited above with respect to claim 1.
4	The product of claim 1, wherein the base in step (b) is KOH or NaOH.	• *See* prior art cited above with respect to claim 1.
5	The product of claim 1, wherein the base B in step (c) is selected from the group consisting of ammonia, N-methylglucamine, procaine, tromethamine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.	• *See* prior art cited above with respect to claim 1.
6	The product of claim 1, wherein the acid in step (d) is HCl or H_2SO_4.	• *See* prior art cited above with respect to claim 1.
7	The product of claim 1, wherein Y_1 is $\_CH_2CH_2\_$; M_1 is α-OH:β-H or α-H:β-OH; $\_C(L_1)$-R_7 taken together is $\_(CH_2)_4CH_3$; and w is 1.	• *See* prior art cited above with respect to claim 1.
8	The product of claim 1, wherein the process does not include purifying the compound of formula (III) produced in step (a).	• *See* prior art cited above with respect to claim 1.
9	A product comprising a compound having formula IV 	• The **'117 patent** claims treprostinil, the same compound and its salt form as the '393 patent. It also discloses a way to synthesize treprostinil via alkylation of benzindene triol followed by the hydrolysis of benzindene nitrile. Col. 20, l. 10-col. 21, l. 12, claims 1-4 • **Phares 2005** discloses the compound claimed by the '393 patent in at least two salt forms and further discloses that the sodium salt of the compound is sold as Remodulin®. It further discloses that treprostinil can be crystallized and that the

	Claim Term	Prior Art Where Limitation Is Found
	or a pharmaceutically acceptable salt thereof, wherein the product is prepared by the process comprising (a) alkylating a compound of formula V with an alkylating agent to produce a compound of formula VI,  (b) hydrolyzing the product of formula VI of step (a) with a base, (c) contacting the product of step (h) with a base B to form a salt of formula IV_s, and  (d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula IV.	diethanolamine salt of treprostinil is particularly preferred. It discloses that the preparation of treprostinil diethanolamine includes a step of adding and dissolving the diethanolamine base to treprostinil that can be further purified to form the purer and more stable crystal form called "form B." pp. [0004], [0024], [0041-42], [0051], [0085-93], [99], [0327], Figures 15-22, Table 16, claim 49 • **Remodulin®** and the **Remodulin® Label** disclose treprostinil sodium and the product claimed by the '393 patent. • **Moriarty 2004** discloses compound 7, the compound that falls within the claimed compound for all claims of the '393 patent. Moriarty 2004 discloses an improved "route for synthesis and subsequent manufacture of a complex drug substance on a multikilogram scale." It further discloses that treprostinil can be crystallized and that the diethanolamine salt of treprostinil is particularly preferred and that the salts of treprostinil can be reacted with diluted HCl to form treprostinil. Moriarty 2004 also discloses that the compound is produced with 99.7% purity. Abstract, pp. 1892, 1895, compound 7, p. 1902 • The **'075 patent** discloses treprostinil and discloses a genus of compounds that encompasses treprostinil. It further discloses that suitable salts of the compounds include the diethanolamine salt. The '075 patent also discloses the synthesis of treprostinil. col. 14, ll. 5-43, Example 33 • **Wade 2005** discloses treprostinil and its salt

	Claim Term	Prior Art Where Limitation Is Found
		forms. ¶¶ [0021], [0024] • **Kawakami 1981** discloses purification through the preparation and use of a base to form a crystalline salt. p. 6 • **Monson 1971** discloses that purification by chromatography is not favored for large-scale industrial production and the use of crystallization and recrystallization as a purification technique. pp. 181-183, 185 • **Eliel 1994** discloses that carboxylate ammonium salts are formed from adding a carboxylic acid with an amine, and that those salts can be purified by recrystallization. p. 322 • **Jones 2000** discloses that carboxylate ammonium salts are formed from adding a carboxylic acid with an amine, and that those salts can be purified by recrystallization. pp. 153-155 • **Lin 1987** discloses alkylation reactions adding $ClCH_2CN$ followed by hydrolysis to the carboxylic acid. p. 5595 • **Aristoff 1985** discloses alkylation reactions adding $ClCH_2CN$ followed by hydrolysis to the carboxylic acid. p. 7971 • **McManus 1959** discloses alkylation reactions adding $ClCH_2CN$ followed by hydrolysis to the carboxylic acid. pp. 1465-1467 • **Ege 1989** discloses that a carboxylate salt can be converted back to a carboxylic acid by treatment with the acid HCl. p. 8

	Claim Term	Prior Art Where Limitation Is Found
		• **Arumugan 2005** discloses that purification by chromatography is not favored for large-scale industrial production. p. 319 • **Yu 2006** discloses that purification by chromatography is not favored for large-scale industrial production. p. 832 • **Harwood 1989** discloses the use of crystallization and recrystallization as a purification technique. pp. 127-134 • **Pavia 1998** discloses that purification by chromatography is not favored for large-scale industrial production. p. 648 • **Sorrell 1999** discloses that purification by chromatography is not favored for large-scale industrial production. pp. 755-758 • **Priscinzano 2002** discloses the well-known technique of purification by crystallization or recrystallization and the use of salts in drug treatment. pp. 4371-4374 • **Ohno 2005** discloses that carboxylate ammonium salts, including diethanolamine salts, are common and well known for use in drugs and drug targets. It further discloses the technique of purification by crystallization or recrystallization and the use of salts in drug treatment. pp. 5279-5294, compound 7. • **Burk 2003** discloses the technique of purification by crystallization or recrystallization and the use of salts in drug treatment. pp. 5731-5734 • **Wiberg 1960** discloses purification of a water-insoluble solid carboxylic acid by

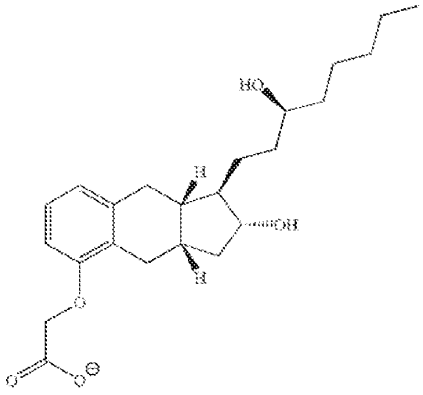
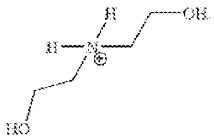
	Claim Term	Prior Art Where Limitation Is Found
		dissolving it in sodium hydroxide, filtering, and then adding an acid. It further discloses that the procedure for use in amines. p. 6 • **Schoffstall 2004** discloses converting carboxylic acid to a salt, adding an acid, which regenerates the carboxylic acid and can then be filtered or extracted into an organic solvent. pp. 3-40 • **PDR 2005 Bicillin® L-A** • **Olmsted** discloses that purification by recrystallization. p. 476 • **Sharp** discloses purification by recrystallization. p. 64
10	The product of claim 9, wherein the purity of product of step (d) is at least 99.5%.	• *See* prior art cited above with respect to claims 2 and 9.
11	The product of claim 9, wherein the alkylating agent is $ClCH_2CN$.	• *See* prior art cited above with respect to claim 9.
12	The product of claim 9, wherein the base in step (b) is KOH.	• *See* prior art cited above with respect to claim 9.
13	The product of claim 9, wherein the base B in step (c) is selected from a group consisting of ammonia, N-methylglucamine, procaine, tromethamine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.	• *See* prior art cited above with respect to claim 9.
14	The product of claim 9, wherein the base B is diethanolamine.	• *See* prior art cited above with respect to claim 9.
15	The product of claim 9, wherein the acid in step (d) is HCl.	• *See* prior art cited above with respect to claim 9.

	Claim Term	Prior Art Where Limitation Is Found
16	The product of claim 9, wherein the process does not include purifying the compound of formula (VI) produced in step (a).	• *See* prior art cited above with respect to claim 9.
17	The product of claim 16, wherein the base B in step (c) is selected from a group consisting of ammonia, N-methylglucamine, procaine, tromethamine, magnesium, L-lysinc, L-arginine, tricthanolamine, and diethanolamine.	• *See* prior art cited above with respect to claim 9.
18	The product of claim 17, wherein the base B is diethanolamine.	• *See* prior art cited above with respect to claim 9.
19	The product of claim 1, wherein the base in step (b) is KOH or NaOH and wherein the base 13 in step (c) is selected from the group consisting of ammonia. N-methyl glucamine, procaine, tromethamine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.	• *See* prior art cited above with respect to claim 1.
20	The product of claim 9, wherein the base in step (b) is KOH or NaOH and wherein the base B in step (c) is selected from the group consisting of ammonia, N-methylglucamine, procaine, tromethamine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.	• *See* prior art cited above with respect to claim 9.
21	The product of claim 1, wherein step (d) is performed.	• *See* prior art cited above with respect to claim 1.
22	The product of claim 21, wherein the product comprises a pharmaceutically acceptable salt	• *See* prior art cited above with respect to claim 1.

	Claim Term	Prior Art Where Limitation Is Found
	formed from the product of step (d).	

EXHIBIT B

The '070 Patent

	Claim Term	Prior Art Where Limitation Is Found
1	A compound having the following structure:  	• The **'222 patent** discloses treprostinil and salts of treprostinil, including amine salts, to treat pulmonary hypertension. It also discloses salts derived from bases, including organic bases, such as dicyclohexylamine. col. 3, ll. 1–20, 35–41; col. 6, ll. 58–63 • **Simonneau** discloses the use of treprostinil sodium to treat pulmonary arterial hypertension. It further discloses drawbacks of subcutaneous infusion. pp. 800, 803, Table 5 • The **'075 patent** discloses treprostinil and a genus of compounds that encompasses treprostinil and the diethanolamine salt of those compounds. The '075 patent further discloses the steps to make treprostinil. col. 3, l. 18, col. 3, l. 21–col. 5, l. 35, col. 74, ll. 25–37; Exs. 31–33 • **Bighley** discloses 38 cationic pharmaceutical salt forms in use at the time of publication, including the diethanolamine salt. The diethanolamine salt was among the more frequently used salts. Bighley also discloses that amine salts frequently have higher aqueous solubilities and bioavailabilities than their corresponding inorganic salts. pp. 456, Table 2, 461. • The **'265 patent** discloses cicaprost, a prostacyclin and carbacyclin derivative. Cicaprost has structural features in common with treprostinil, including the –

	Claim Term	Prior Art Where Limitation Is Found
		0– CH_2COOH group where a salt can form with an amine such as diethanolamine. The '265 patent specifically identifies the diethanolamine salt as a suitable salt of prostacyclin and carbacyclin derivatives. col. 2, ll. 11–21. • The **'713 patent** discloses iloprost, a prostacyclin derivative that is a carboxylic acid. The '713 patent further discloses the diethanolamine salt of iloprost. col. 1, ll. 15–34, 41–49. • The **'095 publication** discloses the diethanolamine salt of a carboxylic acid, zopolrestat, which is "highly water soluble" and an "advantageous" salt form. ¶ 0005. • The **'164 patent** discloses the diethanolamine salt of piroxicam, an acidic benzothiazine. The '164 patent discloses that the diethanolamine salt is "crystalline, non-hygroscopic, rapidly dissolving . . . with high water solubility" and "possess[es] excellent chemical and physical stability properties." col. 8, ll. 37–38, col. 1, ll. 37–65, col. 2, l. 43–col. 3, l. 13. • **Remodulin** discloses the salt of treprostinil. • The **'953 patent** discloses the use of treprostinil for treatment of cardiovascular disease. Col. 2, ll. 8–11.
2	The compound of claim 1, wherein the compound melts at about 107° C.	*See* prior art above with respect to claim 1. • **Halebian 1969 at 911–12, Halebian 1975**

	Claim Term	Prior Art Where Limitation Is Found
		at 1669–70, Threlfall at 2436, Gu at 1878, Vippagunta, and Brittain at 1–2, 5–8 disclose that many pharmaceutical solids exhibit polymorphism that can have different chemical and physical properties. • **McCrone** teaches that every compound has different polymorphic forms and that the number of known forms increases as more time and money is spent researching the compound. p. 727 • **Guillory** teaches that all compounds can crystallize in different polymorphs and that the number increases as the compound is studied. p. 185 • **Hornedo at 657, Gu at 1878, Vippagunta at 3, Byrn at 948, and Bighley at 483** teach that polymorphic transformation should be assessed early in drug development so that the most stable form can be selected. • **FDA Supporting Documentation Guideline** requires that the drug sponsor use analytical procedures to detect polymorphs and stresses the importance of controlling the crystal form of the drug substance during development as a prerequisite to approval. pp. 34–35 • **Brittain** discloses that unstable crystal forms are often obtained first following crystallization. p. 21 • **Caira** also discloses the implications of polymorphism. P. 166

	Claim Term	Prior Art Where Limitation Is Found
		• **Byrn at 948, FDA Supporting Documentation Guideline, Gu at 1878, Vippagunta at 3, Caira at 166, Brittain at 21** disclose that it is desirable to use the most thermodynamically stable polymorphic form. • **Gu at 1878, Caira at 167, Hornedo at 657** teach the risk that a less stable polymorph may convert to a more stable form during manufacture or storage. • **Byrn at 946, Caira at 166, and Guillory at 188–202** disclose techniques for producing different polymorphs and isolating the most thermodynamically stable polymorph. • **Desiraju** discloses the practice of conducting polymorphic screening for a new drug substance. p. 405 • **Shekunov** discloses the use of crystallization for manufacturing drug substances for purification, that tablets are the most widely used solid dosage form, the importance of finding the most stable polymorphic form of substances, and the use of antisolvents in the crystallization process. Introduction, §§ 3.1, 3.3 and 4 • **Berge** discloses that the diethanolamine salt was "potentially useful" and the differences in the characteristics of salt forms and free acid. pp. 2, Table I, 4–10, 15

	Claim Term	Prior Art Where Limitation Is Found
3	The compound of claim 1, wherein the compound has an x-ray powder diffraction pattern having a pattern peak at about 17.2 degrees 2 theta.	*See* prior art cited above with respect to claims 1 and 2.

EXHIBIT C

The '839 Patent

	Claim Term	Prior Art Where Limitation Is Found
1	A pharmaceutical formulation comprising a therapeutically effective amount of a diethanolamine salt of treprostinil and a pharmaceutically acceptable carrier.	• **Simonneau** discloses the use of treprostinil sodium to treat pulmonary arterial hypertension. It further discloses drawbacks of subcutaneous infusion. pp. 800, 803, Table 5 • The **'222 patent** discloses treprostinil and salts of treprostinil, including amine salts, to treat pulmonary hypertension. It also discloses salts derived from bases, including organic bases, such as dicyclohexylamine. The '222 patent discloses the preparation of oral tablets that contain a compound of formula (I), and that such formulations typically contain a carrier. It further discloses that the effective amount of formula (I) for treating pulmonary hypertension is typically between 1 to 50 mg. It also discloses that treprostinil and pharmaceutically acceptable salts of treprostinil are a "particularly preferred compound of formula (I)." col. 2, ll. 53–57, col. 3, ll. 1–20, 35–41, col. 4, ll. 8–19, col. 6, ll. 58–63 • The **'075 patent** discloses treprostinil and a genus of compounds that encompasses treprostinil and the diethanolamine salt of those compounds. The '075 patent further discloses the steps to make treprostinil. It also discloses that the disclosed compounds and their salts can be used to inhibit platelet aggregation and reduce the adhesive character of platelets. col. 3, l. 18, col. 3, l. 21–col. 5, l. 35, col. 12, ll. 39–43, col. 74, ll. 25–37; Exs. 31–33.

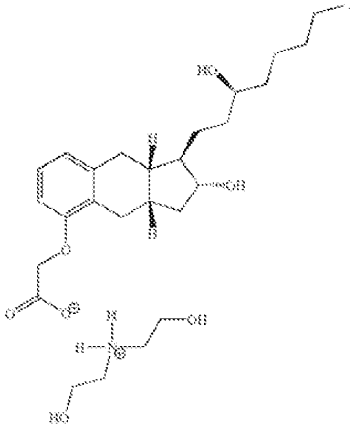
	Claim Term	Prior Art Where Limitation Is Found
		• **Bighley** discloses 38 cationic pharmaceutical salt forms in use at the time of publication, including the diethanolamine salt. The diethanolamine salt was among the more frequently used salts. Bighley also discloses that amine salts frequently have higher aqueous solubilities and bioavailabilities than their corresponding inorganic salts. These characteristics are "desirable formulation characteristics." pp. 456, Table 2, 461. • The **'265 patent** discloses cicaprost, a prostacyclin and carbacyclin derivative. Cicaprost has structural features in common with treprostinil, including the –0– CH_2COOH group where a salt can form with an amine such as diethanolamine. The '265 patent specifically identifies the diethanolamine salt as a suitable salt of prostacyclin and carbacyclin derivatives. col. 2, ll. 11–21. • The **'713 patent** discloses iloprost, a prostacyclin derivative that is a carboxylic acid. The '713 patent further discloses the diethanolamine salt of iloprost and the useful pharmacological properties of the iloprost. col. 1, ll. 15–34, 41–49, 54–col. 2, l.6 • The **'095 publication** discloses the diethanolamine salt of a carboxylic acid, zopolrestat, which is "highly water soluble" and an "advantageous" salt form. ¶ 0005. • The **'164 patent** discloses the diethanolamine salt of piroxicam, an acidic benzothiazine. The '164 patent

	Claim Term	Prior Art Where Limitation Is Found
		discloses that the diethanolamine salt is "crystalline, non-hygroscopic, rapidly dissolving . . . with high water solubility" and "possess[es] excellent chemical and physical stability properties." These properties facilitate the salts' incorporation into pharmaceutical dosage forms. col. 8, ll. 37–38, col. 1, ll. 37–65, col. 2, l. 43–col. 3, ll. 13–17 • **Remodulin®** and the **Remodulin® Label** disclose the salt of treprostinil.
3	The pharmaceutical formulation according to claim 1, wherein the formulation exists in a dosage form selected from a capsule, tablet, liquid, or suspension.	*See* prior art cited above with respect to claim 1. • The **'196 publication** discloses 36 tablet compositions that contain the prostacyclin analog beraprost sodium. The disclosed compositions, including p-glycoprotein inhibitors, successfully delivered beraprost sodium in vivo in a sustained release, oral tablet formulation. Beraprost is similar in structure and function to treprostinil. pp. 9–10, Tables 1–2 • The **'222 patent** discloses that the salts of the compounds in formula I can be incorporated into oral formulations, including capsules, cachets, lonzenges, or tablets. The patent also describes preparation of the tablets, which typically entails mixing a physiologically acceptable salt of a compound of formula (I), for example, with an acceptable carrier. The '222 patent also discloses administration of treprostinil to rats. col. 4, ll. 8–col. 5, l. 2, col. 5, ll. 56–64, col. 6, ll. 42–50 • The **'095 publication** discloses that the diethanolamine salt of zopolrstat, a carboxylic acid, is highly water soluble and therefore an advantageous salt form of zopolrestat. It was well known in in the

	Claim Term	Prior Art Where Limitation Is Found
		art that highly water soluble medicinal preparations, when administered orally, result in efficient absorption of such preparations from the gastrointestinal tract into systemic circulation. ¶ 0005
4	The pharmaceutical formulation of claim 1, wherein the diethanolamine salt of treprostinil comprises a diethanolamine salt of (+)-treprostinil.	*See* prior art cited above with respect to claim 1. • **Remodulin®** discloses the use of (+)-treprostinil as the commercial form of treprostinil.
5	The pharmaceutical formulation of claim 1, wherein the diethanolamine salt of treprostinil comprises a polymorph of a diethanolamine salt of (+)-treprostinil, which polymorph melts at 107° C.	*See* prior art cited above with respect to claims 2 and 3 of the '070 patent.

EXHIBIT D

The '713 Patent

	Claim Term	Prior Art Where Limitation Is Found
23	A method of treating pulmonary hypertension comprising orally administering to a subject in need thereof an effective amount of a compound of the following structure: 	*See* prior art cited above with respect to claim 1 of the '070 and '839 patents. • **Vizza** discloses a clinical study in which the oral prostacyclin analogue beraprost was administered to 13 patients with severe pulmonary hypertension. Oral administration of beraprost avoided problems associated with routes of administration of other pulmonary hypertension drugs. Eleven patients who completed a full trial all showed improvement. p. 661 • **Ansel 1999** teaches the benefits of oral administration, including by way of a tablet, of drugs. p. 120–23 • The **'222 patent** discloses that the salts of the compounds in formula I can be incorporated into oral formulations, including capsules, cachets, lonzenges, or tablets. The patent also describes preparation of the tablets, which typically entails mixing a physiologically acceptable salt of a compound of formula (I), for example, with an acceptable carrier. The '222 patent also discloses administration of treprostinil to rats. col. 4, ll. 8–col. 5, l. 2, col. 5, ll. 56–64, col. 6, ll. 42–50 • The **'095 publication** discloses that the diethanolamine salt of zopolrestat, a carboxylic acid, is highly water soluble and therefore an advantageous salt form of zopolrestat. It was well known in in the art that highly water soluble medicinal preparations, when administered orally, result in efficient absorption of such preparations from the gastrointestinal tract

	Claim Term	Prior Art Where Limitation Is Found
		into systemic circulation. ¶ 0005
24	The method of claim 23, wherein the compound melts at about 107° C.	*See* prior art cited above with respect to claims 2 and 3 of the '070 patent.
25	The method of claim 24, wherein the compound has an x-ray powder diffraction pattern having a pattern peak at about 17.2 degrees 2 theta.	*See* prior art cited above with respect to claims 2 and 3 of the '070 patent.

EXHIBIT E

The '169 Patent

	Claim Term	Prior Art Where Limitation Is Found
8	A pharmaceutical composition for oral administration comprising a therapeutically effective amount of a salt or ester of treprostinil, wherein said composition provides an oral bioavailability of treprostinil at least 50% greater than the oral bioavailability of a composition with treprostinil as a free acid.	• The **'222 patent** discloses treprostinil and salts of treprostinil, including amine salts, to treat pulmonary hypertension. It also discloses salts derived from bases, including organic bases, such as dicyclohexylamine. The '222 patent also discloses that the salts of the compounds in formula I can be incorporated into oral formulations, including capsules, cachets, lonzenges, or tablets. The '222 patent discloses the preparation of oral tablets, which typically entails mixing a physiologically acceptable salt of a compound of formula (I), for example, with an acceptable carrier. It further discloses that the effective amount of formula (I) for treating pulmonary hypertension is typically between 1 to 50 mg. It also discloses that treprostinil and pharmaceutically acceptable salts of treprostinil are a "particularly preferred compound of formula (I)." The '222 patent also discloses administration of treprostinil to rats. col. 2, ll. 53–57, col. 3, ll. 1–20, 35–41, col. 4, ll. 8–col. 5, l. 2, col. 5, ll. 56–63 col. 6, ll. 42–63 • **Simonneau** discloses the use of treprostinil sodium to treat pulmonary arterial hypertension. It further discloses drawbacks of subcutaneous infusion. pp. 800, 803, Table 5 • The **'075 patent** discloses treprostinil and a genus of compounds that encompasses treprostinil and the diethanolamine salt of those compounds. The '075 patent further discloses the steps to make treprostinil. It

	Claim Term	Prior Art Where Limitation Is Found
		also discloses that the disclosed compounds and their salts can be used to inhibit platelet aggregation and reduce the adhesive character of platelets. col. 3, l. 18, col. 3, l. 21–col. 5, l. 35, col. 12, ll. 39–43, col. 74, ll. 25–37; Exs. 31–33 • **Bighley** discloses 38 cationic pharmaceutical salt forms in use at the time of publication, including the diethanolamine salt. The diethanolamine salt was among the more frequently used salts. Bighley also discloses that amine salts frequently have higher aqueous solubilities and bioavailabilities than their corresponding inorganic salts. These characteristics are "desirable formulation characteristics." It further discloses that organic salt forms, such as amines, often have higher aqueous solubilities than inorganic salts and that the dissolution rate often indicates bioavailability, and that high solubility is often associated with high dissolution and absorption. It further discloses that bioavailability of salt is often higher than that of free acid. pp. 453, 456, Table 2, 461, 463–64, 474, 484–86 • **Berge** discloses the relationship between dissolution and bioavailability. pp. 5–6 • The **'265 patent** discloses cicaprost, a prostacyclin and carbacyclin derivative. Cicaprost has structural features in common with treprostinil, including the –0– CH_2COOH group where a salt can form with an amine such as diethanolamine. The '265 patent specifically identifies the diethanolamine

	Claim Term	Prior Art Where Limitation Is Found
		salt as a suitable salt of prostacyclin and carbacyclin derivatives. col. 2, ll. 11–21. • The **'713 patent** discloses iloprost, a prostacyclin derivative that is a carboxylic acid. The '713 patent further discloses the diethanolamine salt of iloprost. col. 1, ll. 15–34, 41–49. The **'095 publication** discloses that the diethanolamine salt of zopolrestat, a carboxylic acid, is highly water soluble and therefore an advantageous salt form of zopolrestat. It was well known in in the art that highly water soluble medicinal preparations, when administered orally, result in efficient absorption of such preparations from the gastrointestinal tract into systemic circulation. ¶ 0005 • The **'164 patent** discloses the diethanolamine salt of piroxicam, an acidic benzothiazine. The '164 patent discloses that the diethanolamine salt is "crystalline, non-hygroscopic, rapidly dissolving . . . with high water solubility" and "possess[es] excellent chemical and physical stability properties." These properties facilitate the salts' incorporation into pharmaceutical dosage forms. Abstract, col. 8, ll. 37–38, col. 1, ll. 37–65, col. 2, l. 43–col. 3, ll. 13–17 • The **'196 publication** discloses 36 tablet compositions that contain the prostacyclin analog beraprost sodium. The disclosed compositions, including p-glycoprotein inhibitors, successfully delivered beraprost sodium in vivo in a sustained release, oral tablet formulation. Beraprost is similar in structure and activity to treprostinil. pp. 9–10, Tables 1–2

	Claim Term	Prior Art Where Limitation Is Found
		• **Vizza** discloses a clinical study in which the oral prostacyclin analogue beraprost was administered to 13 patients with severe pulmonary hypertension. Oral administration of beraprost avoided problems associated with routes of administration of other pulmonary hypertension drugs. Eleven patients who completed a full trial all showed improvement. p. 661 • **Ansel 1999** teaches that benefits of oral administration, including by means of a tablet, of drugs. p. 120–23 • **Remodulin®** and the **Remodulin® Label** disclose the salt of treprostinil and that its absolute bioavailability is approximately 100%. p. 1 • The **'452 publication** teaches effective extended release technology.
9	The composition of claim 8, wherein said composition provides an oral bioavailability of treprostinil at least 100% greater than the oral bioavailability of a composition with treprostinil as a free acid.	*See* prior art cited above with respect to claim 8.
10	The composition of claim 8, wherein the ester is selected from the group consisting of a benzyl ester and an amino acid ester.	*See* prior art cited above with respect to claim 8.
11	The composition of claim 8, wherein the ester is selected from the group consisting of a benzyl ester and a diglycine ester.	*See* prior art cited above with respect to claim 8.

EXHIBIT F

The '311 Patent

	Claim Term	Prior Art Where Limitation Is Found
1	A method of producing a pharmaceutically acceptable salt of treprostinil comprising dissolving treprostinil in a solvent, adding a base, heating, and cooling in an antisolvent to form a pharmaceutically acceptable salt of treprostinil as a crystalline solid.	*See* prior art with respect to the '070 and '393 patents. • **Olmsted at 476, Pavia at 481–82 and Sharp at 65** describe the crystallization and recrystallization process used to remove impurities. • **Byrn** discloses creating crystal forms and the importance of screening for crystal forms (polymorphs) of a particular substance. it also discloses water and ethanol as particular solvents. p. 946 • **Shekunov at 4** discloses the use of antisolvents in the crystallization process. **Sharp** also discloses the use of a "poor" solvent, which functions as an antisolvent. 83–84. • The **'075 patent**, which discloses treprostinil, describes the process of transforming compounds in their free acid form into pharmacologically acceptable salts by adding a base to a solvent. col. 30, l. 41–col. 31, l. 5 • **Byrn** discloses that new crystal forms can be obtained by cooling hot saturated solutions. Byrn also recommends screening for polymorphs of a particular substance p. 946 • **Remodulin®** and the **Remodulin® Label** disclose the salt of treprostinil and its structural formula.
2	The method of claim 1, wherein the base is an inorganic base.	*See* prior art cited above with respect to claim 1. • The **'075 patent** discloses the use of an inorganic base and provides examples.

	Claim Term	Prior Art Where Limitation Is Found
		col. 30, ll. 41–62
3	The method of claim 2, wherein the base is an alkali metal.	*See* prior art cited above with respect to claims 1 and 2. • The **'075 patent** discloses metal salts, and specifically, the sodium salt. it further discloses metal cations that are "[e]specially preferred," including sodium and potassium. col. 14, ll. 56–66 • **Bighley** discloses metallic cations including potassium and sodium, for use in pharmaceutical salts. p. 456, Table 2, 482–83
4	The method of claim 3, wherein the alkali metal is sodium or potassium.	*See* prior art cited above with respect to claims 1–3.
5	The method of claim 1, wherein the base is an organic base.	*See* prior art cited above with respect to claim 1. • The **'075 patent** teaches the use of an organic base, including amine salts. It also specifically discloses the diethanolamine salt. col. 15, ll. 1–25, col. 30, ll. 41–col. 31, ll. 5 • **Bighley** discloses the DEA salt.
6	The method of claim 5, wherein the organic base is diethanolamine.	*See* prior art cited above with respect to claims 1 and 5.
7	The method of claim 3, wherein the solvent comprises ethanol and water.	*See* prior art cited above with respect to claims 1 and 3. • **Sharp** discloses the use of ethanol and water as solvents, as well as mixed solvents. pp. 81–84 • The **'075 patent** discloses water and ethanol as solvents. col. 30, ll. 41–66 • **Olmsted** discloses water and ethanol as

	Claim Term	Prior Art Where Limitation Is Found
		solvents. pp. 458, 476 • **Pavia** discloses a solvent mixture containing ethanol and water. p. 489 • **Byrn** discloses various solvents, including water and ethanol. p. 946
8	The method of claim 5, wherein the solvent comprises ethanol and water.	*See* prior art cited above with respect to claims 1, 5, and 7.
9	The method of claim 1, wherein the antisolvent comprises acetone.	*See* prior art cited above with respect to claim 1. • **Olmsted** describes the use of acetone in solvents. pp. 455, 458 • **Sharp** describes the use of acetone in solvents. pp. 81–82 • **Byrn** discloses the use of acetone to form crystals. p. 946 • **Yeo** discloses ethanol and acetone as antisolvents. p. 1
10	A pharmaceutically acceptable crystalline salt of treprostinil produced by the method of claim 1.	*See* prior art cited above with respect to claim 1 and claims 2 and 3 of the '070 patent. • **Remodulin®** discloses a crystalline salt of treprostinil.
11	A pharmaceutical composition prepared by combining a pharmaceutically acceptable salt of treprostinil produced according to the method of claim 1 and a pharmaceutically acceptable carrier.	*See* prior art cited above with respect to claims 1 and 10, as well as claims 2 and 3 of the '070 patent. • The **'222 patent** discloses a salt of treprostinil in a carrier, as well as the preparation of a formulation of treprostinil and a carrier. col. 4, ll. 8–col. 5, ll. 2 • The **'953 patent** discloses the administration of treprostinil and a suitable composition consisting of a carrier and the active ingredient. col. 6, ll.

	Claim Term	Prior Art Where Limitation Is Found
		8–19

EXHIBIT G

The '897 Patent

	Claim Term	Prior Art Where Limitation Is Found
1	An oral osmotic pharmaceutical dosage form of treprostinil, comprising an osmotically active drug core surrounded by a semi-permeable membrane, wherein the osmotically active drug core comprises A) at least one release enhancing agent selected from a group consisting of wicking agents, complexing agents, and micelle-forming agents, wherein i) the wicking agents are selected from the group consisting of high HLB surfactants, ionic surfactants, and non-swelling hydrophilic polymers, ii) the complexing agents are selected from the group consisting of polyvinyl pyrrolidone, cyclodextrins, and non-ionic surface active agents, and iii) the micelle-forming agents are selected from the group consisting of poly(ethylene oxide) modified sorbitan monoesters, fatty acid sorbitan esters, sodium lauryl sulfate, and sodium docusate, and B) treprostinil as treprostinil diethanolamine, and wherein the semi-permeable membrane includes at least one opening	• The **'452 publication** discloses an osmotic pharmaceutical dosage delivery system (preferably in the form of a tablet) that comprises a single, homogeneous composition within a semipermeable wall that maintains its integrity during pharmaceutical delivery and has at least one passage. The '452 further discloses that the composition within the wall contains a pharmaceutically active agent, a non-swelling solubilizing agent that "enhances the solubility of the pharmaceutically active agent," that the solubilizing agent can be SLS or other potential agents, that the composition contains a non-swelling wicking agent that "enhances the surface area contact of the pharmaceutical agent with the incoming aqueous fluid" to release the agent "in a predominantly soluble form," and that the wicking agent can also be SLS, or other substances. pp. 1–4, 7–8. The '452 publication also discloses that the pharmaceutically active agent can be "any of a broad variety of therapeutically active agents," including "antihypertensives" and that the delivery system can be used to deliver insoluble or poorly soluble actives. p. 9 • The **'283 patent** discloses an osmotic composition that comprises a drug- and osmotic-agent-containing core. The '283 patent also discloses that the osmotic composition comprises a coating that is water permeable and does not dissolve or erode in the environment of use that comprises a

	Claim Term	Prior Art Where Limitation Is Found
	suitable for providing for the osmotic delivery of the treprostinil from the osmotically active drug core.	drug- and osmotic-agent-containing core. The coating is also disclosed to have at least one delivery port. The '283 patent also discloses that the core can contain a solubility-enhancing agent, which can be a surfactant, and that the core can contain SLS or a variety of other listed components. col. 3, ll. 57–65, col. 12, ll. 5–15, 20–23 The '283 patent also discloses that the drug of the composition may be used in the form of a pharmaceutically acceptable salt and may be an antihypertensive agent. It further lists specific prostaglandins, platelet inhibitors, and antihypertensive agents. col. 6, ll. 30–31, 34–35, col. 7, ll. 31–34 • The **'081 publication** discloses a solid, oral, sustained release tablet formulation containing treprostinil diethanolamine. It further discloses and describes the preparation of treprostinil diethanolamine and that the diethanolamine salt is a "particularly preferred" embodiment of the invention and compound for use in treating pulmonary hypertension. The '081 publication also discloses that treprostinil is a weak acid. pp. 4, 8, 9, 22, 82, 84–85 • The **'855 publication** discloses an osmotic oral tablet composition that is surrounded by a semi-permeable wall that may comprise an exit passageway to provide for continuous release of the drug, and that the composition comprises an anionic surfactant. The '855 publication further discloses that use of a surfactant, which increases water solubility, and pharmaceutically acceptable salt improves the amount of

	Claim Term	Prior Art Where Limitation Is Found
		drug delivered and reduces the amount of drug remaining in the composition and in the dosage after delivery. The '855 further discloses that the composition comprises an active ingredient that can be a cardiovascular drug. ¶¶ 0009–0010, 0014, 0018, 0021, 0027, 0031, 0035, 0037, 0060 • The **'212 patent** discloses sustained-release formulations of treprostinil. col. 4, l. 54
2	An oral osmotic pharmaceutical dosage form of claim 1, wherein the treprostinil diethanolamine has water solubility of at least about 30 mg/ml.	*See* prior art cited above with respect to claim 1. • The **'095 publication** discloses that zopolrestat has a water solubility of 100 mg/ml. ¶¶ [0005], [0013] • The '**164 patent** discloses the high water solubility of diethanolamine salts. col. 1, ll. 59–61 • The **Remodulin Label** discloses that Remodulin has an absolute bioavailability approximating 100%. p. 1 • The **'684 publication** discloses a long, non-exclusive list of "highly soluble drugs that can be incorporated into a sustained-release oral dosage form. The publication defines "highly soluble" as more than 100 g/l. §§ [0023], [0026], [0119], [0043], [0049] • The **'283 patent** discloses the use of a prostacyclin in the invention. col. 7, l. 31

	Claim Term	Prior Art Where Limitation Is Found
3	An oral osmotic pharmaceutical dosage form of claim 1 exhibiting an in-vivo release profile that may be predicted from an in-vitro release profile.	*See* prior art cited above with respect to claim 1. • The **'081 publication at 83, '452 publication at 11, '855 publication at ¶ [0051], '684 publication at ¶¶ [0016], [0017], [0023]** disclose that sustained-release in vivio release profiles were well understood.
4	An oral osmotic pharmaceutical dosage form of claim 1, wherein said oral osmotic pharmaceutical dosage form is a sustained-release dosage form.	*See* prior art cited above with respect to claim 1. • The **'081 publication** describes sustained release treprostinil diethanolamine tablets that provided elevated blood drug levels for more than two hours and indicated that this was desirable. pp. 82–85, Figure 14 • The **'452 publication** discloses osmotic formulations that released drug product over a prolonged period of time in *in vitro* tests. pp. 6–9 • The **'283 patent** describes and discloses exemplary sustained release compositions. col. 14, ll. 60–65, col. 17, ll. 57–61
5	An oral osmotic pharmaceutical dosage form of claim 4, wherein the treprostinil diethanolamine has a short half-life.	*See* prior art cited above with respect to claims 1 and 4. • The **'081 publication** discloses the half-life of treprostinil. p. 63
6	An oral osmotic pharmaceutical dosage form of claim 5, wherein said half-life ranges from several minutes to three hours.	*See* prior art cited above with respect to claims 1 and 4.
7	An oral osmotic pharmaceutical dosage form of claim 1, wherein the amount of treprostinil diethanolamine is sufficient to produce a therapeutically effective plasma	*See* prior art cited above with respect to claim 1. • The **'081 publication** discloses the amount of treprostinil diethanolamine

	Claim Term	Prior Art Where Limitation Is Found
	concentration of treprostinil.	used in four different oral treprostinil diethanolamine solutions and the resulting treprostinil blood concentrations and pharmacokinetics. It further discloses that an oral sustained release tablet can provide potentially therapeutic concentrations over an extended period and that the tablets yielded peak blood concentrations of more than 600 pg/ml in humans. pp. 82, 83, Figures 13A–D, 84, 85, Figure 14 • **Remodulin's** prescribing information discloses that the therapeutic steady-state treprostinil blood concentration is about 2 ug/liter. p. 4
8	An oral osmotic pharmaceutical dosage form of claim 7, wherein the therapeutically effective plasma concentration of treprostinil in a human has a C_{min} of 0.1 ng/ml to 0.2 ng/ml.	*See* prior art cited above with respect to claims 1 and 7.
9	An oral osmotic pharmaceutical dosage form of claim 7, wherein the therapeutically effective plasma concentration of treprostinil in a human has a C_{max} of 0.5 ng/ml to 2 ng/ml.	*See* prior art cited above with respect to claims 1 and 7.
10	An oral osmotic pharmaceutical dosage form of claim 9, wherein the therapeutically effective plasma concentration of treprostinil in a human has a T_{max} (time to reach C_{max}) of 2 hours to 8 hours.	*See* prior art cited above with respect to claims 1 and 7. • The **'684 publication** discloses plasma levels that peak at 2 hours and 8 hours. ¶ [0018]
11	An oral osmotic pharmaceutical dosage form of claim 7, wherein the therapeutically effective plasma concentration of treprostinil is maintained to allow for a twice-a-day or once-a-day administration.	*See* prior art cited above with respect to claims 1 and 7. • The **'081 publication** discloses that an 8-hour sustained release treprostinil diethanolamine formulation had already been prepared that provided potentially therapeutic drug concentrations. 82, 84–85, Figure 14

	Claim Term	Prior Art Where Limitation Is Found
		• The **'452 publication** also discloses modification of various ingredients to achieve the desired release profile. p. 11
12	An oral osmotic pharmaceutical dosage form of claim 7, wherein the therapeutically effective plasma concentration of treprostinil results in reduced side effects.	*See* prior art cited above with respect to claims 1, 4, and 7. • The **'081 publication at 62, 79–80, '684 publication at ¶ [0046], and '283 patent at col. 1, ll. 61–col. 2, ll. 10** describe the potential for plasma spikes with treprostinil and the advantages of extended-release dosage forms to include less fluctuation in drug blood levels
13	An oral osmotic pharmaceutical dosage form of claim 1 wherein said at least one release enhancing agent is present in the dosage form in a concentration of 0.5% to 90% by weight.	*See* prior art cited above with respect to claim 1. • The **'452 publication** also discloses SLS, a release-enhancing agent, in this range. Tables 1–6, Figures 3–9
14	An oral osmotic pharmaceutical dosage form of claim 1 wherein said release-enhancing agent is selected from the group consisting of wicking agents and micelle-forming agents.	*See* prior art cited above with respect to claims 1 and 13. • The **'452 publication** discloses that SLS is a wicking agent and a micelle-forming agent. p. 7–8
15	An oral osmotic pharmaceutical dosage form of claim 1, wherein said at least one release enhancing agent is a wicking agent selected from the group consisting of ionic surfactants, and non-swelling hydrophilic polymers.	*See* prior art cited above with respect to claims 1, 13, and 14.
16	An oral osmotic pharmaceutical dosage form of claim 1, wherein said at least one release enhancing agent is a non-swelling hydrophilic polymer selected from the group consisting of polyethylene oxide-polypropylene oxide block copolymers,	*See* prior art cited above with respect to claim 1. • The **'452 publication** discloses a composition that includes a solubilizing agent which can be

	Claim Term	Prior Art Where Limitation Is Found
	cellulose ethers, and polyethylene glycols.	polyethylene glycol. It also discloses specific osmotic compositions that contain a polyethylene glycol and related dissolution data. pp. 3, 8, 14, 15, Tables 1 and 2, Figures 3 and 4
17	An oral osmotic pharmaceutical dosage form of claim 1, wherein said at least one release enhancing agent is a complexing agent selected from the group consisting of polyvinyl pyrrolidone, and non-ionic surface active agents.	*See* prior art cited above with respect to claim 1. • The **'452 publication** discloses a composition that includes a solubilizing agent which can be polyvinyl pyrrolidone. The wicking agent of the disclosed composition also can be polyvinyl pyrrolidone. pp. 3, 7–8, 16–17, Tables 3 and 4, Figures 5 and 6
18	An oral osmotic pharmaceutical dosage form of claim 1, wherein said at least one release enhancing agent is a micelle-forming agent selected from the group consisting of poly(ethylene oxide) modified sorbitan monoesters, fatty acid sorbitan esters, and sodium lauryl sulfate.	*See* prior art cited above with respect to claims 1 and 13.
19	An oral osmotic pharmaceutical dosage form of claim 1, wherein said dosage form is selected from the group consisting of tablets, capsules, and pellets.	*See* prior art cited above with respect to claim 1. • The **'081 publication** discloses the existence of sustained release treprostinil diethanolamine tablets, as well as *in vivo* data • The **'452 publication** discloses a general method for preparing an osmotic tablet and formulations and dissolution data for sustained release, osmotic nifedipine tablets.
20	A method of oral delivery of treprostinil comprising administering to a human patient in need thereof an oral osmotic	*See* prior art cited above with respect to claim 1.

	Claim Term	Prior Art Where Limitation Is Found
	pharmaceutical dosage form of claim 1.	
21	A method of claim 20, where said at least one release enhancing agent is selected from a group consisting of wicking agents, and micelle-forming agents.	*See* prior art cited above with respect to claims 1, 13, and 14.
22	A method of claim 21, wherein said at least one release enhancing agent is a wicking agent is selected from the group consisting of ionic surfactants, and non-swelling hydrophilic polymers.	*See* prior art cited above with respect to claims 1, 13, and 14.
23	A method of claim 22, wherein said at least one release enhancing agent is a non-swelling hydrophilic polymer selected from the group consisting of polyethylene oxide-polypropylene oxide block copolymers, cellulose ethers, and polyethylene glycols.	*See* prior art cited above with respect to claims 1 and 16.
24	A method of claim 22, where said at least one release enhancing agent is a complexing agent selected from the group consisting of polyvinyl pyrrolidone, and non-ionic surface active agents.	*See* prior art cited above with respect to claims 1 and 17.
25	A method of claim 21, wherein said at least one release enhancing agent is a micelle-forming agent selected from the group consisting of poly(ethylene oxide) modified sorbitan monoesters, fatty acid sorbitan esters, and sodium lauryl sulfate.	*See* prior art cited above with respect to claims 1, 13, and 18.
26	A method of claim 20, wherein said treprostinil diethanolamine has a short half-life.	*See* prior art cited above with respect to claims 1 and 4.
27	A method of claim 26, wherein said treprostinil diethanolamine has a half-life ranging from several minutes up to three hours.	*See* prior art cited above with respect to claims 1 and 4.
28	A method of claim 20, wherein the amount of treprostinil diethanolamine is sufficient to produce a therapeutically effective plasma concentration of	*See* prior art cited above with respect to claims 1 and 7.

	Claim Term	Prior Art Where Limitation Is Found
	treprostinil.	
29	A method of claim 28, wherein the therapeutically effective plasma concentration of treprostinil in a human has a C_{min} of 0.1 ng/ml to 0.2 ng/ml.	*See* prior art cited above with respect to claims 1 and 7.
30	A method of claim 28, wherein the therapeutically effective plasma concentration of treprostinil in a human has a C_{max} of 0.5 ng/ml to 2 ng/ml.	*See* prior art cited above with respect to claims 1 and 7.
31	A method of claim 30, wherein the therapeutically effective plasma concentration of treprostinil in a human has a T_{max} (time to reach C_{max}) of 2 hours to 8 hours.	*See* prior art cited above with respect to claims 1 and 7.
32	A method of claim 28, wherein the therapeutically effective plasma concentration of treprostinil is maintained to allow for a twice-a-day or once-a-day administration.	*See* prior art cited above with respect to claims 1, 7, and 11.
33	A method of treating a disease selected from the group consisting of pulmonary hypertension, pulmonary arterial hypertension (PAH), peripheral vascular disease (PVD), ischemic diseases, heart failure, conditions requiring anticoagulation, thrombotic microangiopathy, extracorporeal circulation, central retinal vein occlusion, atherosclerosis, inflammatory diseases, hypertension, cancer and other conditions of unregulated cell growth, comprising administering to a patient in need thereof an oral osmotic pharmaceutical dosage form of claim 1.	*See* prior art cited above with respect to claim 1. • **Remodulin's** prescribing information discloses that Remodulin was indicated for "the treatment of pulmonary arterial hypertension in patients with NYHA [New York Heart Association] Class II–IV symptoms." p. 6
34	A method of claim 33, wherein said at least one release enhancing agent is selected from the group consisting of wicking agents, and micelle-forming agents.	*See* prior art cited above with respect to claims 1, 13, 14, and 33.

	Claim Term	Prior Art Where Limitation Is Found
35	A method of claim 34, wherein said at least one release enhancing agent is a wicking agent is selected from the group consisting of ionic surfactants, and non-swelling hydrophilic polymers.	*See* prior art cited above with respect to claims 1, 13, 14, and 33.
36	A method of claim 35, wherein said at least one release enhancing agent is a non-swelling hydrophilic polymer selected from the group consisting of polyethylene oxide-polypropylene oxide block copolymers, cellulose ethers, and polyethylene glycols.	*See* prior art cited above with respect to claims 1, 16, and 33.
37	A method of claim 33, where said at least one release enhancing agent is a complexing agent selected from the group consisting of polyvinyl pyrrolidone, and non-ionic surface active agents.	*See* prior art cited above with respect to claims 1, 17, and 33.
38	A method of claim 34, wherein said at least one release enhancing agent is a micelle forming agent selected from the group consisting of poly(ethylene oxide) modified sorbitan monoesters, fatty acid sorbitan esters, and sodium lauryl sulfate.	*See* prior art cited above with respect to claims 1, 13, 14, 18, and 33.
39	A method of claim 33, wherein said disease is pulmonary arterial hypertension (PAH).	*See* prior art cited above with respect to claims 1 and 33.
40	An oral osmotic pharmaceutical dosage form of claim 1, which is a tablet comprising treprostinil diethanolamine in an amount equivalent to about 1 mg treprostinil.	*See* prior art cited above with respect to claim 1. • The **'081 publication** discloses that 1 mg sustained release formulations provided "potentially therapeutic drug concentrations" in humans. pp. 84–85 • **Remodulin** was also administered at a rate that totals about 1 mg/day. pp. 9–10
41	An oral osmotic pharmaceutical dosage form of claim 1, which is a tablet comprising treprostinil diethanolamine in	*See* prior art cited above with respect to claims 1 and 40.

	Claim Term	Prior Art Where Limitation Is Found
	an amount equivalent to about 1 mg to 5 mg of treprostinil.	
42	An oral osmotic pharmaceutical dosage form of claim 1, which is a tablet comprising treprostinil diethanolamine in an amount equivalent to about 1 mg to 10 mg of treprostinil.	*See* prior art cited above with respect to claims 1 and 40.
43	An oral osmotic pharmaceutical dosage form of claim 7, wherein the therapeutically effective plasma concentration of treprostinil in a human has a C_{min} of 0.1 ng/ml to 0.2 ng/ml, and a C_{max} of 0.5 ng/ml to 2 ng/ml, and a T_{max} (time to reach C_{max}) of 2 hours to 8 hours.	*See* prior art cited above with respect to claims 1 and 7.
44	A method of claim 20, wherein the oral osmotic pharmaceutical dosage form is a tablet comprising treprostinil diethanolamine in an amount equivalent to about 1 mg of treprostinil.	*See* prior art cited above with respect to claims 1 and 40.
45	A method of claim 20, wherein the oral osmotic pharmaceutical dosage form is a tablet comprising treprostinil diethanolamine in an amount equivalent to about 1 mg to 5 mg of treprostinil.	*See* prior art cited above with respect to claims 1 and 40.
46	A method of claim 20, wherein the oral osmotic pharmaceutical dosage form is a tablet comprising treprostinil diethanolamine in an amount equivalent to about 1 mg to 10 mg of treprostinil.	*See* prior art cited above with respect to claims 1 and 40.
47	A method of claim 20, wherein the oral osmotic pharmaceutical dosage form is administered in an amount sufficient to produce a plasma concentration of treprostinil having a C_{min} of 0.1 ng/ml to 0.2 ng/ml, and a C_{max} of 0.5 ng/ml to 2 ng/ml, and a T_{max} (time to reach C_{max}) of 2 hours to 8 hours.	*See* prior art cited above with respect to claims 1 and 7.
48	An oral osmotic pharmaceutical dosage form of claim 1, wherein the semi-	*See* prior art cited above with respect to claim 1.

	Claim Term	Prior Art Where Limitation Is Found
	permeable membrane comprises cellulose acetate and at least one component select from the group consisting of triethyl citrate (TEC), propylene glycol(PG), mixtures in ratios of TEC to PG ranging from 25:75 to 75:25, Tween 80, polyethylene glycol (PEG); a polyoxyethylene sorbitan ester, triacetin, diethyl phthalate, mineral oil, tributyl sebacate, and glycerol.	• The **'452 publication** discloses a tablet with coating that comprises cellulose acetate and triethyl citrate. pp. 10–11
49	An oral osmotic pharmaceutical dosage form of claim 48, wherein the semi-permeable membrane comprises triethyl citrate.	*See* prior art cited above with respect to claims 1 and 48.
50	An oral osmotic pharmaceutical dosage form of claim 1, which comprises an effective amount of treprostinil diethanolamine up to about 1 mg of treprostinil as treprostinil diethanolamine.	*See* prior art cited above with respect to claims 1 and 40.
51	An oral osmotic pharmaceutical dosage form of claim 1, which comprises an effective amount of treprostinil diethanolamine up to about 5 mg of treprostinil as treprostinil diethanolamine.	*See* prior art cited above with respect to claims 1 and 40.
52	An oral osmotic pharmaceutical dosage form of claim 1, which comprises an effective amount of treprostinil diethanolamine up to about 10 mg of treprostinil as treprostinil diethanolamine.	*See* prior art cited above with respect to claims 1 and 40.
53	An oral osmotic pharmaceutical dosage form of claim 1, wherein the semi-permeable membrane comprises 3% to 10% by weight of the oral osmotic pharmaceutical dosage form.	*See* prior art cited above with respect to claim 1. • The **'452 publication** discloses that the semipermeable wall should be present at 2–15 percent of the tablet weight. p. 6
54	An oral osmotic pharmaceutical dosage form of claim 1, wherein the semi-permeable membrane includes one	*See* prior art cited above with respect to claim 1. • The **'452 publication** discloses that

	Claim Term	Prior Art Where Limitation Is Found
	opening suitable for providing for the osmotic delivery of the treprostinil diethanolamine from the osmotically active drug core.	the "semi-permeable wall of the tablet can contain at least one passageway communicating the contents of the core with the exterior of the device, delivering the beneficial drug through the passageways from the elementary osmotic device." pp. 6–7 • The **'855 publication** discloses that such a hole was routine. ¶ 0037
55	An oral osmotic pharmaceutical dosage form of claim 13, wherein said at least one release enhancing agent is present in the dosage form in a concentration of 1% to 20% by weight.	*See* prior art cited above with respect to claims 1 and 13. • The **'452 publication** discloses compositions that contain a total concentration of release-enhancing agents of from 10 percent to 20 percent. p. 19, Table 6
56	An oral osmotic pharmaceutical dosage form of claim 1, wherein the osmotically active drug core further comprises at least one osmotic agent.	*See* prior art cited above with respect to claim 1. • The **'452 publication** discloses a composition of claim 1 that comprises an osmotic agent. p. 3
57	An oral osmotic pharmaceutical dosage form of claim 56, wherein the at least one osmotic agent is selected from the group consisting of sucrose, xylitol, glucose, lactose, sodium chloride, potassium chloride, cellulose ethers, maltodextrins, and cyclodextrins.	*See* prior art cited above with respect to claims 1 and 56. • The **'452 publication** discloses osmotic compositions that contain xylitol. p. 15, Table 2, 19, Table 6
58	An oral osmotic pharmaceutical dosage form of claim 56, wherein the at least one osmotic agent is present in the dosage form in a concentration of 1% by weight to 90% by weight.	*See* prior art cited above with respect to claims 1 and 57. • The **'452 publication** discloses a number of compositions containing a total concentration of osmotic agent within the claimed range. p. 19, table 6

	Claim Term	Prior Art Where Limitation Is Found
59	An oral osmotic pharmaceutical dosage form of claim 1, wherein the at least one release enhancing agent is sodium lauryl sulfate.	*See* prior art cited above with respect to claim 1. • The **'452 publication** discloses that SLS generally can be used as a solubilizing agent and discloses a number of specific osmotic formulations that contain SLS. pp. 8, 14–19, Tables 1–6
60	An oral osmotic pharmaceutical dosage form of claim 59, wherein the at least one osmotic agent is comprises xylitol.	*See* prior art cited above with respect to claims 1 and 57.

EXHIBIT H

The '892 Patent

	Claim Term	Prior Art Where Limitation Is Found
1	A pharmaceutical product comprising a pharmaceutical packaging; and a solid formulation inside the packaging, wherein the formulation comprises an active agent that is treprostinil diethanolamine, wherein the packing is configured to maintain a moisture level in the solid formulation of greater than 3% and no more than 7%.	• **Phares** teaches the preparation of treprostinil diethanolamine and describes a safety, tolerability, and pharmacokinetic study comparing a sustained-release treprostinil diethanolamine tablet and a sustained-release treprostinil diethanolamine capsule administered to humans. It further discloses that the two treprostinil diethanolamine crystalline polymorphic forms readily absorb moisture. Phares also discloses that treprostinil can be formulated into various dosage forms, including tablets, using known methods and excipients. [0105]–[0107], [0175]–[0184], [0321]–[0349] • **Safdar** discloses phase 2 and phase 3 clinical trials for the treatment of pulmonary arterial hypertension. It further discloses the FREEDOM study that evaluated the efficacy of an oral sustained-release osmotic tablet containing treprostinil diethanolamine. pp. 228–29, Table 1 • **FDA Container Guidance** provides an overview of what information the FDA requires from an applicant regarding the packaging of a drug product in order to obtain approval to sell the drug product in the United States. pp. 20–21, 33, 36, Table 7 • The **Freedom Study** discloses that patients received oral treprostinil for treatment of pulmonary arterial hypertension. • **Lockhart** contains a throughout discussion of pharmaceutical packaging, including the effects of moisture on oral tablets. It further discloses the importance of moisture protection of solid oral

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		preparations. It also discloses factors involving the selection of containers and the use of desiccants. pp. 13–15, 28–29, 30, 93 • **Desiccant delivery systems** discloses various containers and vials for drugs "with airtight and leak proof coinjected desiccant linings, as well as desiccant sheets and film. • **Protective desiccants** discloses a cartridge containing DryGuard desiccants that "are highly effective static adsorbents designed to protect moisture sensitive products from corrosion, mildew, and other humidity related problems during shipping."
2	The pharmaceutical product of claim 1, wherein said formulation comprises at least one pharmaceutically acceptable excipient.	*See* prior art cited above with respect to claim 1. • The **'452 publication** discloses components of the disclosed composition: "[p]referred non-swelling osmotic agents includ[ing]" fructose, lactose, xylitol, and sorbitol. at 3.
3	The pharmaceutical product of claim 2, wherein said at least one excipient comprises at least one of maltodextrin and xylitol.	*See* prior art cited above with respect to claims 1 and 2.
4	The pharmaceutical product of claim 1, wherein the packaging in configured to maintain the moisture level of no less than 3.5% and no more than 6%.	*See* prior art cited above with respect to claim 1.
5	The pharmaceutical product of claim 1, wherein the packaging in configured to maintain the moisture level of no less than 3.5% and no more than 4.5%.	*See* prior art cited above with respect to claim 1.
6	The pharmaceutical product of claim 1, wherein said packaging is a bottle packaging	*See* prior art cited above with respect to claim 1.

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9	A pharmaceutical product comprising: (a) a pharmaceutical packaging; (b) a solid formulation inside the packaging, wherein the formulation comprises a active agent that is treprostinil diethanolamine; and (c) a desiccant inside the packaging, wherein an amount of the desiccant in the packaging is less than an effective amount for maintaining a relative humidity level inside the packaging for a storage time of the formulation below 40%.	*See* prior art cited above with respect to claim 1.
10	The pharmaceutical product of claim 9, wherein said formulation further comprises at least one pharmaceutically acceptable excipient.	*See* prior art cited above with respect to claims 1 and 2.
11	The pharmaceutical product of claim 10, wherein said at least one excipient comprises at least one of maltodextrin and xylitol.	*See* prior art with regard to claims 1 and 2.
12	The pharmaceutical product of claim 9, wherein the packaging is a bottle.	*See* prior art cited above with respect to claim 1.
13	The pharmaceutical product of claim 9, wherein the amount of the desiccant in the packaging is less than an effective amount for maintaining a humidity level in the packaging for 24 months below 40%.	*See* prior art cited above with respect to claim 1.
14	The pharmaceutical product of claim 13, wherein the amount of the desiccant in the packaging is at least two times less than an effective amount for maintaining a humidity level in the packaging for 24 months below 40%.	*See* prior art cited above with respect to claim 1.
15	A storage method comprising: storing a solid formulation inside a pharmaceutical packaging, wherein the	*See* prior art cited above with respect to claim 1.

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	formulation comprises an active agent that is treprostinil diethanolamine; wherein a moisture level in the solid formulation after said storing is greater than 3% and no more than 7%.	
16	The storage method of claim 15, wherein said formulation further comprises at least one pharmaceutically acceptable excipient.	*See* prior art above with respect to claims 1 and 2.
17	The storage method of claim 16, wherein said at least one excipient comprises at least one of maltodextrin and xylitol.	*See* prior art above with respect to claims 1 and 2.
18	The storage method of claim 15, wherein the moisture level in the solid formulation after said storing is no less than 3.5% and no more than 6%.	*See* prior art cited above with respect to claim 1.
19	The storage method of claim 15, wherein the moisture level in the solid formulation after said storing is of no less than 3.5% and no more than 4.5%.	*See* prior art cited above with respect to claim 1.
20	The storage method of claim 15, wherein said storing lasts at least 12 months.	*See* prior art cited above with respect to claim 1.
21	The storage method of claim 15, wherein said storing lasts at least 24 months.	*See* prior art cited above with respect to claims 1 and 2.
22	The storage method of claim 15, wherein the solid formulation is stored inside the packaging together with a desiccant, wherein an amount of the desiccant is less that an effective amount for maintaining a humidity level inside the packaging during said storing below 40%.	*See* prior art cited above with respect to claim 1.
23	The storage method of claim 15, wherein said packaging is a bottle packaging.	*See* prior art cited above with respect to claim 1.

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25	A storage method comprising: storing a solid formulation and a desiccant inside a pharmaceutical packaging, wherein the formulation comprises an active agent that is treprostinil diethanolamine; wherein an amount of the desiccant is less that an effective amount for maintaining a relative humidity level inside the packaging during said storing below 40%.	*See* prior art cited above with respect to claim 1.
26	The storage method of claim 25, wherein said formulation further comprises at least one pharmaceutically acceptable excipient.	*See* prior art cited above with respect to claims 1 and 2.
27	The storage method of claim 26, wherein said at least one excipient comprises at least one of maltodextrin and xylitol.	*See* prior art cited above with respect to claims 1 and 2.
28	The storage method of claim 25, wherein a moisture level in the solid formulation after said storing is no less than 3.5% and no more than 6%.	*See* prior art cited above with respect to claim 1.
29	The storage method of claim 25, wherein a moisture level in the solid formulation after said storing is of no less than 3.5% and no more than 4.5%.	*See* prior art cited above with respect to claim 1.
30	The storage method of claim 25, wherein said storing lasts at least 12 months.	*See* prior art cited above with respect to claim 1.
31	The storage method of claim 25, wherein said storing lasts at least 24 months.	*See* prior art cited above with respect to claim 1.
32	The storage method of claim 25, wherein said packaging is a bottle packaging.	*See* prior art cited above with respect to claim 1.

EXHIBIT I

The '901 Patent

	Claim Term	Prior Art Where Limitation Is Found
1	A method of treating pulmonary hypertension comprising administering to a subject in needed thereof an oral pharmaceutical formulation comprising a pharmaceutically acceptable salt or ester of treprostinil which has an absolute bioavailability of at least 15%, wherein a Cmax in a plasma of the subject increases in a linear fashion with a dose of at least 0.05 mg administered to the subject and wherein a concentration of treprostinil in the plasma of the subject is at least 50 pg/ml for at least 8 hours.	*See* prior art with regard to claims 8 and 9 of the '169 patent. • The **'222 patent** discloses treprostinil and salts of treprostinil, including amine salts, to treat pulmonary hypertension. It also discloses salts derived from bases, including organic bases, such as dicyclohexylamine. The '222 patent also discloses that the salts of the compounds in formula I can be incorporated into oral formulations, including capsules, cachets, lonzenges, or tablets. The '222 patent discloses the preparation of oral tablets, which typically entails mixing a physiologically acceptable salt of a compound of formula (I), for example, with an acceptable carrier. It further discloses that the effective amount of formula (I) for treating pulmonary hypertension is typically between 1 to 50 mg. It also discloses that treprostinil and pharmaceutically acceptable salts of treprostinil are a "particularly preferred compound of formula (I)." The '222 patent also discloses administration of treprostinil to rats. col. 2, ll. 53–57, col. 3, ll. 1–20, 35–41, col. 4, ll. 8–col. 5, l. 2, col. 5, ll. 56–63 col. 6, ll. 42–63 • **Simonneau** discloses the use of treprostinil sodium to treat pulmonary arterial hypertension. It further discloses drawbacks of subcutaneous infusion. pp. 800, 803, Table 5 • The **'075 patent** discloses treprostinil and a genus of compounds that encompasses

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		treprostinil and the diethanolamine salt of those compounds. The '075 patent further discloses the steps to prepare amine salts of the disclosed compounds. It also discloses that the disclosed compounds and their salts can be used to inhibit platelet aggregation and reduce the adhesive character of platelets. col. 3, l. 18, col. 3, l. 21–col. 5, l. 35, col. 12, ll. 39–43, col. 30, l. 41–col. 31, l. 5, col. 74, ll. 25–37; Exs. 31–33. • **Bighley** discloses 38 cationic pharmaceutical salt forms in use at the time of publication, including the diethanolamine salt. The diethanolamine salt was among the more frequently used salts. Bighley also discloses that amine salts frequently have higher aqueous solubilities and bioavailabilities than their corresponding sodium salts. These characteristics are "desirable formulation characteristics." Blighley identifies the diethanolamine salt as one that can provide increased absorption of the drug. pp. 453, 456, Table 2, 461, 484 • The **'265 patent** discloses cicaprost, a prostacyclin and carbacyclin derivative. Cicaprost has structural features in common with treprostinil, including the –0– CH_2COOH group where a salt can form with an amine such as diethanolamine. The '265 patent specifically identifies the diethanolamine salt as a suitable salt of prostacyclin and carbacyclin derivatives. col. 2, ll. 11–21. • The **'713 patent** discloses iloprost, a

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		prostacyclin derivative that is a carboxylic acid. The '713 patent further discloses the diethanolamine salt of iloprost. col. 1, ll. 15–34, 41–49. The **'095 publication** discloses that the diethanolamine salt of zopolrestat, a carboxylic acid, is highly water soluble and therefore an advantageous salt form of zopolrestat. It was well known in in the art that highly water soluble medicinal preparations, when administered orally, result in efficient absorption of such preparations from the gastrointestinal tract into systemic circulation. ¶ 0005 • The **'164 patent** discloses the diethanolamine salt of piroxicam, an acidic benzothiazine. The '164 patent discloses that the diethanolamine salt is "crystalline, non-hygroscopic, rapidly dissolving . . . with high water solubility" and "possess[es] excellent chemical and physical stability properties." These properties facilitate the salts' incorporation into pharmaceutical dosage forms. col. 8, ll. 37–38, col. 1, ll. 37–65, col. 2, l. 43–col. 3, ll. 13–17 • The **'196 publication** discloses 36 tablet compositions that contain the prostacyclin analog beraprost sodium. The disclosed compositions, including p-glycoprotein inhibitors, successfully delivered beraprost sodium in vivo in a sustained release, oral tablet formulation. Beraprost is similar and activity to treprostinil. pp. 9–10, Tables 1–2 • **Vizza** discloses a clinical study in which the oral prostacyclin analogue beraprost

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		was administered to 13 patients with severe pulmonary hypertension. Oral administration of beraprost avoided problems associated with routes of administration of other pulmonary hypertension drugs. Eleven patients who completed a full trial all showed improvement. p. 661 • **Ansel 1999** teaches that benefits of oral administration, including by means of a tablet, of drugs. p. 120–23 • **Remodulin®** and the **Remodulin® Label** disclose the salt of treprostinil.
2	The method of claim 1, wherein the absolute bioavailability of said salt or ester ranges from 21 to 25%.	*See* prior art cited above with respect to claim 1.
3	The method of claim 1, wherein the oral bioavailability of the salt or ester is at least 50% greater than the oral bioavailability of treprostinil as free acid.	*See* prior art cited above with respect to claim 1.
4	The method of claim 1, wherein the oral bioavailability of the salt or ester is at least 100% greater than the oral bioavailability of treprostinil as free acid.	*See* prior art cited above with respect to claim 1.
5	The method of claim 1, wherein the pharmaceutically acceptable salt or ester is the diethanolamine salt of treprostinil.	*See* prior art cited above with respect to claim 1.
6	The method of claim 1, wherein the subject is a human.	*See* prior art cited above with respect to claim 1.
7	A method of treating pulmonary hypertension comprising administering to a subject in needed thereof an oral pharmaceutical formulation comprising	*See* prior art cited above with respect to claim 1.

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	a pharmaceutically acceptable salt or ester of treprostinil which has an absolute bioavailability of at least 15%, wherein an AUCinf in a plasma of the subject increases in a linear fashion with a dose of at least 0.05 mg administered to the subject and wherein a concentration of treprostinil in the plasma of the subject is at least 50 pg/ml for at least 8 hours.	
8	The method of claim 7, wherein the absolute bioavailability of said salt or ester ranges from 21 to 25%.	*See* prior art cited above with respect to claim 1.
9	The method of claim 7, wherein the oral bioavailability of the salt or ester is at least 50% greater than the oral bioavailability of treprostinil as free acid.	*See* prior art cited above with respect to claim 1.
10	The method of claim 7, wherein the oral bioavailability of the salt or ester is at least 100% greater than the oral bioavailability of treprostinil as free acid.	*See* prior art cited above with respect to claim 1.
11	The method of claim 7, wherein the pharmaceutically acceptable salt or ester is the diethanolamine salt of treprostinil.	*See* prior art cited above with respect to claim 1.
12	The method of claim 7, wherein the subject is a human.	*See* prior art cited above with respect to claim 1.