

1 UNITED STATES PATENT AND TRADEMARK OFFICE
2 BEFORE THE PATENT TRIAL AND APPEAL BOARD

3 -----
4 STEADYMED LTD.,
5 Petitioner,

6 v.

7 UNITED THERAPEUTICS CORPORATION,
8 Patent Owner.

9 -----
10 Case IPR2016-00006 (Patent 8,497,393)
11 -----

12
13 VIDEO DEPOSITION OF
14 ROBERT R. RUFFOLO, JR., PHD
15
16 Wilson Sonsini Goodrich & Rosati
17 1700 K Street NW, Suite 500
18 Washington, DC 20006

19
20 Friday, August 19, 2016
21 9:29 a.m.

22
23
24 Reported by:

25 Denise D. Vickery, CRE/RMR JOB NO. 178626

Elisa Dreier Reporting Corp., A U.S. Legal Support Company
950 Third Avenue, New York, NY 10022 (212) 557-5558

P.1

UT Ex. 2058
SteadyMed v. United Therapeutics
IPR2016-00006

IPR2020-00769
United Therapeutics EX2006
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A P P E A R A N C E S

For Petitioner:

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BY: STUART E. POLLACK, ESQ.

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BY: ROBERT DELAFIELD, ESQ.

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

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BY: STEPHEN B. MAEBIUS, ESQ.

Also Present:

Solomon Francis, Videographer

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1 P R O C E E D I N G S

2 - - -

3 THE VIDEOGRAPHER: Good morning.

4 This begins Media Unit No. 1 of the
5 audiovisual deposition of Dr. Robert Ruffolo
6 taken in the matter of SteadyMed Limited,
7 Petitioner versus United Therapeutics
8 Corporation, Patent Owner, before the Patent
9 Trial and Appeal Board, IPR No. 2016-00006.

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

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

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

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

25 MS. CHOKSI: Maya Choksi, DLA

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1 Piper, on behalf of the petitioner.

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

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

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

11 - - -

12 ROBERT R. RUFFOLO, JR., PHD
13 called for examination, and, after having been
14 duly sworn, was examined and testified as
15 follows:

16 EXAMINATION

17 THE VIDEOGRAPHER: Please
18 proceed, counsel.

19 BY MR. POLLACK:

20 Q. Good morning, Dr. Ruffolo.

21 A. Good morning.

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

25 A. Okay. My name is Robert Richard

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

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

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

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

12 A. Yes, I am.

13 Q. Have you been deposed before?

14 A. Yes, I have.

15 Q. How many times have you been
16 deposed before?

17 A. Well, maybe 10.

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

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

1 Q. Those were patent litigation cases?

2 A. Yes, they were.

3 Q. Okay. And about six depositions?

4 A. About -- yeah, about six.

5 MR. POLLACK: Just to get some

6 formalities out of the way, I'm going to

7 mark as Ruffolo Deposition Exhibit 1 the

8 Petitioner's Notice of Deposition of Robert

9 R. Ruffolo, Ph.D.

10 (Document marked for
11 identification purposes as Ruffolo
12 Exhibit 1.)

13 THE WITNESS: Thank you.

14 BY MR. POLLACK:

15 Q. And are you in attendance here
16 today for this deposition in response to
17 petitioner's notice of deposition?

18 A. Yes, I am.

19 Q. Have you testified in any other --
20 you understand this is a proceeding called an
21 inter partes review?

22 A. Yes, I do. Yes.

23 Q. Okay. Have you testified in any
24 other inter partes review?

25 A. No, I don't believe so.

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

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

5 Q. Yeah. Yes.

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

7 Q. Okay.

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

11 Q. Trandolapril?

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

14 Q. Okay.

15 A. Then --

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

19 A. That one was for the generic and --

20 Q. Do you remember which company?

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

23 Q. Okay.

24 A. Then there --

25 Q. Let me ask you. Was that

1 Sanofi-Aventis on the other side or --

2 A. It was Boehringer Ingelheim.

3 Q. Boehringer Ingelheim.

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

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

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

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

17 Q. Right.

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

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

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

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

4 Q. Infringement, invalidity?

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

9 Q. Who won?

10 A. We did.

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

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

17 Q. Okay.

18 A. So that's all I know.

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

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

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

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

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

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

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

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

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

20 Q. Sure.

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

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

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

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

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

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

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

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

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

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

16 A. I --

17 MR. DELAFIELD: Objection.
18 Vague.

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

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

4 BY MR. POLLACK:

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

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

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

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

1 people were doing, I assume, day to day?

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

9 Q. Right. You were the decider?

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

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

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

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

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

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

3 A. Perkins Coie. And --

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

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

8 A. Oh, polymorphs, amorphous, amorphous
9 forms. Mixtures between polymorphs and
10 amorphous, X-ray crystal, X-ray
11 crystallography, XRPD, Raman spectra. All of
12 the technologies involved in determining
13 crystal structure and the pharmaceuticals
14 involved in formulating crystal structures, and
15 there were other. Also, of course, as I said,
16 the R&D process and regulatory process and FDA.

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

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

1 In fact, that's still ongoing and --

2 Q. Fish & Richardson?

3 A. Yes, that's right.

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

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

11 A. Yes.

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

14 A. Both.

15 Q. -- in that case?

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

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

1 A. The patent is about congestive
2 heart failure.

3 Q. What about congestive heart
4 failure?

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

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

25 And so as the person who had to

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

6 Q. That's it?

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

9 Q. Is the patent on the chemical?

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

12 Q. Use in heart failure. Okay.

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

15 Q. Someone else invented the chemical;
16 right?

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

1 failure.

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

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

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

19 Q. Okay. And are there any other
20 cases?

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

23 Q. Okay.

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

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

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

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

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

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

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

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

24 A. No, I had not.

25 Q. When did you first get hired to

1 work on these IPRs?

2 A. I believe it was April of last
3 year.

4 Q. April 2015?

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

7 Q. And how did you get hired?

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

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

12 A. \$500 an hour.

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

15 A. Yes, it is.

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

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

22 Q. About how much less?

23 A. 400 I think.

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

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

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

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

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

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

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

13 MR. DELAFIELD: Objection.
14 Relevance.

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

18 BY MR. POLLACK:

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

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

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

1 A. I'm not sure it would be as high as
2 60.

3 Q. Okay. 30 and 50?

4 A. Maybe.

5 Q. Okay.

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

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

10 Q. Okay.

11 A. It was --

12 Q. Tell you what. Let's --

13 A. Wait till then?

14 Q. Yeah.

15 A. Okay.

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

18 A. Okay.

19 MR. POLLACK: I'm going to mark
20 as Ruffolo Deposition Exhibit 2 UT Exhibit
21 2023, the curriculum vitae of Robert
22 Ruffolo.

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

1 THE WITNESS: Thank you.

2 BY MR. POLLACK:

3 Q. Can you confirm for me that that is

4 your CV?

5 A. Yes, this is my CV.

6 Q. Okay. Are there any corrections

7 you want to make to the CV?

8 A. Not -- not that I know of.

9 Q. And if you can turn to page 13 in

10 the exhibit.

11 A. Okay.

12 Q. I just wanted to look at the

13 section that says "Expert Witness in Lawsuits."

14 A. Uh-huh.

15 Q. So the first two cases, one is a

16 SmithKline Beecham litigation?

17 A. Yes.

18 Q. Okay. And the second is a Wyeth

19 Pharmaceuticals litigation?

20 A. Yes.

21 Q. Were those both product liability

22 kinds of cases?

23 A. Yes, they were. They were the two

24 that I --

25 Q. That you mentioned?

1 A. -- mentioned earlier, yes.

2 Q. What was the SmithKline Beecham one
3 about?

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

6 Q. Fen-Phen?

7 A. Yes.

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

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

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

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

20 Q. Uh-huh. Yeah, right.

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

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

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

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

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

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

16 A. Yes, those first two.

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

19 A. Right.

20 Q. -- correct?

21 And the second is the Goodwin
22 Procter one?

23 A. That's correct.

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

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

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

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

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

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

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

25 Q. Okay. Do you still update your CV

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

3 A. Now I do it myself.

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

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

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

11 A. Okay.

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

15 THE WITNESS: Thank you.

16 BY MR. POLLACK:

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

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

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

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

3 A. Yeah. Yes.

4 Q. -- declaration?

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

8 On page 26, five lines up from the
9 bottom.

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

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

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

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

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

22 A. Yes. Where does it start? Okay.

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

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

7 Can I write that correction on this
8 draft?

9 Q. Sure.

10 A. Just in case we --

11 Q. Yeah.

12 A. (Marking). Okay.

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

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

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

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

22 Q. You didn't?

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

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

4 A. Okay.

5 Q. -- to be --

6 A. Sure.

7 Q. -- into the record?

8 A. Okay.

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

17 Q. And who discovered that error?

18 A. I did when I was reviewing my
19 declaration.

20 Q. Okay. How was this declaration
21 drafted?

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

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

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

4 A. I may have. I may have.

5 Q. Okay.

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

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

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

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

18 A. Oh, probably 20 or 30 times.

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

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

25 THE WITNESS: Not much. This is

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

5 BY MR. POLLACK:

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

8 A. Uh-huh.

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

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

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

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

1 other corrections that you'd like to point out?

2 A. Not that I'm aware of.

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

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

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

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

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

22 A. This document. The contents of
23 my --

24 Q. -- Ruffolo Exhibit 3?

25 A. Correct.

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

3 A. Yes. Yes, it is.

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

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

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

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

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

20 A. I don't understand.

21 Q. Maybe I used too many patent terms.

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

24 MR. DELAFIELD: Objection.

25 Vague.

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

4 BY MR. POLLACK:

5 Q. Well, besides yourself, for
6 example.

7 MR. DELAFIELD: Same objection.

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

11 BY MR. POLLACK:

12 Q. I'm not asking about an
13 improvement.

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

17 MR. DELAFIELD: Objection.

18 Vague.

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

22 BY MR. POLLACK:

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

1 need that was addressed by the '393 patent?

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

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

13 MR. DELAFIELD: Objection.
14 Compound and vague.

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

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

4 BY MR. POLLACK:

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

8 A. Yes.

9 MR. DELAFIELD: Objection.

10 Vague.

11 BY MR. POLLACK:

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

17 MR. DELAFIELD: Objection.

18 Asked and answered.

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

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

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

6 BY MR. POLLACK:

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

12 MR. DELAFIELD: Objection.

13 Asked and answered.

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

23 BY MR. POLLACK:

24 Q. So the FDA changed the
25 specification?

1 A. Ultimately you can't change a
2 specification without FDA approval.
3 Q. Sure, but --
4 A. So they ultimately changed the
5 specification at the request of UTC.
6 Q. They allowed UTC to change the
7 specification?
8 A. They approved the change that UTC
9 had suggested after a detailed analysis.
10 That's one of the things they have to do.
11 These are considered significant changes by the
12 FDA.
13 Q. Can you turn to your paragraph 69
14 and in particular I'm looking on page 34 of
15 your declaration, Exhibit 3.
16 A. Okay. 69 I think starts on 30 --
17 33 it starts.
18 Q. Right.
19 A. Which page would you like me?
20 Q. I'd like you to focus on 34 but,
21 you know, feel free to read whatever you need
22 to read.
23 A. Okay.
24 Q. I'm going to ask you about the
25 first full sentence on 34, which reads:

1 I have repeatably -- excuse me.
2 "I have repeatedly observed during
3 the course of my career that the FDA balances
4 their strong desire for the highest levels of
5 purity against the practical need for a company
6 to be able to manufacture the drug product
7 reliability" -- I'm sorry.
8 A. Reliably.
9 Q. Reliably. Let me read the whole
10 sentence again.
11 A. Okay.
12 Q. "I have repeatedly observed during
13 the course of my career that the FDA balances
14 their strong desire for the highest levels of
15 purity against the practical need for a company
16 to be able to manufacture the drug product
17 reliably."
18 Did I read that correctly this
19 time?
20 A. Yes, you did.
21 Q. Okay. Finally.
22 You still agree with that sentence?
23 A. Oh, yes.
24 Q. Okay.
25 A. Yes.

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

6 MR. DELAFIELD: Objection.
7 Mischaracterizes the document.

8 THE WITNESS: That's only
9 partially correct.

10 BY MR. POLLACK:

11 Q. What's incorrect about it?

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

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

18 A. I don't know.

19 MR. DELAFIELD: Objection.
20 Compound.

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

23 BY MR. POLLACK:

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

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

8 Q. Let me ask you.

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

12 MR. DELAFIELD: Objection.

13 Vague.

14 THE WITNESS: Not necessarily,
15 no.

16 BY MR. POLLACK:

17 Q. But in many cases I can; right?

18 A. Yeah, in some cases you can.

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

23 MR. DELAFIELD: Objection. Lack
24 of foundation.

25 THE WITNESS: Not necessarily.

1 BY MR. POLLACK:

2 Q. But in many cases?

3 MR. DELAFIELD: Same objection.

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

6 BY MR. POLLACK:

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

10 MR. DELAFIELD: Same objection.

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

13 BY MR. POLLACK:

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

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

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

21 MR. DELAFIELD: Objection.

22 Vague.

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

1 BY MR. POLLACK:

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

4 A. Would not.

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

8 What are you referring to? Who
9 would be involved?

10 MR. DELAFIELD: Same objection.

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

19 BY MR. POLLACK:

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

25 MR. DELAFIELD: Objection.

1 Vague and lacks foundation.

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

9 BY MR. POLLACK:

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

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

18 Q. Are you a process research chemist?

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

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

1 A. I was president of research and
2 development.

3 Q. Yeah. So everyone?

4 A. Not --

5 Q. All the scientists?

6 A. Not the company.

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

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

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

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

17 Q. Okay. Let me ask you.

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

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

1 A. Yes, I did.

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

4 A. 24, yes.

5 Q. And you say there:

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

10 A. Yes, I do.

11 Q. Let me start it again then.

12 "I understand that SteadyMed's
13 expert, Dr. Winkler, in his declaration has
14 opined that a person of ordinary skill in the
15 art would have 'a master's degree or a Ph.D. in
16 medicinal or organic chemistry, or a closely
17 related field. Alternatively, a person of
18 ordinary skill would include an individual with
19 a bachelor's degree and at least five years of
20 practical experience in medicinal or organic
21 chemistry.'"

22 Do you disagree with that
23 statement?

24 A. Yes, I do disagree with that
25 statement.

1 Q. Why?

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

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

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

18 Q. Okay. Let me ask you then.

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

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

1 for many, many years.

2 Q. Then let me ask you.

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

7 A. I have --

8 MR. DELAFIELD: Objection.
9 Vague.

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

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

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

1 the pharmaceutical industry.

2 BY MR. POLLACK:

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

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

8 A. Pharmaceutical chemistry,
9 analytical chemistry, stereochemistry, physical
10 chemistry. Another specialized field is
11 physical pharmaceuticals.

12 Q. Anything else?

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

15 Q. Okay. Am I correct then that you,
16 yourself, you don't have a Ph.D. in medicinal
17 chemistry or organic chemistry or physical
18 chemistry or analytical chemistry or physical
19 pharmaceuticals or -- or even pharmaceuticals; is
20 that correct?

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

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

1 we were just discussing, this standard?

2 MR. DELAFIELD: Objection.

3 Vague.

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

9 BY MR. POLLACK:

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

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

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

22 MR. DELAFIELD: Objection.

23 Asked and answered.

24 BY MR. POLLACK:

25 Q. Is that fair?

1 A. I -- well, if you're asking would I
2 include pharmacology with those qualifications
3 that I just listed, I would agree to that.

4 That that would be -- that would fit a POSA.

5 Q. So --

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

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

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

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

21 Q. Do you have experience in
22 analytical chemistry?

23 A. Yes, I do.

24 Q. What's your experience in
25 analytical chemistry?

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

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

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

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

15 A. I believe this is my first one.

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

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

21 Who provided you with those
22 documents?

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

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

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

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

9 THE WITNESS: So I should not
10 answer?

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

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

16 MR. DELAFIELD: I know but --

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

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

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

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

4 BY MR. POLLACK:

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

7 A. There --

8 MR. DELAFIELD: Objection.
9 Vague.

10 THE WITNESS: There is a
11 document on penicillin contamination,
12 cephalosporin contamination, bacterial
13 contamination -- not bacterial -- bacterial
14 component contamination.

15 BY MR. POLLACK:

16 Q. E. coli component?

17 A. E. coli.

18 Q. And that was in insulin?

19 A. That's correct.

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

22 MR. DELAFIELD: Objection.

23 Vague.

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

1 BY MR. POLLACK:

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

4 A. No.

5 Q. Oh, that was concern for which
6 drugs?

7 A. For any --

8 MR. DELAFIELD: Objection.
9 Vague.

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

14 BY MR. POLLACK:

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

18 A. I don't know.

19 Q. You don't know?

20 A. No.

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

23 A. I'm sorry?

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

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

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

6 A. I --

7 MR. DELAFIELD: Objection.
8 Lacks foundation.

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

12 BY MR. POLLACK:

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

16 MR. DELAFIELD: Objection.
17 Asked and answered.

18 THE WITNESS: No, I did not.

19 BY MR. POLLACK:

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

23 MR. DELAFIELD: Objection.
24 Vague.

25 THE WITNESS: No, I did not.

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

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

8 THE WITNESS: Thank you.

9 MR. DELAFIELD: Thank you.

10 BY MR. POLLACK:

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

13 A. Yes, I did.

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

16 A. Yes, that's my understanding.

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

19 Now, do you see claim 1 there?

20 A. Yes, I do.

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

24 MR. DELAFIELD: Objection.

25 Vague. Calls for speculation.

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

5 BY MR. POLLACK:

6 Q. Millions?

7 A. I don't know.

8 Q. You didn't look into that?

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

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

13 MR. DELAFIELD: Objection.

14 Lacks foundation. Calls for speculation.

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

17 BY MR. POLLACK:

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

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

22 A. That misstates --

23 Q. -- number of groups there?

24 A. That misstates --

25 MR. DELAFIELD: Objection.

1 Form.

2 THE WITNESS: -- my prior
3 testimony.

4 BY MR. POLLACK:

5 Q. Okay. Would you correct it for me?

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

9 Q. Okay. Thank you.

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

13 MR. DELAFIELD: Objection.

14 Outside the scope of his declaration. Lacks
15 foundation.

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

21 BY MR. POLLACK:

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

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

1 not part of your opinion?

2 MR. DELAFIELD: Objection.

3 Vague.

4 THE WITNESS: I prepared to talk
5 about treprostiniil and not other compounds.

6 BY MR. POLLACK:

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

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

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

18 MR. DELAFIELD: Objection.

19 Vague.

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

22 BY MR. POLLACK:

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

1 dependent claim, from claim 1?

2 Let me step back a second.

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

5 A. Yes, I think I do.

6 Q. What -- what's your understanding?

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

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

13 MR. DELAFIELD: Objection.

14 Calls for legal conclusion.

15 THE WITNESS: Can you say that
16 again, please?

17 BY MR. POLLACK:

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

22 MR. DELAFIELD: Same objection.

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

1 BY MR. POLLACK:

2 Q. Can you describe it again?

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

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

8 MR. DELAFIELD: Same objection.

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

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

19 BY MR. POLLACK:

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

23 MR. DELAFIELD: Objection.

24 Asked and answered. Outside the scope of
25 his declaration.

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

5 BY MR. POLLACK:

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

8 MR. DELAFIELD: Objection.
9 Mischaracterizes testimony.

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

13 BY MR. POLLACK:

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

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

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

21 Q. And treprostinil only?

22 A. And the diethanolamine salt.

23 Q. And the diethanolamine salt as
24 well?

25 A. Yeah.

1 Q. Okay.

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

5 Q. Well, let me ask you.

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

8 A. Yes.

9 Q. Okay.

10 A. I'm just reading it.

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

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

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

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

23 MR. DELAFIELD: Objection.

24 Vague.

25 THE WITNESS: Those other salts,

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

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

12 BY MR. POLLACK:

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

15 MR. DELAFIELD: Objection.
16 Mischaracterizes testimony.

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

21 BY MR. POLLACK:

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

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

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

3 A. Yes.

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

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

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

13 A. I'm -- yeah.

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

16 A. Yeah.

17 Q. You see that?

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

20 Q. Please.

21 A. The structure -- chemical formula
22 4, Roman numeral 4 in claim 9, is the result of
23 step (d) and -- and so because that compound is
24 part of this patent, step (d) is not optional
25 when it comes to making that compound.

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

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

6 Q. Right.

7 A. -- acceptable salt.

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

11 A. Yes, it is a pharmaceutically
12 acceptable salt.

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

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

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

23 A. It includes the salts.

24 Q. Okay.

25 A. The pharmaceutically acceptable

1 salts.

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

6 MR. DELAFIELD: Objection.

7 Vague.

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

13 BY MR. POLLACK:

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

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

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

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

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

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

14 A. Yes.

15 MR. DELAFIELD: Objection.

16 Vague.

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

25 So, yes, the FDA did have

1 concerns about purity when evaluating the
2 new manufacturing process.

3 BY MR. POLLACK:

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

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

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

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

15 Q. Its exhibit number is 2006.

16 A. Oh, okay. My misunderstanding.

17 Q. Former exhibit number.

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

21 THE WITNESS: Thank you.

22 BY MR. POLLACK:

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

1 A. Yes, it is.

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

5 A. Yes, I do.

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

9 A. Yes, I do.

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

14 A. That's my --

15 MR. DELAFIELD: Objection.
16 Mischaracterizes the document.

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

20 BY MR. POLLACK:

21 Q. And one of the changes in that new
22 manufacturing process is they're going to

23 [REDACTED] instead of [REDACTED]

24 [REDACTED]; isn't that correct?

25 A. That's correct.

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

5 MR. DELAFIELD: Objection.
6 Lacks foundation. Vague.

7 THE WITNESS: Can you repeat the
8 question?

9 BY MR. POLLACK:

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

13 MR. DELAFIELD: Same objections.

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

21 BY MR. POLLACK:

22 Q. Right. And that change in [REDACTED]
23 [REDACTED] has nothing to do with the change in
24 process that concerns the '393 patent in this
25 case?

1 MR. DELAFIELD: Objection.
2 Vague.
3 THE WITNESS: Can you ask that
4 again, please?
5 BY MR. POLLACK:
6 Q. Sure. That change in [REDACTED]
7 [REDACTED] that's not the type of change that's
8 described in the '393 patent?
9 MR. DELAFIELD: Same objection.
10 THE WITNESS: The change in the
11 [REDACTED] ?
12 BY MR. POLLACK:
13 Q. Right.
14 A. Okay. So could you ask it one more
15 time, please?
16 Q. Sure.
17 A. Because now I've got --
18 Q. Okay.
19 A. I'm just trying to figure out what
20 you were asking. It wasn't quite clear to me.
21 I'm sorry.
22 Q. The change in [REDACTED] --
23 A. Yes.
24 Q. -- in this process --
25 A. The change of [REDACTED].

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

3 MR. DELAFIELD: Same objections.

4 THE WITNESS: The '393 patent,
5 the [REDACTED] is not [REDACTED]
6 [REDACTED]. It's something else many steps
7 earlier.

8 BY MR. POLLACK:

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

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

14 Do you know what UT-15C is?

15 A. Yes, I do.

16 Q. Okay. What is it?

17 A. It's treprostinil free acid.

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

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

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

25 Q. Absolutely.

1 A. -- of this letter and review?

2 (Reviewing document).

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

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

9 A. Okay.

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

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

15 A. Yes, I believe so.

16 Q. Okay.

17 -- "is not a compound that was used
18 during the conversion of [REDACTED] to
19 treprostinil."

20 Did I read that correctly?

21 A. Yes.

22 Q. Then they say:

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

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

4 Did I read that correctly?

5 A. Yes, you did.

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

9 A. I believe so.

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

11 A. That's how I would read that.

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

14 A. Yes.

15 Q. -- exhibit; correct?

16 A. Yes.

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

19 "The data in Table 5 from the
20 validation report (VAL-00131) show several
21 impurities detected at low levels below the ICH
22 identification limit of ■■■ percent."

23 Do you see that?

24 A. Yes, I do.

25 Q. Okay. And reading that together

1 with the next sentence, which reads:

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

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

8 MR. DELAFIELD: Objection.
9 Mischaracterizes the document.

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

12 BY MR. POLLACK:

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

15 Did you review Table 5 in your
16 analysis?

17 A. I don't recall.

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

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

23 THE WITNESS: Can I read that
24 paragraph again?

25 BY MR. POLLACK:

1 Q. Absolutely.

2 A. (Reviewing document). Okay.

3 So could you ask the question
4 again, please?

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

9 MR. DELAFIELD: Objection.
10 Mischaracterizes the document.

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

15 BY MR. POLLACK:

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

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

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

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

4 BY MR. POLLACK:

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

9 MR. DELAFIELD: Objection.

10 Vague.

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

14 BY MR. POLLACK:

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

17 A. I --

18 MR. DELAFIELD: Objection.

19 Asked and answered.

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

22 BY MR. POLLACK:

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

25 A. I have --

1 MR. DELAFIELD: Same objections.

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

7 BY MR. POLLACK:

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

11 MR. DELAFIELD: Objection.
12 Vague. Asked and answered. Lacks
13 foundation.

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

17 BY MR. POLLACK:

18 Q. Okay. Let me ask you this then.
19 Can you tell me how the impurities
20 that were found in Table 5 in this process
21 differ from the impurities in any other process
22 used to make treprostinil diethanolamine salt?

23 MR. DELAFIELD: Same objections.

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

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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?

1 A. I saw the Walsh declaration.

2 Q. All right. Anything else?

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

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

11 MR. DELAFIELD: Objection.
12 Lacks foundation.

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

20 BY MR. POLLACK:

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

23 A. Yes.

24 Q. Okay.

25 A. But I simply can't do it from

1 memory.

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

5 A. Yes.

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

9 MR. DELAFIELD: Objection.
10 Lacks foundation. Mischaracterizes the
11 document.

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

16 BY MR. POLLACK:

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

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

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

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

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

3 BY MR. POLLACK:

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

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

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

16 MR. DELAFIELD: Objection.

17 BY MR. POLLACK:

18 Q. Is that fair?

19 MR. DELAFIELD: Objection.

20 Lacks foundation.

21 BY MR. POLLACK:

22 Q. Is that your understanding?

23 MR. DELAFIELD: Objection.

24 Lacks foundation. Mischaracterizes

25 testimony.

1 THE WITNESS: I don't know. I
2 assume that's true. I don't know.
3 BY MR. POLLACK:
4 Q. Okay. But as far as you know, no
5 physician in the public has seen this document?
6 MR. DELAFIELD: Same objections.
7 THE WITNESS: Say it again. I'm
8 sorry, please.
9 BY MR. POLLACK:
10 Q. No physician in the public has seen
11 this document?
12 A. Outside of the FDA?
13 Q. Yeah.
14 A. I assume they haven't.
15 Q. And even at the FDA, only the --
16 most likely only the people who are involved
17 with this application would have seen this
18 document?
19 MR. DELAFIELD: Objection.
20 Lacks foundation.
21 THE WITNESS: The -- there would
22 be a good number of people at the FDA who
23 would have had access to this document. I
24 don't know who would review it, but all the
25 way up to the final signature, which would

1 include a division director would have had
2 access to it. I don't know who would have
3 seen it.
4 BY MR. POLLACK:
5 Q. Right. Well, you're familiar with
6 the FDA process; right?
7 A. Of course.
8 MR. DELAFIELD: Objection.
9 Vague.
10 THE WITNESS: Of course.
11 BY MR. POLLACK:
12 Q. So this kind of detailed chemistry
13 review, about how many people do you think at
14 the FDA would have looked at this?
15 A. Oh.
16 MR. DELAFIELD: Objection.
17 Calls for speculation and vague.
18 THE WITNESS: I could only
19 guess.
20 BY MR. POLLACK:
21 Q. Okay.
22 A. I don't know the exact number.
23 Q. Okay. But it would be a small
24 number?
25 MR. DELAFIELD: Same objections.

1 THE WITNESS: What does "small"
2 mean?

3 BY MR. POLLACK:

4 Q. Five people?

5 MR. DELAFIELD: Same objections.

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

8 BY MR. POLLACK:

9 Q. More than 10?

10 MR. DELAFIELD: Same objections.

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

17 BY MR. POLLACK:

18 Q. Right.

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

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

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

4 A. Yes, I have.

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

8 MR. DELAFIELD: Objection.
9 Vague. Relevance.

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

12 BY MR. POLLACK:

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

17 A. FDA labels don't contain purity
18 information.

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

22 MR. DELAFIELD: Objection.
23 Vague.

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

1 announcements on changes in purity.

2 BY MR. POLLACK:

3 Q. This is all secret information;
4 right?

5 A. This --

6 Q. The purity of this product?

7 MR. DELAFIELD: Objection.

8 Vague. Calls for speculation.

9 THE WITNESS: This document
10 would be, yes.

11 BY MR. POLLACK:

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

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

19 Q. Sure. Sure.

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

25 Q. This is all secret, in fact, which

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

3 MR. DELAFIELD: Objection.

4 Lacks foundation. Calls for speculation.

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

8 BY MR. POLLACK:

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

13 MR. DELAFIELD: Same objections.

14 Asked and answered.

15 THE WITNESS: I would assume
16 that's true.

17 BY MR. POLLACK:

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

20 MR. DELAFIELD: Objection.

21 BY MR. POLLACK:

22 Q. That would also be confidential?

23 MR. DELAFIELD: Objection.

24 Lacks foundation. Calls for speculation.

25 THE WITNESS: That's Table 5 and

1 I would assume that would be confidential as
2 well.

3 BY MR. POLLACK:

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

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

10 Q. Yes. The same paragraph.

11 A. Same paragraph.

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

14 A. (Reviewing document).

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

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

20 Do you see that?

21 A. I see that.

22 Q. Okay.

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

25 Q. Sure. Let me ask you a question

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

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

5 MR. DELAFIELD: Objection.

6 Calls for speculation. Mischaracterizes the
7 document.

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

11 BY MR. POLLACK:

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

18 MR. DELAFIELD: Same objections.

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

23 BY MR. POLLACK:

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

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

3 MR. DELAFIELD: Objection.

4 Calls for speculation. Lack of foundation.

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

8 BY MR. POLLACK:

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

13 A. Ethanolamine.

14 Q. Let me start again.

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

20 MR. DELAFIELD: Objection.

21 Calls for speculation. Lacks of foundation.

22 Asked and answered.

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

1 document, the impurities were very low.

2 BY MR. POLLACK:

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

8 MR. DELAFIELD: Objection.

9 Lacks foundation. Calls for speculation.
10 Asked and answered.

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

15 BY MR. POLLACK:

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

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

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

24 MR. DELAFIELD: Objection.

25 BY MR. POLLACK:

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

3 A. There is not enough information
4 here for me -- for me to make that kind of a
5 conclusion without looking at the -- at Table
6 5, for example, and -- and other sources.

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

10 MR. DELAFIELD: Objection.
11 Vague.

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

16 BY MR. POLLACK:

17 Q. Okay. Let me ask you.

18 Do you know whether step (d)
19 removes impurities from treprostini
20 diethanolamine salt?

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

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

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

4 BY MR. POLLACK:

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

8 MR. DELAFIELD: Objection.

9 Vague. Calls for speculation. Asked and
10 answered.

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

14 BY MR. POLLACK:

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

17 What is your opinion --

18 MR. DELAFIELD: Same objections.

19 BY MR. POLLACK:

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

24 MR. DELAFIELD: Same objections.

25 Outside the scope of his declaration.

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

7 BY MR. POLLACK:

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

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

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

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

19 BY MR. POLLACK:

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

23 Do you have an opinion one way or
24 the other?

25 MR. DELAFIELD: Same objection.

1 Asked and answered six times now.

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

8 BY MR. POLLACK:

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

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

17 A. That's --

18 MR. DELAFIELD: Objection.

19 Asked and answered.

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

22 BY MR. POLLACK:

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

1 prior treprostinil diethanolamine salts?

2 MR. DELAFIELD: Objection.

3 Vague.

4 THE WITNESS: For the
5 diethanolamine salt, I don't remember and I
6 need to look at -- at the data for
7 diethanolamine salt.

8 BY MR. POLLACK:

9 Q. Well, let me ask you. You have in
10 front of you your declaration.

11 Do you express in your declaration
12 an opinion -- and feel free to look through
13 it -- regarding whether or not there was a
14 long-felt need due to a difference in impurity
15 between the claim 9's patented treprostinil
16 diethanolamine salt and prior art treprostinil
17 diethanolamine salt?

18 MR. DELAFIELD: Objection.

19 Vague and compound.

20 THE WITNESS: The -- my comments
21 on long-felt need are based on the FDA's
22 desire to have purity improved, even in an
23 already pure compound, as far as possible
24 and practical. So that would apply to the
25 marketed products free acid and

1 diethanolamine salt.

2 BY MR. POLLACK:

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

6 MR. DELAFIELD: Objection.

7 Vague.

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

14 BY MR. POLLACK:

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

18 A. Which opinion? I'm sorry.

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

22 MR. DELAFIELD: Same objections.

23 Asked and answered.

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

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

5 BY MR. POLLACK:

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

10 A. (Reviewing document).

11 Q. Let me refine my question.

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

17 MR. DELAFIELD: Objection.

18 Vague.

19 THE WITNESS: Okay. Can I? Can

20 I?

21 BY MR. POLLACK:

22 Q. Yes, please.

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

25 Could I make a note on here?

1 Q. Yeah.

2 A. Am I allowed to make a note?

3 (Marking). (Reviewing document).

4 Q. We need to just --

5 A. I'm almost --

6 Q. -- change the tape.

7 A. Oh.

8 Q. We can stay on the record as far as

9 our court reporter is concerned.

10 A. Okay.

11 Q. But I don't think we need video of

12 just him reading.

13 A. Okay.

14 MR. POLLACK: Yes, change the

15 tape.

16 THE VIDEOGRAPHER: The time is

17 11:36 a.m. This completes Media Unit No. 1.

18 We are off the record. Okay. I'm sorry for

19 the delay.

20 The time is 11:37 a.m. This

21 begins Media Unit No. 2. We're on the

22 record. Please proceed, counsel.

23 BY MR. POLLACK:

24 Q. Do you need the question read back?

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

1 if you could indulge me --

2 Q. No, that's fine.

3 A. -- by reading the question back
4 please.

5 Q. No problem.

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

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

14 Q. Can you show me where?

15 A. Yes.

16 Q. Where you're referring to?

17 A. On paragraph 38, the last sentence.

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

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

24 Does it say anything about
25 treprostinil diethanolamine salt?

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

1 A. Yes, I do.

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

5 MR. DELAFIELD: Objection.

6 Vague.

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

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

16 BY MR. POLLACK:

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

23 MR. DELAFIELD: Objection.

24 Asked and answered and vague.

25 THE WITNESS: As I mentioned

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

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

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

12 MR. POLLACK: Oh.

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

16 THE WITNESS: I can go all day.

17 BY MR. POLLACK:

18 Q. Okay.

19 A. Whatever you want. Whatever you
20 like.

21 Q. No, that's fine with me.

22 A. It's up to you.

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

1 A. Yes, I see that.

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

4 MR. DELAFIELD: Objection.

5 Vague.

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

8 So could you repeat the
9 question?

10 BY MR. POLLACK:

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

13 MR. DELAFIELD: Objection.

14 Vague. Asked and answered.

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

19 BY MR. POLLACK:

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

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

24 A. Well --

25 MR. DELAFIELD: Objection.

1 Mischaracterizes the document and vague.

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

8 BY MR. POLLACK:

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

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

15 A. Well, claim 12 --

16 MR. DELAFIELD: Objection.
17 Asked and answered.

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

24 BY MR. POLLACK:

25 Q. You've reviewed the patent; right?

1 A. Oh, of course, yes.

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

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

6 Q. Okay.

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

11 The claim 12 reads:

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

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

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

1 wouldn't have an opinion about it.

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

5 MR. DELAFIELD: Objection.
6 Mischaracterizes his testimony. Asked and
7 answered.

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

14 BY MR. POLLACK:

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

18 MR. DELAFIELD: The same
19 objections.

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

25 BY MR. POLLACK:

1 Q. Okay. And what about for claim 11?

2 It has to do with the alkylating agent.

3 A. Okay.

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

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

8 MR. DELAFIELD: Same objections.

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

15 BY MR. POLLACK:

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

20 MR. DELAFIELD: Objection.

21 Mischaracterizes the document and asked and
22 answered.

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

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

4 BY MR. POLLACK:

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

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

11 MR. DELAFIELD: Objection.

12 Mischaracterizes the document and testimony.
13 Asked and answered.

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

18 BY MR. POLLACK:

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

21 MR. DELAFIELD: Same objections.

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

25 BY MR. POLLACK:

1 Q. Okay.

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

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

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

11 Do you see that?

12 A. Yes, I see that.

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

15 A. I can write on this?

16 Q. Yeah.

17 A. (Reviewing document).

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

22 Q. Okay.

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

1 the diethanolamine salt.

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

5 A. Yes.

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

8 MR. DELAFIELD: Objection.
9 Vague.

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

18 BY MR. POLLACK:

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

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

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

1 need for claim 19?

2 MR. DELAFIELD: Same objections.

3 BY MR. POLLACK:

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

7 MR. DELAFIELD: Objection.

8 BY MR. POLLACK:

9 Q. Unless you feel otherwise --

10 MR. DELAFIELD: Objection.

11 Compound and vague.

12 BY MR. POLLACK:

13 Q. -- that they're different.

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

16 Q. Okay.

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

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

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

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

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

8 A. (Reviewing document).

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

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

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

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

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

3 A. Yes.

4 Q. -- is that fair?

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

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

11 MR. DELAFIELD: Objection.
12 Mischaracterizes the document. Calls for
13 speculation.

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

18 BY MR. POLLACK:

19 Q. Sure.

20 A. -- to me.

21 Q. After step (d) is performed --

22 A. Yes.

23 Q. -- in claim 22 --

24 A. Right.

25 Q. -- the treprostinil acid is

1 converted into a pharmaceutically acceptable
2 salt.

3 Is that a fair interpretation of
4 claim 22?

5 MR. DELAFIELD: Same objections.

6 THE WITNESS: As I understand
7 it, no.

8 BY MR. POLLACK:

9 Q. Okay. How do you understand it?

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

13 Q. Right.

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

16 Q. Do you see the word "salt" in claim
17 22?

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

20 Q. Yeah.

21 A. Claim 21. I apologize.

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

24 A. I'm sorry.

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

1 A. I thought we were working down.
2 MR. DELAFIELD: Same objections.
3 THE WITNESS: My mistake.
4 (Reviewing document).
5 Okay. So, again, as I read the
6 claim and if I understand it correctly,
7 we're taking the product of claim 1, which
8 is the free acid, and reacting it with a
9 pharmaceutically acceptable salt, and there
10 are no specified salts there.
11 So for that particular step,
12 without specifying any salt, and I don't
13 know if they're including diethanolamine in
14 that, I can't say whether it would or
15 wouldn't have a long-felt need. I don't
16 know. They don't specify the salt. So I
17 don't know what they're making.
18 BY MR. POLLACK:
19 Q. Can you take a look at the front of
20 the --
21 A. Sure.
22 Q. -- '393 patent, Ruffolo 4?
23 A. Yes.
24 Q. And do you see there's a number 60
25 on the left and it says "Provisional

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

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

4 Q. Okay. And do you see there's a
5 provisional application filed on December 12,
6 2007?

7 MR. DELAFIELD: Objection.
8 Mischaracterizes the document.

9 THE WITNESS: Yes, I do see
10 that.

11 BY MR. POLLACK:

12 Q. Okay. Did you review the
13 provisional application?

14 A. The '232 patent?

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

17 A. Application.

18 Q. -- number, yeah.

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

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

1 filed at the end of 2007?

2 MR. DELAFIELD: Objection.

3 Lacks foundation.

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

9 BY MR. POLLACK:

10 Q. Okay. Well, let me ask you.

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

14 There's one at line 22.

15 A. I see 2008.

16 Q. Uh-huh.

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

19 Q. Yes.

20 A. Yeah. Okay.

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

22 MR. DELAFIELD: Objection.

23 Vague.

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

1 Okay.

2 BY MR. POLLACK:

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

5 A. Filings?

6 Q. -- when things are filed you see.

7 A. Okay. I see that.

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

13 MR. DELAFIELD: Objection.

14 THE WITNESS: Can I look at --

15 MR. DELAFIELD: Vague.

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

18 BY MR. POLLACK:

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

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

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

1 then.

2 Other than the inventors, can you
3 identify three people anytime between 2007 --
4 well, we'll do it this way -- anytime before
5 2012. Let me start my question again.

6 Can you identify for me at least
7 three people other than the inventors prior to
8 2012 who expressed a long-felt need for a purer
9 treprostinil or treprostinil diethanolamine
10 salt?

11 MR. DELAFIELD: Objection.

12 Vague. Calls for speculation.

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

22 BY MR. POLLACK:

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

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

1 need for lower impurities that you know of.

2 MR. DELAFIELD: Same objection.

3 Relevance.

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

6 BY MR. POLLACK:

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

9 MR. DELAFIELD: Objection.
10 Vague.

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

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

23 BY MR. POLLACK:

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

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

3 MR. DELAFIELD: Objection.
4 Mischaracterizes his testimony.

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

8 BY MR. POLLACK:

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

11 A. It is part --

12 MR. DELAFIELD: Same objection.

13 THE WITNESS: -- of the
14 consideration.

15 BY MR. POLLACK:

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

22 MR. DELAFIELD: Objection.
23 Vague. Relevance.

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

1 BY MR. POLLACK:

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

6 MR. DELAFIELD: Objection.

7 Vague. Calls for speculation.

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

10 BY MR. POLLACK:

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

13 A. No, I did not.

14 Q. Okay. Why not?

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

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

24 A. Oh, yes, of course.

25 Q. Okay. And that department, was

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

3 A. At --

4 Q. -- group?

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

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

12 MR. DELAFIELD: Objection.
13 Vague. Calls for speculation. Lacks
14 foundation.

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

19 BY MR. POLLACK:

20 Q. Yeah.

21 A. The answer would be yes, they
22 would.

23 Q. Okay.

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

1 Q. Right.

2 A. The scientists.

3 Q. Right.

4 A. Okay.

5 Q. Well, what about yourself? Would
6 the people in the regulatory affairs group know
7 more about what the FDA wanted in regard to
8 impurities than -- than you would?

9 MR. DELAFIELD: Same objections.

10 THE WITNESS: Maybe not. I
11 spent a lot of time walking the halls of the
12 FDA and -- and regulatory -- regulatory
13 positions are something that I've been
14 invited to lecture on quite frequently,
15 including to the FDA, and I consult with
16 respect to regulatory positions to most
17 large pharmaceutical companies and many
18 mid-size.

19 So I don't believe everyone in
20 regulatory affairs would know more than me.
21 I'm sure some do, but I wouldn't agree that
22 all of them or even the majority of them do.

23 BY MR. POLLACK:

24 Q. Okay. In forming your opinion
25 today, though, did you -- other than the

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

4 A. No, I did not.

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

8 A. I read his declaration.

9 Q. Did you speak with him --

10 A. No.

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

13 A. I'm sorry.

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

17 A. No, I did not.

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

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

23 Q. Any reason why not?

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

1 could have told me or taught me about
2 regulatory affairs.

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

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

9 Q. No, just in general.

10 A. Oh, I'm sorry.

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

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

17 A. I didn't ask him any questions.

18 Q. Okay. Any reason why not?

19 A. I didn't believe I needed to.

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

22 MR. DELAFIELD: Objection.

23 Vague.

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

1 and I did some calculations based on his
2 data, which appear in my report.
3 BY MR. POLLACK:
4 Q. Let's -- let's take a look at that.
5 I think that's in paragraph 70; is
6 that right?
7 A. I'll have to check. (Reviewing
8 document).
9 Q. I'm sorry. It's in paragraph 67.
10 Is that the calculation you're
11 referring to at paragraph 67?
12 A. (Reviewing document).
13 Yes, that's correct. This is what
14 I was referring to.
15 Q. Are there any other calculations in
16 your declaration?
17 A. I don't think so, but I don't --
18 Q. Yeah, I didn't see any.
19 A. -- recall with certainty.
20 Q. I was just checking.
21 A. Yeah, I don't think so.
22 Q. Okay. Explain to me. What was the
23 calculation you did in paragraph 67?
24 A. I calculated the percentage
25 reduction in total impurities based on the

1 analysis that Dr. Williams did on the
2 treprostini1 free acid by the former process
3 and by the '393 process.

4 Q. Let me ask you.

5 Is what you did -- this number
6 .9545, where did that come from? Did that just
7 come from Dr. Williams?

8 A. Yes, that came from his table.

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

11 MR. DELAFIELD: Objection.

12 Vague.

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

15 BY MR. POLLACK:

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

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

25 Q. Did you calculate any of the

1 averages or standard deviations or anything

2 like that?

3 A. No, I did not.

4 Q. Okay. So you're relying on

5 Dr. Williams' --

6 A. Yes.

7 Q. -- calculation?

8 A. I'm relying on his calculation.

9 Q. Okay. And what about the number
10 .2936? Did you just take that from

11 Dr. Williams?

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

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

16 A. No, I did not.

17 Q. So am I correct, is the calculation
18 that you did is you just subtract .2936 from
19 .9545?

20 MR. DELAFIELD: Objection.

21 Vague.

22 THE WITNESS: No.

23 BY MR. POLLACK:

24 Q. Well, what did you do?

25 A. I divided .2936 by 9545 and

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

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

5 A. Yes.

6 Q. Okay.

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

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

12 MR. DELAFIELD: Objection.

13 Asked and answered.

14 THE WITNESS: I didn't do -- I
15 believe I did a calculation of the absolute
16 percent. It's not in my document, and I
17 forget what number I got. It was something
18 close to █ percent.

19 BY MR. POLLACK:

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

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

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

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

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

7 What's the first one?

8 A. The first one --

9 MR. DELAFIELD: Objection.

10 Vague.

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

14 BY MR. POLLACK:

15 Q. The higher purity of what?

16 A. Of the free acid.

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

20 A. That's correct.

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

24 A. Yes.

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

1 MR. DELAFIELD: Objection.
2 BY MR. POLLACK:
3 Q. Is that what you were referring to?
4 MR. DELAFIELD: Vague.
5 THE WITNESS: Yes.
6 BY MR. POLLACK:
7 Q. Okay. Okay. So you -- you took 1
8 minus .2936 and you divided that by 1 minus
9 .9545?
10 MR. DELAFIELD: Objection.
11 Vague.
12 THE WITNESS: The other way
13 around.
14 BY MR. POLLACK:
15 Q. Okay. I'm sorry.
16 You took 1 minus .94 -- 9545 and
17 divided by 1 minus .2936?
18 A. Yes.
19 MR. DELAFIELD: Same objection.
20 THE WITNESS: Yes. Well, let me
21 see. I just did it on the back of an
22 envelope, so I don't remember.
23 No. I -- 1 minus -- yes. 1
24 minus .2936 divided by 1 minus .9545
25 multiplied by 100 to get the percent higher

1 level of purity.

2 BY MR. POLLACK:

3 Q. All right. What number did you
4 get?

5 A. I don't remember. It was -- it was
6 close to █ percent, between a █ and █
7 percent.

8 Q. Between a █ and █ percent?

9 A. Between █ -- yeah, █ and █
10 percent, something in that range.

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

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

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

25 You're aware of that; right?

1 A. Yes, I am aware of that.

2 MR. DELAFIELD: Objection.

3 Vague.

4 BY MR. POLLACK:

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

7 A. I --

8 MR. DELAFIELD: Same objection.

9 Lacks foundation.

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

13 BY MR. POLLACK:

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

16 A. Yes, that's my understanding.

17 MR. DELAFIELD: Same objection.

18 Lacks foundation.

19 BY MR. POLLACK:

20 Q. Let me ask you.

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

1 MR. DELAFIELD: Objection.
2 Vague. Calls for speculation. Lacks
3 foundation.
4 THE WITNESS: It wouldn't change
5 my opinion.
6 BY MR. POLLACK:
7 Q. So even if the prior art was 99.7?
8 A. It wouldn't change --
9 MR. DELAFIELD: Same objections.
10 THE WITNESS: -- my opinion.
11 BY MR. POLLACK:
12 Q. So you're saying even -- even if
13 there was a 99.7 percent purity level in the --
14 in the prior art, there would still be a
15 long-felt need?
16 A. That 99.7 from Moriarty?
17 Q. Right, from Moriarty.
18 A. Yeah, that wouldn't change my -- my
19 opinion.
20 Q. Okay. So even if all of the --
21 prior to the patent all of the treprostinil
22 that United Therapeutics was selling had a
23 purity of 99.7 percent, you still feel there
24 would be a long-felt need for --
25 A. No, that's not what I was saying.

1 Q. Okay. Explain it to me.

2 MR. DELAFIELD: Objection.

3 Lacks foundation. Calls for speculation.

4 THE WITNESS: I know how

5 Dr. Williams did his analysis. He was

6 pretty clear. And the purities that he got

7 were based on total -- total --

8 BY MR. POLLACK:

9 Q. Related impurities?

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

12 Q. Uh-huh.

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

19 And so you can't compare unless
20 they're apples and apples and there that number
21 99.7 percent didn't mean anything to me because
22 I couldn't tell how he did the analysis. You
23 will get different results with a reference
24 standard versus total related impurities.

25 Q. No, the FDA, though, requires that

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

3 MR. DELAFIELD: Objection.

4 Lacks foundation. Calls for speculation.

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

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

17 BY MR. POLLACK:

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

21 A. Yes, they are --

22 Q. Okay.

23 A. -- in the case of treprostinil.

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

1 MR. DELAFIELD: Objection.
2 Mischaracterizes the documents and his
3 testimony.
4 BY MR. POLLACK:
5 Q. Correct?
6 A. That's correct.
7 Q. Yeah. Okay.
8 A. They -- they do both, but the
9 purity level by HPLC is what is required.
10 Q. Right. Actually --
11 A. Yes.
12 Q. -- you said they did both, but, in
13 fact, they never total up the total related
14 purities and subtract that from 100, do they?
15 MR. DELAFIELD: Objection. Lack
16 of foundation. Calls for speculation.
17 THE WITNESS: No, because that's
18 not a preferred analysis by the FDA. They
19 want a reference standard and that's the
20 HPLC.
21 BY MR. POLLACK:
22 Q. Right. And do you -- do you recall
23 that the Moriarty reference he describes using
24 an HPLC and a UV detector?
25 A. Yes.

1 MR. DELAFIELD: Objection.

2 Lacks foundation.

3 BY MR. POLLACK:

4 Q. Okay. Okay. Why are you then
5 saying you don't -- you're not sure whether or
6 not he used HPLC in a reference standard?

7 A. Well, H --

8 MR. DELAFIELD: Objection.

9 Lacks foundation.

10 THE WITNESS: -- HPLC is used
11 for total related substances, too, but he
12 didn't indicate whether he compared peak
13 heights, which would be total related
14 substances, or a reference standard, which
15 would be the quantitation preferred by the
16 FDA in their certificates of analysis, the
17 release specs.

18 So I couldn't tell what Moriarty
19 used, and I looked for it to see whether
20 that was a number, a comparable number that
21 I could use to compare apples to apples to
22 -- to Dr. Williams.

23 BY MR. POLLACK:

24 Q. Let me ask you this.

25 Moriarty doesn't report anywhere

1 what the total related impurities are; right?

2 MR. DELAFIELD: Objection.

3 Mischaracterizes the document.

4 THE WITNESS: I don't know.

5 BY MR. POLLACK:

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

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

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

12 MR. DELAFIELD: Objection.

13 Lacks foundation. Mischaracterizes the
14 document.

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

21 BY MR. POLLACK:

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

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

25 A. I don't know.

1 MR. DELAFIELD: Same objections.

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

5 BY MR. POLLACK:

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

10 MR. DELAFIELD: Same objections.

11 Asked and answered. Asked and answered.

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

16 BY MR. POLLACK:

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

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

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

24 THE WITNESS: I don't recall.
25 I'd have to go review the paper.

1 BY MR. POLLACK:

2 Q. You're aware that Moriarty is
3 associated with United Therapeutics that that's
4 their patent?

5 A. Yes, of course.

6 Q. Did you ask United Therapeutics,
7 hey, can you tell me how Moriarty did this
8 analysis?

9 A. No, I did not ask.

10 Q. Take a look at the '393 patent.
11 Can you show me in the '393 patent where they
12 report what the impurities are in treprostinil
13 or any other compound?

14 MR. DELAFIELD: Objection.

15 Vague.

16 THE WITNESS: So they report
17 purities in -- I don't see a table number --
18 in column 14 at the bottom, and those are
19 HPLC area under the curve. So those are
20 reference standards.

21 In table -- on column 16, they
22 report a purity and -- and because that is
23 the process that they submitted to the FDA
24 for approval, that has to be an HPLC
25 quantitative assay with a reference

1 standard.

2 BY MR. POLLACK:

3 Q. Uh-huh.

4 A. And in claim 2 -- I'm sorry --
5 claim 2 and claim 10, that is total related
6 substances.

7 Q. Why do you say that if every other
8 place in the patent it reports HPLC assay
9 analysis?

10 A. Because it's my understanding that
11 the document that was submitted by Dr. Walsh to
12 the Patent Office was the last document before
13 approval and that convinced the agency to
14 approve this patent and the claims, and he did
15 total related substances.

16 Q. So you're saying we should look at
17 what Dr. Walsh says, not what's written in the
18 patent?

19 MR. DELAFIELD: Objection.

20 Calls for speculation.

21 BY MR. POLLACK:

22 Q. That is your opinion?

23 A. No, that's not my opinion.

24 Q. Well, then, why aren't we looking
25 at the HPLC analysis in the patent?

1 A. That's not in the claim. I think,
2 actually, you should look at all of them, but
3 what's in the claim was done by a different
4 method, total related substances.

5 Q. So you see the words "total related
6 substances" in the claim?

7 A. No, I don't. As I said, I reviewed
8 Dr. Walsh's analysis and that was submitted
9 just before approval, as I understand, and
10 there were no further actions taken before the
11 decision. And so it makes sense to me that
12 because he reported total related substances
13 that the claims, which is what was in dispute
14 -- dispute, referred to total related
15 substances.

16 Q. Okay. You'd agree with me that
17 within the patent itself, those are all HPLC
18 analyses that are reported?

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

21 THE WITNESS: It's my judgment
22 based on the description of area under the
23 curve and the HPLC assay, as well as the
24 fact that example 6 refers to the process
25 that was approved by the agency, which is an

1 HPLC quantitative assay involving a
2 reference standard, that that is what was
3 used.

4 BY MR. POLLACK:

5 Q. And by "that" you mean HPLC
6 analysis?

7 A. Yes.

8 MR. DELAFIELD: Same objections.

9 THE WITNESS: When you get to a
10 point, I'd like to use the restroom. I
11 don't need lunch if you don't want, but I
12 do -- would like to use the restroom.

13 BY MR. POLLACK:

14 Q. Do you want to break? It's up to
15 you. Do you want to break for lunch now?

16 A. It doesn't matter to me. Whatever
17 you want to do.

18 MR. DELAFIELD: Yeah, it's
19 already 12:30.

20 MR. POLLACK: You guys want to
21 break for lunch? That's fine.

22 MR. DELAFIELD: Sure.

23 THE VIDEOGRAPHER: The time is
24 12:34 p.m. This completes Media Unit No. 2.
25 We're off the record.

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(Whereupon, at 12:34 p.m., a
luncheon recess was taken.)

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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

1 statement there that reads:

2 "For example, if the actual purity
3 of an API is 99.4 percent and the lowest limit
4 of purity in the Drug Specification of the
5 Certificate of Analysis is 99.5 percent, the
6 entire batch of API must be rejected."

7 Do you see that?

8 A. Yes, I do.

9 Q. Okay. So let me see if I -- if I
10 understand this.

11 By the way, do you agree with that
12 statement still?

13 A. Yes. As an example, yes.

14 Q. Okay. So, for example, let's say I
15 have a Certificate of Analysis and it says the
16 HPLC analysis is 99.6.

17 A. Okay.

18 Q. Okay. Would that drug be sold to
19 the public?

20 MR. DELAFIELD: Objection.

21 Vague. Calls for speculation.

22 THE WITNESS: That depends on
23 what the specification was.

24 BY MR. POLLACK:

25 Q. Oh, I'm sorry. I was using --

1 A. Oh, in my example.
2 Q. -- your example. In your example.
3 A. I'm sorry. Yeah, could you repeat
4 that, please? I'm sorry.
5 Q. Yeah. So using your example.
6 A. Okay. Yeah.
7 Q. Let's say I had a drug which its
8 HPLC analysis shows --
9 A. Yes.
10 Q. -- it had a Certificate of Analysis
11 by HPLC of 99.6 percent.
12 Would the FDA allow the company to
13 sell that batch to the public?
14 MR. DELAFIELD: Objection.
15 Vague. Calls for speculation.
16 THE WITNESS: So if it was 99.6
17 and the specification was 99.5, yes, that
18 would be allowed to be approved. I don't
19 know if it could be sold to the public.
20 That depends on many other steps because
21 that API would go into that a drug product,
22 and that has its own specs. So that would
23 determine.
24 BY MR. POLLACK:
25 Q. Sure.

1 A. But it could move on in the
2 manufacturing --
3 Q. It could move on in process?
4 A. -- in the manufacturing process.
5 Q. What if I had an API -- what does
6 API stand for?
7 A. Active pharmaceutical ingredient.
8 Q. If I had an active pharmaceutical
9 ingredient which had, just like your example,
10 Certificate of Analysis, the specification is
11 99.5 percent. So let's say I had a batch and
12 it had an HPLC assay analysis of 99.5 percent.
13 Could that move on in the process?
14 MR. DELAFIELD: Objection.
15 Vague. Relevance. Calls for speculation.
16 THE WITNESS: Yes, that could
17 move on if that 99.5 was the specification.
18 Yes.
19 BY MR. POLLACK:
20 Q. Okay. Now, you're aware the limit
21 for treprostinil that we're dealing with in
22 this case is 98 percent; is that right?
23 MR. DELAFIELD: Objection.
24 Calls for speculation. Lacks foundation.
25 Vague.

1 THE WITNESS: That is the
2 current lower limit.

3 BY MR. POLLACK:

4 Q. Okay. So if I have a batch, let's
5 say I have a -- I make a batch of treprostinil
6 and it -- I measure its HPLC assay and it's 99
7 percent.

8 Do you have my assumptions?

9 A. Uh-huh.

10 Q. Can that batch of treprostinil move
11 on in the process?

12 MR. DELAFIELD: Same objections.

13 THE WITNESS: Assuming all of
14 the other specifications were met, yes, that
15 could move on.

16 BY MR. POLLACK:

17 Q. Okay. And I make another batch of
18 treprostinil API and I measure its HPLC
19 analysis and it's [REDACTED] percent.

20 Could that batch move on in the
21 process?

22 MR. DELAFIELD: Same objections.

23 THE WITNESS: Yes, with that
24 current level spec, that could move on.

25 BY MR. POLLACK:

1 Q. Okay. Based on your experience in
2 the industry, if a company like United
3 Therapeutics made a batch that was █████ percent
4 on the HPLC analysis, it would be the normal
5 expectation that the company would then move
6 that batch into the rest of the process?

7 A. Yes.

8 MR. DELAFIELD: Objection.
9 Relevance. Vague. Calls for speculation.

10 THE WITNESS: Yes, they could do
11 that.

12 BY MR. POLLACK:

13 Q. Okay.

14 A. If they -- if they chose to.

15 Q. Now, Dr. Williams opined that
16 certain batches that he looked at had an
17 average HPLC analysis -- I'm sorry, I'm
18 incorrect -- an average purity based on
19 subtracting related impurities of 99 percent.

20 Is that -- is that what you recall?

21 MR. DELAFIELD: Objection.

22 BY MR. POLLACK:

23 Q. Approximately 99 percent --

24 MR. DELAFIELD: Objection.

25 Vague.

1 BY MR. POLLACK:

2 Q. -- for the Moriarty batches?

3 A. Oh, for the --

4 MR. DELAFIELD: Objection.

5 Vague. Mischaracterizes document.

6 THE WITNESS: I would have to
7 look again at those tables, but it was
8 something close to that. I don't remember
9 the number.

10 BY MR. POLLACK:

11 Q. Okay. Yeah. I'm not trying to --

12 A. Yeah.

13 Q. -- trying to trick you here. If
14 you look at where we were --

15 A. No, I understand. I just don't
16 remember --

17 Q. Yeah.

18 A. -- the number.

19 Q. Remember we were -- we were
20 looking --

21 A. Yeah.

22 Q. -- at your paragraph 67?

23 A. Yeah. Yeah. Okay.

24 Okay.

25 Q. And maybe I misunderstood, but I

1 think here you refer to Dr. Williams'

2 declaration and his Table 1?

3 A. Yes.

4 Q. Do you see that?

5 A. I did, yes.

6 Q. And I think what I'm supposed to
7 conclude here is that the -- well, what am what
8 am I supposed to conclude about the typical
9 purity of the Moriarty process, if anything,
10 from your -- your paragraph 67?

11 MR. DELAFIELD: Objection.

12 Vague.

13 THE WITNESS: That the average
14 relevant impurities are higher in the
15 Moriarty process compared to the '393
16 process.

17 BY MR. POLLACK:

18 Q. Okay. Is there anything I'm
19 supposed to conclude about what the average
20 purity on the scale from zero to 100 percent is
21 of API made by the Moriarty process?

22 MR. DELAFIELD: Objection.

23 Vague. Calls for speculation.

24 THE WITNESS: Oh, I can't answer
25 that because there will be variability.

1 There will be some high, some low, and I
2 haven't analyzed how many would fall below
3 spec. So I don't know.

4 BY MR. POLLACK:

5 Q. Okay. Well, let me ask you this.

6 This number .945. If I subtract
7 that number from 1 and multiply by 100 --

8 A. Uh-huh.

9 Q. -- right, I get approximately 99
10 percent; is that fair?

11 A. About, yes.

12 MR. DELAFIELD: Objection.

13 BY MR. POLLACK:

14 Q. Okay.

15 MR. DELAFIELD: Mischaracterizes
16 the document.

17 BY MR. POLLACK:

18 Q. Would you -- in your view is --
19 does that characterize the average purity of
20 products made by the Moriarty process?

21 MR. DELAFIELD: Objection.

22 Vague.

23 THE WITNESS: I believe that the
24 analysis done by Dr. Williams gives a answer
25 to the question that the Moriarty process

1 produces product that is less pure than the
2 '393. And your question is?

3 BY MR. POLLACK:

4 Q. Okay. I was wondering if it gives
5 an answer to the question of what the average
6 purity was in the Moriarty process.

7 MR. DELAFIELD: Objection.
8 Vague.

9 THE WITNESS: I think it gives a
10 relative purity compared to the '393 process
11 because, remember, it depends on how you do
12 the analysis, whether it's against a
13 reference standard or against total related
14 product.

15 This I know was done against a
16 reference standard, and so it gives an idea
17 of average purity that one would expect with
18 one process to another because you're
19 comparing apples to apples in this case.
20 And I think that's a fair comment what I
21 said and --

22 BY MR. POLLACK:

23 Q. Okay. Let me just make sure you
24 didn't --

25 A. Yeah.

1 Q. -- you didn't make an error here
2 because you just said you know this was done by
3 an HPLC analysis, but here it says total
4 related substances in your paragraph 67.

5 A. Oh, I'm sorry. I'm sorry. I take
6 that back.

7 The comparison is still valid
8 because it's apples to apples total related
9 substances. I apologize. But so it's apples
10 to apples. The same relative purity is
11 comparable. You can compare one to another,
12 and it's higher with '393 than with Moriarty.

13 So I take it back. But you're
14 right. It's total related substances.

15 Q. Okay. Based on this, are we able
16 to say anything about how the HPLC analysis
17 compares --

18 MR. DELAFIELD: Objection.

19 Vague.

20 BY MR. POLLACK:

21 Q. -- for Moriarty versus '393
22 process?

23 MR. DELAFIELD: Objection.

24 Vague. Calls for speculation. Outside the
25 scope of his report.

1 THE WITNESS: Okay. I have not
2 seen that comparison done on -- on HPLC
3 quantitative assay against reference
4 standard. I did look at all of those
5 certificate of release forms where that's
6 done, but I didn't do an analysis.

7 BY MR. POLLACK:

8 Q. Okay.

9 A. But the analysis that Dr. Williams
10 did, because it's apples to apples, gives a
11 good comparison of one process to the other,
12 but I can't relate that to an FDA release spec
13 that's done by different analysis to a
14 reference standard. That's -- that's what I'm
15 trying to say.

16 Q. Okay. Okay. I understand.

17 Okay. So what you're saying here
18 in effect is, look, the '393 patent does
19 another purification step on top of Moriarty,
20 so the purity is going to be higher?

21 A. I'm not --

22 MR. DELAFIELD: Objection.

23 Vague.

24 THE WITNESS: I'm not -- I
25 wouldn't agree with that statement.

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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;

1 correct?

2 MR. DELAFIELD: Objection.

3 Vague. Calls for speculation.

4 THE WITNESS: (Reviewing
5 document). Yes, it says that the compounded
6 formula (VI) does not include that purifying
7 -- that purity step.

8 BY MR. POLLACK:

9 Q. Okay. So that's in claim 16?

10 A. That's in claim 16.

11 Q. Right. So then presumably the
12 other claims you could include the purification
13 of the nitrile.

14 MR. DELAFIELD: Objection.

15 BY MR. POLLACK:

16 Q. Is that your understanding?

17 MR. DELAFIELD: Objection.

18 Vague. Lacks foundation. Calls for
19 speculation.

20 THE WITNESS: That's not my
21 understanding. The process that is the
22 subject of this patent, which is, I think,
23 referenced -- referenced in the claim 1 and
24 claim 9, is referring to a process, which as
25 I understand is the '393 process, which

1 doesn't have purification of the nitrile.
2 BY MR. POLLACK:
3 Q. Okay. I'm not -- I may be asking
4 you something that's a little too legal, but do
5 you have an understanding -- let me step back.
6 Do you have any patents?
7 A. I have a couple of patents, yes.
8 Q. Okay. Do you have any
9 understanding of how patent claims work?
10 A. I have a -- compared to somebody
11 like you -- a relatively low understanding of
12 how patent claims work. I'm not totally
13 ignorant on the subject, but I have some
14 knowledge, but it's certainly nothing that I've
15 devoted a great deal of time to.
16 Q. Are you familiar with the following
17 concept? When a -- when a claim says
18 "comprising" and it has a process comprising,
19 that means the claim is met. If the steps of
20 the claim are performed, plus in addition,
21 because it says "comprising," it also includes
22 processes which have additional steps that
23 that's allowed, that's part of the claim as
24 well.
25 MR. DELAFIELD: Objection.

1 Vague. Calls for a legal conclusion.

2 THE WITNESS: Yeah, that's

3 getting a little bit beyond my -- my --

4 BY MR. POLLACK:

5 Q. Okay.

6 A. -- relative understanding.

7 Q. Yeah, I'm not asking you if that's

8 right.

9 A. Yeah.

10 Q. I was just wondering if you knew

11 about that.

12 A. Not -- not really.

13 Q. Oh, okay.

14 A. Not -- no. Again, I'm not a lawyer

15 -- an attorney and -- and that is beyond my

16 level of expertise.

17 Q. Okay.

18 A. So I'm sorry.

19 Q. Okay. Let me just ask you. Just

20 going back to claim 16 where it said "wherein

21 the process does not include purifying" the

22 nitrile.

23 What was your understanding of how

24 claim 16 was different from claim 9?

25 MR. DELAFIELD: Objection.

1 Vague.

2 THE WITNESS: Well, I -- because
3 claim 9 says it's wherein the product is
4 prepared by the process comprising, and that
5 I understand is the '393 process, which
6 doesn't have a purification step for the
7 nitrile, I -- looks like claim 16 is
8 reaffirming that. That's all I can say.

9 BY MR. POLLACK:

10 Q. Okay. So one of the -- one of the
11 differences between the Moriarty process and
12 what I call the '393 process -- that's what you
13 call it in your declaration; right?

14 A. Yes, I think so.

15 Q. Is that in the '393 process, this
16 purification step is -- of the nitrile has been
17 removed?

18 MR. DELAFIELD: Objection.

19 Vague.

20 THE WITNESS: That's my
21 understanding, yes.

22 BY MR. POLLACK:

23 Q. Yeah. Okay. Are there other -- in
24 addition, there's a further purification step
25 at the end where they make the diethanolamine

1 salt in the treprostiniil that -- that United
2 Therapeutics makes by the '393 process; is that
3 your understanding?

4 MR. DELAFIELD: Objection.
5 Vague. Lacks foundation.

6 THE WITNESS: It's my
7 understanding that that crystallization was
8 done, and it did result in an increase in
9 the level of purity and a decrease in the
10 level of impurities, which is what
11 Dr. Williams analyzed.

12 BY MR. POLLACK:

13 Q. Other than that crystallization and
14 the change in the purification of nitrile, did
15 you identify any other differences between how
16 United Therapeutics made treprostiniil according
17 to the Moriarty process and treprostiniil
18 according to what we're calling here the '393
19 process?

20 MR. DELAFIELD: Objection.
21 Vague. Outside the scope of his
22 declaration.

23 THE WITNESS: I would suggest
24 that the formation of the diethanolamine
25 salt as the step immediately before the

1 crystallization was part of the purification
2 based on my -- on my review of -- of the
3 documents.

4 BY MR. POLLACK:

5 Q. Now, you said that was a
6 purification by crystallization; is that right?

7 MR. DELAFIELD: Objection.
8 Vague. Mischaracterizes testimony.

9 THE WITNESS: That's the step
10 (d), which is reacting the salt formed in
11 step (c) with an acid to form the compound
12 of formula IV, which is treprostinil free
13 acid.

14 BY MR. POLLACK:

15 Q. That's called a crystallization?

16 A. That --

17 MR. DELAFIELD: Same objection.

18 THE WITNESS: -- to me would be
19 a crystallization.

20 BY MR. POLLACK:

21 Q. Let me ask you.

22 Have -- have you seen
23 crystallization used before to purify
24 compounds?

25 A. Oh, yes. Yes, I have.

1 Q. How often?

2 MR. DELAFIELD: Objection.

3 Vague. Calls for speculation.

4 THE WITNESS: It's a process
5 that's used not uncommonly to purify final
6 product of the reaction.

7 BY MR. POLLACK:

8 Q. Wasn't this -- isn't
9 crystallization unique to the '393 patent?

10 MR. DELAFIELD: Objection.

11 Vague and ambiguous.

12 THE WITNESS: The
13 crystallization, as I understand it, is not
14 what's unique to the patent. It's the
15 result of that crystallization that resulted
16 in a different product with a higher purity
17 and lower levels of impurity.

18 BY MR. POLLACK:

19 Q. How long has crystallization been
20 around as a method of purification?

21 MR. DELAFIELD: Objection.

22 Vague. Relevance. Outside the scope of his
23 report.

24 THE WITNESS: I don't know how
25 long it's been around.

1 BY MR. POLLACK:

2 Q. Before 2007?

3 A. Oh, yes.

4 MR. DELAFIELD: Same objections.

5 THE WITNESS: Yes.

6 BY MR. POLLACK:

7 Q. Did you learn about it when you
8 were in college at the university?

9 MR. DELAFIELD: Same objections.

10 THE WITNESS: Yes, I did.

11 BY MR. POLLACK:

12 Q. What course did you -- in what
13 course did you learn about that?

14 MR. DELAFIELD: Same objections.

15 THE WITNESS: The inorganic
16 chemistry, organic chemistry, physical
17 chemistry, medicinal chemistry,
18 pharmaceutical chemistry, analytical
19 chemistry. Maybe some others.

20 BY MR. POLLACK:

21 Q. And when did you go to college?

22 A. In 1968 I started. In 1968.

23 Q. And when did you graduate?

24 A. I graduated with my BS in pharmacy
25 in '73 and then my Ph.D. from the same

1 institution three or four years later.

2 Q. What school was that?

3 A. The Ohio State University, Football
4 Capital of the World.

5 Q. Yeah. (Laugh).

6 And those courses you described
7 taking where they talked about purification
8 with crystallization, did you take those when
9 you were an undergraduate or a graduate?

10 MR. DELAFIELD: Objection.
11 Relevance.

12 BY MR. POLLACK:

13 Q. Or both?

14 A. Both.

15 Q. Okay. Okay. But you're an expert
16 on or at least you have a lot of knowledge
17 about stereochemistry; right?

18 A. Yes.

19 Q. Okay.

20 A. Yes.

21 Q. Okay. But I think it's the case --
22 is it the case that crystallization was not
23 used to separate stereoisomers before 2007?

24 MR. DELAFIELD: Objection.

25 Relevance. Vague. Calls for speculation.

1 THE WITNESS: Crystallization is
2 often used to step -- separate
3 stereoisomers. You have to conversion it to
4 diastereomers by reacting with an optically
5 active salt.

6 BY MR. POLLACK:

7 Q. Okay. But that wouldn't -- that
8 technique of using crystallization to separate
9 stereoisomers, that wouldn't apply to
10 enantiomers, would it?

11 MR. DELAFIELD: Same objections.

12 Outside the scope of his report.

13 THE WITNESS: To just the plain
14 enantiomers?

15 BY MR. POLLACK:

16 Q. Yes.

17 MR. DELAFIELD: Same objections.

18 THE WITNESS: The same
19 enantiomers -- crystallization of the same
20 enantiomers wouldn't -- wouldn't separate
21 them.

22 BY MR. POLLACK:

23 Q. I'm sorry. I didn't mean same
24 enantiomers. I meant, you know, the
25 two-direction, yeah.

1 A. The diastereomers -- excuse me.
2 MR. DELAFIELD: Same objections.
3 THE WITNESS: The enantiomers,
4 dextro and levo --
5 BY MR. POLLACK:
6 Q. Right.
7 A. -- would not be separated alone by
8 crystallization without first reaction with an
9 optically active compound to produce
10 diastereomers which then would be crystallized.
11 Q. Okay. All right. But how far back
12 does doing that process you just described, how
13 far back does that go?
14 MR. DELAFIELD: Objection.
15 Relevance. Vague. Outside the scope of his
16 report.
17 THE WITNESS: Decades.
18 BY MR. POLLACK:
19 Q. Before 2007?
20 A. Oh, yes.
21 MR. DELAFIELD: Same objections.
22 BY MR. POLLACK:
23 Q. Let me ask you some hypotheticals.
24 Suppose the -- just for this
25 argument, for argument, suppose the Moriarty

1 process produced treprostinil and we had a
2 batch of treprostinil made by the Moriarty
3 product -- process and it had a 99 percent HPLC
4 analysis purity.

5 Would United Therapeutics be
6 allowed to send that Moriarty process
7 treprostinil through the rest of the process
8 and out to the public based on the current
9 treprostinil specification?

10 MR. DELAFIELD: Objection.
11 Vague. Calls for speculation. Lacks
12 foundation.

13 THE WITNESS: They would be
14 permitted to move it down the manufacturing
15 process, and if subsequent specifications
16 were met, then it could go out to the
17 public.

18 BY MR. POLLACK:

19 Q. By "subsequent specifications,"
20 you're referring to specifications for the drug
21 product?

22 A. Correct.

23 MR. DELAFIELD: Same -- same
24 objections.

25 BY MR. POLLACK:

1 Q. They wouldn't measure the purity of
2 the API again later in the process?

3 MR. DELAFIELD: Same objections.

4 BY MR. POLLACK:

5 Q. Once it's been formulated for a
6 drug product?

7 MR. DELAFIELD: Same objections.

8 THE WITNESS: If the formulation
9 had other components added to it, the API
10 would not be tested again, but sometimes the
11 API does just become the final product,
12 so...

13 BY MR. POLLACK:

14 Q. Do you know in the case of
15 treprostiniil, does it just become the final
16 product or does it need to be turned into a
17 formulation?

18 MR. DELAFIELD: Objection.

19 Relevance. Lacks foundation.

20 THE WITNESS: It needs to be
21 turned into a formulation. I don't know
22 what else is in the formulation, though.

23 BY MR. POLLACK:

24 Q. Let's suppose that the Moriarty
25 process -- this is a hypothetical, this is my

1 assumption -- produces treprostinil on an HPLC
2 analysis purity of [REDACTED] percent plus or minus
3 [REDACTED] on the standard deviation. All right? So
4 it might be [REDACTED]. It might be [REDACTED], but
5 basically that's the range you're in.

6 In your opinion, would there be a
7 reason for further purification?

8 MR. DELAFIELD: Objection.

9 Vague. Calls for speculation. Outside the
10 scope of his report.

11 THE WITNESS: [REDACTED] -- what did
12 you say?

13 BY MR. POLLACK:

14 Q. [REDACTED] plus or minus [REDACTED].

15 A. As a standard deviation, that
16 doesn't mean -- standard deviation doesn't mean
17 you add 2 and subtract 2.

18 Q. Sure. But it does mean that --
19 what is it? -- 67 percent of the samples will
20 fall between those limits?

21 A. It means that --

22 MR. DELAFIELD: Objection.

23 Lacks foundation. Vague. Calls for
24 speculation.

25 THE WITNESS: It means that the

1 95 percent confidence limit would be
2 approximately plus or minus █.

3 BY MR. POLLACK:

4 Q. █?

5 A. Standard --

6 Q. █ or █?

7 A. █.

8 Q. █?

9 A. Standard deviation is not plus or
10 minus the actual number. Standard deviation is
11 a statistical assessment of the variability,
12 and when you have a standard deviation of 2,
13 you calculate a 95 percent confidence limit
14 which is multiplied by --

15 Q. I'm sorry. I said █ plus or
16 minus █. You may have misheard me.

17 A. Oh, I didn't hear the █ if that's
18 what you said.

19 Q. The point. Yeah, I'm sorry.

20 MR. DELAFIELD: Same objections.

21 THE WITNESS: And the same
22 calculations still -- still you do. It's
23 not plus or minus █. It would be plus or
24 minus something like █.

25 BY MR. POLLACK:

1 Q. And that would be 95 percent of the
2 samples?

3 A. That would be -- would fall in --

4 MR. DELAFIELD: Same objections.

5 THE WITNESS: -- in that range.

6 BY MR. POLLACK:

7 Q. Okay. So 95 percent of the -- of
8 the samples would fall between [REDACTED] and [REDACTED];
9 is that fair?

10 MR. DELAFIELD: Objection.

11 Vague. Lacks foundation. Calls for
12 speculation.

13 THE WITNESS: I forget what
14 number you gave me for the medium purity.

15 BY MR. POLLACK:

16 Q. Ah, okay. Let me write it down
17 [REDACTED].

18 A. Okay.

19 Q. And I'm doing a standard deviation
20 of plus or minus [REDACTED] in my hypothetical.

21 And my question is whether that
22 means that 95 percent of the samples would fall
23 between [REDACTED] and [REDACTED].

24 MR. DELAFIELD: Objection.

25 Vague. Calls for speculation. Lacks

1 foundation.

2 THE WITNESS: Approximately
3 because I did an approximate calculation of
4 confidence limit but...

5 BY MR. POLLACK:

6 Q. Okay. So let me just look back at
7 your paragraph 32 for a second in your
8 declaration, so we don't get confused then.

9 A. I'm sorry. Paragraph?

10 Q. 32.

11 A. Okay.

12 Q. And so you say here -- this is on
13 page 14. I'm looking at your third sentence,
14 and here you say:

15 "Although the FDA provides no
16 absolute level of purity required for any drug,
17 based on my experience of approximately 40
18 years in the pharmaceutical industry
19 interacting with the FDA on regulatory issues,
20 it is commonly assumed that, with rare
21 exception, licensed drugs will have purities in
22 excess of 99%, and often significantly higher."

23 Did I read that correctly?

24 A. Yes, you did.

25 Q. Okay. And you still agree with

1 that statement?

2 A. Yes, I do.

3 Q. Okay. If the Moriarty process is
4 producing [REDACTED] plus or minus [REDACTED], wouldn't it
5 meet the standard you just described there in
6 paragraph 32?

7 MR. DELAFIELD: Objection.

8 Vague. Calls for speculation.

9 Mischaracterizes the document.

10 THE WITNESS: That's -- that's
11 not a standard. That's -- that's what's
12 commonly occurred. A standard is what's in
13 the spec, what's in the specification of the
14 Certificate of Analysis.

15 BY MR. POLLACK:

16 Q. Okay.

17 A. So that's really what matters.

18 Q. Right. Okay. Fair enough. And
19 what's in the specification is 98 percent;
20 right?

21 A. Correct. The lower limit now is 98
22 percent, yes.

23 Q. Right. So material made by the
24 Moriarty process, if it has the limits that I
25 just gave of [REDACTED] plus or minus [REDACTED], it will 95

1 percent of the time meet the spec?

2 MR. DELAFIELD: Objection.

3 Calls for speculation. Lacks foundation.

4 THE WITNESS: Based on those,
5 that number and the standard deviation, in
6 my approximate calculation of 90 percent --
7 95 percent confidence limits, yes, which is
8 from --

9 BY MR. POLLACK:

10 Q. Right. In fact, if we pulled it
11 out to 99 percent confidence limits, we would
12 probably still meet the 98 percent specs?

13 MR. DELAFIELD: Same objections
14 and outside the scope of his report.

15 THE WITNESS: Yeah, I can't do
16 that calculation in my head.

17 BY MR. POLLACK:

18 Q. Okay.

19 A. So I don't know what the 99 percent
20 confidence limits will be.

21 Q. They're going to be greater than 99
22 percent given my numbers; right?

23 MR. DELAFIELD: Same objections.

24 THE WITNESS: I don't know. I'd
25 have to do the calculations and I can't do

1 that one in my head.

2 BY MR. POLLACK:

3 Q. Okay. But as you said here, based
4 on your 40 years of experience, if you're in
5 excess of 99 percent, it's not a rule, but as a
6 kind of a sort of rule of thumb or best guess,
7 better than 99 percent is probably going to be
8 fine with the FDA; right?

9 MR. DELAFIELD: Objection.
10 Mischaracterizes the document.

11 THE WITNESS: No, I wouldn't say
12 that. The rule of thumb would be what's
13 provided in the FDA guidances and, of
14 course, they're guidances. So the FDA can
15 and often does --

16 BY MR. POLLACK:

17 Q. Sure.

18 A. -- tighten them up above 99
19 percent. That's why I said "in excess of" and
20 so it's what they agree with the manufacturer
21 will be the specification for release.

22 Q. Right. But before you get to the
23 FDA, when you were at Wyeth or GSK, your team
24 would have to assess based on the purities you
25 were getting what FDA would probably accept;

1 correct?

2 A. And --

3 MR. DELAFIELD: Objection.

4 Vague.

5 THE WITNESS: And we would -- we
6 would look at the guidance to give us an
7 idea, but it's never a guarantee until the
8 FDA -- until you sit down and discuss with
9 the FDA.

10 They look at the data. They
11 look at your analysis. They look at the --
12 the equipment that you're using. They look
13 at the level of detection and, more
14 importantly, the level of quantitation. And
15 it's through that discussion and negotiation
16 that you end up with a specification.

17 BY MR. POLLACK:

18 Q. Right. Fair enough. But when your
19 team was working on drug approvals, if you saw,
20 you know, a better than 99 percent, did that
21 give you some confidence that yes, we can go to
22 the FDA and see where that discussion goes?

23 MR. DELAFIELD: Objection.

24 Vague. Relevance.

25 THE WITNESS: That depends on

1 when. 20 years ago, yes, I would think that
2 our teams would go to the FDA with that. I
3 don't believe we'd probably do that now on
4 most drugs, but on some drugs we would go to
5 99 or maybe even lower.

6 BY MR. POLLACK:

7 Q. What about 10 years ago? Would
8 you -- would you go with 99?

9 MR. DELAFIELD: Same objections.

10 THE WITNESS: I mean, the -- the
11 criteria get tougher as time goes on and
12 even today, depending on the drug, the FDA,
13 if, for example, if it's a natural product
14 with a very difficult extraction, they go to
15 levels of 85 percent purity. Depends on the
16 drug, the disease.

17 It's not a property of the drug
18 itself. It's a property of the drug, the
19 disease, the patients, whether there are
20 alternate therapies and how serious a
21 disease is, and those really go into
22 determining what the specification will be
23 in terms of purity.

24 BY MR. POLLACK:

25 Q. Okay. I assume in that analysis

1 the more serious a disease, the lower purity
2 the FDA will accept?

3 MR. DELAFIELD: Objection.

4 Relevance. Calls for speculation. Outside
5 the scope of his report.

6 THE WITNESS: It's not that
7 simple. There are serious diseases that
8 have many good therapeutic options, and they
9 may not --

10 BY MR. POLLACK:

11 Q. Sure.

12 A. -- go to that. So that's why I
13 said, it's a very complex dynamic and that's
14 why they issue guidelines and not regulation on
15 these purities. And as you know, there are
16 lots of guidelines on -- from the ICH and the
17 FDA on purity.

18 Q. Sure. I'm just trying to
19 understand how the guidelines work.

20 And so for a disease where there
21 isn't or there aren't therapeutic options,
22 is -- is the FDA a little more forgiving about
23 impurities?

24 MR. DELAFIELD: Objection.

25 Vague. Calls for speculation and outside

1 the scope of his report.

2 THE WITNESS: If the disease is
3 very serious, there are few therapeutic
4 options, or if the therapeutic options
5 aren't very good and the FDA believes this
6 is a drug patients should have and you can't
7 get purity to a level that is typically
8 found in guidance, they may relax that
9 standard after negotiation.

10 But I can tell you, I've seen
11 serious diseases, like cancer, where the FDA
12 wouldn't budge. So it depends on a number
13 of factors, and they take all those things
14 into consideration that I mentioned,
15 including your ability to manufacture a
16 medically necessary drug, and they weigh
17 that.

18 In addition to what I said
19 earlier, how potent the drug is, which means
20 it has a potent pharmacophore, and whether
21 it's acute use or chronic use. And chronic
22 use with a potent pharmacophore gets greater
23 scrutiny.

24 So it's a very complicated
25 analysis and assessment that they do which

1 is why it's the result of often multiple
2 discussions and they -- the amount of data
3 they demand to see before they make that
4 final decision or accept your final
5 recommendation is quite a bit.

6 BY MR. POLLACK:

7 Q. Do you know what disease
8 treprostiniil treats?

9 A. Yes.

10 Q. What disease is that?

11 A. Pulmonary arterial hypertension.

12 Q. Is that a serious disease?

13 MR. DELAFIELD: Objection.

14 Vague.

15 THE WITNESS: I consider that a
16 very serious disease.

17 BY MR. POLLACK:

18 Q. Are there a lot of treatment
19 options for pulmonary arterial hypertension?

20 MR. DELAFIELD: Objection.

21 Vague. Outside the scope of his report.

22 THE WITNESS: There aren't many
23 and they're not particularly effective. So
24 it is a serious disease.

25 BY MR. POLLACK:

1 Q. What about treprostinil? Is it
2 effective for pulmonary arterial hypertension?

3 MR. DELAFIELD: Same objections.

4 THE WITNESS: It is effective.
5 It met the negotiated endpoints that the FDA
6 required for approval in this disease.

7 BY MR. POLLACK:

8 Q. But people still die anyway of
9 pulmonary arterial hypertension even on
10 treprostinil?

11 A. They're --

12 MR. DELAFIELD: Objection.
13 Vague. Calls for speculation. Lacks
14 foundation.

15 THE WITNESS: Very sadly, yes.

16 BY MR. POLLACK:

17 Q. But in 2007, other than
18 treprostinil, there weren't many treatment
19 options for patients with pulmonary arterial
20 hypertension?

21 MR. DELAFIELD: Same objections.

22 THE WITNESS: Not very many.

23 BY MR. POLLACK:

24 Q. Now, if treprostinil had a purity
25 prior to 2007 of [REDACTED] percent on average, would

1 you agree with me that there's not a lot of
2 leeway there to go up? I mean, it's only [REDACTED]
3 percent?

4 MR. DELAFIELD: Objection.
5 Calls for speculation. Mischaracterizes
6 documents and vague.

7 THE WITNESS: If a single lot --
8 because that's all you can be talking about
9 a single lot -- was [REDACTED], that's a --
10 depending on the assay and if it's the --
11 the reference standard assay HPLC, it -- it
12 actually could be further away from 100
13 percent than [REDACTED] because you're basing it on
14 a reference standard, which is not going to
15 be 100 percent.

16 BY MR. POLLACK:

17 Q. Well, if the reference standard is
18 not 100 percent, that raises the number; right?

19 MR. DELAFIELD: Objection.
20 Vague. Calls for speculation. Lacks
21 foundation.

22 THE WITNESS: No. What I said
23 was that that [REDACTED] percent would be further
24 removed -- [REDACTED] percent would be further
25 removed from 100 percent. It would be less

1 than [REDACTED] percent from 100 because the
2 reference standard is less than 100. So it
3 would be [REDACTED] percent of the reference
4 standard, and the reference standard is not
5 100.

6 BY MR. POLLACK:

7 Q. Right. Okay. And actually that,
8 we've been talking about reference standards.

9 Reference standards are just a
10 standard, a known error, in all HPLC assay
11 processes?

12 MR. DELAFIELD: Objection.
13 Lacks foundation. Vague.

14 THE WITNESS: It's not a known
15 error. A reference standard has a known
16 purity.

17 BY MR. POLLACK:

18 Q. Okay. But scientists were well
19 aware about this issue of reference standards
20 and that the value you get in an HPLC assay
21 analysis, one of the sources of error in all
22 HPLC analysis was reference standard?

23 MR. DELAFIELD: Objection.
24 Vague. Lacks foundation.

25 THE WITNESS: That's not a

1 source of error. That's inherent in the
2 assay, and it's related to the reference
3 standard and not the equipment or the
4 procedure relevant to the reference
5 standard.

6 BY MR. POLLACK:

7 Q. You're saying the reference
8 standard is not part of the HPLC procedure?

9 MR. DELAFIELD: Objection.

10 Vague. Lacks foundation.

11 THE WITNESS: No, because you
12 can do total related substances on an HPLC
13 and that's not a reference standard
14 procedure.

15 MR. POLLACK: I'm going to mark
16 as Ruffolo Deposition Exhibit 6 a document
17 formerly called UT Exhibit 2035.

18 (Document marked for
19 identification purposes as Ruffolo
20 Exhibit 6.)

21 THE WITNESS: Thank you.

22 BY MR. POLLACK:

23 Q. And Ruffolo Exhibit 6, is that one
24 of the documents you relied on in your
25 declaration?

1 A. Yes, it is.

2 Q. What is Ruffolo Exhibit 6?

3 A. The -- it's a guide to reviewers of
4 primarily CMC sections of NDAs on
5 chromatographic procedures of different types.

6 Q. Can you just very briefly explain
7 what a CMC is?

8 A. Oh, the chemical, manufacturing and
9 control section of a -- of an NDA. It's a very
10 large and major portion of an NDA.

11 Q. Right. Very briefly, can you
12 explain what's in the chemistry, manufacturers
13 and control section of a New Drug Application?

14 MR. DELAFIELD: Objection.
15 Relevance. It's outside the scope of his
16 declaration.

17 THE WITNESS: I'll do the best I
18 can, but it won't be 100 percent.

19 It will be the chemical
20 synthesis, the purification procedures, the
21 short-term stability, long-term stability,
22 purity, melting point, the packaging,
23 stability of the packaging, stability of the
24 API, stability of the drug product. Many
25 other things.

1 And, importantly, the validation
2 of every single assay done on every single
3 part of everything that I just mentioned and
4 the ones I didn't mention, including the
5 equipment and processes for cleaning
6 equipment, cleaning rooms, cleaning. It's a
7 very detailed document.

8 BY MR. POLLACK:

9 Q. Descriptions of all the factories
10 and the equipment in the factories?

11 A. Descriptions and validation --

12 MR. DELAFIELD: Objection.

13 THE WITNESS: -- processes used
14 for everything that comes in contact with
15 that drug and every analysis done on that
16 drug.

17 BY MR. POLLACK:

18 Q. You mentioned melting point as one
19 of the things that's included in the CMC
20 section.

21 Why do they have melting point in
22 there?

23 MR. DELAFIELD: Objection.

24 Vague. Relevance. Outside the scope of his
25 report.

1 THE WITNESS: Melting point is
2 used as a measure of identity of a compound.

3 BY MR. POLLACK:

4 Q. How does that work?

5 MR. DELAFIELD: Same objections.

6 THE WITNESS: The FDA wants to
7 be sure that the compound that you say
8 you've made is, in fact, the compound you
9 say you've made, and so they include certain
10 spectral analyses. It could be IR,
11 infrared. It could be Raman spectroscopy.
12 It could be UV and -- and melting points.

13 Those are characteristics of
14 compounds that help the FDA confirm that
15 what you've said you've made you've actually
16 made.

17 BY MR. POLLACK:

18 Q. Okay. Do you know if the melting
19 point is affected by the purity of the
20 compound?

21 MR. DELAFIELD: Objection.
22 Relevance. Calls for speculation. Outside
23 the scope of his report.

24 THE WITNESS: There is a
25 relationship to purity and -- between purity

1 and melting point and it's not an absolute
2 relationship but also crystal form,
3 polymorphs, amorphous forms, solvents,
4 crystallization of solvents, crystallization
5 procedure, all of those and other things
6 affect melting point.

7 BY MR. POLLACK:

8 Q. Okay. Let me just ask you.

9 If I have two solids that are the
10 same crystal form of the same drug and they
11 have different melting points, is there a way
12 to compare their purity based on the melting
13 points?

14 MR. DELAFIELD: Objection.

15 Vague. Calls for speculation. Outside the
16 scope of his report.

17 THE WITNESS: As I said, melting
18 point has a relationship to purity, but
19 melting point isn't purity. The FDA doesn't
20 accept melting point as a measure of purity.

21 BY MR. POLLACK:

22 Q. Sure.

23 A. And your question was, if you had a
24 drug with a higher melting point is it more
25 pure?

1 Q. Well, I said, they're the same
2 crystal form.

3 A. Same crystal?

4 MR. DELAFIELD: Same objections.

5 BY MR. POLLACK:

6 Q. Yeah.

7 A. Yeah, in the same crystal form?

8 Perhaps, perhaps not.

9 Q. What's the relationship -- you said
10 there's relationship between melting point and
11 purity?

12 A. Yes.

13 Q. What's the relationship?

14 MR. DELAFIELD: Same objections.

15 THE WITNESS: Often higher
16 melting points have higher purities, but
17 that's not necessarily the case. And when I
18 reviewed all of the -- the Certificate of
19 Analysis sheets on the specs, you can see
20 many examples where higher levels of purity
21 didn't have a higher melting point.

22 BY MR. POLLACK:

23 Q. You didn't put an opinion in your
24 declaration on that, though; correct?

25 A. No. As I said, my -- my task was

1 to deal on long-felt need and so I didn't
2 comment on that.

3 Q. Okay.

4 A. But if I had, I would have
5 commented in the way I've told you and which,
6 in fact, I believe is consistent with
7 Dr. Williams' assessments with melting point.

8 Q. You can look at Exhibit 6, Ruffolo
9 Exhibit 6. If you could turn to page 12.

10 And you reviewed this exhibit in
11 detail, right, before creating your opinion?

12 A. Yes, I did.

13 Q. Okay. You said first paragraph,
14 that first full paragraph, it says "With UVD
15 detectors."

16 A. I'm sorry. I don't -- I don't see
17 that. I must -- I'm on page 12.

18 Q. Page 12.

19 A. Oh, there are two page 12s.

20 Q. Ah, I'm sorry. Yes. I'm looking
21 at the one that's sort of typed at the bottom.

22 A. Okay. I have it. Okay.

23 Q. I think it also says --

24 A. I'm sorry.

25 Q. -- page 9 in the smaller.

1 A. Yeah, I see it.

2 Q. No, you're right.

3 A. Yeah.

4 Q. There's two -- there's two
5 different numbers on there so it's confusing.

6 A. Yeah. Okay.

7 Q. So it's the one that says P.12.

8 A. I see that. Okay.

9 Q. And you see there's a first full
10 paragraph that says "With UV detectors."
11 Is it -- well, let me ask you. UV
12 detectors. Those are the kind of detectors
13 that are used in HPLC assay analysis?

14 A. Oh.

15 MR. DELAFIELD: Objection.
16 Outside the scope of his report. Vague.
17 Calls for speculation.

18 THE WITNESS: Lots of different
19 types of detectors can be used with almost
20 any spectra -- spectra photographic.

21 BY MR. POLLACK:

22 Q. Sure.

23 A. So it's one of them.

24 Q. For example, in Moriarty, Moriarty
25 used a UV detection?

1 A. Are you saying --

2 MR. DELAFIELD: Same objections.

3 THE WITNESS: I don't remember

4 that.

5 MR. POLLACK: I got to do my own

6 work now.

7 I'm going to mark as Ruffolo

8 Deposition Exhibit 7 a document formerly

9 known as Exhibit 1004. It's an article from

10 the Journal of Organic Chemistry by Moriarty

11 and others.

12 (Document marked for

13 identification purposes as Ruffolo

14 Exhibit 7.)

15 THE WITNESS: Thank you.

16 BY MR. POLLACK:

17 Q. And this is what we've been

18 referring to as the Moriarty article?

19 A. Yes.

20 Q. And I think if you turn to the very

21 last page, it says -- I'm going to create

22 ambiguity here, but the one that says page 13

23 in the bottom right-hand corner.

24 A. I see it, yes.

25 Q. It's also known as 1902.

1 A. Okay.

2 Q. Page 1902 from the original
3 article.

4 Looking at page 1902, also known as
5 page 13, does Moriarty report there on the
6 purity of treprostinil that he made according
7 to the Moriarty process?

8 MR. DELAFIELD: Objection.
9 Vague. Calls for speculation. Outside the
10 scope of his report.

11 THE WITNESS: So you're
12 referring to what? I'm sorry.

13 BY MR. POLLACK:

14 Q. I just asked: Does he report on
15 the purity of treprostinil made by the Moriarty
16 process?

17 MR. DELAFIELD: Same objections.

18 THE WITNESS: There is a purity
19 of 99.7 percent listed.

20 BY MR. POLLACK:

21 Q. Okay. And does he say there that
22 it was done by HPLC?

23 MR. DELAFIELD: Same objections.

24 THE WITNESS: It says it was
25 done by HPLC.

1 BY MR. POLLACK:

2 Q. Okay. And prior to that, does he
3 -- does he indicate that UV was used?

4 MR. DELAFIELD: Same objections.

5 THE WITNESS: Prior to that.

6 Can -- can you --

7 BY MR. POLLACK:

8 Q. Just before the words "HPLC." I'm
9 not -- I'm not trying to --

10 A. Where HPLC is methanol --

11 MR. DELAFIELD: Same objections.

12 THE WITNESS: -- 217 nanometers.

13 BY MR. POLLACK:

14 Q. You see the words "UV" before that?

15 A. No.

16 MR. DELAFIELD: Same objections.

17 BY MR. POLLACK:

18 Q. No, you don't?

19 A. Oh, UV. I see. Yes, I'm sorry.

20 Q. Okay.

21 A. Yeah.

22 Q. Based on your review, can you tell

23 me whether or not he used UV detection for

24 HPLC?

25 A. Yes.

1 MR. DELAFIELD: Same objections.

2 THE WITNESS: It appears he did.

3 BY MR. POLLACK:

4 Q. Okay. Let me ask you.

5 The analyses that United
6 Therapeutics did for HPLC analysis, do you know
7 whether they used UV detectors?

8 MR. DELAFIELD: Objection.

9 Vague. Calls for speculation.

10 THE WITNESS: I'd have to, just
11 as with Moriarty, I'd have to -- I'd have to
12 go back and check.

13 BY MR. POLLACK:

14 Q. Okay. You didn't look into that?

15 MR. DELAFIELD: Same objections.

16 THE WITNESS: I probably did. I
17 don't remember. It would be common to do
18 that, but I don't -- I don't remember.

19 BY MR. POLLACK:

20 Q. What about in the '393 patent? Do
21 you know whether they used UV detection?

22 MR. DELAFIELD: Objection.

23 Vague. Outside the scope of his report.

24 THE WITNESS: (Reviewing
25 document). Unless you see it listed

1 someplace, I don't see it, but I'm, you
2 know, I could read the whole thing to find
3 out, and I don't know if it says.

4 BY MR. POLLACK:

5 Q. Yeah, I haven't seen it. I was
6 just wondering --

7 A. I don't -- I don't know.

8 Q. -- if you had any knowledge.

9 A. I don't know.

10 Q. Okay. What about when United
11 Therapeutics looks at total related impurities?
12 Do you know whether they're using UV detection
13 for those impurities?

14 MR. DELAFIELD: Objection.
15 Vague. Calls for speculation. Outside the
16 scope of his report.

17 THE WITNESS: I don't know.
18 That will be in the CMC section, but I don't
19 recall.

20 BY MR. POLLACK:

21 Q. But it would be fairly typical to
22 use UV as a detection?

23 A. It would --

24 MR. DELAFIELD: Objection.

25 Vague. Calls for speculation.

1 Mischaracterizes his testimony.

2 THE WITNESS: It would be -- it

3 would be common --

4 BY MR. POLLACK:

5 Q. Yeah.

6 A. -- to do that.

7 Q. Let me ask you if the following

8 sentence from Exhibit 6 is one you can agree

9 with.

10 "With UV detectors" --

11 A. I'm sorry. Exhibit?

12 Q. And this is on page 12. Yeah.

13 A. Oh, oh, that's the same document.

14 Okay.

15 Q. Yeah. This is the Reviewer

16 Guidance --

17 A. Yeah, got it.

18 Q. -- Validation of Chromatographic

19 Methods.

20 A. Okay.

21 Q. Just to make things clear, this

22 comes from the Center For Drug Evaluation and

23 Research?

24 A. Yes.

25 Q. That's a branch of the United

1 States Food and Drug Administration?
2 A. Yes, that's CEDR, part of the FDA.
3 Q. Right. They're the ones who
4 actually decide drug approvals within the FDA?
5 MR. DELAFIELD: Objection.
6 Calls for speculation.
7 THE WITNESS: For small
8 molecules and, yes, for those types of
9 drugs, yes.
10 BY MR. POLLACK:
11 Q. Right. And treprostinil is a small
12 molecule. It's not a biomolecule?
13 A. Correct.
14 MR. DELAFIELD: Objection.
15 Vague.
16 BY MR. POLLACK:
17 Q. So the CEDR, these are the kinds of
18 people, this is a group that would approve a
19 drug like treprostinil?
20 A. I --
21 MR. DELAFIELD: Objection.
22 Vague.
23 THE WITNESS: I assume --
24 MR. DELAFIELD: Lacks
25 foundation.

1 THE WITNESS: I assume
2 treprostiniil went through CEDR.
3 BY MR. POLLACK:
4 Q. Well, I think you earlier were
5 referring to an NDA rather than a BLA based on
6 that?
7 A. That's -- that's correct.
8 Q. Does that indicate that, therefore,
9 it went through CEDR?
10 MR. DELAFIELD: Same objections.
11 THE WITNESS: It can -- when a
12 drug is used with a device, as this one, it
13 can go through the device division, too. I
14 don't know if it did. I have no -- no
15 reason to believe it, but I don't know.
16 BY MR. POLLACK:
17 Q. Okay. So CEDR says here on page 12
18 of the document, and by that I mean the P.12:
19 "With UV detectors, it is difficult
20 to assure the detection precision of low level
21 compounds due to potential gradual loss of
22 sensitivity of detector lamps with age or noise
23 level variation by detector manufacturer."
24 Do you agree with that statement?
25 A. I agree with that statement, but in

1 the CMC section, as I said, all instrumentation
2 has to be validated and go through, and these
3 are things that would be specified to assure
4 the FDA that this isn't happening.

5 The F -- that's why they're giving
6 this guidance to their reviewers to make sure
7 that that is in there. You couldn't use an old
8 lamp. You couldn't use a device -- a machine
9 with a high noise level because that will
10 affect what they care about, which is the level
11 of quantitation and level of detection.

12 Q. Okay. But noise level is something
13 that really is only a problem when you're
14 trying to detect very small amounts of signal
15 in materials?

16 MR. DELAFIELD: Objection.
17 Vague. Lacks foundation. Outside the scope
18 of his report.

19 THE WITNESS: Not -- not only.
20 It depends on the signal from -- the
21 magnitude of the signal from even the agent
22 you're looking at. If it doesn't give a
23 very powerful signal, then the inherent
24 noise could affect that, too.

25 BY MR. POLLACK:

1 Q. Sure. But if I have a sample
2 where, you know, [REDACTED] percent of it is my drug
3 and [REDACTED] percent of it is an impurity, it's more
4 likely I'm going to have noise problems with
5 the [REDACTED] percent rather than the [REDACTED], is that
6 generally the case?

7 MR. DELAFIELD: Objection.
8 Vague. Calls for speculation. Lacks
9 foundation.

10 THE WITNESS: That would
11 generally be the case.

12 BY MR. POLLACK:

13 Q. And then one of the other things
14 they say here. It's kind of interesting.
15 Going a couple sentences later.

16 A. Uh-huh.

17 Q. It says:

18 "With no reference standard for
19 given impurity or means to assure
20 detectability, extraneous peaks could disappear
21 and appear."

22 Do you agree with that statement?

23 MR. DELAFIELD: Objection.

24 Vague.

25 THE WITNESS: Yes, that's why

1 the FDA on these types of analyses for
2 release specifications have reference
3 standards so that that doesn't happen.

4 BY MR. POLLACK:

5 Q. Right. So reference standards,
6 they're actually preferred in doing HPLC
7 analysis?

8 MR. DELAFIELD: Objection.
9 Vague. Calls for speculation. Lacks
10 foundation.

11 THE WITNESS: They are preferred
12 and almost always insisted on by the FDA.

13 BY MR. POLLACK:

14 Q. Okay. Let's go back to Ruffolo
15 Exhibit 5, and that's the letter that used to
16 be known as Exhibit 2006, from United
17 Therapeutics to Norman Stockbridge dated
18 January 2, 2009.

19 A. Exhibit 5?

20 Q. Exhibit 5.

21 A. Yeah, I have that.

22 Q. I want to look at a statement that
23 United Therapeutics made to the FDA.

24 If you look on page 3, if you look
25 at the second full paragraph, the third

1 paragraph on the page, beginning with the words
2 "In conclusion."

3 Do you see where I am?

4 A. Yes, I do.

5 Q. Okay. It says:

6 "In conclusion, the lots of
7 treprostinil API produced by the new process in
8 Silver Spring are of the same high quality
9 impurity as the commercial lots of API produced
10 by the existing process at the Chicago
11 facility."

12 Did I read that correctly?

13 A. Yes, you did.

14 Q. Okay. And I'm correct that the
15 commercial lots of API produced by the existing
16 process of the Chicago facility, that refers to
17 what we've -- we've been calling the [REDACTED]
18 [REDACTED]?

19 MR. DELAFIELD: Objection.

20 Calls for speculation.

21 THE WITNESS: I'm sorry. Could
22 you repeat that?

23 BY MR. POLLACK:

24 Q. Yes. The -- where it says here the
25 commercial lots of active pharmaceutical

1 ingredient produced by the "[REDACTED]"
2 at the Chicago facility, that refers to what
3 we've been calling the [REDACTED]?

4 MR. DELAFIELD: Same objection.

5 THE WITNESS: Yes.

6 BY MR. POLLACK:

7 Q. Okay. And the "[REDACTED]" in the
8 Silver Spring facility, that refers to the
9 process we've been calling the [REDACTED]?

10 A. Yes, that's my understanding.

11 Q. Okay. And what the -- what United
12 Therapeutics is representing to the FDA here is
13 that the treprostinil made by the '393 process
14 has the same quality and purity as API made by
15 the Moriarty process; isn't that what this
16 says?

17 MR. DELAFIELD: Objection.

18 Mischaracterizes --

19 BY MR. POLLACK:

20 Q. In simpler English?

21 A. Yeah.

22 MR. DELAFIELD: Mischaracterizes
23 this document.

24 THE WITNESS: It says same high
25 purity. They both could have high purity

1 and -- and it's pretty clear from the
2 analyses that I've seen that the purity of
3 '393 process is higher than Moriarty, but
4 that doesn't mean that they're both not
5 highly, highly pure.

6 BY MR. POLLACK:

7 Q. Okay. They're not making a
8 representation here in this conclusion that the
9 [REDACTED] process is superior to the -- the
10 [REDACTED], that is, the '393 process is
11 superior to the Moriarty process in that
12 sentence?

13 MR. DELAFIELD: Objection.
14 Mischaracterizes the document.

15 THE WITNESS: There are no
16 purity levels given and I don't know when
17 the -- the recognition for the high level of
18 purity was made, but also I don't think that
19 changes the fact that both could be high
20 purity. One is higher than the other.

21 BY MR. POLLACK:

22 Q. Okay. Now, let me turn to some of
23 the other representations they made.

24 If you can go to page 6.

25 A. Yes.

1 Q. And you're going to need to look at
2 page 5 as well because, unfortunately, they
3 didn't repeat the headings of the table.

4 A. Okay.

5 Q. Okay. So let me go through the
6 headings on page 5. So the first column is
7 labeled "Test."

8 Do you see that?

9 A. Yes.

10 Q. Okay. And that refers to whatever
11 test or category is described underneath --

12 A. Uh-huh.

13 Q. -- is that fair?

14 A. Yes.

15 Q. Okay. And the second column is
16 called "Currently Approved Specification"?

17 A. Yes.

18 Q. Okay. And that refers to the
19 Moriarty process?

20 A. That's correct.

21 Q. And the third column is called --
22 is called "Proposed New Specification"?

23 A. Yes.

24 Q. Okay. And that refers to the '393
25 process?

1 A. That's correct.

2 Q. And if we go to page 6, under the
3 Test column -- and feel free if you want to
4 write these column headings on top. If you
5 remember, that's fine.

6 A. Okay.

7 Q. So the first column, the Test
8 column, you see it has a chromatographic purity
9 HPLC.

10 Do you see that row?

11 A. Yes, I do.

12 Q. Okay. And then in that row is a
13 set of named impurities?

14 A. Yes, I see.

15 Q. Okay. And these were the purities
16 that -- the impurities that United Therapeutics
17 was able to see in its HPLC instrument?

18 MR. DELAFIELD: Objection.

19 Mischaracterizes the document.

20 THE WITNESS: These are the
21 specifications for those purities. The
22 minimum specifications for allowable levels
23 of these impurities in -- in the product.

24 BY MR. POLLACK:

25 Q. Right. Right.

1 A. The API. API.

2 Q. I'm just -- I'm just saying, yeah,
3 before we get to the spec part.

4 A. Yeah.

5 Q. Just in the Test column, that's a
6 list of the impurities that United Therapeutics
7 saw on their particular HPLC column?

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

10 THE WITNESS: Those are the
11 average characteristic impurities that you
12 see in their analysis.

13 BY MR. POLLACK:

14 Q. Yeah. Okay. And if an impurity
15 for some reason doesn't separate out on their
16 particular HPLC column, we wouldn't see that
17 impurity listed here?

18 MR. DELAFIELD: Same objections.
19 Calls for speculation.

20 THE WITNESS: I'm not sure I
21 agree. Could you repeat that?

22 BY MR. POLLACK:

23 Q. Sure. If an impurity doesn't
24 separate out from the other ingredients in the
25 particular HPLC column material that they

1 selected, we wouldn't see that impurity listed
2 here?

3 MR. DELAFIELD: Same objections.

4 THE WITNESS: That's not true.

5 BY MR. POLLACK:

6 Q. That's not true?

7 A. No.

8 Q. Okay. So you're saying HPLC can
9 separate all impurities from other
10 impurities --

11 MR. DELAFIELD: Objection.

12 BY MR. POLLACK:

13 Q. -- regardless of what column is
14 used?

15 MR. DELAFIELD: Objection.

16 Mischaracterizes testimony.

17 THE WITNESS: No.

18 MR. DELAFIELD: Calls for
19 speculation.

20 THE WITNESS: The FDA requires
21 that you actually conclude that there are
22 not two superimposing peaks, and so they
23 have an assurance of that in the CMC part of
24 the document as part of all of that
25 validation that I mentioned earlier.

1 BY MR. POLLACK:

2 Q. What if an impurity comes out at
3 about the same retention time as the API
4 itself?

5 MR. DELAFIELD: Objection.

6 BY MR. POLLACK:

7 Q. Would they be able to separate
8 that?

9 MR. DELAFIELD: Objection.

10 Vague. Calls for speculation. Lacks
11 foundation.

12 THE WITNESS: The FDA would
13 force you to use a different column with a
14 different bedding that did separate them.
15 The FDA will insist that you confirm that
16 there are no overlapping peaks.

17 BY MR. POLLACK:

18 Q. Even if you don't know if the
19 impurity is there, they would do that?

20 MR. DELAFIELD: Same objections.

21 THE WITNESS: You actually have
22 to go look. So when you report a peak, you
23 have to assure them that there are not --
24 that there's only one material there under
25 that peak. And there are various tests you

1 can do to show them, and you do have to show
2 them that. That's part of the validation
3 for using the technique.

4 BY MR. POLLACK:

5 Q. Do you know whether that was done
6 for treprostiniil?

7 MR. DELAFIELD: Same objections.

8 THE WITNESS: I don't know. If
9 they had two drugs under one peak, it would
10 have been done. It would be required.

11 BY MR. POLLACK:

12 Q. But for treprostiniil you don't
13 know?

14 MR. DELAFIELD: Same objections.

15 THE WITNESS: I don't know, but
16 because I don't recall the -- that part of
17 the CMC, but I do know that United
18 Therapeutics would have to show them that
19 there are not two peaks occurring at the
20 same retention time with one masking the
21 other.

22 And you have to show that by
23 convincing evidence, and there are ways to
24 do that and that's part of the validation of
25 the assay that the FDA requires that United

1 Therapeutics would have had to have been
2 done.

3 BY MR. POLLACK:

4 Q. Okay. You haven't reviewed,
5 though, the CMC other than this letter?

6 A. I reviewed -- no, that's not true.
7 I reviewed quite a bit of the CMC, but I didn't
8 review it all. It would be too much for a
9 single person to review.

10 Q. You didn't attach the CMC to your
11 declaration?

12 A. No, I did not attach the CMC to my
13 declaration.

14 Q. Okay. That's not listed in your
15 materials you reviewed in your -- in the
16 paragraph you have on that in your declaration?

17 MR. DELAFIELD: Objection.
18 Mischaracterizes declaration.

19 THE WITNESS: I don't -- I don't
20 recall if there are CMC sections in my
21 declaration, but I have reviewed parts of
22 the CMC as part of those documents that I
23 mentioned that were sent to me by counsel.

24 BY MR. POLLACK:

25 Q. Which -- which parts did you

1 review?

2 MR. DELAFIELD: Objection.

3 Relevance.

4 THE WITNESS: I reviewed the
5 Certificates of Analysis and I reviewed the
6 injectable NDA component showing how those
7 analyses were done and the calculations that
8 were used. And there was, I think, an ND --
9 annual NDA update or something like that
10 that I reviewed. So I did review components
11 of the CMC.

12 MR. POLLACK: Counsel, I'm going
13 to request that production of all sections
14 of the CMC and any other documents that
15 Dr. Ruffolo reviewed that haven't been
16 produced so far.

17 MR. DELAFIELD: I believe we've
18 produced everything. I think he's only been
19 shown things that we've produced, so...

20 BY MR. POLLACK:

21 Q. So the sections of the CMC you're
22 referring to, were those ones that Dr. Williams
23 relied upon?

24 MR. DELAFIELD: Objection.

25 Calls for speculation.

1 THE WITNESS: I think you have
2 to ask Dr. Williams that. I don't know what
3 he -- what he did, what he looked at.

4 MR. POLLACK: Counsel, are there
5 any documents that he reviewed that were not
6 attached as exhibits provided to the PTAB?

7 MR. DELAFIELD: No, we haven't
8 reviewed anything other than what's been an
9 exhibit.

10 MR. POLLACK: What's been an
11 exhibit to PTAB?

12 MR. DELAFIELD: Yeah.

13 BY MR. POLLACK:

14 Q. Okay. All right. Let's take a
15 look at these.

16 MR. DELAFIELD: One thing. He
17 mentioned that he reviewed the label. I
18 don't think the label is an exhibit. So the
19 label for treprostinil.

20 MR. POLLACK: Okay.

21 MR. DELAFIELD: All right.

22 MR. POLLACK: Would be the only?

23 MR. DELAFIELD: Yeah.

24 MR. POLLACK: If you could
25 produce the label that he reviewed then.

1 MR. DELAFIELD: Okay. We'll
2 take it under advisement.
3 BY MR. POLLACK:
4 Q. So let's look at the second column.
5 A. Yes.
6 Q. And the second column, that is
7 specifications --
8 A. Yes.
9 Q. -- for each of the impurities for
10 the Moriarty process; is that correct?
11 A. Yes, that's correct.
12 Q. Okay. And the third -- third
13 column, those are specifications for impurities
14 for the '393 process; correct?
15 A. That's correct.
16 Q. Okay. And am I also correct that
17 the specification for the impurities in the
18 Moriarty process are identical for every single
19 impurity to the specifications for the '393
20 process?
21 A. Yes.
22 MR. DELAFIELD: Objection.
23 Vague.
24 THE WITNESS: The specification
25 limits are the same for both processes.

1 BY MR. POLLACK:

2 Q. Do you know whether on this
3 document United Therapeutics listed every
4 impurity for which a peak was observed?

5 MR. DELAFIELD: Objection.

6 Vague. Calls for speculation.

7 THE WITNESS: I'm sorry. Would
8 you repeat that?

9 BY MR. POLLACK:

10 Q. Yeah. Do you know whether on this
11 document United Therapeutics listed every
12 impurity for which a peak was observed?

13 MR. DELAFIELD: Same objections.

14 THE WITNESS: They do list
15 unidentified impurities, which are peaks,
16 and if the level of that impurity rose to a
17 level of requiring identification, it would
18 have been identified. That would have been
19 a requirement.

20 BY MR. POLLACK:

21 Q. Right. Now, the final sum there at
22 the bottom, it says "total related substances"?

23 A. Yes, I see that.

24 Q. Okay. What is it -- why does it
25 use the term "related"? Are there unrelated

1 substances?

2 MR. DELAFIELD: Objection.

3 Vague.

4 THE WITNESS: I don't -- I don't
5 recall the exact definition of total related
6 substances. I would have to go research
7 that. Remember, this is not something I
8 prepared for.

9 BY MR. POLLACK:

10 Q. Sure.

11 A. This is, you know, here mainly
12 for -- for the -- for the need. So I'd have to
13 go -- I'd have to go look up and see exactly
14 what the regulatory definition of that is.

15 Q. Okay. You didn't look into that as
16 part of your opinion?

17 A. No, I didn't look into -- into
18 that.

19 Q. Okay. Now, the names of some of
20 these substances are a little, I think, funny.
21 There's one called 1AU90.

22 A. Yes.

23 Q. What is that?

24 MR. DELAFIELD: Objection.

25 Outside the scope of his report.

1 THE WITNESS: Somebody would
2 have to show me the chemical structure on
3 that.
4 BY MR. POLLACK:
5 Q. Well, this -- do you think anyone
6 knows the chemical structure of that?
7 A. Oh, yes.
8 Q. You do?
9 MR. DELAFIELD: Objection.
10 Argumentative.
11 THE WITNESS: The -- if it rose
12 to the level of reporting threshold, it
13 would have to be reported.
14 BY MR. POLLACK:
15 Q. Sure. What's the reporting
16 threshold?
17 A. Well, .05 and -- and .1 would be
18 the identification threshold and they would
19 have to identify it.
20 Q. If it's greater than .1?
21 A. Yeah.
22 Q. Yeah. Do you know if any of these
23 which have just code names have a greater than
24 .1?
25 A. Oh, I -- I don't know.

1 Q. Okay. Do you know whether 1AU90
2 was identified by United Therapeutics?

3 MR. DELAFIELD: Objection.
4 Vague. Outside the scope of his report.

5 THE WITNESS: I don't know.
6 You're, again, asking me questions outside
7 of what I prepared for.

8 BY MR. POLLACK:

9 Q. I mean, this is one of the
10 documents you are heavily relying on. That's
11 why I'm asking you.

12 MR. DELAFIELD: Same objections.

13 THE WITNESS: Yes, but you're
14 asking me questions that are not related to
15 unfelt need. So --

16 BY MR. POLLACK:

17 Q. Your unfelt need has to do with
18 purity; correct?

19 A. It has to do with increases in
20 purity.

21 Q. Right. Okay.

22 A. Yeah.

23 Q. So I'm asking about the impurities
24 here.

25 A. Yeah.

1 Q. Okay.

2 MR. DELAFIELD: Objection.

3 Outside the scope of his report here.

4 BY MR. POLLACK:

5 Q. Outside the group of us here, who
6 are privileged to see this, do you think any
7 member of the public knows what 1AU90 is?

8 MR. DELAFIELD: Objection.

9 Calls for speculation. Argumentative.

10 THE WITNESS: I don't know, but
11 I would assume not, but that's just an
12 assumption.

13 BY MR. POLLACK:

14 Q. By the way, do you have -- do you
15 have any reason to believe that in 2007 --
16 that's when this patent was filed, two years
17 before this document was created -- do you have
18 any evidence that United Therapeutics had any
19 idea what impurities were in treprostini made
20 by the '393 process?

21 A. Before?

22 MR. DELAFIELD: Objection.

23 BY MR. POLLACK:

24 Q. Before 2009. In 2007 where the
25 '393 patent was filed -- first filed.

1 MR. DELAFIELD: Objection.
2 Vague. Calls for speculation.
3 THE WITNESS: Because I reviewed
4 all of the -- the lot specifications on the
5 Certificate of Analysis, these were present
6 before 2007 as well as after.
7 BY MR. POLLACK:
8 Q. Okay. In the '393 patent, is there
9 any mention of what impurities are present or
10 any of these names or similar names?
11 A. Can I refer to the patent?
12 Q. Please.
13 A. (Reviewing document).
14 Okay. Can you repeat the question,
15 please?
16 Q. Is there any evidence in the '393
17 patent regarding what impurities were in the
18 treprostinil made in the '393 patent?
19 MR. DELAFIELD: Objection.
20 Vague. Calls for speculation. Outside the
21 scope of his report.
22 THE WITNESS: I didn't see this
23 list reproduced there.
24 BY MR. POLLACK:
25 Q. Okay. Was -- was there any kind of

1 list of what impurities were in the
2 treprostiniil made in the '393 patent?

3 MR. DELAFIELD: Same objections.

4 BY MR. POLLACK:

5 Q. In the patent itself?

6 A. Without reading the whole thing, I
7 see primarily purities of the parent compound,
8 which is what I believe the invention is
9 related to. And -- and so I see comparisons
10 between the old process and new process with
11 purities, but -- but I don't see, unless I've
12 missed it, I don't see the impurities.

13 Q. Right. All that information -- all
14 the information in the '393 patent is related
15 to the parent compound?

16 A. The overall purity of the parent
17 compound.

18 Q. Right. And that compound is, well,
19 treprostiniil or one of those other compounds
20 that are -- that are in there, the
21 diethanolamine salt or the other ones that are
22 in the claim?

23 MR. DELAFIELD: Objection.

24 Compound.

25 THE WITNESS: The -- yes.

1 BY MR. POLLACK:

2 Q. I want to go back to your paragraph
3 32. There's something else there I was
4 confused about. It's on page 14 of your
5 declaration.

6 A. Okay. I have it.

7 Q. And that's Ruffolo Exhibit 3.

8 If you go about halfway down the
9 page, it says:

10 "There is so much concern with the
11 purity of drug substance and drug product that
12 the highest level of purity possible should be
13 achieved, even if that means changing the
14 synthetic method as has been done in the '393
15 patent."

16 Do you see that?

17 A. Yes, I see that.

18 Q. Okay. And then in -- this is what
19 confuses me.

20 In paragraph 57 -- it's on page 27
21 of your declaration -- you say in the last
22 sentence:

23 "My personal experience has been
24 that when considering the safety and toxicology
25 profiles of impurities, it is often more

1 efficient to reduce the levels of impurities in
2 the drug substance by altering or changing the
3 synthetic method."

4 Do you see that?

5 A. Yes, I do.

6 Q. Okay. So here you're saying change
7 the synthetic method but in 32 --

8 A. I'm saying exactly the same thing.

9 Q. Same thing. Okay. Oh, I see what
10 confused me.

11 But then you say "as has been done
12 in the '393 patent."

13 So I guess what I was wondering is:
14 How has the synthetic method changed in the --
15 in the '393 patent?

16 A. The number of steps was reduced.
17 The purification of the nitrile was taken out.
18 The starting material was changed. The
19 efficiency of the system was increased. The
20 purity, of course, was increased. Fewer
21 solvents were used.

22 And there's a list of -- in the
23 patent, which I could probably find, of things
24 that were changed and improved by the process.

25 Q. Yeah. Can you find me that list?

1 A. (Reviewing document).
2 On column 5 about line 36 or 37.
3 "The present invention provides for
4 a process for producing treprostinil and other
5 prostacyclin derivatives and novel intermediate
6 compounds useful in the process. The process
7 according to the present invention provides
8 advantages on large-scale synthesis over the
9 existing method. For example, the purification
10 by column chromatography is eliminated, thus
11 the required amount of flammable solvents and
12 waste generated are greatly reduced.
13 Furthermore, the salt formation is a much
14 easier operation than column chromatography.
15 Moreover, it was found that the product of the
16 process according to the present invention has
17 higher purity. Therefore the present invention
18 provides for a process that is more economical,
19 safer, faster, greener, easier to operate, and
20 provides higher purity."
21 Q. Okay. Yeah. I didn't see any list
22 there of some of the changes that you
23 described, like the elimination of the
24 purification of the nitrile or --
25 A. I just said that. It's in that

1 paragraph. They -- they specifically state:

2 "For example, the purification by
3 common chromatography is eliminated."

4 That's for the nitrile.

5 Q. Oh, okay. Thanks. Thanks for
6 clarifying that.

7 A. Yeah.

8 Q. And eliminating that purification
9 of the nitrile, how does that affect the purity
10 of the treprostinil?

11 MR. DELAFIELD: Objection.

12 Calls for speculation. Outside the scope of
13 his declaration.

14 THE WITNESS: I don't know how
15 that affects the purity. I'd have to --
16 have to look into that, but it certainly is
17 related to the efficiency and the -- the
18 faster speed of the reaction, easier to
19 operate, and -- and be more economical.

20 That's -- that's quite significant.

21 BY MR. POLLACK:

22 Q. What about the change in solvents?
23 How does that -- does that affect the purity?

24 MR. DELAFIELD: Same objections.

25 THE WITNESS: I give a similar

1 answer.

2 I can't tell what the solvent
3 impact would be on the purity level, but it
4 would certainly be relevant to the easier to
5 operate, the greener, the faster component
6 and, you know, so that's what that would be
7 relevant to.

8 BY MR. POLLACK:

9 Q. Okay. Let me ask you, though,
10 changing the solvents. That's something that
11 you're not sure how much it does it, but it's
12 something that might affect the purity?

13 MR. DELAFIELD: Objection.
14 Calls for speculation. Outside the scope of
15 his report. Vague.

16 THE WITNESS: I don't know.

17 BY MR. POLLACK:

18 Q. Okay.

19 A. It might, it might not.

20 Q. It might or it might not; is that
21 right?

22 A. Yes, that's what I said. I'm
23 sorry.

24 Q. Yeah, okay. That's fine. My
25 hearing is going. (Laugh).

1 A. No. It happens to all of us.

2 Q. And the same for eliminating the
3 purification of the nitrile. That might or
4 might not affect the purity?

5 MR. DELAFIELD: Same objections.

6 THE WITNESS: I -- I don't know.
7 That's what you asked, I think, two or three
8 questions ago. I don't -- I don't know. I
9 haven't seen that assessment done.

10 BY MR. POLLACK:

11 Q. Okay. But it could. It's a
12 possibility?

13 MR. DELAFIELD: Same objections.

14 THE WITNESS: I don't know.

15 MR. POLLACK: Okay. I'm going
16 to mark as Ruffolo Deposition Exhibit 8 a
17 document formerly known as UT Exhibit 2047.
18 It's the "Guidance for Industry on
19 Non-Penicillin Beta-Lactam Drugs."

20 (Document marked for
21 identification purposes as Ruffolo
22 Exhibit 8.)

23 THE WITNESS: Thank you.

24 MR. POLLACK: And I'm going to
25 mark one more exhibit while we're at it.

1 This will be Ruffolo Deposition Exhibit 9
2 formerly known as UT Exhibit 2048.

3 (Document marked for
4 identification purposes as Ruffolo
5 Exhibit 9.)

6 BY MR. POLLACK:

7 Q. And Ruffolo Exhibit 9 is an article
8 called "Clinical Pharmacology of Human
9 Insulin."

10 Are these, Dr. Ruffolo, these two
11 documents that you relied upon in writing your
12 declaration?

13 A. Yes, they are.

14 Q. All right. Starting with Exhibit
15 8, the non-penicillin beta-lactam drugs?

16 A. Uh-huh. Yes.

17 Q. Why did you rely on this document?

18 A. In putting together my -- my
19 report, which relates to the importance of high
20 purity and some of the risks of having
21 impurities even in highly pure drugs, I gave
22 examples that are known so that that -- and
23 these are widely known examples -- that confirm
24 that some impurities that one wouldn't even
25 anticipate could be extremely risky and present

1 high risk to patients.

2 Q. What's this example?

3 A. This example?

4 Q. Yes. I'm sorry.

5 A. The --

6 Q. What is the example in Ruffolo

7 Deposition Exhibit 8?

8 A. So in -- when I first started my
9 career, penicillins and beta-lactams in
10 general, which would include cephalosporins,
11 were manufactured by, for example, my first
12 company Lilly, which was the worldwide leader
13 in antibiotics at the time, but they made many
14 other drugs.

15 And as part of the CMC section in
16 an NDA, you have to show how you cleaned the
17 room, sterilized the equipment, and -- and, you
18 know, run into basically an aseptic room when
19 you manufacture another drug so there's not
20 cross-contamination.

21 With respect to penicillins, even
22 when you do that, penicillins just by being
23 airborne can contaminate other products you
24 make in the same building. And what was
25 learned was that that minute contamination,

1 which you can't even quantify it's so low,
2 produced allergic reactions ranging from very
3 minor to very severe anaphylaxis, resulting in
4 death, and because beta-lactams in general are
5 so highly sensitizing to the immune systems of
6 some people. And this is just what might be
7 existing in a cleaned laboratory in the air.

8 So the FDA first, and then other
9 agencies following shortly thereafter, mandated
10 that you couldn't make a penicillin even in the
11 same building, no matter how much you cleaned
12 that building. You couldn't manufacture any
13 other drug except another penicillin in a
14 building and, of course, you can imagine the
15 difficulty that creates to have a solely
16 dedicated building only for penicillins and you
17 have all these other drugs you manufacture.

18 And so that's what this guideline
19 is. It was the regulators and ultimately the
20 global regulators and, as you can see, the ICH
21 that -- that -- that mandated completely
22 different facilities had to be used. And it --
23 and so those are very, very low levels of
24 contamination that you, as I say, you can't
25 measure.

1 And it even got so significant that
2 when we ordered AP -- starting materials, for
3 example, for other companies, we always had to
4 ask, are there rooms different from penicillin?
5 Because they're not making a drug. They're
6 just making an intermediate.

7 And then, finally, many of these
8 companies that supply intermediates and
9 starting materials would even advertise
10 themselves as non-penicillin producing
11 companies. So that's an example of how
12 dangerous a safe drug, penicillin, can be as a
13 contaminant.

14 Q. Right. In fact, for beta-lactams,
15 those companies that are still making them,
16 they require interlocks right into the
17 buildings?

18 A. Now they've made a concession.
19 They went from completely different buildings,
20 totally separate buildings, and now with
21 improvements in air handling, filtration
22 systems, if you have in one building rooms with
23 completely different ventilation systems that
24 are physically isolated and separate, you now
25 can do it in the same building, but that's

1 rarely done.

2 People still use separate
3 buildings, but you have to have -- again, they
4 relaxed the requirement. You can do it in the
5 same building but completely different -- your
6 interlocking systems that have absolutely no
7 chance of crossover and that even includes air
8 intake, so...

9 Q. Right. And the workers have to
10 actually change their clothes as they go in and
11 out?

12 A. Yeah. Well, they have to do that
13 that anyway, no matter -- no matter what. When
14 you walk into a plant that makes any drug, not
15 just penicillin, the workers have to go through
16 pressure locks, change their clothes, and then
17 go through other double door pressure locks.
18 There are several double door pressure locks to
19 get into any manufacturing facility.

20 Q. To get into the United States?

21 A. That's correct.

22 Q. I don't want to scare you, but you
23 haven't seen what it's like in India, but
24 that's another day.

25 A. But in India, you know -- well,

1 okay. Okay.

2 Q. (Laugh).

3 A. So that's -- that's what that's
4 about.

5 Q. Right. Because beta-lactams, those
6 are drugs that come from a biological source?

7 MR. DELAFIELD: Objection.
8 Lacks foundation.

9 THE WITNESS: Most are synthetic
10 now and don't come from a biologic source.

11 BY MR. POLLACK:

12 Q. Right. But initially there was a
13 biologic source?

14 A. Well --

15 MR. DELAFIELD: Same objection.

16 THE WITNESS: -- way back
17 penicillin was isolated. The pharmacophore
18 that I discussed earlier was isolated, and
19 you would put different decoration on it to
20 change it into different antibiotics with
21 different spectra. Now they're synthetic.
22 They're entirely synthetic and have been for
23 many, many years.

24 BY MR. POLLACK:

25 Q. Treprostinil, though, as far as you

1 know, there isn't a compound like penicillin
2 that requires that kind of isolation in the
3 manufacture of treprostinil; is that fair?

4 MR. DELAFIELD: Objection.
5 Vague. Lacks foundation.

6 THE WITNESS: Well, I don't know
7 what I don't know and there are unidentified
8 peaks, as we've discussed earlier, and --
9 and as we also talked about, there could be
10 peaks below level of detection of a -- of an
11 HPLC. And I don't know what those are.

12 I have no reason to believe it
13 would be this, but the point of this in my
14 document was to highlight that even very
15 safe impurities can be dangerous because
16 penicillin is clearly a safe drug. You
17 give --

18 BY MR. POLLACK:

19 Q. Not for me but maybe for others.
20 (Laugh).

21 A. Yes, that's unfortunate, but it is
22 very safe. You give now -- when I worked in
23 Children's Hospital, they used to give 5
24 million units. The first people to get
25 penicillin in World War II got 10,000 units.

1 So it's a very safe drug, but as a contaminant
2 that you can't even detect, it can be very
3 dangerous.

4 Q. For those who are allergic?

5 A. For those who are allergic.

6 Q. And looking at your second exhibit
7 here, Exhibit Ruffolo 9.

8 A. Uh-huh.

9 Q. This is about insulin?

10 A. Yes.

11 Q. Okay. And insulin is a bio -- it's
12 a biodrug; right? It's not a small molecule?

13 MR. DELAFIELD: Objection.

14 Calls for speculation. Lack of foundation.

15 THE WITNESS: Insulin is a
16 biologic. It's a large molecule.

17 BY MR. POLLACK:

18 Q. And for insulin, the concern, I
19 understand, is the E. coli bacteria?

20 A. It wasn't the bacteria. It was
21 residual impurities from the bacteria in which
22 the insulin was made.

23 Q. Referring to antigens from the --
24 from the bacteria?

25 A. They would --

1 MR. DELAFIELD: Objection.
2 Vague.
3 THE WITNESS: They would or
4 could be antigens, and it was a very high
5 purified -- highly purified product.
6 MR. DELAFIELD: Counsel, I hate
7 to interrupt.
8 MR. POLLACK: No.
9 MR. DELAFIELD: Do you mind if
10 we take a break? He has to catch a flight
11 and I wouldn't mind going to the bathroom.
12 MR. POLLACK: Yeah. Okay.
13 Yeah. No problem like that.
14 THE VIDEOGRAPHER: The time is
15 3:13 p.m. This completes Media Unit No. 3.
16 We are off the record.
17 (Recess - 3:14 p.m. - 3:21 p.m.)
18 (Mr. Maebius no longer present.)
19 THE VIDEOGRAPHER: The time is
20 3:21 p.m. This begins Media Unit No. 4.
21 We're on the record. Please proceed,
22 counsel.
23 BY MR. POLLACK:
24 Q. Okay. We were talking about
25 Ruffolo Deposition Exhibit 9 before the break.

1 A. Yes.

2 Q. This is about the biomolecule
3 insulin?

4 A. That's correct.

5 Q. Correct. And the concern here was
6 about certain antigens from E. coli that could
7 end up in the insulin?

8 A. Yes, that's correct.

9 Q. And that's because E. coli were
10 involved in the production of the -- of the
11 insulin?

12 A. Yeah. Yes, they were.

13 Q. In manufacturing treprostinil, am I
14 correct there are no biological agents that are
15 used in manufacturing treprostinil?

16 MR. DELAFIELD: Objection.

17 Vague. Lacks foundation.

18 THE WITNESS: This, again, was
19 an example of trace contaminants that can be
20 potentially dangerous. But if you do look
21 in the manufacturing process of treprostinil
22 and you look into the specifications,
23 example listed right here in the 2009 letter
24 in the specifications that were sent to the
25 FDA showing an increase in the level of --

1 of purity, you can see that they were
2 looking at endotoxins, which can only come
3 from bacteria, as well as total aerobic
4 count, total yeast count, E. coli,
5 Salmonella, pseudomonas, staphylococcus.

6 So these are -- the reason
7 they're here is they can cause the same kind
8 of allergic reaction that we saw with human
9 insulin.

10 BY MR. POLLACK:

11 Q. Well, these are all lists, if you
12 look at the microbial limits, right, these you
13 would see for any drug? These are all lists of
14 microbes that cause disease; right?

15 MR. DELAFIELD: Objection.

16 Vague.

17 THE WITNESS: Well --

18 MR. DELAFIELD: Mischaracterizes
19 the document.

20 BY MR. POLLACK:

21 Q. Staph?

22 A. E. coli is the same as in the
23 example I gave.

24 Q. Sure.

25 A. And so it was given as an example

1 of how a trace contaminant from a microbe can
2 produce adverse events, and that's the same
3 logic in the specification for treprostinil and
4 many other drugs.

5 Q. Sure. But treprostinil is not made
6 from biologic agents of any kind?

7 MR. DELAFIELD: Objection.
8 Vague. Lacks foundation.

9 THE WITNESS: No, it is not made
10 from a bio -- a cell.

11 BY MR. POLLACK:

12 Q. Right. And the concern here on
13 page 6 where it says "microbial limits," that's
14 about the sterility of the facilities,
15 something we -- one always looks at?

16 MR. DELAFIELD: I'm sorry. Page
17 6 of what?

18 MR. POLLACK: Yeah. Page 6
19 of -- you are right -- Deposition Exhibit 5
20 formerly known as Exhibit 2006 on page 6.

21 BY MR. POLLACK:

22 Q. The microbial limits on this
23 document have to do with the sterility of the
24 facilities; isn't that correct?

25 MR. DELAFIELD: Objection.

1 Mischaracterizes the document. Lacks
2 foundation.

3 THE WITNESS: Yeah, or airborne
4 contaminants, as we discussed, with -- with
5 non- -- with penicillins. They could come
6 in through any process.

7 In fact, in the ICH guidelines
8 on purity, they specifically point out that
9 every single step of every single drug can
10 introduce contaminants and impurities,
11 including every single instrument or vessel.
12 So that's why it's important.

13 BY MR. POLLACK:

14 Q. Okay. But looking at this
15 document, there's nothing on here about
16 penicillin or other beta-lactam antibiotics on
17 Ruffolo Deposition Exhibit 5?

18 A. No, and they weren't intended to.
19 As I said, the examples I gave for contaminants
20 was to show that contaminants that you didn't
21 know were there or you believed were safe or
22 that were there in extremely low and
23 undetectable levels can have significant
24 effects that lead to serious adverse effects.
25 So that's really what these were about.

1 Q. Right.

2 A. And that's also what these numbers
3 in the table on page 6 are related to. They
4 could be introduced the same way. Trace
5 penicillin contaminants can be introduced into
6 a product.

7 But the examples that I gave that
8 you just cite in these last two exhibits was
9 just to show the significance and why the FDA
10 is so concerned about contaminants and why
11 there is an unfelt need to increase purity.

12 Q. Let me ask you.

13 Both of these exhibits, Deposition
14 Exhibit 8 and Exhibit 9, these are examples of
15 contaminants, as you called it, that affect the
16 immune system; correct?

17 MR. DELAFIELD: Objection.

18 Calls for speculation. Vague.

19 BY MR. POLLACK:

20 Q. These are contaminants that create
21 an immune response. That's why they're a
22 problem?

23 MR. DELAFIELD: Same objections.

24 THE WITNESS: In the case of
25 penicillin, it's a sensitization of the

1 immune system after penicillin acts as a
2 hapten binding to a protein.
3 BY MR. POLLACK:
4 Q. And let me try to put that in
5 simpler English.
6 A. Oh.
7 Q. Some people are allergic to
8 penicillin?
9 A. That's -- okay.
10 Q. Is that right?
11 A. That's -- that's correct.
12 Q. Right. And it sets off their
13 immune system?
14 A. Yeah. Yes.
15 Q. Okay.
16 A. But you can be allergic to
17 anything, and as you look at FDA labels for
18 virtually any drugs, one of the precautions is
19 don't take if you're allergic to any of the
20 components in it. So that that's a very common
21 occurrence.
22 Q. But penicillin it is agreed that a
23 fair percentage of the population is allergic
24 to, while other drugs it's a little more rare?
25 MR. DELAFIELD: Objection.

1 Lacks foundation. Vague.

2 THE WITNESS: It's -- it's not
3 that necessarily that the allergic reaction
4 is more rare with other drugs. It can be
5 less severe. So there's a difference
6 between the frequency of allergic and the
7 severity and that's, of course, penicillin
8 and contaminants.

9 BY MR. POLLACK:

10 Q. And similarly with the -- with the
11 E. coli antigens, that's an issue also
12 involving the immune system in Deposition
13 Exhibit 9?

14 A. Yes. That would be antigens that
15 would -- antigens that would cause an immune
16 response.

17 Q. Let me ask you.

18 Looking at the -- let's go back
19 to -- I guess we were already looking at it --
20 Ruffolo Deposition Exhibit 5 at page 6.

21 A. Okay. Yes.

22 Q. Do you know if any of these listed
23 chromatographic impurities have any adverse
24 effects in humans?

25 MR. DELAFIELD: Objection.

1 Vague.

2 BY MR. POLLACK:

3 Q. And if so, what are they?

4 MR. DELAFIELD: Same objections.

5 THE WITNESS: I don't know.

6 What I can tell you is that if you review
7 the FDA label, there are a host of adverse
8 effects produced or observed in patients who
9 are taking treprostinil.

10 BY MR. POLLACK:

11 Q. Sure.

12 A. And --

13 Q. But they're taking purified
14 treprostinil?

15 A. Well, the purified treprostinil
16 still has impurities, and if it's made by the
17 '393 process, it has fewer of them, but there's
18 still some there and including those maybe you
19 don't see.

20 And the -- I lost my train of
21 thought when you asked that second question.
22 What was the question you asked for?

23 Q. Yes. I was asking about the
24 effects of any of these listed impurities.
25 What were those?

1 MR. DELAFIELD: Same objections.

2 THE WITNESS: Oh, yes, I
3 remember my point.

4 In the FDA label, there are
5 adverse events, serious adverse events
6 listed, and the FDA breaks them down into
7 two categories.

8 One that's -- one category are
9 those adverse events that are related to the
10 pharmacology or an extension of the
11 pharmacology of treprostinil, which would be
12 prostaglandin-like activity, and the others
13 don't have an attributable cause.

14 BY MR. POLLACK:

15 Q. Does that mean they could be due to
16 the treprostinil itself?

17 A. Or they -- it could be due to the
18 treprostinil itself or it could be due to a
19 contaminant or it could be due to something
20 else, but the FDA never really knows. They
21 only know what they think is due to the
22 extension of the pharmacology, and it's based
23 on that that they have this desire for
24 impurities to be as low as possible and
25 practical.

1 Q. Did you review -- in forming your
2 opinion on the effect of impurities, did you
3 review adverse event reports for treprostinil
4 for the Remodulin product sold by United
5 Therapeutics?

6 A. I reviewed the adverse events in
7 the label, and -- and those include adverse
8 events observed in clinical trials and also
9 after market. So that that's what I reviewed.

10 Q. Okay. But did you review
11 individual adverse event reports that were
12 provided to the FDA?

13 A. No, I didn't review that section of
14 the NDA.

15 Q. Okay. Do you know whether there
16 were any changes in the adverse event reports
17 after United Therapeutics changed its process
18 of making treprostinil?

19 MR. DELAFIELD: Objection.

20 Vague.

21 THE WITNESS: That would be a
22 very difficult thing to do and is rarely
23 done. Most adverse events occur at a low
24 level and the possibility of seeing a
25 difference statistically -- and the FDA --

1 the FDA would only -- only change a label
2 based on data that solid -- is very low and
3 that's the case with any process change or
4 even any increase in purity.

5 So you wouldn't expect to see
6 that, and at the time you file a change in
7 manufacturing, for example, to give you a
8 decrease in purity, you would not have that
9 information because you don't repeat
10 clinical trials. You repeat and you do
11 studies to match purity standards and
12 release specifications.

13 BY MR. POLLACK:

14 Q. Okay. But as far as you know, from
15 the adverse events reports, there's nothing
16 indicating that there was some change in
17 adverse events over time?

18 MR. DELAFIELD: Objection.

19 Asked and answered.

20 THE WITNESS: Nobody would know
21 that, and I didn't review the adverse events
22 reports -- adverse event reports.

23 BY MR. POLLACK:

24 Q. Go back to your declaration,
25 Ruffolo Deposition Exhibit 3.

1 A. Okay.

2 Q. If you could turn to paragraph 70.

3 A. Okay.

4 Q. And I'm looking on page 35. Near
5 the end of that paragraph, you say here:

6 "Additionally, as shown by the 175
7 batch records, the average purity of the
8 treprostiniil product prepared by the process of
9 the '393 patent is 99.71% while the average
10 purity of the Moriarty product is 99.05%."

11 Do you see that?

12 A. Yes, I do.

13 Q. Where did those two numbers come
14 from?

15 A. Those would have come from
16 Dr. Williams.

17 Q. Okay. That's not something you
18 calculated?

19 A. No.

20 Q. Okay.

21 A. I didn't calculate that.

22 Q. And then it says in the next
23 sentence:

24 "Thus, the average purity of the
25 treprostiniil product prepared by the process of

1 the '393 patent has a 0.7% higher average
2 purity than the Moriarty product."

3 How did you determine that?

4 A. That I also believe was from
5 Dr. Williams.

6 Q. Okay. Do you know where that .7
7 percent number came from?

8 A. I believe it came from -- I don't
9 remember. It came either from his analysis or
10 from his declaration.

11 Q. Okay.

12 A. I'm not sure.

13 Q. I guess I was wondering: Do you
14 know if that came from taking 99.71 and
15 subtracting the 99.05?

16 A. That's -- that's what I believe he
17 did.

18 Q. Okay.

19 A. Yes.

20 Q. You're not certain, though, but
21 that's what you think he did?

22 A. Yes, that's what I believe he did.

23 Q. In view -- in your view, is that a
24 correct way to compare the purity?

25 A. Because he compared apples to

1 apples and had the same -- compared the same
2 analyses on total related substances, yes, I
3 think that's a valid assessment of the
4 difference.

5 Q. Earlier you and I were talking
6 about standard deviation --

7 A. Uh-huh.

8 Q. -- and confidence intervals.

9 Do you remember that?

10 A. Yes, I do.

11 Q. Okay. What role does standard
12 deviation and confidence intervals play in
13 making the comparison between the two purities?

14 MR. DELAFIELD: Objection.

15 Vague. Relevance. Outside the scope of his
16 report.

17 THE WITNESS: Any measurement of
18 means can have associated with it a standard
19 error or standard deviation and from which
20 you can calculate a confidence interval
21 and -- and that would be used to show a
22 statistically significant difference between
23 two pools of numbers.

24 BY MR. POLLACK:

25 Q. You may recall this as well.

1 There's no standard deviation reported by
2 Dr. Williams for these averages.

3 If the confidence interval
4 significantly overlapped, how would that affect
5 your conclusion about the differences between
6 the purity?

7 MR. DELAFIELD: Objection.
8 Vague. Calls for speculation. Relevance.
9 Outside the scope of his report.

10 THE WITNESS: It wouldn't change
11 my interpretation because there would still
12 be a numerically higher number level of
13 purity with the Moriarty process -- with the
14 -- excuse me -- '393 process and that also
15 translated to a -- what did I have? -- ■
16 some odd percent reduction in impurities,
17 and that's a number that is impressive and
18 regulators would like to see.

19 BY MR. POLLACK:

20 Q. That reduction you just described,
21 the ■ some percent, that's based on these two
22 numbers here, isn't it?

23 A. Yes.

24 Q. Okay. And earlier in one of
25 your -- in your answer just two answers ago,

1 you used the word "statistical significance" I
2 believe?

3 A. Yes.

4 Q. What were you referring to?

5 A. Numbers can differ and when they
6 differ by what's called a statistical
7 significance that's assuming a 95 percent
8 probability, that's called statistical
9 significance, and when they don't, it's called
10 a trend.

11 Q. If you only see a trend, what
12 conclusions can you draw from the difference
13 between numbers that are only a trend, as you
14 called it?

15 MR. DELAFIELD: Objection.
16 Vague. Relevance. Calls for speculation
17 and outside the scope of his report.

18 THE WITNESS: The trends that
19 are not statistically significant don't mean
20 that they're not real. I think the more
21 important part is based on these data, the
22 FDA agreed to change the specification for
23 purity from a mean of 99 percent to a mean
24 of 100 percent, resulting in a higher
25 quality product.

1 BY MR. POLLACK:

2 Q. Actually, didn't they change the
3 specification from 98 percent to 102?

4 A. That's --

5 MR. DELAFIELD: Objection.

6 Vague. Mischaracterizes the document.

7 THE WITNESS: That's the range.

8 I was talking about the mean centered around
9 that.

10 BY MR. POLLACK:

11 Q. Okay.

12 A. But we can talk about both because
13 the answer is the same.

14 If you have a mean purity of 99
15 percent that they move up to 100, that's a
16 higher quality product. If you take the lower
17 level of 97 percent and move it up to 98
18 percent, which is what the FDA did.

19 Q. Right. Did the FDA do that or did
20 United Therapeutics do that?

21 A. Oh, United Therapeutics made the
22 request and the FDA, which doesn't have to do
23 it and they don't make changes that they don't
24 believe are -- are not important. The FDA
25 approved, agreed and approved those changes to

1 the FDA's standard. It met their long-felt
2 need, and they made that change.

3 Q. The FDA made that change or United
4 Therapeutics made that change?

5 A. United Therapeutics --

6 MR. DELAFIELD: Objection.
7 Vague.

8 THE WITNESS: -- can't make a
9 change. They can only propose a change.
10 Only the FDA can make a change.

11 BY MR. POLLACK:

12 Q. At the time that United
13 Therapeutics was making an -- making an
14 amendment to their application, they were
15 asking to move, factories, correct from Chicago
16 to Silver Spring?

17 MR. DELAFIELD: Objection.
18 Lacks foundation.

19 THE WITNESS: I don't recall the
20 timing. I think the document, the letter
21 suggests that they were about the same time.

22 BY MR. POLLACK:

23 Q. Actually, the letter is about the
24 change --

25 A. Yeah. Okay.

1 Q. -- of the factory from Chicago to
2 Silver Spring; correct?

3 A. I think so, yes.

4 Q. Yes. And the letter is also about
5 the -- that's a major change, by the way,
6 moving from one factory to another; right?

7 MR. DELAFIELD: Objection.

8 Vague.

9 THE WITNESS: That is considered
10 a major change.

11 BY MR. POLLACK:

12 Q. Yes. And in addition, they -- the
13 people at United Therapeutics decided that they
14 would change what [REDACTED] were used
15 for the process; right?

16 MR. DELAFIELD: Objection.

17 Vague.

18 THE WITNESS: United
19 Therapeutics decided to change the process,
20 and as part of that change in process, they
21 also changed the [REDACTED].

22 BY MR. POLLACK:

23 Q. Right. Now, changing [REDACTED]
24 [REDACTED] has nothing to do with what's
25 discussed in the '393 patent; correct?

1 MR. DELAFIELD: Objection.
2 Vague.
3 THE WITNESS: Sorry. Could you
4 say that again, please?
5 BY MR. POLLACK:
6 Q. Yeah. A change in [REDACTED]
7 [REDACTED] that has nothing to do with what's
8 discussed in the '393 patent?
9 A. The '393 patent describes a change
10 in process from a more lengthy process to a
11 much abbreviated process, and as part of that
12 process, the starting material changed from
13 whatever it was in Moriarty many, many, many
14 steps earlier to the benzindene triol.
15 So, yes, both the process and the
16 starting material did change, and that's the
17 subject of the patent.
18 Q. The [REDACTED] change,
19 though, was not; right? In the patent, they
20 describe making the product from other
21 materials, correct, not from benzindene triol?
22 MR. DELAFIELD: Objection.
23 Vague. Mischaracterizes the document.
24 THE WITNESS: It's my
25 understanding that the starting material of

1 the '393 process in the patent is the
2 benzindene triol.

3 BY MR. POLLACK:

4 Q. The patent describe -- doesn't
5 describe using materials to make the benzindene
6 triol as well?

7 MR. DELAFIELD: Objection.
8 Vague.

9 THE WITNESS: When I -- when I
10 look at the process, for example, in
11 Example 1, it looks to me like the starting
12 material is benzindene triol. That's one of
13 the four compounds that occur in the entire
14 process and that to me seems very different
15 than the Moriarty process.

16 BY MR. POLLACK:

17 Q. The Moriarty process doesn't go
18 through benzindene triol?

19 MR. DELAFIELD: Objection.
20 Calls for speculation.

21 THE WITNESS: Your question --

22 MR. DELAFIELD: Lack of
23 foundation.

24 THE WITNESS: -- was the
25 starting material, and the starting material

1 in the Moriarty process is not the
2 benzindene triol. It's something many, many
3 steps earlier.

4 BY MR. POLLACK:

5 Q. And if we look at the '393 patent
6 at column 7?

7 A. Yes.

8 Q. There's a formula there 10.
9 Do you see that?

10 A. Formula?

11 Q. It's in column 10. It says "X."
12 There's an X and under that it's X11. It's
13 around line 20.

14 A. Oh, I see. Yes, I see that.

15 Q. Isn't that the starting material
16 for the process described in the '393 patent?

17 MR. DELAFIELD: Objection.

18 Vague. Outside the scope of his report.
19 Lacks foundation.

20 THE WITNESS: When I look at the
21 steps that they're talking about -- steps A,
22 B, C, and D -- they start at the benzindene
23 triol, not at compound X.

24 BY MR. POLLACK:

25 Q. Sure. So you're saying the claims

1 only claim that part of the process; correct?

2 A. Yes.

3 MR. DELAFIELD: Objection.

4 Vague.

5 THE WITNESS: And I, you know,
6 again, am not a lawyer.

7 BY MR. POLLACK:

8 Q. Right.

9 A. I wasn't prepared for this, but it
10 looks to me like the process that they're
11 patenting is starting at benzindene triol and
12 ending with treprostinil free acid.

13 Q. Okay. You understand that in the
14 patent it describes the process as starting
15 from compound 10?

16 MR. DELAFIELD: Objection.

17 Vague. Lacks foundation.

18 THE WITNESS: That's not my
19 understanding. I see that they're referring
20 to that reaction from another patent and I
21 -- that to me doesn't look like the starting
22 material for this process, nor is it what
23 they told the FDA was their new process.

24 The new process started with
25 benzindene triol, which is a major change,

1 and then, of course, the [REDACTED] of that
2 [REDACTED], which was going to be
3 [REDACTED] and none of that involves this
4 material.

5 BY MR. POLLACK:

6 Q. Right.

7 A. Compound X.

8 Q. And one of the issues is, it's
9 going to be [REDACTED]. So now the United
10 Therapeutics doesn't have [REDACTED] over how
11 some [REDACTED] is [REDACTED] the [REDACTED]
12 [REDACTED]; correct?

13 MR. DELAFIELD: Objection.
14 Vague. Calls for speculation. Lacks
15 foundation.

16 THE WITNESS: No, that's not
17 correct.

18 BY MR. POLLACK:

19 Q. Okay. Explain to me.

20 A. In the letter where the -- the 2009
21 letter where UTC is requesting this change in
22 process as well as a change in [REDACTED]
23 [REDACTED], both of which are major changes, the
24 FDA is so concerned about purity, as we've said
25 all day, that they were worried about the

1 purity of the [REDACTED] and
2 carryover of any impurities into the final
3 product. It's a major change. That's a very
4 difficult question.

5 And the response you can see shows
6 that the [REDACTED] of the [REDACTED]
7 was subject to specifications that were put in
8 place by the [REDACTED] that matched [REDACTED]
9 specifications for [REDACTED].

10 So they did have [REDACTED] over that
11 [REDACTED] and that's basically what the FDA was
12 asking and that's what satisfied the FDA and
13 allowed them to start this new process starting
14 benzindene triol.

15 Q. Right. But United Therapeutics is
16 not -- they're getting a [REDACTED] from
17 that [REDACTED], but they're [REDACTED]
18 [REDACTED]; is that
19 fair?

20 MR. DELAFIELD: Objection.

21 BY MR. POLLACK:

22 Q. Of the [REDACTED]?

23 MR. DELAFIELD: Objection.

24 Vague. Calls for speculation. Lacks
25 foundation. Outside the scope of his

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report.

THE WITNESS: It's been my experience that when a late-stage [REDACTED] [REDACTED] is [REDACTED] and [REDACTED] we actually place somebody at that [REDACTED] to make sure that the [REDACTED] [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] [REDACTED], the [REDACTED] [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,

1 but in that letter, they -- UTC indicates
2 that the process is -- I don't remember --
3 either the same or virtually the same.

4 BY MR. POLLACK:

5 Q. Okay. Do you know where that is in
6 the letter?

7 A. I can find it.

8 Q. Is that the bottom -- bottom of the
9 first page that you're referring to?

10 A. (Reviewing document).

11 Yes, beginning on the bottom of
12 page 1 and extending through about the first
13 third of page 2.

14 Q. Okay. So I'm right. I think I'm
15 right. One of the things that needs to get --
16 one of the changes that needs to get approved
17 here as a major amendment is that the

18 [REDACTED] is now being [REDACTED] from a
19 [REDACTED] called [REDACTED] or [REDACTED] called [REDACTED]
20 [REDACTED]; is that right?

21 A. Yes.

22 Q. Okay. And so the FDA is approving
23 all of these changes; right? The change in
24 factory, the change -- and the change in
25 [REDACTED] and the change in crystallization in

1 the process?

2 A. And process and starting material,
3 yes.

4 Q. So there's a large number of
5 changes in here instead of three changes, big
6 changes?

7 MR. DELAFIELD: Objection.
8 Mischaracterizes the document.

9 THE WITNESS: There were --
10 these are considered major changes, and so
11 UTC had to go through all of the
12 documentation necessary to satisfy the FDA
13 because this is a major concern of the FDA
14 because of ultimately quality of the
15 material produced and purity.

16 And, again, in the three
17 questions raised by the FDA, two of them had
18 to deal with purity.

19 BY MR. POLLACK:

20 Q. Right. One of those had to do with
21 the purity of the benzindene triol; right?

22 A. One of those was the purity of the
23 benzindene triol and the concern by the FDA of
24 the carry-through of any impurities in the
25 benzindene triol to the final product. That's

1 how concerned they are about purity and
2 contaminants.

3 Q. Right.

4 A. And they were obviously satisfied
5 by the fact that the process were the same and
6 the release specs remained the same for
7 ██████████, and then also the fact that
8 there was a higher level of purity by this new
9 process. That was considered significant
10 enough by the FDA to allow a change to the drug
11 specification.

12 Q. You keep saying the FDA considered
13 it significant enough.

14 Can you show me where in the letter
15 they said they thought it was significant?

16 A. No, it doesn't say that in the
17 letter. The fact that they approved it when
18 they don't like to make changes unless they're
19 considered important. You can't simply change
20 it yourself.

21 And when you submit this change for
22 approval, it involves a great, great, great
23 deal of analysis by the FDA. It takes a long
24 time, a lot of people and, again, they have to
25 balance that between their desire to increase

1 purity and their belief that you can make this
2 product consistently so that there are no drug
3 shortages.

4 Q. And that last reason, the drug
5 shortages, that's why they allow, for example,
6 a purity of 98 percent?

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

9 THE WITNESS: The -- the FDA,
10 again because of their strong desire to have
11 the highest levels of purity as possible,
12 and I keep saying practical, the practical
13 part is to make sure that they get the
14 highest level of purity, which they
15 obviously we're happy with.

16 They made -- they approved the
17 change, but they would not have approved
18 that if they thought the company couldn't
19 make the material or that a subsequent
20 company, after the drug loses its patent,
21 couldn't make that material, which would
22 result in drug shortages.

23 BY MR. POLLACK:

24 Q. But, in fact, all the material made
25 under the [REDACTED] process, at least all the

1 material we've seen, met the 98 percent
2 standard, didn't it?

3 MR. DELAFIELD: Objection.

4 Calls for speculation. Lacks foundation.

5 THE WITNESS: Well, all of the
6 batches, I don't know whether they all met
7 that. I'd have to go look at the data. I
8 don't know what the variability was and, you
9 know, I reviewed 170 something Certificates
10 of Analysis. I don't remember if any did or
11 didn't. So I don't know.

12 BY MR. POLLACK:

13 Q. Okay. I'll represent to you that
14 all of the ones made under the [REDACTED] process
15 made the 98 percent level.

16 MR. DELAFIELD: Same objections.

17 BY MR. POLLACK:

18 Q. Given that, how does that affect
19 your opinion?

20 A. That doesn't change my opinion at
21 all. Because when the FDA agrees to allow a
22 mean range to center from 99 to 100 percent and
23 a lower level from 97 to 98 percent, they are
24 assured of having a higher quality product than
25 would have been allowed under the other

1 guidelines, and that makes them feel good.
2 That's what they shoot for. That's their --
3 it's an unfelt need or the -- I'm blanking on
4 the words. That's what their need is. That's
5 what they desire.

6 MR. POLLACK: Let's -- let's
7 take a break for 10 minutes. I want to look
8 at --

9 THE WITNESS: Okay.

10 MR. POLLACK: -- what other
11 things we want to ask you?

12 THE WITNESS: Sure. Okay.

13 MR. POLLACK: Why don't you guys
14 out.

15 THE WITNESS: Yeah, I'll leave.

16 THE VIDEOGRAPHER: The time is
17 4:03 p.m. We're going off the record.

18 (Recess - 4:03 p.m. - 4:21 p.m.)

19 (Document marked for
20 identification purposes as Ruffolo
21 Exhibit 10.)

22 THE VIDEOGRAPHER: The time is
23 4:21 p.m. We're back on the record. Please
24 proceed, counsel.

25 MR. POLLACK: Okay.

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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

1 about the date?

2 BY MR. POLLACK:

3 Q. The date, yeah.

4 A. But, you know, this is a problem
5 with -- and I've had it with many FDA
6 documents. It can't find the date. I see a
7 stamped date. I don't know whether that's when
8 it was received. So I don't -- I don't know
9 anything. I can't confirm the date.

10 Q. Okay. You haven't seen that kind
11 of stamp on all of the FDA's official
12 documents?

13 A. No.

14 Q. No? Okay.

15 A. No.

16 Q. Remodulin. You see the name
17 Remodulin?

18 A. Yes.

19 Q. Okay. That's the -- that's United
20 Therapeutics treprostinil product?

21 A. Yes.

22 Q. Yes? Okay.

23 And now you haven't reviewed this
24 letter before; is that -- is that correct?

25 A. No, I've never seen this.

1 Q. Okay. But you see this is a letter
2 responding to a citizen's petition? You see
3 that in the first sentence?

4 MR. DELAFIELD: Objection.
5 Vague. Relevance. Beyond the scope of his
6 declaration.

7 THE WITNESS: (Reviewing
8 document). I see that it says it's a
9 citizen's petition.

10 BY MR. POLLACK:

11 Q. Okay. It's a letter responding to
12 a citizen's --

13 A. Yeah.

14 Q. -- petition; right?

15 A. Yeah.

16 Q. And it's a citizen's petition that
17 was filed by United Therapeutics?

18 MR. DELAFIELD: Objection.
19 Relevance. Beyond the scope of his
20 declaration.

21 THE WITNESS: I don't -- I don't
22 know.

23 BY MR. POLLACK:

24 Q. Well, it says there; right?

25 "This letter responds to a

1 citizen's petition submitted to the FDA by
2 United Therapeutics Corp."

3 Did I read that correctly?

4 A. You -- yes, you did.

5 Q. Okay. Do you have any reason to
6 believe it's -- that United Therapeutics Corp.
7 did not file a citizen's petition?

8 A. I don't know.

9 MR. DELAFIELD: Objection.

10 THE WITNESS: Did they?

11 MR. DELAFIELD: I'd just like to
12 enter a standing objection for any questions
13 relating to this regarding relevance and
14 that it's outside the scope of his
15 declaration.

16 THE WITNESS: And I, you know, I
17 don't know what United Therapeutics did.
18 You know, I guess if they're responding to
19 it, they probably did, but I don't -- I
20 don't know. I have no idea what this is
21 about.

22 BY MR. POLLACK:

23 Q. Okay. You know -- do you know what
24 a citizen's petition is?

25 MR. DELAFIELD: Objection.

1 Outside the scope of his testimony and lacks
2 foundation.

3 THE WITNESS: I've heard -- I've
4 heard the word a number of times. I
5 actually don't really know what it means.

6 BY MR. POLLACK:

7 Q. Okay.

8 A. It's -- despite my experience, I
9 don't -- I never had to deal with one. So I
10 really don't know what -- exactly what it is.

11 Q. Okay. I mean, I assume when you
12 were at Wyeth they did file citizen's petitions
13 with the FDA?

14 MR. DELAFIELD: Objection.
15 Lacks foundation. Vague.

16 THE WITNESS: I assume they did.
17 Again, I'm familiar with the words, but I'm
18 not familiar with what it is --

19 BY MR. POLLACK:

20 Q. Okay.

21 A. -- and what was done with them.

22 Q. Okay. Are you aware that a
23 citizen's petition is part of the -- a process
24 of challenging regulatory approvals at the FDA?

25 MR. DELAFIELD: Objection.

1 Lacks foundation. Same objections as
2 before.

3 THE WITNESS: I was not familiar
4 with that. I haven't seen many of them, and
5 I don't know --

6 BY MR. POLLACK:

7 Q. Okay.

8 A. -- what that is.

9 Q. So this goes beyond your regulatory
10 expertise?

11 A. This?

12 Q. Citizen's petitions.

13 A. Citizen's? Yes, I would say this
14 goes beyond my regulatory expertise.

15 Q. Okay. If you could turn to --
16 indulge me and turn to page 8 of Ruffolo
17 Deposition Exhibit 10.

18 A. Oh.

19 Q. This one.

20 A. Oh, oh, oh. I'm sorry.

21 Q. If you could turn to page 8.

22 A. 8. Okay. (Pause). Okay.

23 Q. Let me ask you this first.

24 Are you aware that -- are you --
25 are you aware of what the Orange Book is?

1 MR. DELAFIELD: Objection.

2 Relevance. Outside the scope of his
3 declaration.

4 THE WITNESS: I have heard of
5 the Orange Book. I have a little bit of
6 knowledge, but I -- it's not something that
7 I've paid a lot of attention to. So it's --
8 I put that in the same category of -- of the
9 citizen's petition.

10 Most of my regulatory experience
11 focuses on regulations, guidelines,
12 approval, and -- and that goes not just for
13 the FDA, but the three major agencies in the
14 world, EMA and PMDA.

15 And I know the Orange Book has
16 something to do with patents, but as I said,
17 I'm not a patent lawyer and I don't really
18 follow that very much. So that also is
19 beyond my area of expertise in regulatory.

20 BY MR. POLLACK:

21 Q. Okay. But let me ask you this.

22 Were you aware that in filing a New
23 Drug Application, the drug companies that you
24 worked for are required to file a list of
25 patents that covered the drug in the New Drug

1 Application?

2 MR. DELAFIELD: Same objections.

3 THE WITNESS: I am aware of

4 that.

5 BY MR. POLLACK:

6 Q. Okay. And were you aware that

7 those patents would then get listed in

8 something called the Orange Book, which today

9 is just a website?

10 MR. DELAFIELD: The same

11 objections.

12 THE WITNESS: I was not aware of

13 that.

14 BY MR. POLLACK:

15 Q. Okay. But you're aware that

16 patents are filed with New Drug Applications?

17 MR. DELAFIELD: Same objections.

18 THE WITNESS: Yes, I was.

19 BY MR. POLLACK:

20 Q. Okay. And are you aware regarding

21 whether or not United Therapeutics filed any

22 patents with the FDA in their NDA for

23 Remodulin?

24 MR. DELAFIELD: Objection.

25 Relevance. Outside the scope of his

1 declaration.

2 THE WITNESS: Not -- not -- no,
3 I don't know that. Again, as I said, I was
4 focused on -- on need and -- and I haven't
5 had a chance to look at this, think about
6 this. And even if I did, this falls outside
7 my area of expertise.

8 BY MR. POLLACK:

9 Q. Let me ask you this.

10 Have you compared the claims of the
11 '393 patent to United Therapeutics' Remodulin
12 product?

13 MR. DELAFIELD: Objection.

14 Vague.

15 THE WITNESS: I'm sorry?

16 BY MR. POLLACK:

17 Q. Yes. Have you compared the patent
18 claims in the '393 patent to United
19 Therapeutics' Remodulin product?

20 MR. DELAFIELD: Same objection.

21 THE WITNESS: You have to
22 clarify. Compare what and how?

23 BY MR. POLLACK:

24 Q. Oh, okay. So by that I mean, did
25 you go through, say, claim 9, compare the

1 element -- do you know what the elements of a
2 claim are?

3 A. Sorry.

4 Q. Okay.

5 A. I'm not a patent attorney. I...

6 Q. Did you compare the language in
7 claim 9 to United Therapeutics' treprostinil
8 product?

9 MR. DELAFIELD: Same objection.

10 THE WITNESS: Still I don't know
11 how -- what you mean "compare." Compare to
12 what?

13 BY MR. POLLACK:

14 Q. I'll see if I can make it simpler.

15 Did you analyze claim 9 and
16 determine whether it covers United
17 Therapeutics' Remodulin product?

18 MR. DELAFIELD: Same objection.

19 THE WITNESS: I -- again, I'm
20 still not quite sure what you mean but, you
21 know, that wasn't what I was asked to do,
22 and I don't believe I did make any
23 comparison like that.

24 BY MR. POLLACK:

25 Q. Do you know if anyone else in this

1 case made that comparison?

2 A. No.

3 MR. DELAFIELD: Same objection.

4 THE WITNESS: I haven't spoken
5 to anyone outside of Mr. Delafield.

6 BY MR. POLLACK:

7 Q. Okay. All right. If we can turn
8 back to page 8 in Ruffolo Deposition Exhibit
9 10.

10 A. Yes.

11 Q. And as you'll see here, the issue
12 is whether a generic treprostinil injection
13 product can emit material that's on the
14 Remodulin label and, in particular, the use of
15 something called a "high pH glycine diluent."

16 Do you see that?

17 MR. DELAFIELD: Objection.

18 Outside the scope of his declaration. Lacks
19 foundation.

20 THE WITNESS: I mean, I can't
21 interpret that. I'd have -- even if I had
22 read this, I may not be able to interpret
23 it. But is there a section you would like
24 me to read?

25 BY MR. POLLACK:

1 Q. Why don't you feel free to read
2 this section starting from the word
3 "Discussion" on the page before.
4 A. "Discussion." Oh.
5 Q. Yep.
6 A. (Reviewing document). Okay.
7 Q. Have you read enough or you want to
8 read more?
9 A. I don't know. It depends on your
10 question.
11 Q. Okay. Fair enough.
12 Do you understand from this that
13 United Therapeutics was allowed by the agency
14 to add to their label for Remodulin
15 (treprostinil) information about using a high
16 pH glycine diluent to reduce the risk of BSIs?
17 MR. DELAFIELD: Objection.
18 Mischaracterizes the document. Relevance.
19 Outside the scope of his declaration.
20 THE WITNESS: No, I wasn't aware
21 of that. The section I read didn't define
22 BSIs and, again, I focused on long-felt need
23 with respect to purity and I -- and
24 impurities and I didn't see anything here
25 related to any of that.

1 So I really don't know what this
2 letter is in response to and I don't
3 understand. Here we're talking about drug
4 product and that wasn't the focus of my
5 review. It was on --

6 BY MR. POLLACK:

7 Q. Uh-huh.

8 A. It was on contaminants and
9 impurities in the synthesis of API. So I'm
10 sorry. I don't even know how to respond.

11 Q. Yeah. I'm not going to ask you
12 about BSIs and whether that's true or anything
13 else.

14 A. Yeah.

15 Q. I just wanted to know is, you know,
16 based on the letter, is it -- is it the case
17 that the FDA had allowed United Therapeutics to
18 add to their label information about the use of
19 high pH glycine diluent?

20 MR. DELAFIELD: Objection.
21 Relevance. Calls for speculation.
22 Mischaracterizes the document and outside
23 the scope of his declaration.

24 THE WITNESS: And what was your
25 question?

1 BY MR. POLLACK:

2 Q. Yeah. I was just asking whether or
3 not United Therapeutics was allowed by the FDA
4 to add information about the use of a high pH
5 glycine diluent, whatever that may be, to their
6 -- to their label.

7 MR. DELAFIELD: Same objections.

8 THE WITNESS: I don't know
9 anything about that at all, and reading a
10 couple of paragraphs on this letter that
11 don't even define some of the abbreviations
12 used, I can't -- I can't do anything with
13 this. This doesn't mean anything to me.

14 BY MR. POLLACK:

15 Q. Well, do you see -- let's take a
16 look at the second full paragraph on page 8.

17 A. The which? The --

18 Q. The one beginning with "More the
19 point." "More to the point." I want to take
20 a look at the second sentence. Do you see
21 there it says:

22 "When we approve the addition of
23 this information to Remodulin's label in
24 September 2013."

25 Do you see where I'm reading?

1 A. Yes, I do.

2 Q. Okay. Reading that, am I correct
3 that the FDA approved adding certain
4 information to Remodulin -- that's the same
5 product we've been talking about -- to the
6 labeling of Remodulin; is that fair?

7 MR. DELAFIELD: Same objections.

8 THE WITNESS: I guess so. I
9 don't know.

10 BY MR. POLLACK:

11 Q. Okay. That's what the letter says;
12 right?

13 A. That's --

14 MR. DELAFIELD: Same objection.

15 BY MR. POLLACK:

16 Q. I know you don't know
17 independently, but in the letter that's what it
18 says?

19 MR. DELAFIELD: Same objection.

20 THE WITNESS: That's what, two
21 sentences out of a 10-page letter I never
22 saw before that's related to something I
23 didn't prepare for. It doesn't mean
24 anything to me.

25 BY MR. POLLACK:

1 Q. Okay.

2 A. In fact, the only thing that means
3 anything to me is the signature of Janet
4 Woodcock, who's a good friend of mine.

5 Q. Okay. That's the same Janet
6 Woodcock --

7 A. Yes.

8 Q. -- that you refer to in your
9 declaration?

10 A. Correct.

11 Q. She's the author of this letter?

12 A. She's the signatory of this letter.

13 Q. Letter is issued with her approval;
14 correct?

15 A. That's correct.

16 Q. Okay. And if we go back to page 8?

17 A. Okay.

18 Q. Okay. In Janet Woodcock's letter,
19 she says "We" and by 'we' she's referring to
20 the FDA?

21 MR. DELAFIELD: Objection.
22 Calls for speculation. Lacks foundation.
23 Relevance. Outside the scope of his
24 declaration.

25 THE WITNESS: Which "we"? "We

1 did not take these acts"?

2 BY MR. POLLACK:

3 Q. Yes, or we did -- all of the
4 "we's." "We approved." "We did so in the
5 interest."

6 That's referring to the FDA; right?

7 MR. DELAFIELD: Same objections.

8 THE WITNESS: I guess so. I
9 suppose she would.

10 BY MR. POLLACK:

11 Q. Right? It's a letter from the FDA;
12 is that fair?

13 A. Yeah.

14 MR. DELAFIELD: Same objections.

15 BY MR. POLLACK:

16 Q. Okay. And it says here --

17 A. I should point out.

18 Q. Uh-huh.

19 A. Letters come from the FDA that
20 don't represent the entire FDA opinion. During
21 the entire NDA process, you get letters from
22 the FDA. That's -- that's a --

23 Q. Yeah. This is an official response
24 to a citizen's petition?

25 MR. DELAFIELD: Same objection.

1 THE WITNESS: Again, I don't
2 know.
3 BY MR. POLLACK:
4 Q. You don't know what those are?
5 A. Yeah. I'm sorry.
6 Q. Okay. And they say here they made
7 a label change; right?
8 They did so in the interest of
9 "providing healthcare providers with up-to-date
10 information on the use of high glycine diluents
11 and not out of the concern that the
12 administration of IV treprostinil with a
13 neutral diluent should always be avoided
14 because it poses a risk to patients. The
15 agency had been concerned about the safety of
16 neutral diluents" -- I'm sorry.
17 "If the agency had been concerned
18 about the safety of neutral diluents, it could
19 have revised the labeling to require the use of
20 high pH glycine diluents only and taken steps
21 to raise awareness about the effect that choice
22 of diluent has on the risk of BSIs."
23 Now, in the case of the changes
24 that we're talking about here that were
25 approved by the FDA, the manufacturing changes,

1 those changes don't even appear on the label;
2 correct?

3 MR. DELAFIELD: Same objections.

4 THE WITNESS: That's correct.

5 BY MR. POLLACK:

6 Q. Right. Here we're talking about
7 changes that were approved by the agency that
8 do appear on the label; correct?

9 MR. DELAFIELD: Same objections.

10 THE WITNESS: I don't know. I
11 don't remember it from the label. I
12 reviewed the label. I don't remember this.

13 BY MR. POLLACK:

14 Q. Okay. But here the agency is
15 saying, just because we approved it on the
16 label, that doesn't mean we endorsed your
17 statements about the effect of these high pH
18 glycine diluents; isn't that what they're
19 saying?

20 MR. DELAFIELD: Objection.

21 Vague. Mischaracterizes the document.
22 Relevance. Lacks foundation. Outside the
23 scope of his declaration.

24 THE WITNESS: To be honest, I
25 don't know what the agency is saying here.

1 You know, I'm sorry. In a 10-page letter,
2 looking at a couple of paragraphs, I don't
3 know what they mean. I don't know what
4 they're referring to. I don't know what
5 their intent is. And this is an area that I
6 have not been involved with before.

7 BY MR. POLLACK:

8 Q. Okay. Well, you said you had some
9 regulatory expertise.

10 Based on your regulatory expertise,
11 can you explain what's being described here?

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

14 THE WITNESS: I said I had a
15 great deal of regulatory expertise. But I
16 also said that I didn't know everything
17 about regulatory affairs and that there were
18 people in regulatory affairs that knew more
19 than me and many who knew less, but this is
20 something that I have not had to deal with.

21 And this is -- again, I don't
22 know what this is.

23 BY MR. POLLACK:

24 Q. Okay. I'm only asking this because
25 earlier I believe you stated the opinion that

1 by approving United Therapeutics' changes from
2 97 to 98 percent, the FDA was endorsing that as
3 a change in purity. And you seem to have the
4 expertise to opine on that or that was your
5 view that there was an endorsement, or maybe I
6 misunderstood you.

7 And yet here you're not able to
8 tell me whether the FDA considers an approval,
9 as they did here, to be an endorsement.

10 A. They --

11 MR. DELAFIELD: Objection.

12 Mischaracterizes testimony. Relevance and
13 outside the scope of his declaration.

14 THE WITNESS: The area I
15 testified to before I've had a great deal of
16 experience in at every level with the FDA.

17 BY MR. POLLACK:

18 Q. Uh-huh.

19 A. This I have not had any experience
20 and I know for -- I know that the FDA does not
21 like to make changes in specifications unless
22 they believe they are significant. I don't
23 know what Janet is saying about whatever label
24 -- labeling change she's talking about.

25 Q. Well, you said earlier that you had

1 reviewed the label?

2 A. I did review the label, yeah.

3 Q. Okay. If you reviewed the label,
4 you saw a discussion about what diluents should
5 be used with Remodulin?

6 MR. DELAFIELD: Objection.
7 Lacks foundation.

8 THE WITNESS: It --

9 MR. DELAFIELD: Outside the
10 scope of his declaration. Relevance.

11 THE WITNESS: Well, and because
12 it was outside the scope, it's not an area
13 that I would have focused on. I focused on
14 other parts of the label, and I do know a
15 good deal about labeling negotiations as far
16 as NDA approval.

17 This in citizen's petition I
18 don't -- is an area that I have not been
19 involved with, not focused on, and I don't
20 have the experience in. What I testified to
21 I have great deal of experience in. Sorry.

22 BY MR. POLLACK:

23 Q. Yeah. Okay. But in regard to
24 whether or not the FDA endorses statements made
25 by applicants, what's your evidence of that?

1 MR. DELAFIELD: Objection.

2 Mischaracterizes his testimony. Relevance.

3 THE WITNESS: The applicant
4 can't make a change without the FDA's
5 agreement and approval.

6 BY MR. POLLACK:

7 Q. Uh-huh.

8 A. And when they do that in the
9 context of a specification, they wouldn't
10 permit it if they didn't believe it was
11 significant and important enough to do so.

12 I have no idea what this letter is
13 talking about, and I don't even understand the
14 argument that's being made here. Again, maybe
15 if I studied this for a couple of days but, you
16 know, this is not something I've seen or been
17 involved with.

18 Q. Okay. But you don't have any
19 statements, articles, documents, evidencing
20 that the FDA endorses statements made by
21 applicants merely because they approved the
22 change?

23 MR. DELAFIELD: Objection.

24 Vague. Asked and answered. Relevance.

25 THE WITNESS: The FDA doesn't

1 allow change unless they agreed with that
2 change and approved that change. That's
3 their job.

4 BY MR. POLLACK:

5 Q. Sure.

6 A. And with respect to specifications
7 and release of batches and all of the pre-NDA
8 work and NDA work, their approval is required
9 and that approval is so important that it's
10 what allows you to sell a new product. That's
11 a big deal.

12 Q. Uh-huh.

13 A. So that acknowledgement by the FDA
14 is important, it has a legal meaning, and it's
15 not done trivially.

16 Q. Okay. I understand that.

17 A. So --

18 Q. But that's not what I asked you.

19 A. Well, but, again, I have no idea
20 what you're asking me. I'm sorry.

21 Q. Oh. I was asking if you had any --

22 A. I can't say it in any other words.

23 Q. Sure. I was asking if you had any
24 documentation regarding the statement you just
25 made. Not -- not your -- not your opinion but

1 what -- do you have any documents with those
2 statements on them from the FDA? Do you have
3 any other written materials from anyone --

4 A. Well --

5 Q. -- supporting those statements?

6 MR. DELAFIELD: Same objections.
7 Compound.

8 THE WITNESS: There are numerous
9 documents that define the changes that we
10 spoke about earlier, and I've referenced
11 those, on how sponsors deal with the FDA and
12 what the FDA requires.

13 So, yes, there are documents
14 that lay out what the FDA requires.

15 And as I said earlier, the
16 changes that were made by UTC with respect
17 to the manufacturing process, the starting
18 material, those are defined in FDA and ICH
19 documents as major changes requiring
20 validation, documentation, and ultimately
21 approval by the FDA.

22 So, yeah, those documents exist,
23 and I've cited them.

24 BY MR. POLLACK:

25 Q. Well, actually --

1 A. This is --

2 Q. Uh-huh.

3 A. You know, again, I don't even know
4 what this is.

5 Q. This is just a document regarding
6 the same product that we're talking about in
7 this case; right?

8 MR. DELAFIELD: Objection.
9 Argumentative.

10 THE WITNESS: Yeah. It's --

11 BY MR. POLLACK:

12 Q. Yeah. Okay.

13 A. I understand from the title it's
14 the same product we're talking about, but I
15 don't know what they're talking about.

16 Q. Okay. Looking back at Exhibit --
17 what was called Exhibit 2006, the letter from
18 the --

19 A. Oh, yeah.

20 Q. -- from United Therapeutics to the
21 FDA.

22 As we discussed earlier, there were
23 two other major amendments that were made;
24 right? One regarding the [REDACTED] of the
25 product and one regarding the location of the

1 facility?

2 MR. DELAFIELD: Objection.

3 Mischaracterizes the document.

4 THE WITNESS: Yes, that's
5 correct.

6 BY MR. POLLACK:

7 Q. Okay. Given that those -- those
8 two were changes requiring major amendments in
9 the first place, how do we know that changing
10 the spec from 97 to 98 was also a major
11 amendment? Is there any indication that they
12 considered that to be a major amendment?

13 A. Sure.

14 MR. DELAFIELD: Objection.
15 Compound. Vague.

16 BY MR. POLLACK:

17 Q. What's the indication?

18 A. You -- the documents that I've
19 cited consider those changes to be amendment.
20 They specifically address changes in
21 specifications.

22 Q. Can you -- can you show me where it
23 says that a change in purity from 97 to 98
24 percent is considered a major amendment?

25 A. They wouldn't have listed something

1 as a change in purity from 97 to 98 percent.
2 That's not what guidelines do. They talk about
3 changes in specifications, which that would --
4 would be.

5 Q. Okay. Can you show me where they
6 say a change -- in the documents you've
7 cited -- a change increasing the minimum HPLC
8 assay purity is a major amendment?

9 MR. DELAFIELD: Objection.
10 Vague.

11 THE WITNESS: The increasing the
12 stringency of a -- of a specification is not
13 a major amendment. What is a major
14 amendment was the change in the process, the
15 change in the starting material. Those are
16 major changes, and those major changes
17 resulted in an increase in purity that the
18 FDA ultimately approved.

19 MR. POLLACK: I'm going to mark
20 as Ruffolo Deposition Exhibit 11.

21 (Document marked for
22 identification purposes as Ruffolo
23 Exhibit 11.)

24 THE WITNESS: Thank you.

25 BY MR. POLLACK:

1 Q. Ruffolo -- and Ruffolo 11 is a
2 document entitled "Patent Owner Response to
3 Petition."
4 A. Yes.
5 Q. Have you seen this document before?
6 A. Yes, I believe I have.
7 Q. Okay. When did you see this
8 document?
9 A. I saw this maybe a year ago. Oh,
10 I'm sorry. This is the response. This is not
11 the --
12 Q. Yeah. I don't want to trick you or
13 anything.
14 A. Right. Yeah.
15 Q. If you turn to the last page?
16 A. Yeah.
17 Q. You'll see it's dated July 6, 2016?
18 A. Oh, okay. Sorry. I would have
19 read this in the last couple of weeks.
20 Q. Oh, okay. Were you involved at all
21 in creating Ruffolo Deposition Exhibit 11?
22 A. No, I was not --
23 Q. Okay.
24 A. -- involved in the creation of this
25 document.

1 Q. Okay. And had you read this
2 document at any time before you wrote your
3 final draft of your declaration?

4 A. I don't believe so because I
5 believe my document was submitted on this day
6 because it was the day before a family vacation
7 where I had to finish mine. So I don't know if
8 I could have read this in advance.

9 Q. Okay. Let me ask you.
10 Did you read any prior drafts of
11 Ruffolo Deposition Exhibit 11?

12 A. Oh. No.

13 Q. Okay.

14 A. No.

15 Q. So Ruffolo Deposition Exhibit 11
16 you first read in preparation for today's
17 deposition?

18 A. Yes, that's correct.

19 Q. Okay. Was there anything in
20 Ruffolo Deposition Exhibit 11 that you
21 disagreed with?

22 A. Could you be more specific?

23 Q. Well, did you see any mistakes
24 or -- let me start with that. Did you see any
25 mistakes in Ruffolo Deposition Exhibit 11?

1 A. Not that I recall.

2 Q. Okay. Did you see opinions or
3 statements that you thought were maybe just
4 slightly inaccurate?

5 A. Can you be more specific on whose
6 opinions you're talking about?

7 Q. Yeah. Any of the opinions that
8 were written in here by -- this was submitted
9 -- this was submitted by United Therapeutics.

10 A. I understand.

11 Q. Okay.

12 A. Yeah.

13 Q. Were any of the statements in here
14 -- I assume this was -- these were written by
15 United Therapeutics attorneys.

16 Were there any statements in this
17 document that you looked at and said, well, I
18 don't know if I completely agree with --

19 A. Okay.

20 Q. -- that statement?

21 MR. DELAFIELD: Objection.

22 Vague.

23 THE WITNESS: This document, as
24 I recall, quotes some opinions from -- from
25 either Dr. Winkler or from the -- the Board,

1 that Board.

2 BY MR. POLLACK:

3 Q. The Board? The Board that's --

4 that's hearing this case?

5 A. Many of those I wouldn't have

6 agreed with.

7 Q. Okay.

8 A. Obviously the opinions that relate

9 to mine --

10 Q. Uh-huh.

11 A. -- my declaration and the opinions

12 that relate to Dr. Williams' declaration I do

13 agree with.

14 Q. Okay. So there was nothing --

15 there were no statements in here that United

16 Therapeutics was advancing that you thought, I

17 don't -- I don't completely with that?

18 A. Not that I recall.

19 MR. DELAFIELD: Objection.

20 Asked and answered.

21 BY MR. POLLACK:

22 Q. Let me just -- I just wanted to

23 check one thing with you.

24 If you turn to page 34?

25 A. Okay.

1 Q. At the top of the page, this is
2 under a heading that says "The '393 Patent
3 Product is Structurally and Functionally
4 Distinct from Moriarty's Product."

5 A. Yes, I see that.

6 Q. Okay. Do you know what that means?

7 A. I believe I do.

8 Q. What -- what does it mean?

9 A. "Structurally different" I believe
10 means a difference in the chemical that was
11 produced as a result of the reaction, and
12 "functionally" I believe means the clinical or
13 perhaps patient significance. That's -- that's
14 my understanding.

15 Q. Is there a difference between the
16 approved Moriarty treprostinil product that was
17 shown clinically that's different from the '393
18 product?

19 MR. DELAFIELD: Objection.

20 Vague. Compound. Outside the scope of his
21 declaration.

22 THE WITNESS: Not -- not to my
23 knowledge.

24 BY MR. POLLACK:

25 Q. And you said that -- we were

1 mentioning structurally.

2 Is there a difference between the
3 structure of treprostinil as made by the
4 Moriarty product and the structure of
5 treprostinil as made by the '393 patent?

6 A. Yeah. As I -- as I indicated,
7 structure to me represents the result of the
8 chemical reaction, and the purity of the
9 material produced by '393 is higher and the
10 levels of all but one of the impurities are
11 lower in the '393 process compared to Moriarty.

12 Q. Let me ask you a hypothetical.

13 If the -- here you point out that
14 the difference in purity is .7 percent; right?

15 A. That's --

16 MR. DELAFIELD: Objection.

17 Vague.

18 THE WITNESS: That's -- yes,
19 that's from my declaration.

20 BY MR. POLLACK:

21 Q. Okay. Is that a fair
22 characterization of your declaration that's
23 made on page 34? A .7 percent difference in
24 average purity?

25 A. Yes, I believe it is.

1 Q. Okay. And in your view, is that
2 being used to show that the '393 product is
3 structurally different from the Moriarty
4 product?

5 A. Yes, in that it contains two-thirds
6 less impurity than the Moriarty process.

7 Q. Okay. Let me ask you.

8 If instead of .7 percent
9 difference, what if the difference was █
10 percent? Would that still be a structural
11 difference, in your view?

12 MR. DELAFIELD: Objection.

13 Calls for speculation. Outside the scope of
14 his declaration.

15 THE WITNESS: If it was █, that
16 would represent about a █ percent
17 reduction. Yeah, that -- that would be
18 important to me.

19 BY MR. POLLACK:

20 Q. Okay. What about a █ percent
21 difference? Would that be a structural
22 difference, in your view?

23 MR. DELAFIELD: Same objections.

24 THE WITNESS: That would be
25 about a █ percent -- would be, yeah, █

1 percent reduction in overall impurities.
2 Maybe. I don't know. I'd have to think
3 about that.

4 BY MR. POLLACK:

5 Q. Okay. What if it were a [REDACTED]
6 percent difference in impurity? Would that --
7 between the '393 and treprostinil product,
8 would that be a structural difference, in your
9 view?

10 MR. DELAFIELD: Same objections.

11 THE WITNESS: Well, certainly if
12 I have to think about [REDACTED], I'd have to think
13 about [REDACTED], and I haven't thought about that.

14 BY MR. POLLACK:

15 Q. Do you -- you're giving an opinion
16 that .7 is a structural difference.

17 I'm trying to figure out where is
18 that borderline between structural difference
19 and one that's not a structural difference.

20 MR. DELAFIELD: Same objections.

21 THE WITNESS: I don't know, but
22 I do believe that a [REDACTED] percent reduction
23 in -- in purity is. I don't know what the
24 cutoff is at the low end, but I'm confident
25 that [REDACTED] percent reduction in purity is.

1 BY MR. POLLACK:

2 Q. Okay. Are there -- is there a
3 number that I could give you that you would
4 agree that that would be too small a difference
5 to make a structural difference?

6 MR. DELAFIELD: Objection.
7 Relevance. Outside the scope. Lacks
8 foundation.

9 THE WITNESS: You know, not --
10 if you're asking me can I set the lower
11 limit?

12 BY MR. POLLACK:

13 Q. Yeah.

14 A. I'm telling you, I'd have to think
15 about that. I haven't thought about that, and
16 I don't know off the top of my head what it
17 would be.

18 Q. In your view, is there no lower
19 limit?

20 MR. DELAFIELD: Objection.
21 Asked and answered.

22 THE WITNESS: There is a lower
23 limit to everything. I just don't know
24 where it is off the top of my head.

25 BY MR. POLLACK:

1 Q. You haven't thought of that?

2 A. No.

3 MR. DELAFIELD: Same objections.

4 BY MR. POLLACK:

5 Q. What if there were no difference in
6 the average purity for the Moriarty process and
7 the '393 process? How would your [REDACTED]
8 change then?

9 MR. DELAFIELD: Objection.

10 Vague. Calls for speculation.

11 THE WITNESS: Well, first off,
12 there isn't no difference. There is a
13 difference in the purity of treprostinil
14 that's higher and a difference in the
15 overall level of impurities that are lower
16 in the '393 process. So the hypothetical
17 doesn't mean anything to me.

18 BY MR. POLLACK:

19 Q. I understand, but I'm asking you to
20 give an opinion based on my hypothetical and
21 you're here as an expert. So --

22 MR. DELAFIELD: Same objections.

23 BY MR. POLLACK:

24 Q. -- I'd like to you do that.

25 A. So if you're asking me are two

1 identical preparations?

2 Q. Uh-huh.

3 A. Is there a difference between two
4 identical preparations?

5 Q. Well, they're two different
6 processes; right?

7 A. Well --

8 Q. But let's say they give around the
9 same average purity.

10 A. Then there could be a difference
11 depending on which contaminant -- which
12 contaminants are or aren't different, which
13 ones are elevated or which are lower, and I
14 wouldn't know that in a hypothetical example.

15 Q. How come you don't know that?

16 MR. DELAFIELD: Objection.

17 THE WITNESS: Because I can't --

18 MR. DELAFIELD: Calls for
19 speculation.

20 THE WITNESS: Because I can't
21 make it up.

22 BY MR. POLLACK:

23 Q. Okay.

24 A. You're asking me to make up
25 information that doesn't exist and I -- that's

1 not how I think.

2 Q. So, in your opinion, it's not just
3 a difference in purity, but also the exact
4 identity of each of those impurities that --

5 A. Sure.

6 Q. -- matters to the claim?

7 A. Sure.

8 MR. DELAFIELD: Objection.

9 Calls for speculation.

10 BY MR. POLLACK:

11 Q. Okay.

12 A. Absolutely. Absolutely. It's what
13 I referred to as the -- the characteristic
14 impurities.

15 Just to give you an example. If
16 two processes that were different and had
17 exactly the same purity, but one of them had a
18 very high level of one single impurity. It
19 would be very high that made up all of that
20 impurity, and the other one had much lower
21 levels. You bet that would make a difference.

22 Q. Right. Wouldn't that depend on the
23 FDA, the guidelines, how --

24 A. Of course.

25 Q. Whether or not that impurity

1 mattered? So it may make no difference at all;
2 isn't that right?

3 MR. DELAFIELD: Objection.

4 Vague. Incomplete hypothetical. Calls for
5 speculation.

6 THE WITNESS: You know, if the
7 purity was █ percent and that █ percent was
8 all one single peak, that would get a great
9 deal of attention by all those groups you
10 said: the FDA, the reviewers, and including
11 the company itself.

12 BY MR. POLLACK:

13 Q. All right. But that's not the case
14 for the Moriarty process?

15 MR. DELAFIELD: Same objections.

16 THE WITNESS: The Moriarty
17 process doesn't fit your hypothetical
18 example where you ask me to make up data.

19 BY MR. POLLACK:

20 Q. Uh-huh.

21 A. The Moriarty process produces █
22 plus fold increase in impurities compared to
23 '393 and that I'm more comfortable with because
24 that's real and not made up.

25 Q. Okay. Yeah, but I'm just asking

1 that weren't real, you know, how far would your
2 opinion go?

3 MR. DELAFIELD: Objection.

4 Calls for speculation. Outside his expert
5 evaluation.

6 THE WITNESS: Well, I mean, as I
7 said, I can't off the top of my head think
8 of that.

9 But in the example that you gave
10 me where you required me to make up data,
11 which is something scientists don't really
12 do well, at least not good scientists -- we
13 go on real information like this .7 percent
14 data, you know -- I have difficulty
15 answering that question.

16 And I gave you an example of
17 made-up data that you requested where it
18 would make a big deal, a big difference but,
19 I mean, I guess you can ask me to make up
20 data all day long and I could come up with
21 lots of silly examples where it would make a
22 difference. And I'm happy to do that if you
23 like. It's just not something I do for a
24 living.

25 BY MR. POLLACK:

1 Q. All right. No further questions.

2 A. Thank you.

3 MR. DELAFIELD: I have no
4 questions.

5 MR. POLLACK: Thanks so much for
6 your time.

7 THE WITNESS: Thank you. Thank
8 you.

9 THE VIDEOGRAPHER: The time is
10 5:11 p.m. This concludes today's
11 audiovisual deposition of Dr. Robert R.
12 Ruffolo. We're off the record.

13 (Off the stenographic record.)

14 THE REPORTER: Mr. Delafield, do
15 you wish a copy of the transcript?

16 MR. DELAFIELD: Yes, if I could
17 get it expedited.

18 MR. POLLACK: I need it
19 expedited.

20 THE REPORTER: What time frame?

21 MR. POLLACK: Three days.

22 THE REPORTER: Do you wish a
23 rough?

24 MR. DELAFIELD: I want one.

25 MR. POLLACK: Sure. Yeah, I'll

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get a rough, too.

MR. DELAFIELD: If I could get expedited, both the rough and final.

THE REPORTER: When do you want the final?

MR. DELAFIELD: When can I get it?

THE REPORTER: Three days.

MR. DELAFIELD: Okay. If that's the quickest, yes.

(Signature having not been waived, the taking of the deposition concluded at 5:11 p.m.)

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DECLARATION UNDER PENALTY OF PERJURY

I declare under penalty of
perjury that I have read the entire transcript of
my Deposition taken in the captioned matter
or the same has been read to me, and
the same is true and accurate, save and
except for changes and/or corrections, if
any, as indicated by me on the DEPOSITION
ERRATA SHEET hereof, with the understanding
that I offer these changes as if still under
oath.

Signed on the _____ day of
_____, 2016.

ROBERT R. RUFFOLO, JR., PHD

CERTIFICATE OF REPORTER

DISTRICT OF COLUMBIA)

I, DENISE D. VICKERY, CRR/RMR and
Notary Public, hereby certify the witness was by
me first duly sworn to testify to the truth; that
the foregoing deposition was taken at the time
and place stated herein; and that the said
deposition was recorded stenographically by me
and thereafter reduced to printing under my
direction; that said deposition is a true record
of the testimony given by said witness.

I certify the inspection, reading and
signing of said deposition were NOT waived by
counsel for the respective parties and by the
witness; and that I am not a relative or employee
of any of the parties, or a relative or employee
of either counsel, and I am in no way interested
directly or indirectly in this action.

Denise D. Vickery, CRR/RMR

My Commission expires February 14, 2018

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Page No. 8 Line No. 4 Change to: _____
"and" to "am"

Page No. 10 Line No. 9 Change to: _____
"Trandolapril" To "Trandilapril"

Page No. 10 Line No. 10 Change to: _____
"Trandolapril" To "Trandilapril"

Page No. 10 Line No. 11 Change to: _____
"Trandolapril" To "Trandilapril"

Page No. 83 Line No. 21 Change to: _____
"Their" To "There are"

Page No. 113 Line No. 19 Change to: _____
"reactive" to "reacted"

Page No. 142 Line No. 15 Change to: _____
"purity" To "impurity"

Page No. 142 Line No. 17 Change to: _____
"purity" To "impurity"

Page No. 164 Line No. 24 Change to: _____
"a" to "an"

Page No. 204 Line No. 20 Change to: _____
"Spectra photographic" To "Spectrophotometric"

Page No. 245 Line No. 3 Change to: _____
"for" To "from"

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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"

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DECLARATION UNDER PENALTY OF PERJURY

I declare under penalty of perjury that I have read the entire transcript of my Deposition taken in the captioned matter or the same has been read to me, and the same is true and accurate, save and except for changes and/or corrections, if any, as indicated by me on the DEPOSITION ERRATA SHEET hereof, with the understanding that I offer these changes as if still under oath.

Signed on the 1st day of September, 2016.



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2 BEFORE THE PATENT TRIAL AND APPEAL BOARD

3
4 STEADYMED LTD.,
5 Petitioner,

6 vs.

7 UNITED THERAPEUTICS
8 CORPORATION,
9 Patent Owner.

10 -----
Case IPR2016-000006 (Patent 8,497,393)

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12
13
14 VIDEOTAPED DEPOSITION OF ROBERT M. WILLIAMS, PH.D.

15
16 Friday, August 26, 2016

17 9:30 a.m.

18
19 12235 El Camino Real
20 San Diego, California

21
22
23 Reported by:
24 Harry Alan Palter
25 CSR No. 7708, Certified LiveNote Reporter

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ROBERT M. WILLIAMS, PH.D.

SteadyMed Ltd. vs. United Therapeutics Corporation

Friday, August 26, 2016

Harry Alan Palter, CSR No. 7708

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1 San Diego, California

2 Friday, August 26, 2016; 9:30 a.m.

3

4

5 THE VIDEOGRAPHER: Good morning. We are
6 on the record. This is the videotaped deposition of
7 Robert M. Williams, Ph.D., in the matter of
8 SteadyMed, Ltd., vs. United Therapeutics
9 Corporation.

10 This deposition is taking place at 12235
11 El Camino Real, Suite 200, San Diego, California
12 92130, on August 26, 2016, at 9:30 A.M.

13 My name is Kory Ross. I'm the
14 videographer with U.S. Legal Support. Video and
15 audio recording will be taking place unless all
16 counsel agree to go off the record.

17 Would all present please identify
18 themselves, beginning with the witness.

19 THE WITNESS: Robert M. Williams.

20 MR. POLLACK: Stuart E. Pollack, DLA
21 Piper, LLP U.S., on behalf of SteadyMed, Ltd., the
22 petitioner. I'm joined with Maya Choksi from the
23 same law firm.

24 MS. HASPER: Katherine Hasper of Wilson,
25 Sonsini, Goodrich & Rosati, on behalf of United

1 Therapeutics and the witness.

2 MR. MAEBIUS: And Steve Maebius from
3 Foley & Lardner on behalf of patent owner.

4 THE VIDEOGRAPHER: Thank you, Counsel.

5 The certified court reporter is Harry
6 Palter.

7 Will you please swear in the witness.

8

9

10 ROBERT M. WILLIAMS, PH.D.,
11 having been duly administered an oath in accordance
12 with the California Code of Civil Procedure
13 Section 2094, was examined and testified as follows:

14

15

16 EXAMINATION

17 BY MR. POLLACK:

18 Q Good morning, Dr. Williams.

19 A Good morning, Counselor.

20 Q Just as a formality to start today, could
21 you state your name for the record and your current
22 position.

23 A Robert M. Williams, university
24 distinguished professor at Colorado State
25 University.

1 Q Okay. Now, I know you've been deposed
2 before; correct?

3 A Yes.

4 Q How many times have you been deposed?

5 A I don't know the exact number. It's
6 somewhere around 17, 15 -- 16, 17, somewhere in
7 there. I lost count, actually.

8 Q Okay. Were all of those patent cases?

9 A Yes.

10 Q And how many of those cases were for
11 United Therapeutics?

12 A Let me see. Three. I think this would
13 be my third deposition with United Therapeutics.
14 But I'd have to -- I can check -- check. It may be
15 three or four. I don't remember. I think it's for
16 sure three.

17 Q Okay. But you understand all the rules
18 of depositions at this point?

19 A Yes.

20 Q Okay. And there's no reason today that
21 you can't give your best testimony?

22 A No.

23 Q All right.

24 MR. POLLACK: I'm going to mark as
25 Williams Deposition Exhibit 1 the Petitioner's

1 Notice of Deposition.

2 (Exhibit 1 marked)

3 BY MR. POLLACK:

4 Q And Dr. Williams, are you here today in
5 response to Petitioner's Notice of Deposition of
6 Robert M. Williams, Ph.D.?

7 A Yes, that's my understanding.

8 Q So you've done two other depositions for
9 United Therapeutics. Did both of those cases also
10 involve treprostinil?

11 A Yes.

12 Q And those were two cases in New Jersey
13 involving generic challenges to United Therapeutics
14 Remodulin product?

15 A Yes.

16 Q Do you remember the names of the two
17 defendants in those cases?

18 A Sandoz in the first case, which went to
19 trial, and then Teva.

20 Q Okay. And the type of case is still
21 ongoing?

22 A I believe so.

23 Q Have you submitted an expert report or
24 Declaration in the Teva case?

25 A Yes.

1 Q And have you -- and you've been deposed
2 already in that Teva case?

3 A Yes.

4 Q Did your expert Declaration or deposition
5 concern the '393 patent at all?

6 A Yes.

7 Q Okay. Did you opine on the validity or
8 invalidity of the '393 patent in that case?

9 A No.

10 Q Okay. What did you opine on?

11 A Claim construction.

12 Q Okay. And what were the issues regarding
13 claim construction in that case?

14 MS. HASPER: Objection. Relevance.

15 THE WITNESS: I don't -- I don't recall
16 off the top of my head.

17 BY MR. POLLACK:

18 Q Okay. Were they similar to the claim
19 construction issues in the current IPR?

20 A I believe there was some overlap, yes.

21 Q Which ones were an overlap?

22 A Again, I'd have to go back and look at my
23 Declaration.

24 Q You don't recall --

25 A It's -- I don't recall exactly.

1 Q Okay.

2 A I don't want to give an inaccurate
3 answer.

4 Q Absolutely.

5 Do you recall if there was any discussion
6 of the meaning of the term "product" in the '393
7 case with either -- with Teva?

8 MS. HASPER: Objection. Relevance.

9 You may answer to the extent it doesn't
10 reveal privilege.

11 THE WITNESS: Again, my -- I haven't
12 looked at that material for awhile, so I'm hesitant
13 to give an answer right now.

14 BY MR. POLLACK:

15 Q You're not sure?

16 A I'm not 100 percent sure.

17 Q Okay. What about the word "comprising"?
18 Was there any issue about the meaning of the word
19 "comprising" in the '393 case?

20 MS. HASPER: Same objection.

21 THE WITNESS: I'd have to give the same
22 answer. I don't exactly recall.

23 BY MR. POLLACK:

24 Q Well, do you know did you -- whether
25 there was an issue or not, did you make any comments

1 or provide any opinions regarding the meaning of the
2 word "comprising" in the Teva case?

3 MS. HASPER: Same objection.

4 THE WITNESS: I didn't hear you,
5 Katherine?

6 MS. HASPER: Same objection.

7 THE WITNESS: And your question again
8 was? Did I give --

9 BY MR. POLLACK:

10 Q Did you give any opinion of any form
11 regarding the meaning of the term "comprising" in
12 the Teva case regardless of what the -- ultimate
13 issue was?

14 A I'd need to refresh my recollection by
15 looking at the Declaration I submitted.

16 Q You don't recall as you sit here?

17 A I don't recall.

18 Q And do you know whether the Declaration
19 you submitted, whether it was -- whether it was
20 stamped "confidential"?

21 A I believe so.

22 MR. POLLACK: Counsel, to the extent it's
23 available, we'd like to get a copy of his
24 Declaration from the Teva case.

25 MS. HASPER: I'll look into it for you.

1 BY MR. POLLACK:

2 Q And are you also involved in certain
3 other generic challenges to the Remodulin product,
4 also pending the District of New Jersey?

5 A I know that there's a case now that I've
6 been retained for involving Watson Laboratories.

7 Q Any others?

8 MS. HASPER: Objection. Privilege.

9 To the extent that you can answer without
10 revealing attorney-client communications or
11 confidential information, you may do so.

12 THE WITNESS: Not that I'm aware of.

13 BY MR. POLLACK:

14 Q Not that you're aware of? Okay.

15 And in the Watson case, have you
16 submitted any opinions or formed any opinions in
17 that case?

18 A Not yet.

19 Q Not yet? Do you know what the issues are
20 in the Watson case?

21 MS. HASPER: Again, objection.

22 Privilege.

23 I caution the witness not to answer to
24 the extent that doing so would reveal privileged
25 information.

1 THE WITNESS: That's at a very early
2 stage, so I haven't done any --

3 BY MR. POLLACK:

4 Q You haven't done anything?

5 A No.

6 Q Okay. About how many hours in total have
7 you worked on cases for United Therapeutics at this
8 point?

9 MS. HASPER: Objection.

10 Mr. Pollack, this is -- you're asking
11 about how much time he's spent either on his own
12 with counsel working on --

13 MR. POLLACK: Okay. Stop the speaking
14 objections now; all right?

15 MS. HASPER: I'm trying to explain that
16 you're asking a line of questions which assumes --

17 MR. POLLACK: Okay. Just -- just say
18 your objection.

19 (Indiscernible crosstalk)

20 THE WITNESS: Excuse me, Counselor?

21 BY MR. POLLACK:

22 Q Yes. How many hours have you worked on
23 cases for United Therapeutics?

24 MS. HASPER: Objection. I instruct the
25 witness not to answer to the extent doing so will

1 reveal privileged information.

2 THE WITNESS: I have no idea.

3 BY MR. POLLACK:

4 Q Well, more than a hundred?

5 MS. HASPER: Objection. Privileged.

6 THE WITNESS: I don't know.

7 MR. POLLACK: Are you instructing him not
8 to answer?

9 MS. HASPER: The objection -- so I'm
10 going to give you a standing instruction to this
11 entire line of questioning, that to the extent
12 Mr. Pollack asks you about privileged information,
13 including your communications with counsel for
14 United Therapeutics, that we request you not answer.

15 MR. POLLACK: I'm not asking about his
16 communications.

17 BY MR. POLLACK:

18 Q About how much income have you received
19 so far from United Therapeutics working on their
20 cases?

21 MS. HASPER: Objection. Relevance.
22 Prejudicial.

23 THE WITNESS: I don't recall.

24 BY MR. POLLACK:

25 Q Over \$100,000?

1 MS. HASPER: Objection. Relevance.

2 Prejudicial.

3 THE WITNESS: I'd have to go look at my
4 invoices.

5 BY MR. POLLACK:

6 Q Over \$50,000?

7 MS. HASPER: Objection. Relevance.

8 Prejudicial.

9 THE WITNESS: Likely.

10 BY MR. POLLACK:

11 Q Likely over 50 -- between 50 and 100? Is
12 that fair?

13 MS. HASPER: Objection. Relevance.

14 Prejudicial.

15 THE WITNESS: I don't know.

16 BY MR. POLLACK:

17 Q It could be over hundred?

18 MS. HASPER: Objection. Relevance.

19 Prejudicial. Asked and answered.

20 BY MR. POLLACK:

21 Q It could be over a hundred thousand
22 dollars?

23 A I'm thinking I'd have to go look.

24 MS. HASPER: Objection. Relevance,

25 privilege, asked and answered.

1 THE WITNESS: I'd have to look.

2 BY MR. POLLACK:

3 Q You'd have to look.

4 I'm asking if it's possible whether it
5 was over a hundred thousand dollars?

6 MS. HASPER: Objection. Relevance.
7 Privileged. Asked and answered.

8 THE WITNESS: I just remember I've been
9 working on a lot of different cases at the same
10 time.

11 BY MR. POLLACK:

12 Q Sure.

13 A I don't remember.

14 Q Sure.

15 What's your hourly rate?

16 A \$650 an hour.

17 Q Okay. Have you worked over a hundred
18 hours on United Therapeutics cases?

19 MS. HASPER: Same objection.

20 THE WITNESS: I'd have to give the same
21 answer. I'd have to go back and look at my
22 invoices. I don't -- I don't recall off the top of
23 my head.

24 BY MR. POLLACK:

25 Q Okay. What about in this IPR? About how

1 many hours have you worked in this IPR?

2 MS. HASPER: Same objection.

3 THE WITNESS: I don't know.

4 BY MR. POLLACK:

5 Q No idea?

6 A No.

7 Q "No." More than 40 hours?

8 MS. HASPER: Same objection.

9 THE WITNESS: Again, I don't want to give
10 an inaccurate answer, so I would need to look at my
11 invoices.

12 BY MR. POLLACK:

13 Q I understand. But I'm asking just for an
14 approximate answer. Is it more than 40 hours?

15 MS. HASPER: Same objection.

16 THE WITNESS: I don't know.

17 BY MR. POLLACK:

18 Q About how much have you invoiced for in
19 this matter?

20 MS. HASPER: Same objection.

21 THE WITNESS: Between two and three
22 invoices, so I'm not really sure.

23 BY MR. POLLACK:

24 Q Okay. About how much was this at each
25 invoice?

1 A I do not recall.

2 MS. HASPER: Same objection.

3 BY MR. POLLACK:

4 Q Was each invoice larger than \$50,000?

5 A No.

6 MS. HASPER: Same objection.

7 BY MR. POLLACK:

8 Q Were some of the invoices larger than
9 \$50,000?

10 A No, I don't think so.

11 Q You think all of them were below \$50,000?

12 A Yes.

13 Q Okay. And there were about three
14 invoices?

15 MS. HASPER: Same objection.

16 THE WITNESS: Again, I can't exactly
17 recall.

18 BY MR. POLLACK:

19 Q Okay. Can you give --

20 A Because I'm working on other matters.
21 Completely different matters, not for United
22 Therapeutics. So --

23 Q Sure.

24 A I have a very accurate record on my
25 computer, but I don't remember.

1 Q How many matters are you working on now?

2 MS. HASPER: Objection. Relevance.

3 THE WITNESS: Around nine right now.

4 BY MR. POLLACK:

5 Q Okay.

6 A I'm paid for about nine different

7 matters.

8 Q All right. About how much do you earn a

9 year doing matters?

10 MS. HASPER: Objection. Relevance.

11 THE WITNESS: Which -- what do you mean

12 "a year"? It varies from year to year.

13 BY MR. POLLACK:

14 Q How about this year? How much in --

15 MS. HASPER: Same objection.

16 BY MR. POLLACK:

17 Q -- 2016 so far?

18 A I haven't tabulated that yet from my

19 accountant. He's been buggin' me to give him

20 numbers to him before September 15th. So I'll be

21 doing that soon. I don't know.

22 Q Okay. Approximately how much?

23 A I don't know.

24 Q How about 2015? How much?

25 MS. HASPER: Same objection.

1 BY MR. POLLACK:

2 Q How much have you earned in 2015 on
3 patent matters?

4 A It was somewhere around \$800,000.

5 Q And what about 2014? A similar amount?

6 MS. HASPER: Same objection.

7 THE WITNESS: I don't recall.

8 BY MR. POLLACK:

9 Q Of that \$800,000 last year, about how
10 much of that was from United Therapeutics?

11 A I have no idea.

12 MS. HASPER: Same objection.

13 BY MR. POLLACK:

14 Q Would you say half of your time --
15 (Indiscernible crosstalk)

16 THE WITNESS: I have no idea.

17 BY MR. POLLACK:

18 Q No idea at all?

19 A No.

20 Q Okay.

21 MS. HASPER: I'll just repeat what got
22 lost in the crosstalk was me saying, "Same
23 objection." Also, "privilege."

24 BY MR. POLLACK:

25 Q Have you done work in other -- you

1 understand this is a proceeding called an "inter
2 partes review"?

3 A Yes.

4 Q Have you done work in other inter partes
5 reviews?

6 A Not yet, no.

7 Q This is your first one?

8 A Yes.

9 Q Okay. And how many cases have you
10 testified at trial in?

11 A Four times.

12 Q Four times?

13 A Four different cases.

14 Q Okay. One of those was the Sandoz case?

15 A Yes.

16 Q That case didn't involve the '393 patent;
17 is that right?

18 A No.

19 Q Okay. Are you involved also -- I think
20 there's another Sandoz case involving the '393
21 patent? Are you involved in that one?

22 MS. HASPER: Objection. Foundation.

23 THE WITNESS: Not that I'm aware of.

24 BY MR. POLLACK:

25 Q No?

1 Okay. The Declaration?

2 MR. POLLACK: I'm going to mark as
3 Williams Deposition Exhibit 2 the Declaration of
4 Robert M. Williams, Ph.D., in support of patent
5 owner response to petition.

6 (Exhibit 2 marked)

7 BY MR. POLLACK:

8 Q If you could just verify me that that's a
9 fair and accurate copy of your Declaration?

10 A (Examining document) So this is -- yes.
11 This is a copy of my Declaration as submitted.

12 Q Okay. Were there any mistakes in your
13 Declaration that you discovered?

14 A Yes.

15 Q Okay. What are those mistakes?

16 A There is two minor mistakes. At
17 paragraph 88, there's a typographical error. One,
18 two, three, four -- fifth line down, middle,
19 Exhibit 2034 should be Exhibit 2044.

20 Q Okay.

21 A And the second error is there is a small
22 change to Exhibit B, entry --

23 Q I'm sorry, where are you?

24 A Exhibit B.

25 Q Okay.

1 A Page 50, the entry [REDACTED] was
2 inadvertently a duplicate. So that -- that one
3 entry needs to be crossed out.

4 Q Okay. Could you tell me what page we're
5 looking at?

6 A 50.

7 Q And which entry is it?

8 A It's the -- I believe it's the [REDACTED]
9 was inadvertently a duplicate of another -- another
10 entry.

11 Q And that is the 17th one down?

12 A Yes. I think that's correct.

13 Q Okay. Other than those two corrections,
14 are there any other corrections you want to make?

15 A Not that I have found.

16 Q Okay. Are all of your opinions in this
17 matter -- are they all contained in your
18 Declaration?

19 A Yes.

20 Q Okay. Who did the first draft of your
21 expert Declaration?

22 A I actually made the draft of -- sort of
23 the template of the first draft and, Counsel, Bobby
24 Delafield, and I also worked with Katherine here.
25 We went back-and-forth by e-mail assembling

1 different drafts as we went along, and discussed
2 issues and --

3 Q What's Katherine's last name?

4 A Hasper.

5 Q All right. Anyone else you worked with
6 at counsel?

7 MS. HASPER: You can answer to the extent
8 it doesn't reveal privileged information.

9 THE WITNESS: I primarily worked with
10 Bobby and Katherine, as I recall.

11 BY MR. POLLACK:

12 Q Who assembled the appendices "A" and "B"?

13 A Counsel did.

14 Q Did you have any questions about how
15 counsel assembled Exhibits A and B -- or appendices
16 "A" and "B"?

17 A What do you mean?

18 Q Did you ask them: How were these
19 assembled?

20 A Yes. I worked with them, and there was
21 underlying batch data that I was provided with, and
22 I was able to cross-check that the entries were all
23 accurate.

24 Q Okay. Who selected the particular
25 batches that were chosen to the analyzed?

1 A These were -- I think these were
2 requested by counsel from United Therapeutics.

3 Q Okay. You had nothing to do with the
4 selection?

5 A Other than asking for as much batch data
6 as was available.

7 Q Okay. Did you get all batch data that
8 was available?

9 A I believe so.

10 Q Okay. Was there any batch data that you
11 saw that's not included in appendices "A" and "B"?

12 A No.

13 Q Did you ask whether there was any other
14 batch data that you could include?

15 A I did ask.

16 Q Okay. And what was the answer?

17 A That this was all they were able to find.

18 Q Okay. If we can go in your Declaration
19 to paragraph 27.

20 Here in paragraph 27, you list some
21 patent litigation matters that you were working on?

22 A Yes.

23 Q Is that right? Okay.

24 Are there -- it says here, "Process
25 chemistry patent litigation." Are there other kinds

1 of litigation matters that you were working on that
2 aren't in this list?

3 A Yes.

4 Q Okay. About how many other matters?

5 A So this lists, I believe, seven. And
6 I've worked on somewhere around 27. So 20 other
7 matters that -- that were not dealing with process
8 chemistry issues.

9 Q Just briefly what were those other
10 matters concerning?

11 A I would need to look at my list of -- of
12 cases. I don't have a memory of all of 'em.

13 Q Sure. Do you have a recollection of some
14 of them?

15 A I did a couple of cases on behalf of
16 Apotex in Canada early on.

17 Q Apotex is a generic pharmaceutical
18 company?

19 A Yes.

20 Let me see. I did a formulation case
21 where I testified at trial on behalf of Hospira and
22 Apotex against Sanofi-Aventis. That wasn't process
23 chemistry. That was formulations. I've done a
24 bunch of formulation cases.

25 Q I see on this list there are some cases

1 that name United Therapeutics.

2 A Hmm-hmm.

3 Q Okay. The first one lists United
4 Therapeutics is United Therapeutics Corp. versus
5 Sandoz. And there are two cases listed. Do you see
6 that?

7 A Yes.

8 Q Is the first case the case that went to
9 trial already?

10 A Yes.

11 Q Okay. And --

12 A I believe so.

13 Q And that case didn't involve the '393
14 patent?

15 A No.

16 Q Okay. And then there's a second case.
17 Do you see that? 13-316?

18 A 13 --

19 Q It's in the same -- sorry. It's in the
20 same phrase on page 11.

21 A That was -- I think that was a
22 consolidated thing where there were two different --
23 there was a formulation patent and a process patent
24 that were litigated at the trial --

25 Q Okay.

1 A -- as I recall.

2 Q And neither of them involved the '393
3 patent? Neither of those cases?

4 A No, I don't think so. No.

5 Q At the very bottom of the page, we see
6 the words United Therapeutics starting?

7 A Yes.

8 Q And then it says, "versus Teva." That's
9 the matter you're working on now?

10 A I believe that matter is over. I believe
11 the parties settled.

12 Q Okay. Okay.

13 The matter in which you've given an
14 expert on claim construction, that's a new Teva
15 matter that's not listed here?

16 A Boy, I -- you know, just looking at the
17 case numbers, I don't remember. I'd have to look at
18 my -- at my records.

19 Q Okay. Looking here, you see this is a
20 matter filed -- this Teva matter was filed in 2014.
21 Is the matter you're working on now the one that was
22 more recent?

23 A Well, as far as I -- as far as I can
24 recall, the only two matters for UTC I'm working on
25 right now is this one.

1 Q Right.

2 A The IPR matter.

3 Q Okay.

4 A And then the upcoming Watson case.

5 Q Okay. Okay. And you see it also lists
6 here yet another matter for Sandoz?

7 A Oh, I'm sorry, the Sandoz one is the one
8 I believe that settled. The Teva one might still be
9 ongoing. I just don't recall. Nothing's happened
10 in a while, so I don't remember.

11 Q Okay. Okay. And in addition to these,
12 there's this Watson matter?

13 A Yes.

14 Q Are you working on any matters for United
15 Therapeutics involving their -- the oral form of
16 treprostinil?

17 MS. HASPER: Objection. Privilege.

18 THE WITNESS: Not that I can think of.

19 BY MR. POLLACK:

20 Q Okay. Nothing comes to mind?

21 A No.

22 Q Okay. When did you first get hired to
23 work on this matter?

24 A I don't recall the exact date of -- when
25 I signed my Retainer Agreement. I believe it was

1 either late -- late last year or early this year.

2 I'm not exactly sure of the timing.

3 Q And when -- when do you actually start
4 working substantively on the matter?

5 MS. HASPER: Objection. Privilege.

6 I instruct the witness not to answer to
7 the extent doing so will reveal privileged
8 communications with counsel.

9 THE WITNESS: I just don't recall.

10 BY MR. POLLACK:

11 Q Well, was it in the Spring? You start
12 working on it in the Spring.

13 MS. HASPER: Same objection.

14 THE WITNESS: I don't remember.

15 BY MR. POLLACK:

16 Q Don't recall at all?

17 A No.

18 Q How about as late as Summer?

19 MS. HASPER: Same objection.

20 THE WITNESS: I was certainly working on
21 it by the Summer, but I don't remember how early in
22 the year or if there was anything late in 2015. I
23 just don't remember.

24 BY MR. POLLACK:

25 Q Okay. Well, you recall -- you can look

1 at your Declaration. You filed that on or around
2 July 6th. Do you recall that?

3 A This (Indicating)?

4 Q Yes.

5 A Yes. Okay.

6 Q Okay. So using that date, about how many
7 months earlier did you start working on the IPR?

8 MS. HASPER: Objection. Privileged.

9 THE WITNESS: I just don't remember the
10 timing.

11 BY MR. POLLACK:

12 Q Three months before?

13 MS. HASPER: Objection. Privileged.

14 THE WITNESS: Counsel, I said, "I don't
15 remember."

16 BY MR. POLLACK:

17 Q Okay. But I'm trying to -- you know,
18 could it have been six months before?

19 MS. HASPER: Objection. Privileged.

20 Asked and answered.

21 THE WITNESS: I just don't recall the
22 timing. I could easily look at my invoices.

23 MR. POLLACK: I'd like to request
24 Dr. Williams's invoices in this matter.

25 MS. HASPER: I hear your request.

1 BY MR. POLLACK:

2 Q Okay. Do you think you started working
3 on it substantively in late 2015?

4 MS. HASPER: Objection. Privileged.
5 Asked and answered.

6 THE WITNESS: I -- I don't recall.

7 BY MR. POLLACK:

8 Q Nothing at all, whether --

9 A I just don't recall.

10 Q No idea?

11 How soon after you were retained did you
12 start working on that?

13 MS. HASPER: Objection. Privileged.
14 Asked and answered.

15 I instruct the witness --

16 MR. POLLACK: None of this is privileged.

17 And your speaking objections are going so far. If
18 this continues, I'm going to ask for a second
19 deposition of him. Understood?

20 Go ahead.

21 THE WITNESS: I don't recall.

22 BY MR. POLLACK:

23 Q Okay. Other than your hourly rate, is
24 there any other compensation you expect for working
25 on this IPR?

1 A No. Other than the opportunity to play
2 golf in Southern California tomorrow.

3 (Laughter)

4 BY MR. POLLACK:

5 Q Could you tell me about why you're
6 playing golf in Southern California tomorrow?

7 A Because there's a great golf course near
8 here that I like.

9 Q Oh, Okay.

10 A But United Therapeutics is not paying for
11 it. I am.

12 Q How many -- how many matters have you
13 worked with the law firm of Wilson Sonsini on?

14 MS. HASPER: Objection. Privileged.

15 This also refers -- it sounds like you're
16 asking about case others than this case.

17 THE WITNESS: So give me your question
18 one more time, please.

19 BY MR. POLLACK:

20 Q Sure. How many matters have you worked
21 on with the Wilson Sonsini law firm?

22 A By "matters," do you mean litigation
23 matters, because -- --

24 Q Any kind of matter.

25 A -- I was a cofounder of a biotechnology

1 company that used Wilson Sonsini's patent counsel.

2 Q Okay.

3 A That was microcide pharmaceuticals, and
4 we use the Wilson Sonsini. So I have -- and that
5 was their Palo Alto office.

6 Q Did they take -- in exchange for that
7 legal work, did they take any kind of equity or any
8 kind of compensation of that type?

9 A That, I don't remember. It was a long
10 time ago.

11 Q Okay.

12 A It was the early '90s. I just don't
13 remember. But I know Wilson Sonsini was patent
14 counsel to Microcide.

15 Q Okay. How many other matters?

16 A Um, let me see.

17 MS. HASPER: Objection. I instruct the
18 witness not to answer to the extent doing so would
19 reveal any privileged information.

20 THE WITNESS: I have a current spinoff
21 company that I founded and am president of in Fort
22 Collins. And we have patent counsel from Wilson
23 Sonsini who volunteered to work for free.

24 BY MR. POLLACK:

25 Q Really?

1 A Yeah.

2 Q Why did they do that?

3 A It's active-retirement-sort-of situation.
4 So retired attorney who actually still is associated
5 with Wilson Sonsini but wants to do something
6 interesting instead of just playing golf, and skiing
7 or something like that.

8 Q Okay.

9 A We were very lucky to get a very
10 qualified attorney who's interested in our company
11 and our technology.

12 Q Okay. All right. Anything else?

13 A I was retained to work on one other case
14 that never materialized. So there was no -- no
15 expert reports or anything. So I was retained, no
16 invoices that I can recall, and the matter settled
17 before anything happened.

18 Q Okay. Anything else?

19 A Not that I can think of.

20 Q Okay. I mean, other -- there's also a
21 bunch of matters with United Therapeutics. Those
22 were all the Wilson Sonsini firm?

23 A Yes.

24 Q Okay. And same set of questions for the
25 Foley & Lardner firm. How often have you worked

1 with that firm?

2 A Who?

3 Q Do you know Mr. Maebius?

4 A Oh, I just met him for the first time
5 yesterday.

6 Q Oh, okay. Okay.

7 Have you met anyone else from
8 Mr. Maebius's firm?

9 A I don't think so.

10 Q Okay. And did you meet with Mr. Maebius
11 yesterday to prepare for today's deposition?

12 A He came to the preparation that I was
13 doing with Counselor Hasper.

14 Q Okay. Who else was at that preparation?

15 A One other attorney from UTC. Shaun -- I
16 can't remember his last name.

17 Q Okay. Anyone else?

18 A No.

19 Q And other than yesterday, were there
20 other meetings in-- that you had with counsel in
21 preparation for today's deposition?

22 A No.

23 Q About how long did you meet with counsel
24 yesterday?

25 A About nine hours.

1 Q And prior to yesterday's meeting with
2 counsel, did you have telephone -- you know,
3 meetings by telephone or other means of
4 communication -- with counsel?

5 A A few with Counselor Delafield.

6 Q Okay. Other than Counselor Delafield,
7 anyone else?

8 A No.

9 Q What else did you do to prepare for
10 today's deposition?

11 A I reread lots of documents, patents, prior
12 art, my own Declaration.

13 Q Did you search for prior art?

14 A Did I search for prior art?

15 I don't -- I don't recall.

16 Q You don't know, one way or the other?

17 A No, I don't know, one way or the other.

18 Q Okay. Did you search for any papers,
19 articles, or documents that were relied upon in your
20 Declaration?

21 A Well, I already had a vast amount of
22 literature from the other cases. So I was already
23 fairly familiar with a massive volume of literature
24 and information relative to treprostinil. So --

25 Q Did any of the articles that were

1 attached to your Declaration -- let me rephrase.

2 Were all of the articles attached to your
3 Declaration provided by counsel?

4 A I guess I'd need to look at my list of
5 exhibits. I don't remember. I'd have to look --

6 Q Okay. If you look at paragraph 28 of
7 your Declaration, there's a description of what you
8 considered.

9 A Well, this isn't a list.

10 Q Well, that's the only list you provided,
11 sir.

12 A Okay.

13 Q Let me ask you: It says there, "I have
14 also reviewed a number of documents in this case,
15 including all documents cited by SteadyMed and UTC,
16 as well as the materials I have cited in the
17 Declaration."

18 Other than those documents, were there
19 any other documents not described in that sentence
20 that you reviewed?

21 A No.

22 Q Okay. You say in the last sentence, "If
23 I am provided additional information or documents in
24 this proceeding, I may offer further opinions
25 regarding the additional information."

1 Were you provided any additional
2 information or documents?

3 A No.

4 Q Okay. And, therefore, you will not be, I
5 assume, offering further opinions regarding any
6 additional information?

7 A Not at this time.

8 Q Okay. Was there anything that you asked
9 for from counsel that you wanted to review?

10 A I actually -- can I go back to a previous
11 question you asked me?

12 Q Absolutely.

13 A You asked me if I -- if I did my own --
14 any literature searching?

15 Q Yes, yes.

16 A So I actually did pull up every single
17 one of Dr. Winkler's publications.

18 Q Okay.

19 A I did that myself. And I provided all of
20 those papers to counsel and looked through all of
21 his papers.

22 Q Okay.

23 A So that was -- so I would consider that a
24 literature search. It was actually a lot of work.

25 Q Okay. He's written a lot of papers;

1 right?

2 A That's all relative. Relative to me, no.

3 Q Okay.

4 A I've published maybe three or four times
5 the number of papers of Dr. Winkler.

6 Q Okay.

7 A So it was actually, from my point of
8 view, a modest amount. But it was still over a
9 hundred papers, I think it was.

10 Q Yeah. You know Dr. Winkler; right?

11 A Yes, I do.

12 Q In fact, you're together in a network of
13 experts; is that right?

14 A I wouldn't characterize it that way.
15 Dr. Winkler has a -- an expert witness head-hunting
16 firm called Cymedex, and he's contacted me at least
17 a half a dozen times as a potential candidate to
18 work on cases that came to his company. And none of
19 them materialized in a retained engagement, but
20 we've certainly talked on the phone. He's had my
21 CV. He obviously thinks I'm a very good expert, so
22 he's been trying to find, you know, an engagement
23 for his company that uses me.

24 Q Okay. The two of you know each other;
25 right?

1 A Oh, yes.

2 Q Yeah.

3 A Yeah. Organic chemistry is a small
4 community.

5 Q Yeah. Would you say Dr. Winkler's a
6 distinguished organic chemist?

7 A I think he's a very solid organic
8 chemist.

9 Q How does "solid" differ from
10 "distinguished"?

11 A So I would reserve the characterization
12 "distinguished" to be with more accolades, national
13 awards, and things like that, and I don't think he's
14 quite hit that bar.

15 Q Okay. What about you? Have you hit that
16 bar?

17 A Very fortunately, yes, I would say so. I
18 got a major -- two major national ACS awards
19 recently. I'm university distinguished professor,
20 Colorado State University, which is a lifetime
21 appointment, and there's only 12 in a campus of more
22 than 1,200 faculty.

23 Q Okay.

24 A I don't mean to disparage Dr. Winkler.
25 He's a very nice man, and he's a very good chemist.

1 Q Other than searching for Dr. Winkler's
2 articles, do you recall any other documents that
3 were provided solely by you for use in this
4 proceeding?

5 A I provided counsel with some of my own
6 papers.

7 Q And what did those papers concern? Why
8 did you provide those?

9 A So I cited those in my Declaration that
10 had to do with how I have used the word "product" in
11 my own publications. And I also -- some of the
12 papers from -- that I found from Dr. Winkler, how he
13 also very, very -- in the very same way uses the
14 word "product" in his own publications.

15 Q Okay.

16 A So we use the word the same way.

17 Q Other than those papers which were
18 attached from you regarding the meaning of the word
19 "product," was there anything else that you provided
20 for use in this proceeding?

21 A Not that I can think, off the top of my
22 head.

23 Q When counsel provided you with the data
24 for appendices "A" and "B," who did the calculations
25 based on those appendices?

1 A Counselor Hasper did.

2 Q You didn't do the calculations?

3 A No. But I checked them.

4 Q Okay. As I understand it, one of your
5 main opinions here is that the product of the '393
6 patent has an average purity of █████ percent, while
7 the product of the Moriarty patent has an average
8 purity of 99.0 percent, approximately. Is that --
9 is that fair?

10 A There's more to it than that. Just the
11 overall purity. There's also impurity --
12 significant impurity profile differences between the
13 product of the two patented processes.

14 Q How are those different profiles
15 significant?

16 A In what context?

17 Q Well, are any of those impurities known
18 to be particularly harmful?

19 A Well, by "harmful," what do you mean
20 "harmful"? In what context?

21 Q In any context.

22 A Well, I mean, in process chemistry, the
23 goal is to try to get as pure an API as possible
24 that is free of any type of extraneous impurities.
25 And so sometimes, depending on the API material,

1 impurities may have deleterious biological
2 consequences; sometimes they don't. Um --

3 BY MR. POLLACK:

4 Q Do any of the -- as far as you know, any
5 of these particular impurities have deleterious
6 biological consequences?

7 MS. HASPER: Objection. Beyond the scope
8 of his expert Declaration.

9 THE WITNESS: I'm not a clinician, so I
10 don't know.

11 BY MR. POLLACK:

12 Q You don't know?

13 A I don't know.

14 Q Okay. So other than the percentage of
15 the impurities, if there's no knowledge about the
16 biological deleterious effects of any of these
17 impurities, what difference does it make which ones
18 they are?

19 A So I think the stereoisomer impurities
20 would be the ones that a process chemist would be
21 particularly wary of. The dimer impurity and the
22 ethyl and methyl ester impurities are hydrolyzable
23 back to treprostinil to API.

24 So those are both -- I guess,
25 operationally, you can recover, actually,

1 treprostinil from those impurities if you needed to.
2 And, you know, in vivo, they can be hydrolyzed in
3 treprostinil. So they're not going to have a
4 deleterious effect, presumably.

5 Q But no one knows that?

6 A Not for -- not that I've seen.

7 MS. HASPER: Same objection.

8 BY MR. POLLACK:

9 Q Let me ask you this: If -- let's say the
10 difference in impurities between the '393 patent and
11 the Moriarty prior art patent was ██████ for the
12 '393 -- same number you're relying on -- and 99.5
13 for the Moriarty patent, how would that change
14 your -- your opinion?

15 MS. HASPER: Objection. Foundation.

16 THE WITNESS: Well, there's a lot more to
17 it than just the -- and you're talking about
18 average --

19 BY MR. POLLACK:

20 Q Average. Yeah.

21 A -- over --

22 Q Yeah. I'll give you average.

23 A 50, 100 batches or something like this?

24 Q Sure.

25 A Again, it's not just a simple matter of

1 that one of the significant advantages of the '393
2 process is the elimination of chromatography, which
3 from a process chemist point of view is exceedingly
4 important because chromatography is expensive, it's
5 time-consuming, it adds cost of goods, there's
6 safety issues, waste issues. And eliminating that
7 is a -- is always a very, very desirable goal.

8 So the '393 process allows for the
9 elimination of chromatography in the preparation of
10 the final drug substance. So that's very important.

11 Q I don't see that opinion expressed in
12 your Declaration, though, sir.

13 A Hmmm?

14 Q That opinion is not expressed in your
15 Declaration, is it?

16 A About the elimination of chromatography?

17 Q Yeah.

18 A I -- I think it's in there, and it's
19 certainly in the patent. The patent talks about the
20 advantages of the elimination of chromatography.

21 Q Okay. But in your opinion, you talk
22 about the difference in the impurities; correct?

23 A Yes. I certainly spend quite a bit of
24 time on the impurity profiles.

25 Q Right. Okay.

1 A The differences.

2 Q If the difference in the quantity of
3 impurities was only [REDACTED] versus 99.5, how would that
4 affect your opinion?

5 MS. HASPER: Objection.

6 THE WITNESS: I'd have to look at actual
7 data and impurity profiles. You're asking me a
8 hypothetical --

9 BY MR. POLLACK:

10 Q Yes.

11 A -- that I'm reticent to just give an
12 opinion on without actually seeing what you're
13 talking about.

14 Q Well, you gave an opinion on the
15 difference between 99.0 and [REDACTED]. I'm trying to
16 understand how your opinion changes when it's [REDACTED]
17 versus 99.5.

18 A Again, I would need to see data and the
19 way in which the two processes operate that rendered
20 the material of those relative impurities.

21 Q So the 99.5 is the Moriarty process. Got
22 it? And the [REDACTED] is the '393 process. How would
23 your opinion change if those were the average
24 results?

25 MS. HASPER: Objection. Asked and

1 answered.

2 THE WITNESS: So I would need to see the
3 distribution of actual impurities, and I would also
4 need to understand the process that resulted in
5 those materials.

6 BY MR. POLLACK:

7 Q What would you need to understand about
8 the process?

9 A Well, like the '393 process I just
10 mentioned eliminates chromatography. So
11 crystallization gets an incredibly pure salt.

12 Q Let me ask you this: The claims of the
13 '393 patent, you're allowed to do chromatography and
14 practice those claims; right?

15 A Yes.

16 Q Okay.

17 A But the patent enables you to eliminate
18 that step.

19 Q Okay. But the claims would include that
20 step; right?

21 A They can --

22 Q Yeah.

23 A -- but again, the process -- very
24 important part of the process is that it enables you
25 to eliminate that step.

1 Q The --

2 A We've been going almost an hour, and my
3 63-year-old bladder is not as robust as it used to
4 be. So could we take a quick break?

5 MR. POLLACK: Absolutely. Absolutely.

6 THE VIDEOGRAPHER: We are off the record.

7 The time is 10:18 A.M.

8 (Off the record)

9 THE VIDEOGRAPHER: We are back on the
10 record. The time is 10:25 A.M.

11 BY MR. POLLACK:

12 Q Welcome back, Dr. Williams. I have --
13 we've already marked as Williams Deposition
14 Exhibit 3 a patent -- U.S. Patent No. 8,497,393, the
15 patent at issue in this proceeding.

16 (Exhibit 3 marked)

17 BY MR. POLLACK:

18 Q And I've marked as Williams Deposition
19 Exhibit 4, U.S. Patent 6,765,117, the Moriarty
20 patent, also known as Exhibit 1003 in the
21 proceeding.

22 (Exhibit 4 marked)

23 BY MR. POLLACK:

24 Q If we could start with Deposition
25 Exhibit 4.

1 This is the Moriarty patent; correct?

2 A Yes.

3 Q Okay. And you've -- you've reviewed that
4 thoroughly for your opinion in this proceeding?

5 A Yes.

6 Q If you could turn to column -- columns 9
7 and 10. Do you see there's a compound toward the
8 bottom -- a compound 14? Do you see that?

9 A Yes.

10 Q Okay. And there's a step where it's
11 being turned into compound 15? Do you see that?

12 A Yes.

13 Q Okay. I wanted to compare that to the
14 claims in Exhibit 3, the '393 patent. And what I
15 want to know is whether or not that change from 14
16 to 15 -- is that what the '393 patent refers to as
17 "step (a)"?

18 A Okay. Which page of the '393 patent?

19 Q The claims are -- they start at column
20 17 --

21 A Oh, I'm sorry.

22 Q -- and then they go through to column 21.

23 A (Examining document) Okay. So your
24 question was, is the conversion of 14 to 15
25 step (a)? Is that your question?

1 Q That's correct. Yes.

2 A Yes.

3 Q Okay. And my next question is: The
4 conversion from 15 to 16 in Exhibit 4, the '117
5 Moriarty patent, is that what is known as "step (b)"
6 in the claims of the '393 patent?

7 A Yes.

8 Q And looking at Exhibit 4, the '117
9 patent, this is showing a scheme for making
10 compounds of the type claimed in the '393 patent but
11 by the Moriarty method. Is that -- is that fair?

12 A Yes.

13 Q Okay. On pages 9 and 10, compound 16, is
14 that the final compound of the process? The
15 Moriarty process.

16 A Structure 16?

17 Q Yes.

18 A So that would be true where R1 is H. M
19 in brackets on both sides is 1. All three Ms are 1.
20 That would be treprostnil.

21 Q Treprostnil. But the '393 patent has a
22 lot of other compounds to the final products; right?

23 A Yes.

24 Q Okay. Would that be a structure of final
25 products -- let me start again.

1 Would structure 16 in the Moriarty
2 patent, Exhibit -- Deposition Exhibit 4 -- would
3 structure 16 be a structure of final compounds made
4 in, for example, claim 1 of the '393 patent?

5 A No, because there's an additional step in
6 the '393 step (c).

7 Q The purification step?

8 A The contact and the product in step (b)
9 with a base to form a salt, which is then optionally
10 reactive with an acid to form the carboxylic acid
11 16.

12 Q Okay. Okay. So if you did step (1) all
13 the way through step (d) -- where step (d) is
14 optional, though, you would get a compound of 16?

15 A You said, step (1) through D? What do
16 you mean?

17 Q Sorry. I may have misspoken, then.

18 If you performed claim 1 through
19 step (d), you would get a compound of structure 16?

20 MS. HASPER: Objection. Mischaracterizes
21 the document.

22 THE WITNESS: So --

23 BY MR. POLLACK:

24 Q I was just trying to understand your last
25 answer, but --

1 A Okay. So --

2 Q -- we can move on.

3 A Structure 16, where I specify what the
4 variables were, R1 and M, where R1 is H, and M is
5 the number 1, that structure would then be
6 treprostinil acid. And included in the Markush or
7 the more generic formula shown in claim 1, you would
8 get treprostinil after step (d).

9 Q Okay. So structure 16 would be included
10 in the products would you get in claim 1 after
11 step (d)?

12 MS. HASPER: Objection. Mischaracterizes
13 the document.

14 THE WITNESS: So included in the formula
15 1S -- I think that's what you're referring to;
16 right? In --

17 BY MR. POLLACK:

18 Q Yes. 1 --

19 A So in formula 1 -- 1S where the
20 stereochemistry of the secondary hydroxyl group,
21 there's a wavy line that has to be defined as
22 down -- would be a dashed line. And then these
23 other variables, Y1, W, M1, L1, R7 -- and I believe
24 that -- I'm certain, actually, that the definitions
25 they call out when you plug them in correctly reads

1 on the structure of treprostinil.

2 Q Okay. Okay. I didn't want to confuse
3 you. And I may have confused you. I was actually
4 referring to structure 1, which is -- just turn to
5 the very beginning of the claim, claim 1; right?

6 The structure -- structure Ss with the base; right?

7 A Wait. So you've lost me now.

8 Q Right.

9 A We're at column 17.

10 Q Yes.

11 A On the '393.

12 Q Yeah.

13 A And you're asking me to look at structure
14 1; right?

15 Q You can look at anything you want to.
16 You referred to, just now, to structure 1S, and that
17 shows the salt -- the base salt; right?

18 A Yes.

19 Q Okay.

20 A That's the salt.

21 Q Okay.

22 A And after D, you get to formula 1, the
23 treprostinil acid.

24 Q Right.

25 A Acid.

1 Q And 16 would be included in formula 1?

2 MS. HASPER: Objection. Mischaracterizes
3 the document.

4 BY MR. POLLACK:

5 Q The '117 patent?

6 A Well, the molecular structure of 16 reads
7 onto formula 1 where the variables are defined
8 appropriately --

9 Q Okay.

10 A -- which the claim calls out.

11 Q Okay. Looking at the -- looking at

12 columns 9 and 10, which show how to make

13 treprostinil in similar structures, do you see a

14 chromatography step?

15 A Well, I can see a chromatography step in
16 every step.

17 Q One could do it optionally?

18 A Yeah. And the way organic chemistry
19 works is that when you're going through a synthesis
20 of this complexity the first time, every
21 intermediate product is typically isolated by
22 chromatography to get an analytical sample and
23 characterize it to get it as pure as possible for
24 analytical purposes. And then as you go from small
25 scale to large scale, one hopes to eliminate

1 chromatography steps, and you take Cree material on
2 it or crystallize intermediates if they're
3 crystalline.

4 Q Okay. But here on pages 9 and -- column
5 9 and 10, the '117 patent, it doesn't say anything
6 about chromatography?

7 A Well, a person skilled in the art looking
8 at this would understand that this is just a
9 reaction scheme structure with no details. One
10 would need to look at the actual experimental --
11 detailed experimental procedures for each step and
12 see if any of these steps require chromatography.

13 Q Okay. But as Moriarty lays out the
14 reaction here, chromatography may be optional, but
15 he doesn't -- here on pages 9 and 10 -- columns 9
16 and 10 require chromatography; is that fair?

17 A Well, that's --

18 MS. HASPER: Objection. Asked and
19 answered. Mischaracterizes the document.

20 THE WITNESS: There's not enough
21 information here. Again, I just said this is a
22 reaction scheme. One would need to look at the
23 actual published procedures, the experimental -- the
24 recipe, the detailed how to do each step.

25 ///

1 BY MR. POLLACK:

2 Q Let me ask you this: The claims for the
3 '117 patent -- the claims, which is in the back at
4 columns 21 to 24 --

5 A Okay.

6 Q -- do the claims of the Moriarty patent
7 require a chromatography step?

8 A No, I did not see the word
9 "chromatography" in the claims. But I know that the
10 reality of doing synthesis like this, it does entail
11 chromatographic separation.

12 Q Okay. Could we go back to your
13 Declaration? That's Exhibit 2. I'd like to turn to
14 paragraph 98 of your Declaration. It's on page 33.

15 In the last two sentences, those appear
16 to be the conclusion sentence of your paragraph.
17 And it says there, "The treprostiniil product of the
18 '393 patent has an average purity of ██████ percent,
19 while the Moriarty product has an average purity of
20 99.05 percent. Thus, the treprostiniil product of
21 the '393 patent has an average purity that
22 is .7 percent higher than that of Moriarty's."

23 Do you see -- did I read that correctly?

24 A Yes.

25 Q Why is that difference important to you?

1 A Well, that's -- that's one important
2 difference. This is the overall average purity.
3 And then inside those numbers are the actual
4 characteristic impurity profiles that come along as
5 a signature of the synthesis. And the '393 patent
6 process allows for elimination or significant
7 reduction of a significant number of those
8 impurities. And that's important.

9 Q Well, what if the reduction in each of
10 those impurities was only .02 percent? Why is that
11 important?

12 MS. HASPER: Objection. Foundation.

13 THE WITNESS: So you're -- I'm trying to
14 understand. This is a hypothetical question?

15 BY MR. POLLACK:

16 Q Hypothetical question.

17 A Okay. And so you're asking me if the
18 difference between -- just re --

19 Q Just pick one impurity. Let's pick
20 1AU90. That's one of the impurities?

21 A Yes.

22 Q What is 1AU90?

23 A That's one of the stereoisomers.

24 Q Which one?

25 A There's 32 stereoisomers. I don't have

1 the structure memorized, but I recall that it's a

2 [REDACTED] stereoisomer. I

3 think --

4 Q Okay.

5 A -- but I'd have to check.

6 Q All right. Anything particularly
7 significant about that stereoisomer?

8 A Well, it's a carboxylic acid like
9 treprostinil. And so in terms of separating it from
10 the desired molecule, treprostinil, that's a
11 challenging impurity to remove, because it has very
12 similar PKA. They're both carboxylic acids. They
13 have the same molecular skeleton. They're just
14 different in stereochemistry.

15 Q But biologically, is there any difference
16 between 1AU90 and treprostinil?

17 MS. HASPER: Objection. Beyond the
18 scope.

19 THE WITNESS: I don't know, but certainly
20 treprostinil is the biologically active principal.
21 And I'm not aware of any biological data on 1AU90.
22 But there may be some, but I'm not a biologist.

23 BY MR. POLLACK:

24 Q That's not something you looked into?

25 A No.

1 Q You didn't speak to anyone else working
2 on this case who looked into that?

3 A No.

4 Q Did you speak to any -- other than the
5 attorneys, did you speak to anyone else in working
6 on this case?

7 A No.

8 Q And are you familiar with a Dr. Ruffolo
9 who submitted a Declaration in this case?

10 A I don't know him.

11 Q Okay. You never spoke to him?

12 A No.

13 Q Did you read his Declaration?

14 A Briefly and very recently.

15 Q Was that only in preparation for your
16 deposition?

17 A No. So that was part of the big -- sort
18 of master file that I saw, and I -- I briefly
19 scanned through his -- his Declaration.

20 Q Let me ask you: Did you read his
21 Declaration before you signed and completed your
22 Declaration on July 6th?

23 A No.

24 Q Okay. So it was only after --

25 A Only after.

1 THE REPORTER: Try to pause a little bit,
2 please.

3 THE WITNESS: I'm sorry.

4 BY MR. POLLACK:

5 Q We both have that habit.

6 THE REPORTER: Yes, do you.

7 THE WITNESS: I will try and speak much
8 slower. Is that what you want?

9 THE REPORTER: Like that will happen.

10 BY MR. POLLACK:

11 Q Are you originally from New York?

12 A How did you guess?

13 Q I'm a New Yorker, also. So we're both
14 fast-talkers.

15 A Huntington.

16 Q I'm Brooklyn, lucky you.

17 A But I hate the Yankees. Red Sox fan.

18 Q Oh, Mayor Bloomberg was; right?

19 Let me ask you -- you make this point
20 about the ██████ versus the 99.05. I'm really trying
21 to understand, how far can the 99.05 number increase
22 before that point is no longer that significant to
23 your opinion?

24 A You know, I didn't -- I didn't do that
25 analysis or consider -- consider that.

1 Q Understand. I'm asking you to just
2 consider that now.

3 A I'd need to look at data -- impurity
4 profiles and data.

5 Q Let's say the impurity profiles were all
6 the same as we're seeing now, just the number has
7 changed. So if the number is changed, and they
8 change in such a way that we go from 99.05 to 99.5,
9 how would that change your opinion?

10 MS. HASPER: Objection. Incomplete
11 hypothetical. Beyond the scope.

12 THE WITNESS: Okay. So you're asking me,
13 again, sort of a make-believe Moriarty series of
14 batches that I've never seen. I haven't seen any
15 such material. And Dr. Winkler didn't produce any
16 Moriarty material batches, or he didn't do his own
17 experiments to show that he would get that. But,
18 again, I -- you know, I -- I'd -- I'd have to look
19 at the data.

20 BY MR. POLLACK:

21 Q Let me ask you: What if -- what if the
22 Moriarty batches -- the average value for the
23 Moriarty batches was [REDACTED] -- the very same as your
24 number there --

25 MS. HASPER: Same objection.

1 BY MR. POLLACK:

2 Q -- how would that change your opinion?

3 MS. HASPER: Same objection.

4 BY MR. POLLACK:

5 Q So no difference in the purity level.

6 MS. HASPER: Same objection.

7 THE WITNESS: Okay. So, again, I think
8 your question's about overall impurity -- overall
9 purity, █████ percent, which is total related
10 substances, which is known, plus unknown
11 impurities -- so it's just not a simple matter of
12 overall purity. You also have to look at the
13 impurity profiles, because that is the significant
14 difference in the product between the '393 and the
15 Moriarty process.

16 BY MR. POLLACK:

17 Q So you're saying even if the overall
18 purity is the same, the distribution of those
19 impurities -- which we don't know anything about in
20 regard to their biological property -- but that
21 really matters? That's your opinion?

22 A That's my understanding, that in
23 product-by-process patents, the -- the new product
24 by the new process has to have structural,
25 functional differences. And impurity profiles are

1 structural differences.

2 Q Are there any functional differences,
3 though, between a material -- a new material which
4 has a impurity level -- or purity level of [REDACTED] and
5 another material which has a purity level of, say,
6 [REDACTED]?

7 MS. HASPER: Objection. Beyond the
8 scope. Incomplete hypothetical.

9 THE WITNESS: I don't know. And, again,
10 the -- you know, the -- really, the significant
11 thing about the '393 process is the elimination of
12 the chromatography. The way I view it, that's a
13 functional difference. It reduces cost of goods,
14 and solvent safety. So it's -- it's not a
15 insignificant matter.

16 BY MR. POLLACK:

17 Q Let me ask you something: In the -- if
18 you go to the '393 patent -- pick up Exhibit 3,
19 again -- there's a claim 16. Do you see that claim?

20 A Yes.

21 Q It's in column 20.

22 A Yes.

23 Q Now, do you have any patents?

24 A Yes.

25 Q Okay. You understand how patent claims

1 work; correct?

2 A Generally.

3 Q Okay.

4 A I'm not a patent expert, but --

5 Q You know -- do you know what an
6 independent and a dependent claim is?

7 A Yes.

8 Q Okay. What's your understanding of what
9 a dependent claim is?

10 MS. HASPER: Objection to this, that it
11 seeks a legal conclusion.

12 THE WITNESS: Well, generally, a
13 dependent claim is -- follows an independent claim
14 and typically narrows down the scope of the
15 independent claim to a more -- some type of
16 parameter.

17 BY MR. POLLACK:

18 Q It adds something the independent claim
19 doesn't require; is that fair?

20 A Again, I'm not a lawyer. I don't know if
21 that's ubiquitously true, but that sounds
22 reasonable.

23 Q Is claim 16 -- is that a dependent claim?

24 A Yes. It's dependent from claim 9.

25 Q Okay. What is claim 16 adding?

1 MS. HASPER: Same objection.

2 THE WITNESS: So claim 16 says, "The
3 product is claim" --

4 THE REPORTER: Speak up, please.

5 BY MR. POLLACK:

6 Q If you could read more slowly. He's got
7 to type it all.

8 A "The product of claim 9 wherein the
9 process does not include purifying the compound of
10 formula VI produced in step (a), which is the
11 nitrile."

12 Q What does that mean?

13 A So this is -- this claim is saying that
14 you do -- you perform step (a) and then carry the
15 nitrile through to the next step without doing a
16 purification step, like a chromatography.

17 Q Okay. In your understanding, though,
18 does that mean that claim 9 could be carried through
19 with the chromatography?

20 A It could, but importantly, this patent
21 and the process that's being used eliminates that.

22 Q Right. But claim 9 doesn't; right?
23 Claim 9, you can do the chromatography.

24 A You could if you wanted to. It seems
25 like a nonsensical thing to do when we know it works

1 really great without.

2 Q But claim 9 does include with the
3 chromatography?

4 A It's agnostic as to chromatography;
5 right? Doesn't say, one way or the other.

6 Q Sure. But claim 16 is very specific.
7 That's done without the chromatography; right?

8 A Yes.

9 Q So that means claim 9 includes both with
10 or without the chromatography; is that fair?

11 A Again, I'm not -- I'm not a patent
12 lawyer, so I'm not sure that that is necessarily the
13 way that's read.

14 Q What's your understanding?

15 A Yeah. It's -- I mean, it's silent on
16 that issue. So --

17 Q And based on that, what do you conclude
18 about whether chromatography is included in claim 9?

19 MS. HASPER: Objection to the extent it
20 seeks legal conclusion.

21 THE WITNESS: So, you know, I think a
22 person skilled in the art looking at this, again,
23 would be informed by the specification and column
24 15, a real-world 5-kilogram example, says no column
25 for that step. Whereas in the prior art process,

1 there's a purification column chromatography step.

2 So --

3 BY MR. POLLACK:

4 Q Let's take a look at claim 1.

5 Now, you'll agree with me that claim 1
6 also would include the chromatography; is that fair?

7 A I don't know if I would read in the
8 requirement for chromatography. It doesn't say
9 anything about it. It's also silent on that issue.

10 Q But it couldn't -- since it's silent and
11 there's a claim that says, "Don't use
12 chromatography," we could probably conclude that it
13 does include chromatography, just on basic logic?

14 A Yeah. I suppose it could, but we --
15 again, the patent talks in several places about the
16 advantage of elimination of the chromatography step.

17 Q Let me ask you: About how many compounds
18 do you think there are in claim 1?

19 A Oh, lots. I don't know the -- I don't
20 know the exact number.

21 Q Hundreds of thousands? At least?

22 A Very likely. But I'm not sure.

23 Q Okay. So for all of those hundreds of
24 thousands of compounds, is there any information in
25 the '393 patent about whether those hundreds of

1 thousands of compounds will be pure without
2 chromatography?

3 A Well, the specification only deals with
4 treprostinil itself so that's the -- I guess the
5 important enabling example that's in the
6 specification of the patent. But the patent teaches
7 that if you applied this salt formation,
8 crystallization, that -- in this structural family,
9 one would have a reasonable expectation that you'd
10 also be able to crystallize and purify just as was
11 done for treprostinil.

12 Q Okay. You don't see any data in this
13 patent, though, about the purity of any of these
14 other thousands of compounds, do you?

15 A No. There's no data for the other
16 compounds, but there is really great data for
17 treprostinil.

18 Q Now, do you understand that claim 9 also
19 includes treprostinil diethanolamine salt as a
20 product?

21 A Yes.

22 Q Okay. And, in fact, if I don't carry out
23 step (d), the optional step, and I use
24 diethanolamine as my salt, I'm going to get
25 treprostinil diethanolamine salts; correct?

1 A Yes.

2 Q If I don't carry out step (d), does the
3 claim include chromatography?

4 A So your question is, if I do not carry
5 out --

6 Q Let me rephrase my question.

7 If I don't carry out step (d), would it
8 be necessary to use chromatography?

9 A If I -- so your question is, if you do
10 not carry out step (d) --

11 Q Right.

12 A -- would it be necessary to use
13 chromatography?

14 Q Correct.

15 A So I would say that you're forming a
16 salt. And it's -- salts are perhaps the most
17 obnoxious compounds to purify by chromatography.
18 And it's very, very rare to, in fact, purify salts
19 by chromatography. So the whole reason a person
20 skilled in the art would form a salt in the first
21 place is by trying to avoid chromatography, 'cause
22 you can crystallize salt. Salts -- and particularly
23 salts like this that are water soluble, that's the
24 whole purpose of forming the salt.

25 Q Okay. However, if I carry out steps (a)

1 through (c), the claim 9 allows me to do
2 chromatography if I so wish; correct?

3 A Chromatography at which step? A? I
4 don't know where you're talking about.

5 Q At any of the steps.

6 A Well, could you, but the whole purpose of
7 this invention is to eliminate the chromatography
8 step.

9 Q Okay. By the way, you don't see in the
10 claims where it says the invention is carried out
11 without the chromatography step, other than the one
12 claim, claim 16?

13 A No. But the spec also prominently talks
14 about the elimination of chromatography.

15 Q Okay.

16 A And a process chemist really would zero
17 in on that important advantage.

18 Q What can you tell me about the impurity
19 profile of the thousands of compounds in claim 1?

20 MS. HASPER: Objection. Beyond the
21 scope.

22 THE WITNESS: I could tell you about the
23 impurity profile of one of the thousands of
24 compounds in claim 1, treprostinil, because I have
25 data on that.

1 BY MR. POLLACK:

2 Q Does any person of ordinary skill in the
3 art or any person of any skill in the art know
4 anything about the purity [sic] profile of the
5 thousands of compounds in claim 1, other than
6 treprostininl?

7 MS. HASPER: Objection. Beyond the
8 scope.

9 THE WITNESS: Well, because all the
10 structures that are called out under claim 1 have
11 the same molecular framework as treprostininl, one
12 would expect that the impurity profiles would very
13 likely be similar in that you'd have to
14 stereoisomeric impurities, and dimers, and esters,
15 and the triol and so on.

16 It's very similar types of species would
17 very likely be present, if you change the variables,
18 like added a carbon atom to the side chain, or what
19 have you.

20 BY MR. POLLACK:

21 Q But some of the species would be
22 different; correct?

23 A What do you mean by "different"?

24 Q Some of the impurities would be ones not
25 seen in treprostininl; correct?

1 MS. HASPER: Objection. Foundation.

2 THE WITNESS: Well, they would
3 necessarily be different because you've already
4 changed the structure. So -- so if you change even
5 by one carbon atom, now longer -- you can't get the
6 same exact impurities from treprostinil because
7 you've already changed the molecular structure to a
8 different molecule.

9 BY MR. POLLACK:

10 Q So all of those molecules would have
11 different impurity profiles from treprostinil; is
12 that fair?

13 MS. HASPER: Objection.

14 THE WITNESS: So -- I think -- I'm trying
15 to give a good answer here, that you would have
16 similar -- I guess you call them "homologous series
17 of impurities," stereoisomeric impurities, that
18 would almost certainly be similar. So they'd be the
19 -- like 1AU90 could be 1AU90 prime for another
20 compound, but it would be a similar stereoisomeric
21 impurity, because they're made by the same kind of
22 chemical steps.

23 BY MR. POLLACK:

24 Q You referred to 1AU90. Is that a name
25 used in the literature?

1 A No. I think that's a UTC code number
2 for -- for that.

3 Q It's a secret code number; right?

4 A I don't know if it's secret or not. I
5 know that in Moriarty's GOC paper, he used UT-15 or
6 something, which is the United Therapeutics code
7 number. So that one wasn't secret. So I don't know
8 if they're secret or not.

9 Q Right. UT-15 is the published name for
10 treprostinil; correct?

11 A Yes.

12 Q Okay. But 1AU90, you've never seen that
13 in the literature; correct?

14 A Not that I can recall.

15 Q Okay. None of the -- have you seen in
16 the literature where any of these impurities are
17 characterized?

18 A I don't recall.

19 Q What about in the '393 patent? Do you
20 see any mention in Exhibit 3 of what impurities are
21 present in any of the compounds in the '393 patent?

22 A No. I don't believe they're specifically
23 called out.

24 MR. POLLACK: To make things a little
25 easier for us, I'm going to mark as separate

1 exhibits your appendices to your Declaration. I'm
2 going to mark Appendix A as Williams Deposition
3 Exhibit 5.

4 (Exhibit 5 marked)

5 MR. POLLACK: And I'll mark Appendix B as
6 Williams Deposition Exhibit 6.

7 (Exhibit 6 marked)

8 BY MR. POLLACK:

9 Q If you could just verify for me that
10 Deposition Exhibits 5 and 6 are true and accurate
11 copies of your appendices A and B, respectively?

12 A (Examining documents).

13 (Brief pause)

14 Okay. Appendix A is identical. And
15 Appendix B is identical to the one submitted but
16 does not have the one correction that we made at the
17 beginning of the deposition.

18 Q Could you do me a favor? Could you take
19 Exhibit 6 and make the correction on there by pen?

20 A Okay. I don't have a pen. Can I borrow
21 yours?

22 And I think it was -- oh. I think it's
23 this one. 11 -- wait. I think it's this one.

24 Okay. So I've just crossed out that [REDACTED].

25 Q Okay. I'd like to turn to Exhibit 5.

1 That's Appendix A.

2 A Okay.

3 Q Okay. And I want to look at your Data
4 Source column. Do you see you have a column that
5 says, "Data Source"?

6 A Yes.

7 Q Okay. This is a column that counsel
8 created for you -- right? -- and then you checked
9 this?

10 A Yes.

11 Q Okay. So the first -- well, let's
12 count 'em -- one, two, three, four, five, six,
13 seven, eight, nine, ten -- the first ten entries are
14 all solely from an exhibit called "Exhibit 2052."
15 Do you see that?

16 A Yes.

17 Q Okay. And then after that, all of the
18 entries are included in an exhibit called "2036"
19 that you attached to your Declaration. Do you
20 recall that?

21 A Well, no. I think it's 2053, page 19.
22 And then Exhibit 2036. So there's two --

23 Q But those were identical; right?

24 A Okay.

25 Q The 2053 and 2036, did you check that,

1 that they were identical?

2 A I don't recall right now.

3 Q Okay. Let me say, I also misspoke as
4 well.

5 If you look on page 44, there are two
6 samples, UT-15-011001 and UT-15-020101, about four
7 and five rows up from the bottom? Do you see where
8 I'm reading?

9 A Hmm-hmm.

10 Q Okay. Those two were listed as -- wait.
11 Did I -- I think I did -- as just being from 2053;
12 is that correct?

13 A That's what it says, yeah.

14 Q Okay. But all of the other ones are in
15 both 2053 and 2036; is that fair?

16 A Yes.

17 MR. POLLACK: Okay. If we can mark as
18 Deposition Exhibit 7 what was formerly called
19 "Exhibit 2036."

20 (Exhibit 7 marked)

21 BY MR. POLLACK:

22 Q Did you review in detail all of the
23 Certificates of Analysis in Exhibit 2036?

24 A I laid my eyes on every page, and I
25 cross-checked some of them in detail. I didn't look

1 at every number on every batch record.

2 Q Okay. You didn't compare each one to
3 make sure it was correct on your table?

4 A I said I spot-checked them, and they all
5 seemed fine.

6 Q Okay. By spot-checking, though, you
7 didn't do every single one, you --

8 A I didn't do every single one. I just
9 randomly picked and found no errors.

10 Q Okay. Did you calculate what the average
11 purity was of the samples in Exhibit 2036?

12 A Well, counsel did the calculation. And
13 that's the summary at the bottom.

14 Q That's all of the samples; right? That's
15 2036 and 2052 and 2053; correct?

16 A Yes.

17 Q Okay. Did you calculate just what it
18 would sum up to in 2036?

19 A So, in other words, eliminating the 2052,
20 the development batches is what you're asking?

21 Q Yes.

22 A No.

23 Q Why -- do you have an understanding why
24 2052 was added -- why the samples from 2052 were
25 added to the samples from 2036?

1 A Yes, because we also added development
2 batches for the '393 process. And we -- and I
3 thought that the fairest comparison was to look at
4 the development batches that were used in UTC's
5 development of the Moriarty process and the
6 development batches from the '393 as well. I
7 thought that was the fairest comparison.

8 Q That was your idea or counsel's idea?

9 A We discussed it. I -- I don't remember
10 if who -- who came up with the first idea, but we
11 agreed this was a reasonable thing to do.

12 Q Okay. Guess what? Ms. Choksi did the
13 calculation for us, so I'm going to provide that to
14 you.

15 So I'm going to mark as Williams
16 Deposition Exhibit 8 a chart of all of the purities
17 and total related impurities from the Appendix A,
18 Deposition Exhibit 5.

19 (Exhibit 8 marked)

20 BY MR. POLLACK:

21 Q And I'm also going to mark -- just so you
22 can see how we created this -- I'm going to mark as
23 Deposition Exhibit 9 a chart containing all samples,
24 including the ones from 2052.

25 (Exhibit 9 marked)

1 BY MR. POLLACK:

2 Q What we've done here is, we've just
3 marked in highlighting which ones are from 2052.
4 And so what we've done here is, we've used all of
5 the samples that you did, and we also used the HPLC
6 analysis. Do you know what I mean by that?

7 A Why don't you explain.

8 Q Yeah. If you look at, for example, 2036,
9 Deposition Exhibit 7 -- let's go to the third page
10 of the document, the one that says, "Page 3 of 3."
11 And on the bottom, it says -- well, it says,
12 "Page 3" at the bottom center. Do you see where I'm
13 looking?

14 A Hmm-hmm.

15 Q Okay. Now, do you see there's a -- it
16 says, "Test," and there's a number, "Assay HPLC."
17 Do you see that?

18 A Yes.

19 Q And do you see it says, "98.4"?

20 A Yes.

21 Q Okay. So what we've done on this chart
22 is, we've put in all of those values as well. Do
23 you see where it says, "Assay Purity"?

24 A Okay. Which --

25 Q You can pick either 8 or 9. The only

1 difference is, we highlighted the ones from 2052 on
2 9.

3 A Okay.

4 Q Okay. So do you understand what I mean
5 by the HPLC assay?

6 A So this one corresponds to --

7 Q Let's see. This one here that we're
8 looking at is lot UT15-99H001. Do you see that on
9 Exhibit 2036?

10 A Yes. So that's entry 11; right?

11 Q That's correct.

12 A Okay.

13 Q Okay. Is that number recorded fairly?

14 A It appears to be.

15 Q Okay. And what we've done at the end is,
16 we've taken -- we'll let you go through,
17 electronically, these spreadsheets -- we've taken
18 all the data you used, and we did an average, as did
19 you, and we got 99.0 by both methods, whether you
20 use the HPLC assay, or what I'm calling "implied
21 purity" where you subtract the total related
22 substances.

23 A Wait. What --

24 Q On the very last page of either document.

25 A Oh.

1 Q Do you see that?

2 A Yes.

3 Q Okay. That's the same number you got;
4 correct? Appendix A.

5 A Yes. Basically the same.

6 Q Okay. Now what I'm going to mark as
7 Deposition Exhibit 10 is the same document, except
8 with the first ten samples, the ones that came from
9 Exhibit 2052 removed.

10 (Exhibit 10 marked)

11 BY MR. POLLACK:

12 Q If you would verify for me that
13 Exhibit 10 is the same as 8 or 9 except with the
14 highlighted exhibit -- lots removed.

15 A Okay. That appears to be the case.

16 Q Okay. And then what we did is, we -- we
17 did the same thing you did. We took the average,
18 but we did it two ways. We did it with the HPLC
19 assay --

20 A Hmm-hmm.

21 Q -- so taking each of those numbers from
22 2036. You understand what I'm referring to?

23 A Yes.

24 Q And we also did it the way you did it,
25 subtracting the total related substances from 100.

1 A Yes.

2 Q Okay. If you look on page 5, there's the
3 result of our average. Do you see that?

4 A Yes.

5 Q And do you see that the HPLC assay -- the
6 average was [REDACTED]?

7 A I see that.

8 Q Okay. Instead of 99.0. Do you see that?

9 A Hmm-hmm.

10 Q And doing it your way, the way you
11 prefer, the result was 99.5. Do you see that?

12 A What do you mean --

13 Q Subtracting the total related substances
14 from 100, the average was 99.5.

15 A Okay.

16 Q Do you see that?

17 A I'm not sure what this implied impurity
18 is. I don't -- I don't -- what's implied impurity?

19 Q So that's the language I'm using. If you
20 want to call it "purity," that's fine. It is the
21 100 minus the total related substances.

22 A Okay.

23 Q How did you calculate the purity of each
24 sample?

25 A Okay. So the total related substances is

1 the -- the sum of the known impurities plus the
2 unknown impurities.

3 Q Is it?

4 A That's my understanding.

5 Q Well, let's take -- let's take, for
6 example -- let's go to the top of page 44; all
7 right? So there's all of the impurities, and that
8 sum is .4. Do you see that in the right?

9 A Yes.

10 Q Okay. Now, do you get .4 when you add
11 all those numbers up?

12 A I have to do the calculation. Can I use
13 my phone --

14 Q Absolutely.

15 A -- here? (Using phone).

16 MS. HASPER: Counsel, while Dr. Williams
17 does the math, may I ask a question to clarify
18 something, perhaps to avoid an extraneous objection?

19 You introduced Exhibit 10 and said that
20 the highlighted rows had been removed. I noticed
21 highlighting on two rows. Is that merely a printing
22 error, or is that --

23 MR. POLLACK: Those are just simply --
24 I'll point that out to him. Those are simply the
25 highlighted two rows from Exhibit 2053. Different

1 exhibit.

2 MS. HASPER: They're not also in 2036?

3 MR. POLLACK: -36. Correct.

4 MS. HASPER: All right. Thank you.

5 THE WITNESS: So that line -- we're
6 talking about the top line on the top of page 44?

7 BY MR. POLLACK:

8 Q Correct.

9 A Let me check this again. First time I
10 got .55.

11 Q That's what I get. But please feel free
12 to do it again.

13 A Okay. So it's -- I get .55, the addition
14 of those.

15 Q Yes.

16 A Known -- and those are all known
17 impurities, I believe.

18 Q Right. And then the total related
19 substances is .4?

20 A So I believe the reason that the -- that
21 the numbers don't add up is that the -- the -- where
22 the amount of impurity was less than .05, a number
23 of .05 was put. So it's -- it's estimated
24 conservatively high. But the actual total, which
25 comes from, I believe, these batch documents, is

1 what's in this column.4.

2 Q Right. But, in fact, what's in that
3 column is not the sum of the known impurities listed
4 in your prior columns; correct?

5 A Again, I just explained what -- is there
6 any confusion to what I just said?

7 Q Yes.

8 A Hmm?

9 Q Yes, there is. The -- you said earlier
10 that the sum of total related substances was the sum
11 of each of the known impurities; correct?

12 A And unknown impurities.

13 Q And unknown impurities.

14 A Yes.

15 Q Okay.

16 (Mr. Snader entered the deposition at
17 11:24 A.M.)

18 BY MR. POLLACK:

19 Q And here we see that summing those up,
20 they don't equal the same number; correct?

21 A So maybe the place to go is the source
22 document here. This is 20 -- so the source document
23 at page 36 shows total related substances as
24 .4 percent.

25 Q I see that.

1 A So that's -- that's -- where these
2 numbers came from. They weren't from the linear
3 addition here (Indicating).

4 Q Right.

5 A Yeah.

6 Q Okay. We're both agreed on that; right?

7 A Yeah.

8 Q Okay. And, actually, your way of putting
9 in what the total related substances are for
10 compounds that are not detected or ones which are
11 less than .05, that's sort of arbitrary, isn't it?

12 A No. Arbitrary?

13 Q Well, you could have done instead of .05,
14 you could have made it zero for example; right?

15 A Yeah. So I was conservative and
16 estimated on the high side. So less than .05 could
17 be .000001; okay?

18 Q And, actually, putting it on the high
19 side, that makes the purity lower, doesn't it? It
20 makes it seem like it's less pure than it actually
21 is, doesn't it?

22 A Yes. And I did the same thing for the
23 '393 process batches. So they -- so the same -- to
24 be fair, that same conservative method was used to
25 compare both.

1 Q Okay. Here's what I want to know: So
2 when -- the batches 2036 all done by Magellan, even
3 the ones from 2053, are included to make an average,
4 the average value is either [REDACTED] percent pure for
5 HPLC analysis or a total of .5 percent impurities by
6 total related substances. What I want to know is,
7 who, then, decided to go out and find ten other
8 pieces of data to try to drag that number lower to
9 99?

10 A I sort of don't like the way you just
11 characterized that, 'cause it sounds like this was
12 done deliberately to make the Moriarty process look
13 worse than it is. That's not really fair.

14 Q Really?

15 A So what we did was, we looked at
16 development batches from the '393, and we also
17 looked at development batches from Moriarty. And,
18 you know, either way -- I mean, if you put them in
19 or drop them out, the impurity profiles between the
20 two processes are different; okay? So you can't
21 just look at the overall total related substances
22 purity; you have to look at the actual distribution
23 of the impurities. Because the '393 process
24 unexpectedly -- okay? -- because of the
25 crystallization of the salt, removes stereoisomeric

1 impurities -- two of them completely -- and leaving
2 only the very small amount of the enantiomer, which
3 is [REDACTED].

4 Q Okay.

5 A So just doing these -- these overall
6 impurity comparisons and percentages, I don't think
7 is -- is valid.

8 Q But you actually submitted this to the
9 Patent and Trademark Office and told them that that
10 was one of the significant differences between
11 Moriarty and the '393 process, that the purity was
12 99.0 versus [REDACTED], isn't that true?

13 A I didn't submit anything to the Patent
14 and Trademark Office.

15 Q You understand this is your Declaration
16 that you signed.

17 A Yes.

18 Q That was submitted to the Patent and
19 Trademark Office. You understand that?

20 A I thought you were talking about the --
21 the batch records.

22 Q Well, those are submitted as well.

23 A Yeah.

24 Q You understand that --

25 ///

1 (Indiscernible crosstalk)

2 THE WITNESS: I'm sorry. I don't
3 understand where you're --

4 BY MR. POLLACK:

5 Q You understand your Declaration?

6 A Yeah.

7 Q That it was used as evidence at the
8 Patent and Trademark Office in this proceeding. You
9 understand that; right?

10 A Yes.

11 Q Okay. And in that Declaration, you
12 represented to the Patent and Trademark Office that
13 the difference between Moriarty -- one of the
14 differences between Moriarty and the '393 patent was
15 that Moriarty produced an average of only 99.0,
16 while the '393 patent produced an average of [REDACTED].
17 You recall saying that; right?

18 A Yes.

19 Q Okay. And now what we're seeing is, if
20 we take only the data, the two data sets, created by
21 Magellan, one for the '393 and one for the Moriarty
22 process, in fact, the numbers are [REDACTED] and [REDACTED].

23 A But, again, you're talking about the
24 overall purity. You're not talking about impurity
25 profile.

1 Q Sure. I understand. I'm not disagreeing
2 with you on that. I'm just saying, you told the
3 Patent Office that these two differed. And one of
4 the ways they differed was one was 99.0 and the
5 other was [REDACTED]. Now we see that both are [REDACTED]. How
6 does that jive with acceptable scientific conduct?

7 A Well, the -- again, the '393 batches were
8 produced without chromatography. So you could
9 repurify and purify anything you want --

10 Q Of course.

11 A -- by chromatography to [REDACTED] percent
12 if you wanted to --

13 Q Right.

14 A -- okay? -- but, you know, in large-scale
15 manufacturing, that's not practical. It's not
16 economical. It's not safe. It's not
17 environmentally appropriate; okay? So -- but,
18 again, I think the -- what I was focused on was
19 looking at -- the -- the -- the structural
20 differences between the impurities between the two
21 processes is different. And that is not reflected
22 in the overall purity, no matter however you want to
23 eliminate batches, and cherry-pick batches or
24 however you want to do that.

25 Q You'd agree with me somebody here

1 cherry-picked some batches, didn't they?

2 A No, I don't think so.

3 Q You don't think somebody added 10 batches
4 to take the number down from ██████ to 99.0?

5 A No. We -- my understanding is, we asked
6 for -- these were all the batches we could find
7 records for. And these were the same -- I think
8 these are the same 56 batches that were used by
9 Dr. Aristoff in the -- the Sandoz litigation.

10 THE VIDEOGRAPHER: Sorry to interrupt, we
11 have five minutes of video left.

12 MR. POLLACK: Why don't we take a short
13 break.

14 THE WITNESS: Sure.

15 MR. POLLACK: Whatever you want.

16 THE WITNESS: Yeah. 15 minutes? I need
17 a bathroom break, anyway.

18 THE VIDEOGRAPHER: This ends Media No. 1
19 in the deposition of Robert M. Williams, Ph.D. The
20 time is 11:32 A.M.

21 (Off the record)

22 THE VIDEOGRAPHER: This begins Media
23 No. 2 in the deposition of Robert M. Williams, Ph.D.
24 We are back on the record. The time is 11:53 A.M.

25 MR. SNADER: And this is Shaun Snader,

1 United Therapeutics Corporation, Washington, D.C.,
2 counsel for patent owner.

3 BY MR. POLLACK:

4 Q Welcome back, Dr. Williams.

5 A Hmm-hmm.

6 Q During the break, did you speak to
7 counsel about this case, the deposition, or any --
8 any matter having to do with treprostinil?

9 A No. We talked about golf, hotels, and
10 restaurants.

11 Q Okay. If you can go back to your
12 Exhibit 2 -- that's your Declaration.

13 A Okay.

14 Q If you turn to paragraph 98, you see
15 there, it says, "The treprostinil product of the
16 '393 patent has an average purity of ██████ percent,
17 while the Moriarty product has an average purity of
18 99.05." Do you see that statement?

19 A I see that statement.

20 Q And then you say, "Thus, the treprostinil
21 product of the '393 patent has an average purity
22 that is .7 percent higher than that of Moriarty's."
23 Do you see that statement?

24 A Yes, I do.

25 Q And you understand that those statements

1 were given to the Patent and Trademark Office --
2 right? -- in this proceeding?

3 A Yes.

4 Q Are those statements not important to
5 your opinion?

6 A They're important. But if we also read
7 above, I say, "It is clear the treprostinil product
8 produced by the '393 patent process has a markedly
9 different impurity profile than the treprostinil
10 product of the Moriarty prior-art process and as
11 such is physically distinct from the prior-art
12 product."

13 So my opinion in total is important in
14 paragraph 98, not just that one little aspect.

15 Q Okay. Although, I know that one little
16 aspect is the -- what's called a "conclusory
17 sentence"?

18 A I don't know if I would label that as the
19 final conclusion.

20 Q Even though it follows the word, "Thus"?
21 Begins with the word, "Thus"?

22 A Well, I sort of begin the paragraph, ". .
23 . from these data." That's also -- I'm making a
24 conclusion about the impurity profile. So I'm
25 actually making two different important conclusions

1 in this paragraph. So the overall purity, and I
2 think very significantly, the impurity profile,
3 which is different. That's the structural
4 difference.

5 Q But it seems like you made the impurity
6 profile point in paragraph 97, isn't that right?

7 A Let me just read that.

8 Well, I talked about the differences in
9 impurity -- I talked about salient features of the
10 impurity profile for the '393 patent process in
11 paragraph 97.

12 Q Now, you said that the statement about
13 the [REDACTED] versus the 99.5 was also important. Why
14 was it important to your opinion?

15 A Well, it shows that in addition -- in
16 addition to the differences in impurity profile, the
17 structural differences is also an overall purity
18 difference.

19 Q And why didn't you think that was
20 important?

21 A Well, because you're looking at various
22 aspects of the product. The overall purity, as well
23 as the detailed components of the impurities.

24 Q Yeah. So why was the overall purity
25 important for distinguishing -- if it was -- for

1 distinguishing the '393 product from the Moriarty
2 product?

3 A Well, the Moriarty product, again,
4 involves a very time-consuming, expensive
5 chromatography. And if that step weren't conducted,
6 you'd get an even worse product. So you have to
7 perform that step, which is very, very deleterious
8 in so many ways, as we discussed earlier. And so
9 you still want to have a high overall purity. But
10 it's also important to recognize that there is a
11 difference in the individual impurities between the
12 two processes. And the data shows that so
13 incredibly clearly.

14 Q Let me ask you -- you have a
15 paragraph 103, if you go a couple pages later. And
16 you see there, again, you talk about the difference
17 in purity between Moriarty or Phares and the '393
18 patent. Do you see that?

19 A So this is with regard to the
20 treprostinil diethanolamine salt?

21 Q Yes. The first sentence is, but further
22 down, you say, "Regardless of the purity identified
23 in Moriarty, a further analysis of all batches made
24 by the Moriarty process up to the time of the
25 reference itself, reveals an average purity of

1 99.05 percent, while the average purity of the '393
2 patent batches is [REDACTED]." Do you see that sentence?

3 A I see that.

4 Q Okay. And that's referring to the
5 treprostinil free acid; correct?

6 A Um, so the -- the [REDACTED] percent, this is
7 the 121 batches in the table that I have. And that
8 includes some batches of just salt, but most of them
9 are acid.

10 Q So you actually looked at both salt and
11 acid in your analysis?

12 A Yes. And the salt is amazing. The salt
13 is just stunningly pure.

14 Q Salt, in fact, is somehow purer than the
15 free acid, isn't it?

16 A That's correct.

17 Q Even though the last acidification step
18 hasn't been performed?

19 A On the salt.

20 MS. HASPER: Objection.

21 BY MR. POLLACK:

22 Q On the salt.

23 A Sorry.

24 Q Yes.

25 MS. HASPER: Objection. Mischaracterizes

1 the document.

2 THE WITNESS: Yeah. So at the salt
3 stage, the step (d) has not been performed.

4 BY MR. POLLACK:

5 Q Right.

6 Why did you think it was important in
7 this one paragraph -- 103 that's about the salt to
8 point out the differences in the purity of 99.05
9 versus [REDACTED] in the prior art versus the patent?

10 A So you've already asked me this question
11 and I've already given you have the answer. So
12 you're asking me the same question over and over.

13 Q So what's the answer?

14 MS. HASPER: Objection. Asked and
15 answered.

16 THE WITNESS: I told you that the overall
17 purity is important, but I also looked at the
18 individual components of the impurities. And
19 they're different.

20 BY MR. POLLACK:

21 Q Okay. Since it is an important point
22 that the overall purity is important, isn't it a
23 problem for your opinion if data points were
24 cherry-picked to try to bring the actual purity down
25 from [REDACTED] to 99.0?

1 MS. HASPER: Objection. Mischaracterizes
2 his testimony and the document.

3 THE WITNESS: No. So I -- I -- I don't
4 like your question, because it's -- it's accusatory
5 and mischaracterizes the analysis that I did that I
6 thought was very fair. I included development
7 batches for both the Moriarty process, and I also
8 included development batches for the '393 process.
9 So the development batches for the '393 are also
10 poorer than the later commercial batches. And so by
11 the same token, those numbers bring down the average
12 purity of the '393 process. So I thought I was
13 being very fair.

14 BY MR. POLLACK:

15 Q Oh, really? To bring it down when it's
16 [REDACTED], even with those batches?

17 What did it bring it down from?

18 A Well, I didn't -- I didn't do the
19 calculation to eliminate those. I included both.
20 But if you did eliminate the development batches, it
21 would certainly improve the overall purity of the
22 '393 batches.

23 MR. POLLACK: I'm going to mark as
24 Williams Deposition Exhibit 11 a document known as
25 "Exhibit 2052" in the case, the UT-15 injection

1 drug-substance chemistry manufacturing and controls
2 submission for an NDA No. 21-272.

3 (Exhibit 11 marked)

4 MS. HASPER: And just to let you know, my
5 realtime has not been working since we came back
6 from the break.

7 THE REPORTER: Off the record.

8 THE VIDEOGRAPHER: Off the record. The
9 time is 12:03 P.M.

10 (Off the record)

11 THE VIDEOGRAPHER: We are back on the
12 record. The time is 12:05 P.M.

13 BY MR. POLLACK:

14 Q All right, Dr. Williams, I've put in
15 front of you the Exhibit 2052, which is the source
16 of the ten additional data points you added to your
17 analysis. Is this 2052 the document that you relied
18 upon?

19 A (Examining document) Yes.

20 Q Okay. Now, if you would turn to what's
21 called at the bottom of the document in the center,
22 "Page 25"?

23 A Okay.

24 Q Are these the lots that you added to the
25 analysis of the average purity of the Moriarty

1 process?

2 MS. HASPER: Objection. Mischaracterizes
3 his testimony and the documents.

4 THE WITNESS: So I don't think I would
5 agree with the way you phrased your question -- that
6 I added these. I was given all of the data
7 together.

8 BY MR. POLLACK:

9 Q By counsel?

10 A Yes.

11 Q Hmm-hmm.

12 A So there was no importing separately
13 these batches to try and obfuscate the data.

14 Q Right. 'Cause counsel had already
15 calculated the average value so that you just
16 checked that calculation; correct?

17 A Yes. I checked the calculation, and we
18 did the same thing for the '393 batches. We
19 added -- the development batches were there to do a
20 fair comparison.

21 Q When you did the check of the
22 calculation, you didn't say: Hey, why are we adding
23 that other exhibit? Let me see how these numbers
24 come out if I just use the set that was presented as
25 existent 2036.

1 MS. HASPER: Objection.

2 BY MR. POLLACK:

3 Q You didn't do that; right?

4 MS. HASPER: Objection. Mischaracterizes
5 the document and the testimony.

6 THE WITNESS: So I didn't do a separate
7 calculation. I certainly looked at the charts, the
8 exhibits. And either way you slice it, if you want
9 to include the development batches, or you want to
10 exclude them, my opinion does not change; okay?

11 Because with the -- with the -- the Moriarty
12 process, you're starting with an inferior process.

13 So the development batches were not as
14 nice as the development batches that you started
15 with the '393, 'cause it's a better, distinct,
16 process; okay? But even if you wanted to eliminate
17 both of them either way, the impurity profiles are
18 different. And the '393, no matter how you slice
19 it, gives you a superior product, a different
20 product.

21 BY MR. POLLACK:

22 Q Okay. But one part of your opinion --
23 and you definitely stated this a number of places in
24 your Declaration -- was that the Moriarty process
25 gave you 99.0 while the '393 process gave you [REDACTED];

1 right? That was one opinion that you stated?

2 A That's one aspect of my opinion.

3 Q It's one opinion that you stated?

4 A One aspect of my opinion.

5 Q Looking now and seeing that certain of
6 the data points were added from these older
7 development batches and that brought down the purity
8 from ██████ to 99.0, do you want to now remove just
9 that one aspect of your opinion?

10 MS. HASPER: Objection. Mischaracterizes
11 his testimony and the documents.

12 THE WITNESS: No, because, you know, the
13 development batches are compared fairly to
14 development batches between two processes; okay?
15 So, again, we're looking at an average of many, many
16 batches over time. And so what I did not do is, I
17 did not cherry-pick a single batch from the '393 and
18 compared it to a single batch of the Moriarty
19 process. So I thought it was much more significant
20 to look at the overall picture. And I think my
21 report very fairly and accurately provides the
22 overall picture with the exception of that one
23 duplicate entry, which doesn't change the number
24 very much.

25 ///

1 BY MR. POLLACK:

2 Q Let's think about it this way: So 46
3 batches show an average value for the purity of
4 [REDACTED]. And 10 batches bring that number down to
5 99.0.

6 Is it not true that, fairly, one should
7 take the 46 rather than throwing in 10 outliers?
8 Isn't that how science is done?

9 MS. HASPER: Objection. Mischaracterizes
10 the documents.

11 THE WITNESS: No. I don't -- I don't
12 agree.

13 BY MR. POLLACK:

14 Q Let's take a look at this page 25 that I
15 asked you to look at in Exhibit 11. The dates of
16 manufacture of these lots -- do you see them?
17 There's a line that says, "Date of Manufacture."

18 A Okay.

19 Q The first two lots are dated in 19 --
20 they're both in 1986. My eyes are a little weak,
21 but I think one's July 1986, and the other one is
22 August 1986? Do you see that?

23 A Okay.

24 Q And then the next batches are all dated
25 in -- their date of manufacture is either 1997 or

1 1998; correct?

2 A Yes.

3 MR. POLLACK: I'm going to mark as
4 Williams Deposition Exhibit 12 a document known in
5 this case as "Exhibit 1004," which is the Moriarty
6 Journal of Organic Chemistry Article.

7 (Exhibit 12 marked)

8 BY MR. POLLACK:

9 Q And can you verify for me that Exhibit 12
10 is the Moriarty article that's prior art that we've
11 been referring to in this deposition?

12 A Yes.

13 Q What's the date on the Moriarty article?

14 A 2004.

15 Q Okay. What date was it received by the
16 journal?

17 A June 5th, 2003.

18 Q Okay. How many years after was this
19 article published compared to when these lots were
20 manufactured in -- sorry. Let me ask my question
21 again.

22 How many years are there between the lots
23 described in Exhibit 2052 and the Moriarty article?

24 MS. HASPER: Objection. Vague.
25 Relevance.

1 THE WITNESS: So the earliest -- the
2 earliest date is July of '86 to 2003. Is that -- is
3 that the year-spread that you're asking me about?

4 BY MR. POLLACK:

5 Q Year-spread. Right. Okay.

6 Many of the lots are from 1998 and 1999?

7 A So there's the date of manufacture and
8 date of testing.

9 Q I'm asking the date of manufacture.

10 A Yes.

11 Q Isn't that what's relevant here, date of
12 manufacture?

13 A Relevant -- relevant to what?

14 Q Relevant to -- I'll withdraw that
15 question.

16 Okay. So, for example, one of the lots
17 you included -- and you're free to look at your
18 chart -- is lot No. LRX97J01, made in October 1997.
19 Do you see that?

20 A I see that.

21 Q Okay. That is seven years before the
22 Moriarty article was published?

23 A Yes.

24 Q Okay. Let me ask you: There's two lots
25 you didn't include in your analysis. They're the

1 two that are made by -- you see there's also a line
2 that says "Manufacturer"; correct? On the top?

3 A Yes.

4 Q Okay. And -- by the way, none of these
5 lots that are on page 25 were manufactured by United
6 Therapeutics; correct?

7 A So I believe that Steroids and SynQuest
8 are contract manufacturers that were making the drug
9 for United Therapeutics.

10 Q Right. It wasn't made by United
11 Therapeutics itself?

12 A I'm not really privy to the detailed
13 relationship between United Therapeutics and its
14 suppliers. But if a supplier is making the drug for
15 UTC, I believe that UTC would be the -- you know,
16 ultimately be the manufacturer.

17 Q Okay. Do you know who makes treprostinil
18 now for United Therapeutics?

19 A I know that there's suppliers that --
20 different suppliers that make different -- do
21 different parts of the synthesis, but I'm actually
22 not sure of the whole picture of how -- who's
23 contributing what pieces, what companies.

24 Q Okay. Now, you understand the first two
25 lots were made by Upjohn back in the '80s; correct?

1 A Yes.

2 Q Okay. And you'll agree with me that it
3 can't be the case that way back in the '80s, Upjohn
4 was using the Moriarty process; correct?

5 A No. It's not possible.

6 Q Okay. Now, do you notice that there's a
7 footnote -- it's a little hard to read the typeface
8 is small -- it's footnote 4. Do you see that
9 footnote 4?

10 A Yes.

11 Q Can you read footnote 4 for us into the
12 record?

13 A "These lots were manufactured by
14 Pharmacia and Upjohn using a slightly different
15 route of synthesis."

16 Q In reading that, is it your understanding
17 that what they mean by that is all the other lots
18 here were made in a way that's only slightly
19 different from the way Upjohn made treprostinil?

20 MS. HASPER: Objection. Calls for
21 speculation.

22 THE WITNESS: Yeah. I don't know.

23 BY MR. POLLACK:

24 Q What's your understanding of what that
25 says?

1 A What? Footnote 4?

2 Q Yeah. Footnote 4.

3 A So --

4 MS. HASPER: Objection. Relevance.

5 THE WITNESS: That these -- these two
6 1986 lots were made by Pharmacia and Upjohn using a
7 different -- a slightly different route of
8 synthesis.

9 BY MR. POLLACK:

10 Q Okay.

11 A That's what it says.

12 Q Sure. Okay. And is it your
13 understanding that the other lots, then, were not
14 made exactly the way Upjohn made them but a fairly
15 similar process was used?

16 MS. HASPER: Objection.

17 THE WITNESS: You know, I don't know the
18 details.

19 BY MR. POLLACK:

20 Q You don't know the details of how all
21 these lots were made?

22 A No. I haven't seen the detailed batch
23 records of what went into those lots.

24 Q Okay. So you don't know whether or not
25 these lots were made by the '393 process, the

1 Moriarty process, the older Aristoff process; is
2 that right?

3 MS. HASPER: Objection. Mischaracterizes
4 testimony and the documents.

5 THE WITNESS: Um, you know, I -- I'd have
6 to investigate further. I don't know.

7 BY MR. POLLACK:

8 Q Right. You -- you don't know if any of
9 these are from the Moriarty process?

10 A Um --

11 Q At least not the ones on page 25?

12 A So the Moriarty paper came out in 2003.

13 Q 2004 it came out.

14 A Well, yes. Yeah. The paper was
15 published in 2004, but the technology had been put
16 together as easily as early as 2003.

17 Q Okay.

18 A So I don't think it's possible that any
19 of these could have been made by Moriarty process
20 just based on the dates.

21 Q And yet these are the ten additional
22 samples that you added to your analysis that brought
23 the value down from ██████ to 99.0; correct?

24 MS. HASPER: Objection. The testimony --
25 mischaracterizes testimony and the documents.

1 THE WITNESS: So I -- I guess I don't
2 know.

3 BY MR. POLLACK:

4 Q Well, do you want to compare the lot
5 numbers here to the lot numbers on -- if you take
6 the exhibit that has the yellow highlighting --
7 that's our Exhibit 9 -- this one here (Indicating).
8 Or you can compare it to your appendix. Either one.

9 A (Examining documents) So it begins with
10 9 -- 97J01.

11 Q Right. That's the third -- third column?

12 A Yes.

13 Q And that's on your -- that is on one of
14 the ones you analyzed on your -- on your chart?

15 A Yes.

16 Q Okay. And LRX99801, you analyzed that
17 one, too?

18 A Yes. That's the second entry. And then
19 BO-1. And then they go to -- the next one is UT,
20 but it's -- oh, that's -- yeah. So they're just in
21 sequential order.

22 Q Okay. And each of these lots were
23 just -- we were just reviewing, you're not sure what
24 method was used to make any of these. You haven't
25 seen the batch sheets?

1 A I haven't seen the batch sheets.

2 Q Does that -- looking at this data now,
3 are you prepared to change your opinion about
4 whether or not the Moriarty method, in fact, gives a
5 [REDACTED] percent purity just like the '393 patent?

6 A No.

7 And you keep asking me the same question
8 30 different ways, and I already told you: If you
9 wanted to throw out all the development batches from
10 both processes and both analyses, fine --

11 Q Okay.

12 A -- that doesn't change the differences in
13 impurity profile. And it also is not going to
14 change the overall fact that the '393 process gives
15 an overall higher purity than Moriarty.

16 So, you know, fine. Scratch out those 10
17 entries if you want to. It doesn't change my
18 opinion.

19 Q Okay. You understand if we scratch out
20 those 10 entries, we're going to get [REDACTED] for
21 impurity --

22 A We're still never going to change the
23 impurity profile.

24 Q I understand. I'm just talking about the
25 one -- you said twice, at least -- I think much more

1 than twice -- in your opinion that the purity
2 profile between Moriarty and the '39 -- I'm sorry --
3 that the purity level between the '393 patent and
4 Moriarty were different -- let me start my question
5 again.

6 You've said -- now seeing, at least twice
7 -- and I think there were some more times -- in your
8 Declaration that the -- an important point is that
9 the purity level between Moriarty and the '393
10 patent is different, and it's different by 99.0
11 versus [REDACTED]. I just want to focus on that one
12 opinion, nothing else.

13 A Okay.

14 Q Do you want to retract that opinion now,
15 having seen this information at this deposition?

16 MS. HASPER: Objection. Asked and
17 answered.

18 THE WITNESS: No.

19 BY MR. POLLACK:

20 Q No? Why not?

21 A Because, you know, even if the -- you
22 eliminate these development batches, the overall
23 purity for both processes goes up, but Moriarty's
24 never going to catch the '393 purity.

25 Q Okay.

1 A So no matter how you want to add or
2 eliminate data, the -- the important -- the really
3 important thing that these spreadsheets show of
4 these -- from these batch records is that the
5 Moriarty process does not provide, on average, a
6 purer material than the '393, and the impurity
7 profiles are distinctly different. And it was
8 unexpected that you would be able to eliminate, for
9 example, two to three stereoisomeric impurities
10 entirely.

11 Q Okay. You said it doesn't provide -- the
12 Moriarty process doesn't provide on average a higher
13 purity than the '393. But let me ask you another
14 direction. Does the '393 process significantly
15 provide a higher purity than the Moriarty process?

16 MS. HASPER: Objection. Asked and
17 answered.

18 THE WITNESS: Yes, on average, that is
19 definitely the case. That's what the data shows.

20 BY MR. POLLACK:

21 Q Did you include standard deviation -- you
22 know what standard deviation is; right?

23 A Yes.

24 Q And I notice you didn't calculate any
25 standard deviations for your average, isn't that

1 true?

2 A That is true. I did not. That's not the
3 sort of thing anyone would do.

4 Q Isn't that the standard scientific
5 method?

6 A It may be for some sciences, but organic
7 chemistry and even process chemistry, you know, it's
8 very rarely, in my experience, done.

9 And, you know, if you wanted to put
10 instead deviations, I didn't calculate that. You
11 know, I don't think it's going to change the
12 picture. The impurity profiles are different, and
13 the '393 process produces a superior product.

14 Q I'm going to -- and we'll provide this
15 spreadsheet electronically to counsel -- but for you
16 for now --

17 MS. HASPER: Is there a way I can see the
18 spreadsheet?

19 MR. POLLACK: You can go look over his
20 shoulder. That's perfectly fine.

21 BY MR. POLLACK:

22 Q We have calculated the averages and the
23 standard deviations for all of the samples,
24 excluding 2052. And I've given you the spreadsheet
25 there.

1 You know how to use Excel; right?

2 A Yes.

3 Q Okay. So I've given you the Excel
4 spreadsheet there. You're free to play with it and
5 verify we did everything correctly. You'll see the
6 standard deviations are recorded there; right?

7 A I see them.

8 Q Okay. And those were calculated using
9 the standard Excel method. And you see that for the
10 HPLC assay, I believe it's .6 is the standard
11 deviation? Do you see that?

12 A I see that.

13 Q And .24, the total impurities.

14 A I see that.

15 Q Okay. Let's start with the .6.

16 If the standard deviation -- if it's
17 ██████, plus or minus .6, is there any value that the
18 '393 patent purity could have that would be
19 statistically different from ██████, plus or minus .6?

20 MS. HASPER: Objection. Beyond the
21 scope.

22 THE WITNESS: So, Counsel, I know that
23 your focus is on this overall average purity, but my
24 opinion is not on this average overall purity in
25 isolation; it's the overall purity in combination

1 with the impurity profile. And I can't separate
2 those two, because they're inseparable from the
3 reality of how this drug is made and what the
4 characteristics of the product are.

5 BY MR. POLLACK:

6 Q Okay. Yeah. I'm not trying to attack
7 the whole of your opinion. You can keep the
8 impurity profile part. I'm trying to understand the
9 other prong -- the total impurities level. Is
10 that -- you've said it's important to your opinion.
11 So I'm now exploring why it's important to your
12 opinion. And now seeing that that value really
13 doesn't change much, how does removing that one leg
14 change your opinion?

15 A It doesn't.

16 Q Okay. And should we -- since your
17 opinion is fine without that one leg -- without the
18 purity comparison, should we just eliminate the
19 purity comparison from your opinion and just rely on
20 the difference in impurity profile?

21 MS. HASPER: Objection. Mischaracterizes
22 his testimony.

23 THE WITNESS: No.

24 BY MR. POLLACK:

25 Q Why not?

1 A Because, even if you eliminate these
2 development batches, the -- the overall purity of
3 the '393 product that is being manufactured on a
4 commercial scale is still better than what UTC was
5 getting with the Moriarty process. And
6 significantly, we've eliminated chromatography, and
7 the impurity profiles themselves are distinct.

8 Q You understand that the two purity-level
9 values hardly change. You understand that --
10 right? -- between the Moriarty process and the '393
11 process?

12 A I don't agree.

13 Q Why not?

14 A Well, again, if -- even if we're going to
15 chop off the tops of both of those Exhibit A and B
16 charts, the overall -- the overall purities are
17 still different.

18 Q Let me ask you something: Did you notice
19 that the HPLC assay analysis of the -- all of the
20 samples, excluding those ten that were made by
21 method -- you're not even sure what method was
22 used -- just including those, did you notice that
23 the value was █████ and that that's the same value
24 reported in the Moriarty prior art? Did you notice
25 that?

1 A For the single batch made in the Moriarty
2 paper?

3 Q Yes. Yes.

4 A Yeah. So that's not in my opinion
5 representative.

6 Q Well, having now seen 56 batches that
7 average [REDACTED], doesn't that show that, in fact, the
8 [REDACTED] number is quite representative is? Isn't that
9 so?

10 MS. HASPER: Objection. Objection.
11 Mischaracterizes the documents.

12 THE WITNESS: Ask me your question one
13 more time, please?

14 BY MR. POLLACK:

15 Q Sure. Having seen 56 samples now which
16 came to an average of [REDACTED] for the purity level --
17 and comparing that to the [REDACTED] number that Moriarty
18 reported, doesn't that show that Moriarty's value,
19 in fact, was representative?

20 MS. HASPER: Objection. Same objection.

21 THE WITNESS: No. So 56 batches give
22 99.1 percent.

23 BY MR. POLLACK:

24 Q I'm sorry. 46 batches -- I apologize.

25 Having seen now that 46 batches give a

1 value of [REDACTED], isn't that consistent with the [REDACTED]
2 value reported by Moriarty in the prior art?

3 A So those -- they're the same number.

4 MS. HASPER: Objection.

5 THE WITNESS: Sorry.

6 MS. HASPER: Objection. Mischaracterizes
7 the document.

8 THE WITNESS: So, you know, I'm not
9 really sure -- so you're referring to in here --

10 BY MR. POLLACK:

11 Q Yes.

12 A -- [REDACTED] percent of, apparently,
13 recrystallized treprostinil in the JOC paper; right?

14 Q Yes.

15 A That's the number you're referring to;
16 right?

17 Q Yes. That's the number that Moriarty
18 reports; correct?

19 A Right.

20 Q That is on, for the record, if we look
21 at -- let's call it page 13 of the exhibit --
22 page 1902 of the original article. The right-hand
23 column, and it's just above where it says,
24 "Acknowledgement"; right?

25 A Yes.

1 Q Is that where we're looking?

2 And there, it refers to a purity of
3 [REDACTED] percent, and that is for the compound
4 treprostinil, which was also known as UT-15;
5 correct?

6 A Yes.

7 Q Okay. And that number, [REDACTED], is
8 consistent with the [REDACTED] we see for the average of
9 46 samples; correct?

10 MS. HASPER: Objection. Mischaracterizes
11 the document.

12 THE WITNESS: So -- okay. So, you know,
13 even if those numbers are the same, if you eliminate
14 development batches from the '393, that number goes
15 up. And I -- again, the data in the '393 chart is
16 very conservative because less than [REDACTED] was put in
17 as [REDACTED] -- as [REDACTED]. So it's actually much purer.

18 BY MR. POLLACK:

19 Q What's much purer?

20 A The '393 product.

21 Q Well, the same is true for the Moriarty
22 product.

23 A No. So you've -- you might max out if
24 you do your own type of cherry-picking of
25 eliminating these early development batches, but the

1 '393 data, again -- all of those -- all of those
2 percentages are going to be improved if you
3 eliminate those -- whatever it was -- number of
4 development batches that were also -- that I also
5 included for the '393.

6 Q Oh, what if I represent to you that
7 actually that's not the case that they won't be
8 improved?

9 A Okay. But, again, you can look at the
10 impurity profiles, and there is -- 1AU90 appears in
11 only one batch and 2AU90 only appears in one batch
12 and the rest of them have zero. You cannot say the
13 same for any -- any -- for the Moriarty on average.
14 So the -- there's only two batches: [REDACTED]
15 and [REDACTED]. Those are the only two batches where
16 the stereoisomeric impurities appear. And then if
17 you scan down the column 0000000 -- all the way
18 down.

19 So that crystallization step completely
20 obliterates those two stereoisomeric impurities.
21 And a person skilled in the art couldn't have
22 predicted that. And the triol, t-r-i-o-l, also was
23 completely obliterated.

24 Q And did you look at -- if you look at
25 Appendix A -- and Appendix A, that's the Moriarty

1 method; right?

2 A I'll give you your computer back.

3 MS. HASPER: Could I just ask counsel --
4 since you've been showing him an electronic
5 document, can we get that in electronic form
6 immediately?

7 MR. POLLACK: We will provide it after
8 the --

9 MS. HASPER: Perhaps before lunch?

10 No, I'd like it before the deposition is
11 over, please.

12 MR. POLLACK: I don't know if we'll be
13 able to do that.

14 MS. HASPER: Well, I'm going to insist on
15 it.

16 MR. POLLACK: I heard what you said.

17 BY MR. POLLACK:

18 Q Sir, take a look at Appendix A.

19 A Okay.

20 Q And if you look at 1AU90 starting below
21 the ten lots -- the first ten lots on your chart,
22 you notice they're all zeros.

23 A Okay. Which entry?

24 Q Let's start on page 43.

25 A Okay.

1 Q Okay. And let's start below where --
2 below the 2052s that you used; okay? So look at
3 Data Source and get to the line that's below the
4 2052s.
5 A Okay.
6 Q Okay? Do you see a bunch of zeros for
7 1AU90?
8 A Yes. And I see [REDACTED] for 2AU90.
9 Q Right. But those are [REDACTED] you put in
10 because it said less than [REDACTED]; right? That's why
11 they're all [REDACTED]?
12 A Some of them may be actually [REDACTED]. [REDACTED] or
13 --
14 Q Or less?
15 A Or less.
16 Q Okay.
17 A But they're detectable.
18 Q Okay. But, similarly, though, even under
19 Moriarty 1AU90, barely detectable, in most cases?
20 A Okay. But the profiles are still
21 different, on average.
22 Q I'm going to mark --
23 A So I'm -- I need a nature break, and
24 maybe this is a good time for lunch, perhaps?
25 MR. POLLACK: It's up to you.

1 THE WITNESS: Yeah. And it's gotten
2 warmer in here.

3 MS. HASPER: Yes, it has.

4 THE WITNESS: Maybe we can adjust the
5 thermostat again?

6 MS. HASPER: Why don't we go ahead and go
7 off the record, and maybe we can adjust the
8 environmental.

9 THE VIDEOGRAPHER: We are off the record.
10 The time is 12:38 P.M.

11 (Luncheon recess taken at 12:38 P.M.)

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1 A F T E R N O O N S E S S I O N
2 Commenced at 1:34 P.M.
3
4 THE VIDEOGRAPHER: We are back on the
5 record. The time is 1:34 P.M.
6
7 EXAMINATION (Resumed)
8 BY MR. POLLACK:
9 Q Welcome back from lunch, Dr. Williams.
10 A Thank you.
11 Q Over lunch, did you have a chance to
12 review the spreadsheet of the 46 data points in
13 Excel form?
14 A No.
15 Q Okay. You didn't look at that at all?
16 A No. I ate lunch.
17 Q Okay. That was it. Okay.
18 I'm going to mark as -- let me just do
19 one more, sort of, housekeeping thing. I think what
20 we'll do is, we'll mark the spreadsheet in
21 electronic form which we've now sent to United
22 Therapeutics' counsel, and we've now e-mailed it to
23 the court reporter as well.
24 MR. POLLACK: We'll mark that as Williams
25 Deposition Exhibit 13 so it exists on the record.

1 (Exhibit 13 marked)

2 MR. POLLACK: Now, I'm going to mark as
3 Williams Deposition Exhibit 14 a document currently
4 called on the record "Exhibit 2006."

5 (Exhibit 14 marked)

6 BY MR. POLLACK:

7 Q Exhibit 2006, also known as "Williams
8 Deposition Exhibit 14," appears to be a letter from
9 United Therapeutics to the FDA, dated January 2nd,
10 2009.

11 Dr. Williams; is that correct? Is that
12 what this is?

13 MS. HASPER: Objection. Beyond the
14 scope.

15 THE WITNESS: Wait. What are you asking
16 me?

17 BY MR. POLLACK:

18 Q I'm asking you if Williams Deposition
19 Exhibit 14 is a letter from United Therapeutics to
20 the FDA, dated January 2nd, 2009.

21 A That's the date, and it's on United
22 Therapeutics letterhead, and it's addressed to the
23 Division of Cardiovascular and Renal Products --
24 FDA, yes.

25 Q Is my answer -- is the answer "yes"?

1 A Yes.

2 Q Okay. And this is one of the documents
3 you relied upon in forming your opinion?

4 A I looked at a lot of documents. I
5 believe I've seen this before.

6 Q If you turn to page 3 of the document --
7 no, let me step back.

8 Let me ask you: Do you know what this
9 letter is about?

10 A I have to refresh my memory. I don't
11 remember --

12 Q Okay.

13 A -- just by looking at the face page.

14 Q Let me ask you -- if you don't remember,
15 you can just tell me.

16 If we go to page 3, you see there's a
17 paragraph that begins, "In conclusion . . ."

18 A I'd like to read the letter --

19 Q Absolutely.

20 A -- to just familiarize myself with the
21 content if you don't mind.

22 Q I don't mind.

23 A (Examining document) Okay. I've had a
24 chance to review the document.

25 Q Okay. Was this a documented you used in

1 forming your opinion?

2 A Yes. I -- I remember looking to this.

3 This is the change in the spec for the API.

4 Q Okay. So if we turn to page 3,
5 Exhibit 14, you see there's a paragraph that says,
6 "In conclusion . . .," just above the bolding? Do
7 you see that?

8 A Yes.

9 Q And the conclusion says, "In conclusion,
10 the lots of treprostinil API" -- that means "active
11 pharmaceutical ingredient"; is that right?

12 A Yes.

13 Q "In conclusion, the lots of treprostinil
14 active pharmaceutical ingredient produced by the new
15 process in Silver Spring are of the same
16 high-quality impurity as the commercial lots of API
17 produced by the existing process at the Chicago
18 facility."

19 Did I read that correctly?

20 A That's what it says.

21 Q Okay. Do you have any reason to disagree
22 with that statement?

23 A No.

24 Q Okay. And when it says here, "the new
25 process in Silver Spring," that's a process that now

1 includes the '393 process, is that your
2 understanding?

3 A That's correct. Yes.

4 Q And the -- in that process, the quality
5 and purity are being compared to the existing
6 process at the Chicago facility. Do you see that?

7 A Yes.

8 Q Okay. And the existing processes at the
9 Chicago facility, that was done using the Moriarty
10 process; is that correct?

11 A I believe that's correct. That's what
12 I've been told.

13 Q Okay. Go down just a couple paragraphs.
14 There's a paragraph that begins with the word,
15 "During." Do you see that?

16 A Yes.

17 Q And it says, "During the initial
18 analytical method validation for the treprostini
19 assay, the results indicated that there is about
20 2 percent variability in the assay." Did I read
21 that correctly?

22 A That's what it says.

23 Q Okay. Do you have any reason to disagree
24 with that statement?

25 A No.

1 Q Okay. When referring to the treprostinil
2 assay, that's the HPLC assay of how pure the
3 treprostinil is?

4 A I don't know for certain. It doesn't
5 say, "HPLC assay."

6 Q What's your understanding?

7 A That sounds reasonable, but I can't be
8 certain.

9 Q Well, did you review this document in
10 forming your opinion; correct?

11 A Yeah.

12 Q Okay. And when you read that, did you
13 wonder what it was referring to?

14 A Not in that context, no.

15 Q Maybe I can help you. Let's go to
16 page 6. And do you see there, it says, "Assay
17 HPLC"? Do you see that row?

18 A Yes.

19 Q Okay. And do you see it refers to
20 certain numbers --

21 A Yes.

22 Q -- in the next two rows -- columns? Yes?

23 A Yes.

24 Q Okay. Looking at page 6 and then looking
25 back at page 3, reading those sections, can you now

1 conclude for me that the 2 percent variability in
2 the assay refers to the HPLC assay?

3 A Yeah. I believe that's what they're
4 talking about.

5 Q And so what this sentence on page 3 says
6 is that the HPLC assay analysis for treprostinil has
7 a plus or minus 2 percent variability; is that fair?

8 A So variability -- but -- I don't think
9 that's accuracy -- variability.

10 Q Am I correct that what that means is that
11 the HPLC assay analysis can only be controlled such
12 that the outcome falls somewhere between plus
13 or minus 2 percent of the desired amount?

14 A Yeah, I'm not sure about that. I mean,
15 HPLC is an extremely sensitive technique, and you
16 can detect levels of impurities at much, much lower
17 than 2 percent.

18 Q Let me ask you: Are you an expert at
19 analytical chemistry?

20 A I have a lot of expertise in analytical
21 chemistry, yes.

22 Q What's your expertise in analytical
23 chemistry?

24 A I have extensive experience with NMR --
25 nuclear magnetic resonance spectroscopy -- infrared

1 spectroscopy, HPLC, thin-layer chromatography, mass
2 spectrometry, ultraviolet spectroscopy, X ray
3 crystallography.

4 Q Okay. And you've used all those
5 techniques?

6 A Yes.

7 Q Okay. But your research area is not
8 analytical chemistry; is that fair?

9 A I wouldn't say it that way. My research
10 area relies, on a daily basis, on analytical
11 technologies and instrumentation.

12 Q Sure.

13 A So I can't -- my laboratory can't
14 function without daily routine access to all the
15 techniques I just enumerated.

16 Q Sure. But your specialty is not the
17 design, development, construction of analytical
18 instruments; is that fair?

19 A I have not designed analytical
20 instruments. But for my entire career as a chemist,
21 I have been using extensively all these analytical
22 instruments, including with my own hands.

23 Q Let me ask you: Did you take analytical
24 chemistry in graduate school?

25 A I actually didn't take any courses in

1 graduate school.

2 Q Okay. Even for the master's?

3 A Hmmm?

4 Q Even for the master's portion of your
5 graduate school?

6 A So my master's degree, the way it works
7 at MIT when you get a Ph.D. degree, you
8 automatically get a master's degree. It wasn't like
9 a separate thesis. I sat in on a lot of courses,
10 but I didn't actually take any courses in graduate
11 school.

12 Q Did you sit in on analytical chemistry?

13 A No.

14 Q Did you take analytical chemistry in
15 college?

16 A Yes.

17 And I also taught graduate level
18 spectroscopy courses when I started my independent
19 career at Colorado State University. So I have also
20 taught mass spec and NMR and HPLC to graduate
21 students.

22 Q Okay. That course didn't include HPLC?

23 A The course I taught was mostly centered
24 on spectroscopy. We did talk a little bit about
25 HPLC, but I also teach my own graduate students

1 about HPLC.

2 Q Okay. And as part of your teaching of
3 HPLC, do you discuss error analysis of the HPLC
4 instrument?

5 A Yes, because sometimes we have to report
6 very accurate data based on HPLC. So, yes, HPLC is
7 much, much more sensitive than NMR.

8 Q I think one of the things you say in your
9 Declaration, though is that -- let me ask you this:
10 Is there in your view any preference for using HPLC
11 assay analysis where you measure the peak of the
12 substance of interest versus measuring the total
13 related impurities?

14 A I didn't quite follow your question.

15 Q Yeah. In determining the purity of a
16 substance, which technique is better? Using the
17 HPLC peak of the substance of interest or using a
18 sum of the peaks of the impurities?

19 A I really am sorry. I'm not following
20 your question. It doesn't make sense to me.

21 Q Let me break it down, then.

22 The HPLC assay analysis described here --
23 that's an analysis in which the area under the curve
24 for -- in this case, treprostinil, but for any other
25 substance as well -- is compared to a reference

1 standard; is that fair?

2 A Yes.

3 Q Okay. And that's one technique of
4 determining the purity of a substance; right?

5 A Yes.

6 Q Now, something else that you did in your
7 Declaration, I believe, is you looked at a table of
8 total related substances; correct?

9 A Yes.

10 Q And you subtracted those from 100 to get
11 the purity analysis; right?

12 A Yes.

13 Q Okay. Which of those two techniques is
14 preferable?

15 A Well, I think you need to do both. In
16 fact, in my own research, I don't rely exclusively
17 on HPLC. I always ask my students to corroborate
18 through NMR as well, because some compounds are
19 invisible by HPLC if they don't have a chromophore,
20 if you're using a UV detector.

21 Q Right.

22 A So it's -- but for industrial process
23 validation, you know, the assumption is that the
24 analytical group who has established the protocols
25 and methods is already thoroughly vetted and

1 confirmed and verified that the analytical technique
2 that's going to be use San Diego reliable and
3 sensitive within a given set of parameters for a
4 given type of compound and impurities.

5 Q Right. But there could be some
6 compounds -- some impurities in there that don't
7 have a chromophore and wouldn't be seen in a
8 particular HPLC analysis?

9 A That's possible, yes.

10 Q Okay. And you said you would do both.
11 Is there any preference for one or the other, or
12 they're both equal?

13 A Well, HPLC is typically faster,
14 particularly if you have it set up in a -- you know,
15 a robotic auto-sampler type of thing.

16 So NMR takes more time. You gotta
17 prepare the samples, you have to get the
18 spectrometer, and you have to look at everything in
19 the spectrum. But in my own research, I insist that
20 my students use every technique available to figure
21 out what's in that product mixed or purified
22 product.

23 Q Now, let me also ask you, though -- so I
24 can do HPLC and just look at the peak for the
25 substance of interest, say, treprostinil or

1 something else.

2 A Hmm-hmm.

3 Q Or I could look at the total related
4 substances. And I think you said it's probably best
5 to do both. Is there a preference, though, for
6 total related substances or for the looking at the
7 larger peak?

8 MS. HASPER: Objection. Asked and
9 answered.

10 THE WITNESS: Okay. I'm not sure about
11 this preference issue. I mean, it's important to
12 understand -- like for batches -- you know,
13 commercial batches of treprostinil with what the
14 individual impurities are and how pure the main
15 component is, and so there's impurities that are
16 known, we know exactly what -- like the enantiomer
17 where that --

18 BY MR. POLLACK:

19 Q Right.

20 A -- peak is and that type of thing, as
21 well as unidentified impurities -- these other
22 things that are there that you're not sure exactly
23 what that is.

24 Q Okay.

25 A May be a mixture of things.

1 Q Okay. Now, in your Declaration -- and
2 you may have misunderstood -- I thought there was
3 some criticism of the use of reference standards.

4 Did I misinterpret?

5 A You want to point me to where you think
6 I've got a criticism?

7 Q Let me just ask you first: Do you have
8 any criticism of reference standards?

9 A In general or specifically with respect
10 to this matter?

11 Q Both.

12 A Well, it's important -- I mean, the
13 reference standard itself has to be a highly
14 purified material, and there's no such thing
15 anywhere on this planet of something that's
16 100.0 percent pure.

17 So no matter how many times you
18 recrystallize or do chromatography over and over
19 again, you can approach 100 percent, but you can
20 never get there.

21 So the goal is to try and have as pure a
22 reference standard as possible, and then you measure
23 against that, if you can ascertain what the purity
24 of the reference standard is.

25 Q And that's an initial that's inherent in

1 all HPLC measurements; is that right?

2 A Yes.

3 Q And that's true, even if you're measuring
4 the total related substances, you need to use a
5 reference standard, isn't that correct?

6 A Well, I think -- the reference standard
7 is the same reference standard, and they're just
8 measuring area under the curves of other peaks. And
9 that's added to the known ones.

10 Q Okay. They're not using reference
11 standards for each impurity?

12 A I don't believe so, no. I mean, they
13 know what each -- they use reference standards
14 because they've identified for example where
15 1AU90 -- what the retention time is that so they
16 know where that comes.

17 Q Right.

18 A For the known ones.

19 Q They would use a reference standard for
20 the known ones?

21 A Well, they know where that is. I don't
22 know -- I do not believe that they separately
23 calibrate the small peak for, like, 1AU90 against
24 the reference standard for 1AU90. It's a single
25 reference standard for treprostinil.

1 Q Okay.

2 A Otherwise, it would just take too long.

3 Counselor, I apologize. The coffee here
4 after lunch just came --

5 MR. POLLACK: No problem.

6 THE VIDEOGRAPHER: Going off the record,
7 the time is 2:00 P.M.

8 (Off the record)

9 THE VIDEOGRAPHER: We are back on the
10 record. The time is 2:03 P.M.

11 MS. HASPER: Mr. Pollack, just before you
12 begin, I'd like to interject a posthumous objection
13 to the introduction of the electronic document that
14 was introduced as Exhibit 13. It's just irregular
15 to introduce an electronic copy of something, rather
16 than a printed copy.

17 MR. POLLACK: I believe we did provide a
18 printed copy as well, which was --

19 MS. HASPER: Are you saying that what you
20 introduced as Exhibit 13 was identical to what you
21 printed out and provided as a printed copy?

22 MR. POLLACK: Yes. The information is
23 identical.

24 MS. HASPER: Could you show me which of
25 the other exhibits is the same as --

1 MR. POLLACK: We can do that off the
2 record at some other time.

3 MS. HASPER: Okay. Until I have that,
4 then I will let the objection stand. I may retract
5 it later.

6 BY MR. POLLACK:

7 Q If you could go to -- back to an exhibit
8 we had looked at before -- it's Exhibit 11. It's
9 this giant book here that is also known as
10 "Exhibit 2052."

11 If you could turn to -- there's a lot of
12 numbers, I know, on these pages, but there's a P.43
13 at the bottom of the page.

14 A Okay.

15 Q Okay. Do you see on that page it has an
16 explanation of total related substance equals some
17 of all reported peaks except UT-15? Do you see
18 that?

19 A Yes.

20 Q Okay. And what I was trying to
21 understand here is, when it says, "reported peaks,"
22 those are peaks of the known and identified
23 substances; is that right?

24 A My understanding was that total related
25 substances includes known plus unknown.

1 Q Where did you get your understanding?

2 A I don't remember what document. I know
3 that we -- I discussed this several times with --
4 with counsel, and we referred to documents. I can't
5 remember off the top of my head which one confirmed
6 that, but that was my understanding, anyway.

7 Q And that was your understanding from
8 counsel?

9 A Yes.

10 Q Okay. Looking here, can you tell whether
11 -- from this definition whether unidentified
12 substances are included?

13 A So reported peaks is not, to me,
14 synonymous with known species. So there could be a
15 peak that's reported, but -- it has a certain height
16 and area under the curve. And --

17 Q Okay.

18 A So I'm not really sure what you're asking
19 me.

20 Q Yeah. I was asking you whether this
21 indicated that it was only those peaks which were
22 identified with a code number or other kind of name.

23 A No. So I believe at the -- the batch
24 records themselves show separately the known
25 impurities, and then unknown impurities, and then

1 total related substances. They're broken out
2 separately.

3 Q Right. Right. Right. Earlier, though,
4 remember we went through those numbers, and we
5 weren't able to sum them to the number which was the
6 total related substances? Do you recall that?

7 A Yes.

8 Q Okay.

9 A But I -- I explained that that's because
10 they come from two different types of -- and that
11 the .05 was less than .05 and the actual total
12 related substances gives the net amount of other
13 things besides UT-15.

14 Q Okay. Do you know how the less than .05s
15 were handled?

16 A Well, the less than .05s were given a
17 value in my chart of .05. So rounded up,
18 essentially.

19 Q Right. I'm asking you how -- United
20 Therapeutics, or whoever else, was compiling that
21 data, how did they handle it?

22 A Well, they're reported just like that.
23 It's less than .05. So it was detectable, but then
24 the sum of those end up -- my understanding is, the
25 sum of those all end up in the total related

1 substances value. So known plus unknown.

2 Q But if one's not detected or .05, how is
3 that handled by UT or whoever was reporting the
4 values?

5 MS. HASPER: Objection. Asked and
6 answered.

7 THE WITNESS: You're -- I think I just
8 explained exactly the answer to your question.

9 BY MR. POLLACK:

10 Q What was the answer? Maybe I didn't
11 follow it.

12 MS. HASPER: Same objection.

13 THE WITNESS: I said, so if you look in
14 the batch records themselves, they split out the
15 individual known impurities and the unknown
16 impurities; okay? And so the ones that are --
17 record a value of less than .05 percent in the
18 summary that I gave were given a value of .05.

19 So that's erring on the high side --
20 okay? -- 'cause it could be .00001 percent, but the
21 total related substances value, then, would have
22 built in, you know, say one peak was .0003 -- okay?
23 -- so it wouldn't be added in as .05. It comes just
24 through the standard protocols that they have for --
25 for measuring this.

1 BY MR. POLLACK:

2 Q So you're saying even though they don't
3 report a value, they have some value for these very,
4 very small peaks in your view?

5 A Yeah. Of course, there's a value.
6 They're visible in the chromatogram. And the
7 computer, you know, measures the area under the
8 curve, and you get a -- you know, this total related
9 substances number.

10 Q Okay. And that -- even for peaks that
11 are so small that there's a signal to noise problem?
12 Those are included?

13 A I can't speak to signal to noise. I
14 don't -- you know -- you know, I'm sure this has all
15 been vetted in their validation procedures for that.

16 Q Okay. I mean, did you speak to anyone
17 or --

18 A No.

19 Q -- look into --

20 A No.

21 Q Let me ask my question again: Did you
22 speak to anyone or look into how United Therapeutics
23 determined those values?

24 A No.

25 Q Okay.

1 A No. I took these -- this data -- I mean,
2 these are all things that are produced to the FDA,
3 and they have to be validated, and confirmed and --
4 so I didn't question the veracity or authenticity,
5 accuracy, because these are, you know, important
6 documents.

7 Q Let me ask you -- if you go back to
8 Exhibit 2006, also known now as "Williams Deposition
9 Exhibit 14" --

10 A Okay.

11 Q -- if you could turn to page 6. You see
12 it says, "Assay HPLC"; right?

13 A Yes.

14 Q Okay. And in the right-hand column,
15 they've set a standard for that; right? It says,
16 "not less than 98 percent and not more than
17 102 percent"?

18 A Yes.

19 Q Okay. So if I have a batch and I run an
20 HPLC assay on the batch, and the purity comes out as
21 98.0 percent -- by the way, that's done by -- let me
22 make sure I understand.

23 These assay HPLCs, those are done by
24 taking the area under the curve for the treprostiniil
25 and comparing that to the standard?

1 A I believe so, yes.

2 Q Okay. So if I have -- if I make a batch
3 of treprostinil, and I measure its HPLC assay, and I
4 get 98.05 percent, that batch passes the FDA
5 specification; right?

6 A Yes.

7 Q I can sell that batch to the public?

8 A That's my understanding, yes.

9 Q Okay. In fact, as far as the FDA is
10 concerned, any batch that has a purity better than
11 98 percent -- so long as it meets these other
12 specifications -- that batch can be sold to the
13 public; right?

14 MS. HASPER: Objection. Beyond the
15 scope.

16 THE WITNESS: Well, I'm not an FDA
17 expert, but my understanding is, it has to be
18 between 98 percent and 102 percent.

19 BY MR. POLLACK:

20 Q Fair enough.

21 But if it's between those numbers, then
22 it can be sold to the public?

23 MS. HASPER: Same objection.

24 THE WITNESS: As far as I know, but I'm
25 not an FDA expert.

1 BY MR. POLLACK:

2 Q You've done a lot of ANDA litigation? Do
3 you know what I mean by, "ANDA litigation"?

4 A Yes. "Abbreviated New Drug Application."
5 The Hatch-Waxman Act.

6 Q And that's where a generic company tries
7 to sell a copy of something very similar?

8 A Yes.

9 Q And the ANDA litigation you've been
10 involved in, including some for treprostinil; right?

11 A Yes.

12 Q The ANDA filer, they report a purity as
13 well -- right? -- for their API?

14 A I believe so.

15 MS. HASPER: Objection. Beyond the
16 scope.

17 THE WITNESS: I believe so. That's what
18 I've seen previously.

19 BY MR. POLLACK:

20 Q Okay. Have you seen that in your other
21 litigations?

22 A I have.

23 Q Yeah. Okay.

24 And they need to meet the same purity
25 specifications for their active pharmaceutical

1 ingredient that the brand name does; right?

2 MS. HASPER: Same objection.

3 BY MR. POLLACK:

4 Q Is that your understanding?

5 A So, again, I'm not an FDA expert, but I
6 know that the generic also has to meet some target
7 specification. I don't know if it's the same as the
8 branded drug or not in every case.

9 Q Okay. In your experience, when you've
10 done your ANDA cases, have you seen that the generic
11 company meets the same purity specification as the
12 brand name?

13 MS. HASPER: Same objection.

14 THE WITNESS: You know, I just don't -- I
15 just don't recall, because in the ANDA cases that I
16 have worked on, this is all prelaunch, end of
17 product, so they have a proposed product and a
18 proposed spec. So I don't know what happens at --
19 you know, after, when they're actually selling, if
20 they, you know, start to sell their product.

21 BY MR. POLLACK:

22 Q Although, they've created a -- a batch
23 which they provide to the FDA. You've seen that;
24 right?

25 A Yes.

1 Q Okay. And they've made purity
2 measurements of their batches in order to try to
3 gain approval of their ANDA?

4 MS. HASPER: Same objection.

5 THE WITNESS: I think that's generally
6 how it works, yeah.

7 BY MR. POLLACK:

8 Q Okay. And they've done an HPLC assay
9 purity analysis of their active pharmaceutical
10 ingredient. You've seen that; right?

11 MS. HASPER: Objection. Scope.
12 Relevance.

13 THE WITNESS: Perhaps, if that's the
14 assay that's used for that particular drug. I would
15 assume they would be doing the same thing. But I
16 suppose there could be other types of assays.

17 BY MR. POLLACK:

18 Q Okay. What about for treprostinil? Did
19 companies like Sandoz, or Watson or Teva, did they
20 submit an HPLC assay analysis for their active
21 pharmaceutical ingredient?

22 MS. HASPER: Objection. Scope.
23 Relevance.

24 I advise the witness not to answer if it
25 would reveal privileged or confidential information.

1 THE WITNESS: I actually don't recall.

2 BY MR. POLLACK:

3 Q Okay. Let me ask you this: When a
4 generic company is measuring the purity of their
5 active pharmaceutical ingredient by HPLC assay
6 analysis, they, too, need to use a reference
7 standard; right?

8 MS. HASPER: Same objection.

9 THE WITNESS: I presume they also have to
10 do that as well to validate their Assay Purity to
11 the FDA.

12 BY MR. POLLACK:

13 Q And when they're doing that with their
14 reference standard, they don't have access to the
15 brand-name company's reference standard; right?
16 They have to create their own?

17 MS. HASPER: Same objection.

18 THE WITNESS: I actually don't know.

19 BY MR. POLLACK:

20 Q Okay. No idea?

21 A I have no idea.

22 Q Okay.

23 MR. POLLACK: I'm going to mark as
24 Williams Deposition Exhibit 15, an article by
25 Terence L. Threlfall titled, "Analysis of Organic

1 Polymorphs," a review that appeared in "The
2 Analyst," October 1995.

3 (Exhibit 15 marked)

4 BY MR. POLLACK:

5 Q Let me ask you: Are you familiar with
6 Terry Threlfall?

7 A I don't recall. I think I've seen this
8 before.

9 Q Okay.

10 A Are you going to tell me that I cited it
11 in my Declaration?

12 Q No, I'm not. I'll tell you that you have
13 not.

14 A I actually don't recognize this.

15 Q Okay. Do you know Dr. Threlfall?

16 A No.

17 Q Okay. I want to turn to -- if you look
18 on the first page, 2435 and going over to 2436,
19 there's a discussion there about how to name
20 polymorphs.

21 What are polymorphs, if you could --

22 A Actually, polymorphs are different
23 crystalline forms of solid compounds. They adopt
24 different crystal-lattice configurations.

25 Q Do you consider yourself an expert on

1 crystal forms of organic molecules?

2 A No.

3 Q But you're -- you've heard of this
4 phenomenon before?

5 A Yes, yes.

6 Q So, Dr. Threlfall discusses here, there's
7 no clear choice on how to designate polymorphs. And
8 one of the suggestions he has is numbering, based on
9 order of discovery. Were you familiar with that
10 system for naming polymorphs?

11 MS. HASPER: Objection. Beyond the
12 scope.

13 THE WITNESS: No.

14 BY MR. POLLACK:

15 Q No? Okay.

16 You've never seen polymorphs named "Form
17 1," "Form 2," "Form 3"?

18 A I have.

19 Q Are you aware that's usually based on the
20 order of discovery?

21 A I have no idea.

22 MS. HASPER: Same objection.

23 BY MR. POLLACK:

24 Q Okay. Now, further down, he has some
25 other suggestions. If we go on to 2436, top of the

1 page, he says -- the second sentence, "The addition
2 of a melting or upper transition point to a Roman
3 numeral is possibly the best compromise, although
4 care must be taken to distinguish the melting point
5 of the polymorph and that of the transformed
6 product."

7 Do you see where I'm reading?

8 A Yes.

9 Q Okay. Did I read that correctly?

10 A That's what it says.

11 Q Am I correct that one of the ways of
12 naming polymorphs that's been proposed is to name
13 them by assigning their -- the melting point in
14 addition to a Roman numeral?

15 MS. HASPER: Objection. Scope.
16 Relevance.

17 THE WITNESS: Yeah. So I'm not a
18 polymorph expert. So --

19 BY MR. POLLACK:

20 Q Well, why do you think they do that?

21 Why do you think they append a melting
22 point to each polymorph?

23 MS. HASPER: Same objection.

24 THE WITNESS: Well, certainly, that's a
25 physical characteristic of an individual solid form.

1 BY MR. POLLACK:

2 Q The melting point is something that's
3 unique to that particular solid form?

4 MS. HASPER: Same objection. Also
5 speculation.

6 THE WITNESS: Yes. But I know enough
7 about crystallization that melting points are highly
8 dependent upon the solvent that was used, the
9 conditions that the crystals were grown under, time,
10 scale. There's lots of variability in that. And
11 I've run into this many, many times over the years
12 in my own research.

13 BY MR. POLLACK:

14 Q Okay. But those conditions create
15 different polymorphs, isn't that the issue?

16 A No. It could be the same --

17 MS. HASPER: Same objection.

18 THE WITNESS: It could be the same
19 polymorph, but depending on how the crystal was
20 grown, there's lots of -- you know, I've consulted
21 on this issue. Inclusion of solvent can sometimes
22 affect melting ranges and things like this.

23 BY MR. POLLACK:

24 Q Well, if there's solvent in it, then it's
25 known as a "solvate"; right?

1 A Not necessarily.

2 Q Why not?

3 A Solvates are different. Solvates are
4 actually -- for example, hydrates are solvates where
5 there's a certain number of water molecules that
6 will be noncovalently associated with a molecule in
7 the crystal lattice. And sometimes these can be
8 highly well-defined numbers like a trihydrate. So
9 every molecule -- say a treprostinil trihydrate,
10 each one would have three molecules of water
11 associated with it. And sometimes there is a range
12 that, you know, it's not exactly 3; it's 3.6. Okay.

13 Q You know, we're talking about -- in this
14 proceeding, we're talking about treprostinil
15 diethanolamine salt Form B. You'll agree with me
16 that they've verified that that salt is neither a
17 hydrate nor a solvate in the Phares reference;
18 right?

19 MS. HASPER: Objection.

20 THE WITNESS: I don't recall. I'd have
21 to look at --

22 BY MR. POLLACK:

23 Q Do you want to look at it?

24 A Sure.

25 Q You could have "Exhibit 1005" as it was

1 called.

2 MR. POLLACK: I'm going to mark as
3 Williams Deposition Exhibit 16 a document currently
4 known in the case as "Exhibit 1005," also known as
5 the "Phares," P-h-a-r-e-s, "reference."

6 (Exhibit 16 marked)

7 BY MR. POLLACK:

8 Q In order to make this a little bit easier
9 for you, the discussion of the characterization of
10 treprostinil diethanolamine salts starts on what's
11 called "Page 90" in the bottom right-hand corner of
12 the document. It's page 87 in the original
13 pagination.

14 A (Examining document) Okay. I've looked
15 at the paragraph on that page 90, or 87.

16 Q Okay. If you could move on to the
17 section on Form B, which starts at the bottom of --

18 A I'm sorry.

19 Q -- 87 and goes onto 88. I particularly
20 wanted to focus on moisture sorption/desorption data
21 and thermal data, but feel free to read all of it.

22 A (Examining document) Okay. I've read
23 that.

24 Q Okay. Based on what you've read here,
25 can you tell whether or not the Form B described

1 here is a hydrate solvate or is otherwise wet with
2 solvent?

3 A Well, in contrast to Form A, where it
4 specifically says -- indicated the material is not
5 solvated, they don't make such an affirmative
6 statement with Form B. But I'm not a polymorph
7 expert, so -- you know, I'm -- I wouldn't be
8 certain.

9 Q Okay. So you don't understand what it
10 says there about the minimum weight loss. That's
11 not an indication to you that there's -- no water
12 was contained in the crystal?

13 A Well, it's certainly hydroscopic.
14 Absorbs water.

15 Q Hmm-hmm. Okay. But this information
16 here, can you tell from that -- the fact that water
17 is not desorbing? Does that indicate to you -- and
18 I recognize you're not a crystal-form expert, but
19 does it indicate to you that it's not a solvate, or
20 is this outside of your area?

21 A It's really outside of my area.

22 Q Okay. And what about -- you see there it
23 says -- do you know what a "TG" is? It says, "A TG
24 shows minimum weight loss up to 100 degrees C."

25 A I've seen that acronym before. I don't

1 remember off the top of my head exactly what it
2 means.

3 Q Have you ever seen the acronym "TGA" as
4 it's sometimes referred to?

5 A Is that "thermographic metric analysis"?
6 Yeah.

7 Q Yes. Are you familiar with how that
8 technique is used with polymorphs?

9 A Not intimately, no.

10 Q Okay. You're not aware that technique is
11 sometimes used to show that there's a solvent or
12 solvate in a -- in a polymorph?

13 MS. HASPER: Objection. Asked and
14 answered. Scope.

15 THE WITNESS: Yeah. I mean, I'm not very
16 familiar with the technique, so --

17 BY MR. POLLACK:

18 Q Okay. Fair enough.

19 If we could go back just quickly in the
20 Threlfall article.

21 You know, never mind.

22 A Okay.

23 MR. POLLACK: I'm going to mark as
24 Exhibit Williams Deposition Exhibit 17 an excerpt
25 from the book "Solid-State Chemistry of Drugs," by

1 Steven R. Byrn, Ralph R. Pfeiffer and Joseph G.
2 Stowell.

3 (Exhibit 17 marked)

4 BY MR. POLLACK:

5 Q And, no, this wasn't attached to your
6 report.

7 Have you either seen or read this book,
8 ever, before?

9 A No.

10 Q Okay. Do you know any of the authors?

11 A No.

12 Q Okay. Are there any textbooks on the
13 solid-state form of drugs that you have read?

14 A Not that I can think off the top of my
15 head, no.

16 Q Okay. Turn to the first page of this
17 document. This is Chapter 10 on polymorphs. Let me
18 just ask you about the second sentence which says
19 that, "Compounds that crystallize as polymorphs can
20 show a wide range of different physical and chemical
21 properties, including different melting points and
22 spectral properties."

23 I just want to know if you agree with
24 that sentence or have any reason to disagree with
25 it?

1 MS. HASPER: Objection. Scope.

2 THE WITNESS: I don't have any reason to
3 disagree.

4 BY MR. POLLACK:

5 Q Okay. Do you agree with it?

6 A I have no reason to disagree.

7 Q Okay. One of the things that
8 characterizes a polymorph is its melting point.
9 It's one of the things that uniquely identifies a
10 polymorph; is that right?

11 MS. HASPER: Objection. Scope. Asked
12 and answered.

13 THE WITNESS: Again, based on my limited
14 understanding that this can be quite dependent on
15 conditions, the solvent that was used, the scale.

16 BY MR. POLLACK:

17 Q If you look a little further down on
18 page 143, there's a second paragraph. This, again,
19 talks about how polymorphs are made. Do you see --
20 or named. Do you see that?

21 A Yes.

22 Q Okay. And they point out there's no
23 standard numbering systems for polymorphs; right?

24 A That's what it says.

25 Q Okay. And if you go down about three,

1 four, five sentences, there's a sentence beginning
2 with the word, "It." Do you see that sentence?

3 It says, "It has been suggested . . .?"

4 A Yes.

5 Q Okay. And I'll read it into the record.

6 "It has been suggested that polymorphs be
7 numbered consecutively in the order of their
8 stability at room temperature or by their melting
9 point."

10 Did I read that correctly?

11 A That's what it says.

12 Q Okay. And so what he's proposing here is
13 that a polymorph would be identified by its melting
14 point. Do you see any place where he says: And it
15 needs to be further identified by what solvent was
16 used?

17 MS. HASPER: Objection. Relevance.

18 THE WITNESS: No, but I guess I'd have to
19 read a lot more on -- on this -- in this article.
20 It may be discussed later.

21 BY MR. POLLACK:

22 Q Okay. Well, this is a -- I'll represent
23 to you, it's not discussed later. But this is the
24 second time we've seen a proposal that polymorphs be
25 named by their melting point; right? You saw that

1 in the Threlfall article as well?

2 A Okay. Yes. That's what it says.

3 Q And Threlfall also, he doesn't suggest:

4 Oh, it needs to be named also by what solvent was
5 used -- right?

6 A I didn't see that mentioned, no.

7 Q While we're getting that out, could you
8 go back to the patent for me.

9 A The patent? Which patent?

10 Q The patent. The '393 patent,
11 Exhibit 1001, now known as "Williams Deposition
12 Exhibit 3."

13 A Okay.

14 Q And I'd like to turn to what's called
15 "Page 8" in this exhibit. It's column 12 of the
16 patent. And if you look in that column in the
17 paragraph starting -- two paragraphs starting around
18 line 35, you see it refers to, "Polymorph B of the
19 treprostinil diethanolamine salt"; right?

20 A What line?

21 Q I'm sorry. Line 40 -- it starts around
22 line 42 and continues down the page.

23 A Okay.

24 Q Okay. Now, that polymorph B, that's the
25 same polymorph B that's referred to in Exhibit 1005,

1 the Williams Deposition Exhibit 16, the Phares
2 reference?

3 A I can't be certain they're the
4 same, 'cause Phares doesn't tell us where the
5 treprostiniil comes from.

6 Q It's the same polymorph, though; is that
7 fair?

8 A Well, that's what it's called, "polymorph
9 B."

10 Q Okay. They're both polymorph Bs; right?

11 A That's what they're called.

12 Q Do you have any reason to believe that
13 they're different?

14 A Well, I certainly know where polymorph B
15 in the patent comes from. In Phares, they do not
16 identify the source of the treprostiniil.

17 Q Yeah. I'm not asking about how it was
18 made or other differences. I'm just asking in
19 regards to what crystal form it is.

20 Are both of these the same crystal form,
21 the crystal form of treprostiniil diethanolamine salt
22 in the '393 patent and the crystal form in the
23 Phares prior art reference, which are both called
24 Form B? Are they the same crystal form?

25 A I can't be 100 percent certain. This

1 melts at 104, and I think the Phares melts the 107.

2 So I'm not certain.

3 Q Okay. Now, the Phares reference,
4 that's -- that's a patent application written by
5 people at United Therapeutics; right?

6 A Yes.

7 Q Okay. Did you ask anyone at United
8 Therapeutics: Hey, do you have information about
9 that particular Form B that you made in the Phares
10 patent?

11 A No.

12 Q But you knew they -- if anyone had that
13 information, it would be United Therapeutics; right?

14 A Presumably.

15 Q Right. You don't think I'm going to have
16 that information; right?

17 A No.

18 Q Right. And if they were different --
19 right? -- if the Form B in the Phares reference and
20 the Form B in the '393 patent -- if they were
21 different, don't you think that your counsel would
22 have given you documents showing that they were
23 different crystal forms?

24 A All I know is what's stated in the
25 documents.

1 Q That you received.

2 A Yes.

3 Q And you didn't ask for any further
4 information on this issue?

5 A No. No. I didn't think there was a need
6 to.

7 Q So we were looking at the patent,
8 Exhibit 1001, also known as "Williams Deposition
9 Exhibit 3." I want to go to the next paragraph that
10 begins with, "At this stage . . ."

11 Do you see that paragraph? In column 12.

12 A Okay. Column 12 and -- where -- okay.

13 Q It's about line 53.

14 A Hmm-hmm.

15 Q I'll read it into the record so we know
16 where we are?

17 A Okay.

18 Q It says, "At this stage, if the melting
19 point of the treprostinil diethanolamine salt is
20 more than 104 degrees C, it was considered polymorph
21 B."

22 Did I read that correctly?

23 A That's what it says.

24 Q Okay. So if you're in the '393 patent,
25 they are identifying whether a treprostinil

1 diethanolamine salt is Form B by its melting point;
2 right?

3 A Yes.

4 Q Okay. And if the melting point is
5 greater than 104, that indicates that it must be the
6 Form B; correct?

7 A Your question again?

8 Q Let's just put it this way: The melting
9 point is a signature for Form B.

10 A It's one characteristic, physical
11 property, yes.

12 Q They're not just saying it's one
13 characteristic property; they're saying it is the
14 property which tells you it's Form B. Isn't that
15 what that sentence says?

16 A Well, its X ray defraction pattern is
17 going to be much more diagnostic.

18 Q Okay. I'm just asking: What does this
19 sentence say?

20 A Well, it says, "At this stage if melting
21 point of the treprostini diethanolamine salt is
22 more than 104 degrees, it was considered polymorph
23 B." That's what it says.

24 Q Okay. Let me ask you this: The people
25 at United Therapeutics, they know how to take PXRDs;

1 right?

2 MS. HASPER: Objection. Speculation.

3 THE WITNESS: I'm not sure if they do
4 that in in-house, or if they contract that out to
5 another lab that has deep expertise in this or not.
6 I don't know if they do it in-house or not. I don't
7 know.

8 BY MR. POLLACK:

9 Q Okay. They have access to the technique;
10 right?

11 A Sure.

12 Q We saw in the Phares reference, they have
13 a PXR for Form B; right?

14 A Yes.

15 Q So presumably, they did a PXR of what
16 they did here in the '393 patent, Exhibit 1001;
17 right?

18 MS. HASPER: Same objection.

19 THE WITNESS: You're asking me presumably
20 they did a PXR?

21 BY MR. POLLACK:

22 Q Yeah.

23 A I don't know if there was data on that or
24 not in here.

25 Q There's no data in here.

1 Let me ask it to you this way: Do you
2 think that the people at United Therapeutics would
3 have reported that this is Form B without do doing a
4 PXR? Is that your opinion?

5 A I don't have an opinion.

6 Q One way or the other?

7 Okay. I mean, the people at United
8 Therapeutics, they're not amateurs at these
9 techniques; right?

10 MS. HASPER: Objection. Scope.

11 BY MR. POLLACK:

12 Q You don't know?

13 A I don't know.

14 Q Okay.

15 A We've been going for another an hour,
16 could we possibly have a break?

17 THE VIDEOGRAPHER: This ends media No. 2
18 in the deposition of Robert M. Williams, Ph.D.
19 We're off the record at 2:45 P.M.

20 (Off the record)

21 THE VIDEOGRAPHER: This begins Media
22 No. 3 in the deposition of Robert M. Williams, Ph.D.
23 We are back on the record. The time is 2:57 P.M.

24 MR. POLLACK: I'm going to mark as
25 Williams Deposition Exhibit 18, a Guidance for

1 Industry from the FDA titled, "ANDAs:
2 Pharmaceutical Solid Polymorphism."

3 (Exhibit 18 marked)

4 BY MR. POLLACK:

5 Q I'm going to represent to you, this
6 wasn't attached to your report. But I'm wondering
7 if you've reviewed this document in the past in the
8 course of your various ANDA litigations or
9 consulting?

10 A Not that I can recall.

11 Q Okay. This is -- well, can you explain
12 to me what is -- what this document is?

13 A No.

14 Q Okay.

15 A I've never seen it before.

16 Q Sure. Do you know what a Guidance for
17 Industry is -- I mean -- from the FDA?

18 A I've seen FDA guidance things. These are
19 things the FDA puts out to help pharmaceutical
20 companies jump through all the hoops with the FDA to
21 get approval.

22 Q Okay. And I'm right -- this one is about
23 pharmaceutical solid polymorphism?

24 MS. HASPER: Objection.

25 THE WITNESS: That's what it says.

1 MS. HASPER: Scope.

2 BY MR. POLLACK:

3 Q Okay. And in simple language, that's
4 about different crystal forms of drugs; right?

5 MS. HASPER: Same objection.

6 THE WITNESS: Yes.

7 BY MR. POLLACK:

8 Q Okay.

9 MS. HASPER: Counsel, if I could clarify:
10 You said this was a -- Exhibit 18. I thought the
11 previous exhibit was 18.

12 THE REPORTER: No, the last one was 17.

13 MS. HASPER: Thank you. I'll correct
14 that, then.

15 BY MR. POLLACK:

16 Q Let me ask you: Are you familiar with
17 any guidances from either the FDA or -- are you
18 familiar with the ICH?

19 A I'm trying to remember what the acronym
20 stands for. I don't remember now.

21 Q Okay.

22 A But, yes, I've seen -- I've seen each
23 before. I was trying to remember what the acronym
24 is.

25 Q Have you looked at any either ICH or FDA

1 documents concerning polymorphism in the past?

2 MS. HASPER: Objection. Relevance.
3 Scope.

4 THE WITNESS: Not that I can think of.

5 BY MR. POLLACK:

6 Q Okay. Let me ask you just to turn to
7 page 9 of Exhibit 18. You see here this is a -- a
8 guidance setting forth specifications for polymorphs
9 in drug substances for solid, oral, and suspension
10 dosage-form products.

11 And you see that in the first square, the
12 question is: Is there a polymorph specification in
13 the USP -- the USP -- that's the United States
14 Pharmacopeia?

15 A Pharmacopeia.

16 Q What is the United States Pharmacopeia?

17 A Oh, it's a compendium of drug substances
18 that is indexed and catalogued by this organization.

19 Q Okay. And the organization which is
20 known as the "USP"; is that right?

21 A I think so, yes.

22 Q The USP puts in specifications for each
23 drug substance, including things like purity,
24 crystal form, melting point -- is that your
25 understanding?

1 A I don't recall off the top of my head
2 exactly what data's in there.

3 Q Okay. You've used the USP; right?

4 A I have.

5 Q Okay. What do you recall from your use
6 of it? What that -- what is in there?

7 A It's been a while since I looked at one,
8 so I don't exactly remember.

9 Q Okay. About how long did you look at
10 one?

11 A I don't remember.

12 Q More than a year ago?

13 A Well, you know, my father was a
14 pharmacist, and he has a whole bunch of old ones
15 that we just had to move from one place to another.
16 I looked at those, but those are ancient.

17 Q Okay. Have you ever looked at the
18 U.S. -- you understand there will be a USP monograph
19 for treprostinil?

20 A Yeah.

21 Q And there's also one for treprostinil
22 diethanolamine salt; correct?

23 A I guess so. I'll take your
24 representation.

25 Q Okay. You haven't looked?

1 A No.

2 Q Okay. Now, you see here, one of the
3 things that the FDA asks the ANDA applicant to do is
4 to look if there's a polymorph specification in the
5 USP, and then it says, for example, "melting point."
6 Do you see that?

7 A Yeah, I see that.

8 MS. HASPER: Objection. Scope.

9 BY MR. POLLACK:

10 Q So melting point is one of the things the
11 FDA calls out. In fact, it's the only thing in here
12 that they give as an example as associated with a
13 polymorph. Do you see that?

14 MS. HASPER: Same objection.

15 THE WITNESS: It says, "example." "For
16 example."

17 BY MR. POLLACK:

18 Q There's other things; right?

19 A Certainly.

20 Q Right. But melting point is the one that
21 they gave in this document?

22 A As an example.

23 MS. HASPER: Same objection.

24 BY MR. POLLACK:

25 Q Because melting point is something that

1 uniquely identifies a polymorph; right?

2 MS. HASPER: Same objection.

3 Mischaracterizes the underlying document.

4 THE WITNESS: I would not necessarily
5 agree with that.

6 MR. POLLACK: Let me mark as Williams
7 Deposition Exhibit 19 a document that's been called
8 "Exhibit 2030" in this case. It's an article by --
9 rather than try to say the name, it's an article
10 that appeared in the International Journal of
11 Pharmaceutics in 2006.

12 (Exhibit 19 marked)

13 BY MR. POLLACK:

14 Q Let me ask you: Is Williams Deposition
15 Exhibit 19 an article you relied upon in your
16 Declaration?

17 A Yes.

18 Q Okay. Do you have any idea how to
19 pronounce the author's first name?

20 A "Adhiyaman."

21 Q Okay. We'll call this the Adhiyaman
22 article?

23 A Okay.

24 Q Okay. Now, in the Adhiyaman article, we
25 see -- I think my understanding of this -- or at

1 least of your opinion of it -- is that there are a
2 number of crystals of certain chemical called
3 "dipyridamole"? Is that a decent pronunciation of
4 it, or how would you pronounce that?

5 A "Dipyridamole."

6 Q Okay. And they're all made in different
7 solvents; is that fair?

8 A Yes.

9 Q Okay. And each of them has a different
10 PXRD pattern; is that fair?

11 A I think that's what they're illustrating
12 in the article, yes.

13 Q Okay. Isn't it correct that a different
14 PXRD pattern means that the crystal has a different
15 three-dimensional structure in a solid form?

16 A Yes.

17 Q Okay. So each of these is really a
18 different crystal form of the same drug; is that
19 fair?

20 A I think that's fair.

21 Q Okay. So what we learned about in this
22 article is sometimes when you use different
23 solvents, you get different crystal forms of the
24 same drug; right?

25 A Yes.

1 Q Okay. So there's nothing in here saying
2 that two crystals that have the same crystal form
3 and same PXRD structure made from different solvents
4 are different?

5 MS. HASPER: Objection. Mischaracterizes
6 the document.

7 THE WITNESS: Please state your question
8 one more time?

9 BY MR. POLLACK:

10 Q Sure. Sure.

11 So there are no -- let me make the
12 following clear: There are no examples in Williams
13 Deposition Exhibit 19 of two crystals having the
14 same PXRD pattern but which are different crystal
15 forms.

16 A You'll have to ask me that one more time.

17 Q Sure. There are no examples in Williams
18 Deposition Exhibit 19 of two crystals, made with
19 different solvents, having the same PXRD pattern but
20 different -- but are different crystal forms?

21 A I'm not sure I can come to that
22 conclusion.

23 And what I did cite from this article is
24 that the conclusion, which I quoted in my
25 Declaration, and it's also based on my experience of

1 crystallizing the same compound on different days
2 from different solvents under slightly different
3 conditions, you can get a different melting point.

4 And it depends on the scale and lots of things.

5 Q Okay. But could you get a different
6 melting point because you've gotten a different
7 crystal form. Isn't that the issue?

8 A Not necessarily.

9 Q So your testimony today is, I can have --
10 let me ask you this: If I have two crystals that
11 have the same PXRD pattern, can I get two different
12 melting points?

13 A Yes.

14 Q Okay. And what is the reason for that in
15 your opinion?

16 MS. HASPER: Objection. Scope.

17 THE WITNESS: So the way these melting
18 points, which are done typically today with this
19 differential scanning calorimetry, the melting
20 ranges can depend on the rate of heating, the sample
21 size, and even the individual instrument that's
22 used. There can be variability.

23 BY MR. POLLACK:

24 Q Sure. You're saying there can be errors
25 in the measurement?

1 A Yes.

2 Q Fair enough. Okay.

3 But assuming that the appropriate scan
4 rate is used and appropriate sample size is used and
5 all of those things are the case, will two crystals
6 which have the same PXRD pattern have the same
7 melting point?

8 A I don't know if that's ubiquitously true.
9 I wouldn't agree with that.

10 Q Do you not know, or do you formally
11 disagree with that?

12 A I disagree.

13 Q Okay. Do you have any -- is there
14 anything in this article that supports your opinion?

15 A Well, the conclusion is that -- it says
16 right here, "In conclusion, it can be said that the
17 crystallization conditions" --

18 Q Read that slowly.

19 A Sorry.

20 "In conclusion, it can be said that the
21 crystallization conditions and the medium used have
22 a major effect on dipyridamole crystals habit
23 modification under ambient conditions. The crystals
24 showed significant changes in the shape, size,
25 melting points, dissolution rate, XRD patterns and

1 DSC curves."

2 And I quoted that in my --

3 Q But here, they pointed out they all had
4 different XRD patterns, right?

5 A Okay.

6 Q Right?

7 And, in fact, that's what the data shows
8 in here. They all had different XRD patterns?

9 A Hmm-hmm.

10 Q Right. I'm asking about two crystals
11 having the same XRD pattern.

12 A So in my own research, we do a lot of
13 x-ray crystallography. And I work pretty closely
14 with an expert crystallographer, Orrin Anderson.
15 And we've had crystals that had the exact same XRD
16 pattern that were produced on different days that
17 had slightly different melting points. So I've seen
18 this myself.

19 Q Okay.

20 A So what you're trying to say is just
21 simply not ubiquitously true.

22 Q Okay. Do you have any literature or any
23 papers -- other than your own personal anecdotal
24 experience, do you have any scientific literature or
25 papers that support that opinion?

1 A I'm sure I could find it if I was asked
2 to, but that was based on my own experience.

3 Q Okay.

4 A And that's -- it happened not just once.
5 It's happened numerous times.

6 Q Okay. But as part of this proceeding,
7 you didn't look for any papers that supported that
8 opinion?

9 A Well, I think the main point here is that
10 you can't compare the polymorph form and Phares to
11 what's in the '393. That was the main underlying
12 theme here.

13 Q Right. But your opinion on that was
14 based on the idea that the same polymorph could have
15 two different melting points; correct?

16 MS. HASPER: Objection. Mischaracterizes
17 the document and the testimony.

18 THE WITNESS: I mean, what's
19 characterized is the same polymorph -- or what's
20 called -- but there wasn't enough information to
21 ascertain that that was the case.

22 BY MR. POLLACK:

23 Q The people who called it the same
24 polymorph, that's United Therapeutics?

25 A Okay.

1 Q The people you're working for; right?

2 A That doesn't mean they're infallible.

3 Q Okay. It wasn't -- it wasn't me; right?

4 A No.

5 Q It wasn't Dr. Winkler?

6 A No.

7 Q No?

8 And -- okay. You think maybe they made a
9 mistake in identifying the polymorphs?

10 MS. HASPER: Objection.

11 Mischaracterizes -- testimony.

12 THE WITNESS: Yeah. I was addressing

13 Dr. Winkler's analysis.

14 BY MR. POLLACK:

15 Q That's not what I asked you.

16 I said, do you think they made a mistake
17 in identifying the polymorphs of each of those
18 papers? United Therapeutics made a mistake?

19 MS. HASPER: Objection. Mischaracterizes
20 testimony. Asked and answered.

21 THE WITNESS: I cannot be 100 percent
22 certain.

23 BY MR. POLLACK:

24 Q Okay. You didn't do anything to
25 investigate whether they made a mistake in

1 identifying those two polymorphs?

2 A No. I just have the documents as they
3 read.

4 Q And the documents called both of those
5 "polymorphs Form B"?

6 A Yes. Made under different conditions,
7 and Phares doesn't provide any information on
8 solvent that was used, scale, source of the
9 treprostinil, and so on. So it's just not enough
10 there.

11 Q You know, you've brought up the term
12 "scale" several times in this deposition. Looking
13 back at Exhibit 1001, is there anything --

14 A What's Exhibit 1001?

15 Q Exhibit 1001 is the '393 patent. It's
16 also known as "Williams Deposition Exhibit 3."

17 A Okay.

18 Q I'd like you to look at claims in the
19 '393 patent. Do you see anything in there that says
20 what scale the reaction is being carried out at?

21 A No.

22 Q Okay. So the reaction covers any scale;
23 right?

24 A Certainly.

25 Q Could be bench; laboratory reaction, like

1 Moriarty did in his Journal of Organic Chemistry
2 article?

3 A Yes.

4 Q That could be included -- and it could be
5 a large clinical batch; correct?

6 A Yes.

7 Q Okay. Let me go back to the Phares
8 reference, Exhibit 1005, known as "Williams
9 Deposition Exhibit 16." If you could turn to
10 page 42. And we have a lot of page 42s here, so let
11 me be a little more specific.

12 Page 42 in the lower right-hand corner of
13 the document, original page 40 of the reference --

14 A Yes. I'm there.

15 Q Okay. -- I was wondering if you could
16 help me understand some of the chemistry in -- you
17 see there's a synthesis at the top of page; right?

18 A Yes.

19 Q Okay. Here's what I was not fully
20 understanding: There's -- if you go to this
21 synthesis scheme, there's a structure on the lower
22 right-hand corner in the scheme. And next to it,
23 there's an arrow, and there's a letter "L" above it.
24 Do you see that?

25 A Yes.

1 Q Okay. And now, what's -- to the right of
2 the arrow with the letter "L," that's the mirror
3 image of the -- some of the compounds that are shown
4 in claim 9 of the '393 patent; is that right?

5 A So which -- which structures are you
6 asking me to compare?

7 Q Yeah. Let's take a look at -- there's a
8 structure called "5" in claim 9.

9 A Okay. That's the so-called "benzindine
10 triol."

11 Q Hmm-hmm. And is that structure and
12 claim 5 -- is that the mirror image of the structure
13 on page 42 also known as "40," in the lower
14 right-hand corner?

15 A That would be 11-B where R is H. That
16 would be the mirror image of the benzindine triol.

17 Q Okay. Thanks.

18 And then in step (1), if you look down in
19 the paragraph, it tells you what step (1) is. And
20 step (1) seems to have two parts to it; is that
21 fair?

22 There's a little (i) and then a two
23 little (ii) part?

24 A Yes.

25 Q Okay. Those are two separate steps in

1 (1); right?

2 A Yes.

3 Q Okay. And the first step -- the
4 letter -- single (i) step where it says, "CL,"
5 "CH2," "CN," and then it says "K2," "CO3" -- is that
6 the -- is that the alkylating step like is done in
7 step (a) of claim 9, except for the mirror-image
8 compound?

9 A Yes.

10 Q Okay. And then there's a step where it
11 says "KOHCH3OH reflux 83 percent." Is that the
12 hydrolyzing step of -- which is called "step (b)" in
13 the '393 patent being applied to the mirror-image
14 compound?

15 A Yes.

16 Q Okay. So what we see here is there's an
17 alkylating step (a) and a hydrolyzing step (b) on
18 page 42 of the Phares reference.

19 A Yes.

20 MR. POLLACK: I'm going to mark as
21 Williams Deposition Exhibit 20 an excerpt from
22 Exhibit 1002, and it's a small section from that
23 exhibit which was the prosecution history. And it's
24 called the "Declaration of David Walsh."

25 (Exhibit 20 marked)

1 BY MR. POLLACK:

2 Q You've reviewed this document in
3 preparation for this deposition and for -- in
4 preparing your Declaration; correct?

5 A Yes.

6 Q I think we discussed earlier that
7 according to this document -- if we turn to the
8 document called "Page 348" in the lower right-hand
9 corner. I think we discussed earlier how for the
10 treprostinil diethanolamine salt, that's what's
11 presented at the top of the page -- the salt?

12 A Yes.

13 Q Okay. And then below that is the free
14 acid?

15 A Yes.

16 Q Okay. And we see in the free acid, the
17 impurities are 0.2 percent; right? Total related
18 substances.

19 A No.

20 Q Oh, I'm sorry. What is the impurities by
21 HPLC for total related substances for the
22 treprostinil free acid on the Walsh Declaration?

23 A Oh, you were asking me about the salt,
24 which is .1 pertinence.

25 Q I'm sorry. Misspoke, then. I was not --

1 okay.

2 Want to do the salt first or the free
3 acid?

4 A You're asking the questions.

5 Q Okay.

6 A You pick the order.

7 Q All right. Let's do the free acid.

8 A Okay.

9 Q Am I correct that the total related
10 substances for the free acid is 0.2 percent?

11 A Yes.

12 Q And for the treprostiniol diethanolamine
13 salt, the total related substances is 0.1 percent?

14 A Yes.

15 Q Okay. So, in fact, there are -- well,
16 let me ask you this: The treprostiniol free acid,
17 it's made the same way as the diethanolamine salt,
18 except step (d) is then executed; is that correct?

19 A That's correct.

20 Q Okay. And so when step (d) was executed,
21 the amount of total related substances actually
22 increased; correct?

23 A Yes.

24 Q And, in fact, the spec, even, for
25 treprostiniol free acid made using the step (d) is

1 actually set to not more than 3 percent. Do you see
2 that?

3 A Yes.

4 Q And for the salt, the level of impurities
5 is set to only not more than 1-1/2 percent. Do we
6 see that?

7 A Yes.

8 Q So carrying out an additional step,
9 step (d), on the treprostinil diethanolamine salt
10 actually increases the impurity level of the
11 product; right?

12 MS. HASPER: Objection. Mischaracterizes
13 the document.

14 THE WITNESS: So what's going on here --
15 this is actually fairly easy to understand.

16 BY MR. POLLACK:

17 Q Okay.

18 A -- is that the salt, which is incredibly
19 pure. Seven to eight impurities is not present.
20 The only thing that's detectable is an tiny amount
21 of the enantiomer 3AU90. All the others have been
22 eliminated. And when you treat the salt with acid,
23 the impurities that now come back are the two
24 dimers: 750W93, 751W93; and the ethyl ester.

25 And that's because those are formed by

1 acid-catalyzed self-condensation to make the two
2 dimers, and the tiny residual amount of ethanol that
3 was used to recrystallize the diethanolamine salt
4 forms a small amount of the ethyl ester.

5 Q Okay. If you could turn to -- we had an
6 exhibit we were looking at before, Williams
7 Deposition Exhibit 14. That was a letter from the
8 FDA.

9 A Okay. I've got the letter.

10 Q If you could turn to the second page of
11 the letter, the one that says "2" in the center at
12 the bottom. If you look -- you see there's a bullet
13 point in the middle of the page?

14 A Yes.

15 Q Okay. And in that first paragraph there,
16 they say, "Historically at our Chicago facility,
17 UT15C intermediate is not a compound that was used
18 during the conversion of [REDACTED] to
19 treprostinil." Did I read that correctly?

20 A That's what it says.

21 Q And UT15C intermediate, that's a code
22 name for treprostinil diethanolamine salt. You know
23 that; right?

24 A Okay. I actually -- I don't remember
25 that that's the code name. Here in this -- Walsh

1 Declaration it's called "UTW-11-0327." So --

2 Q You're not familiar with the code name
3 "UT15C" from the documents?

4 A I mean I didn't -- I saw UT15C. I was
5 real -- I focused more on the more explanatory names
6 like benzindine triol, the diethanolamine salt.

7 Q Maybe this next sentence will help you
8 recall what UT15C was. It says, "This new process
9 was necessary for the production of our UTC15C API"
10 -- "API" stands for "active pharmaceutical
11 ingredient"?

12 A Yes.

13 Q -- "for investigational oral
14 formulation."

15 Are you aware of that United Therapeutics
16 sells an oral treprostinil diethanolamine salt drug?

17 A Yes.

18 Q Okay. Reading this now, does that
19 refresh your recollection that UT15C is treprostinil
20 diethanolamine salt?

21 A Yeah.

22 Q Okay.

23 A That's fine.

24 Q Okay. Now, it says here that, "The data
25 in table 5 from the validation report" -- which

1 apparently has a number, [REDACTED] -- "showed several
2 impurities detected at low levels, below the ICH
3 identification limit of [REDACTED] percent. These
4 impurities are not carried through to the final API
5 treprostinil as described below."

6 Did I read that correctly?

7 A That's what it says.

8 Q So here, what they're saying is, there's
9 a bunch of impurities in treprostinil diethanolamine
10 salt. And those ones are not carried forward to the
11 free acid. Did you see that?

12 A Okay. I see that.

13 Q Okay. I'm not mischaracterizing that --
14 right? -- that's what they're saying?

15 A That's what it says.

16 Q Okay. And so, in fact, here, what
17 they're telling the FDA is, the treprostinil free
18 acid is cleaned of all these impurities by the acid
19 step, and yet Walsh's Declaration doesn't list these
20 impurities and claims that the diethanolamine salt
21 is purer than the free acid.

22 Do you see that?

23 MS. HASPER: Objection. Mischaracterizes
24 the documents.

25 THE WITNESS: So in Walsh's Declaration,

1 there are unidentified impurities. So -- so I can
2 only assume that that's what this is referring to.

3 BY MR. POLLACK:

4 Q Here, it shows that there are several
5 impurities. Do you see that?

6 A Well, it says --

7 MS. HASPER: Objection. Vague.

8 Where are you referring to?

9 THE WITNESS: I'm sorry.

10 BY MR. POLLACK:

11 Q In page 2.

12 A Yeah. So in the Walsh Declaration, it
13 says, "unidentified impurities," plural.

14 Q Right.

15 A Okay.

16 Q Hmm-hmm.

17 A And so there's 0.7 percent of those. And
18 then in the acid, those are not detected.

19 Q Yeah. Except here, you notice how here
20 it says they're below the ICH identification limit
21 of 0.1. That doesn't say they're below the .05
22 identification limit where you don't have to report
23 them; right?

24 MS. HASPER: Objection. Mischaracterizes
25 the documents.

1 THE WITNESS: Okay. I haven't thought
2 about this. You know, I haven't --

3 BY MR. POLLACK:

4 Q That's why I'm asking you to think about
5 it now.

6 A Okay.

7 MS. HASPER: Objection. Beyond the scope
8 of his report.

9 THE WITNESS: You know, I'd have to think
10 about this deeply and figure out what the
11 significance, if any, of that is.

12 BY MR. POLLACK:

13 Q Okay. You agree with me they're saying
14 here -- reading this sentence fairly, that there are
15 a number of impurities that are above the .05 level
16 but below the .01 level which are in the salt, and
17 those are being cleaned out by the acidification
18 process.

19 MS. HASPER: Objection. Mischaracterizes
20 the --

21 BY MR. POLLACK:

22 Q That's what they're saying to you; right?

23 MS. HASPER: Objection. Mischaracterizes
24 the documents.

25 THE WITNESS: So I'd have to think about

1 this, but I -- I actually -- anyway, I'd have to
2 think about it.

3 BY MR. POLLACK:

4 Q What were you going to say?

5 A I'd need more time to consider.

6 Q You agree with me there appears to be
7 some contradiction here between what Walsh is
8 presenting and what is being presented to the FDA in
9 Exhibit 2006?

10 MS. HASPER: Objection. Mischaracterizes
11 the testimony and the documents. Also asked and
12 answered.

13 THE WITNESS: Yeah. I wouldn't -- I -- I
14 don't have an opinion on that. So --

15 BY MR. POLLACK:

16 Q You have no opinion, one way or the
17 other?

18 A I have no opinion.

19 Q This isn't something you looked at in
20 forming your opinion for this case?

21 A No.

22 Q Let me ask you: What kinds of impurities
23 that would be in the diethanolamine salt would be
24 cleaned out by the acidification step?

25 MS. HASPER: Objection. Foundation.

1 THE WITNESS: You know, I could only
2 speculate what would be reasonable to a person
3 skilled in the art, since the diethanolamine salt --
4 the only basic species is diethanolamine.

5 Diethanolamine may also come with some other basic
6 impurities: Maybe ethanolamine, triethanolamine.

7 So I'm always speculating.

8 I have no data, but it's possible that
9 those are basic impurities that are removed when you
10 proteinate the salt because you also get rid of
11 diethanolamine. So it would make sense that
12 molecules like that would also disappear.

13 BY MR. POLLACK:

14 Q And I'm correct if we look on Walsh or
15 Williams Deposition Exhibit 20 here, on page 348 as
16 it's styled in the bottom right-hand corner, those
17 kinds of impurities were not included on the list
18 for the treprostinil diethanolamine salt?

19 A I'm not -- I didn't follow you. I'm
20 sorry, counselor.

21 Q The kind of impurities you just described
22 that could be cleaned out by the acid, those
23 impurities are not on the list that Walsh presented
24 of impurities for the diethanolamine salt.

25 MS. HASPER: Objection. Mischaracterizes

1 the document.

2 THE WITNESS: Well, those presumably
3 could be unidentified impurities, because there's
4 .07 percent that are in the salt that are not
5 detected in -- or there's -- there's "ND" for
6 unidentified impurities in the final acid. So --

7 BY MR. POLLACK:

8 Q If we have, let's say, just two
9 impurities that are above the .05 nonreporting level
10 for ICH, that already gets us to above .1 -- right?
11 -- .1 and above in total unidentified impurities?

12 A I'm not quite following your question.
13 Just --

14 Q Here, it refers to the -- I'm sorry.
15 Here it refers to, there are some
16 impurities in 2006 that are referred to. And it
17 says it shows several impurities. Not one, but
18 several impurities.

19 Let's imagine there's just two for this
20 hypothetical. At low levels, they're below the ICH
21 identification limit of .1 -- or presumably, if they
22 were below the .05 level -- right? -- for ICH -- in
23 which case, you don't even have to discuss them --
24 that would have been mentioned.

25 So there are several impurities that are

1 below .1 but above .05. If we just have two of
2 those, that's already going to put us greater than
3 point .07 that you referred to in the Walsh
4 Declaration; right?

5 MS. HASPER: Objection. Mischaracterizes
6 the documents.

7 THE WITNESS: So since I don't know what
8 they are, how many unidentified impurities are in
9 that number of .07 percent, I can't say anything.

10 BY MR. POLLACK:

11 Q All right.

12 A I'd only be guessing, and I don't want to
13 guess.

14 Q Okay. Okay.

15 But -- seem a little strange to you that
16 Walsh doesn't mention this to the Patent Office in
17 providing this Declaration that there are other
18 impurities?

19 MS. HASPER: Objection. Mischaracterizes
20 the document. Beyond the scope.

21 THE WITNESS: You know, I have no idea
22 what was inside Dr. Walsh's mind and what the actual
23 exchange was between him and the Patent Office. You
24 know, these are individual batches that he
25 represented as being representative.

1 And I think that is fair, because the
2 analysis that I did on 121 batches of treprostinil
3 made by the '393 are as good, if not significantly
4 better, than these. So it's consistent. I don't
5 think he's hiding anything. I don't think there's
6 anything sinister going on here.

7 BY MR. POLLACK:

8 Q I mean, earlier, we were talking about
9 the one Moriarty batch, and you were complaining
10 that that [REDACTED] batch was not representative, even
11 though it was the one that Moriarty presented in his
12 paper. Now you're saying one batch from Walsh is
13 representative?

14 A Well -- that's what he represented to the
15 FDA, and the data I've looked at corroborates that.

16 Q Well, we saw earlier -- right? -- there's
17 a [REDACTED] percent that's corroborated by 46 samples;
18 right?

19 MS. HASPER: Objection. Mischaracterizes
20 the document.

21 THE WITNESS: I mean, I haven't done the
22 comparison. You threw, like, a spreadsheet in front
23 of me and --

24 BY MR. POLLACK:

25 Q Do you want to do it now? We can go

1 through the spreadsheet, and you can check that
2 every number is correct.

3 A I'll -- you're asking the questions. Not
4 me.

5 Q Okay. Let's do that now. We'll put up
6 the spreadsheet, and you can go through it and
7 verify that each number is correct. Is that fair?

8 Okay.

9 THE REPORTER: Let's go off the record.

10 THE VIDEOGRAPHER: We're off the record.

11 The time it 3:37 P.M.

12 (Off the record)

13 THE VIDEOGRAPHER: We are back on the
14 record the. The time is 3:55 P.M.

15 BY MR. POLLACK:

16 Q Welcome back, Dr. Williams.

17 Before the break, we were -- you had
18 asked to see the spreadsheet regarding the 46 values
19 for purity from the Certificates of Analysis that we
20 averaged and took a standard deviation of. What
21 we've put in front of you is what's been previously
22 marked as "Williams Deposition Exhibit 13." It's an
23 electronic copy of the documents we were showing you
24 before.

25 And you can feel free to manipulate them

1 on the computer, examine them, and compare them to
2 the data you reported in your Declaration in
3 Appendix A or any other place and verify that the
4 calculation is correct.

5 MS. HASPER: Objection. Mischaracterizes
6 the testimony.

7 Also, I've previously lodged an objection
8 to the use of this electronic exhibit. I'm going to
9 maintain that objection at this time.

10 And also, if counsel would permit, I'll
11 enter a standing objection to the entire line of
12 questioning regarding this exhibit so I don't have
13 to keep making it.

14 MR. POLLACK: That's fine.

15 MS. HASPER: All right.

16 THE WITNESS: And, actually, I didn't ask
17 to see this again.

18 BY MR. POLLACK:

19 Q Okay. You did not ask to see that again?

20 A I did not.

21 Q Let me ask you: Do -- so I had asked
22 you -- do you trust that these calculations are
23 correct?

24 A I haven't had a chance to look through
25 them. So, no, I don't trust them.

1 Q Okay. Well, now you have a chance to
2 look through them. Why don't you take a look
3 through them and see if you trust the calculation.

4 A Can I use this -- so these supposedly
5 correspond to entries on Exhibit A.

6 Q That's correct.

7 A Is that right?

8 Q Yes. Except we've removed the first ten
9 as we've discussed.

10 A Okay. So we started there. Okay.
11 First of all, I'm -- I have not seen
12 "implied impurity." That was nowhere in my charts.

13 Q Okay. You have seen "total related
14 substances," though?

15 A Yes.

16 Q Okay. You'd agree with me that the --
17 whether you like the phrase "implied purity" or not,
18 based on total related substances, the purity for
19 each sample is determined by taking 100 and
20 subtracting total related substances?

21 A Yes.

22 Q Okay.

23 A So this first one has a -- what the
24 results are -- that 1.0 -- that's 1 percent -- that
25 was in the second to last column of this; right?

1 Q Yes.

2 A And so your implied impurity is 100 minus
3 1, so 99. That's what that second --

4 Q Correct.

5 A -- entry means?

6 Q Yes.

7 A And that's the source document.

8 Q Is there another name, other than
9 "implied purity," that you would like to use?

10 A Not -- no. I don't have any other fancy
11 name for this.

12 Q Okay. That calculation was done
13 correctly; right?

14 A Yeah. So Assay Purity -- where did that
15 number come from?

16 Q That is from the original Certificate of
17 Analysis.

18 A Ah. So where are those?

19 Q That is Exhibit 2036, which is among
20 your --

21 A Is it this big, thick thing?

22 MR. POLLACK: Did we mark it already?

23 MS. HASPER: Yeah.

24 MR. POLLACK: Yeah. I'll give you the
25 number in a second.

1 It's Williams Deposition Exhibit 7.

2 THE WITNESS: You don't have -- do you
3 have a printout of this?

4 BY MR. POLLACK:

5 Q So we have --

6 A Making life much easier for me.

7 Actually, with these glasses on, these are my -- not
8 my computer glasses. These are my driving glasses.

9 Q A printout of the spreadsheet?

10 A Yeah.

11 Q Yes. We have --

12 THE REPORTER: Would this help

13 (Indicating)?

14 BY MR. POLLACK:

15 Q If you look, there's a Deposition

16 Exhibit 10 in your documents. Williams Deposition

17 Exhibit 10.

18 A That's what this is?

19 So what's missing from this spreadsheet

20 that you prepared are the individual impurities.

21 Q You didn't rely on the individual

22 impurities either -- right? -- for this calculation?

23 You used the total related substances; correct?

24 A For which calculation are you talking

25 about?

1 Q For your calculation of the average
2 purity.

3 A Oh, right. That was total related
4 substances. But I relied on the individual
5 impurities for my opinion that the '393 product is
6 distinct and more pure and different.

7 Q I understand that. But here we're just
8 looking at the calculation. I just want you to
9 verify for me that the calculation we've done of the
10 average purity is correct.

11 A 2036 -- okay. (Mumbling).

12 THE REPORTER: Sir, please don't mumble.

13 THE WITNESS: Okay. I'm sorry. I'm just
14 going through this, one entry at a time.

15 (Brief pause while witness works with
16 exhibit)

17 BY MR. POLLACK:

18 Q Dr. Williams, those two we haven't given
19 you that exhibit yet -- why don't you finish the --

20 A The yellow? Okay.

21 Q Yeah. When you finish, we'll give you
22 those two as well.

23 A Okay.

24 (Brief pause)

25 MS. HASPER: Counsel, while Dr. Williams

1 is still looking at the document, I'd like to take
2 the time to make this statement on the record that,
3 previously, you made the representation that the
4 electronic document was the same as the printouts
5 that had been provided earlier and marked as
6 Exhibits 8 through 10; is that correct?

7 MR. POLLACK: Yes.

8 MS. HASPER: Okay. Having reviewed at
9 least Exhibit 10, I see several -- at least a few
10 changes -- differences between the electronic
11 version that you provided to me and the document.

12 So I'm going to be maintaining my
13 objection to the entirety of Exhibit 13.

14 THE WITNESS: So I did all the ones from
15 here. 2036.

16 BY MR. POLLACK:

17 Q And you have two more to check; right?

18 A I think there were four -- four.

19 Q Which ones do you still want to check?

20 A So there's 20101, 20201, and 20302 and
21 20303 -- oh, wait. The -- oh, these, I can get from
22 here. I'm sorry.

23 Q Okay.

24 A Two, yeah. Let me pull these off here
25 while I've got this document open.

1 Q Yeah.

2 (Brief pause)

3 A Okay. Just the remaining two.

4 MR. POLLACK: Okay. We're going to mark
5 as Williams Deposition Exhibit 21 a document known
6 in the case as "Exhibit 2053."

7 (Exhibit 21 marked)

8 BY MR. POLLACK:

9 Q Dr. Williams, is this the Exhibit 2053
10 you relied on in listing batch data in your
11 Appendix A?

12 A Yes.

13 (Brief pause)

14 All right. So I've finished checking
15 them.

16 Q Okay. Let the record reflect you spent
17 more than 30 minutes checking them.

18 A Okay.

19 Q Okay. And you checked every single data
20 point; right?

21 A I did.

22 Q Okay. You didn't spot-check them. This
23 is a check of every single point?

24 A Right. Yes.

25 Q Okay. What -- did you see any mistakes

1 or differences?

2 A Yes.

3 Q Okay. Which ones did you see?

4 A So entry No. 16, which was UT lot --
5 UT15-000901. And the discrepancy apparently comes
6 from the actual batch record from Exhibit 2036, has
7 total related substances at .5, and thus the -- your
8 implied purity is 99.5 instead of 100. And I think
9 it's because on the other document -- which was a
10 summary at page 19 --

11 Q 2053?

12 A Right. -- 2053 at page 19 for that
13 lot 901, it's listed as .05 percent. So this is
14 probably a typo (Indicating); and this is probably
15 accurate (Indicating), the original source document.

16 Q Let's -- take a look at the entry on here
17 for -- this is lot -- which one? UT15-00901?

18 A Yes.

19 Q Okay. Let's just take a look at --
20 you're referring to this number here, the .1
21 (Indicating)?

22 A Yes.

23 Q Okay. If we look there, do you see up
24 there at the top of the screen that says, ".05"?

25 A Well, I actually -- my -- I can't see

1 that.

2 Q You can look -- why don't you take a look
3 up there on the big screen.

4 A Okay.

5 Q Can you see it there?

6 A Yeah.

7 Q Okay. And so you see that on Excel, we
8 set the number -- the digits with one decimal
9 place -- right? -- on the printout?

10 A Okay. So where you got that from was
11 Exhibit 2053, but the source document for that shows
12 that it's 0.5.

13 Q 0.5 or 0.05?

14 A 0.5.

15 Q Oh.

16 A While you're checking that, could I take
17 a short break?

18 MR. POLLACK: Sure.

19 THE VIDEOGRAPHER: We are off the record.
20 The time is 4:44 P.M.

21 (Off the record)

22 THE VIDEOGRAPHER: We are back on the
23 record. The time is 4:48 P.M.

24 MR. POLLACK: Okay.

25 ///

1 BY MR. POLLACK:

2 Q So we just -- you just said that entry 16
3 should be changed to .5; is that right?

4 A Yeah, I believe that's correct.

5 Q Okay. So should we change that here,
6 this being the spreadsheet and see what we get? Is
7 that fair?

8 MS. HASPER: I'm just going to reiterate
9 my standing objection to this entire line of
10 questioning using this document.

11 MR. POLLACK: Okay.

12 BY MR. POLLACK:

13 Q So now it says, ".5"; right? Fair
14 enough?

15 A Okay.

16 Q Okay.

17 A You have to change the number below it.

18 Q Oh, okay. There you go.

19 All right. Any other changes?

20 A Yes.

21 Q Okay.

22 A So I found for entry 33 --

23 Q Okay.

24 A -- UT15-020202 --

25 Q Okay.

1 A -- what was reflected -- I was looking at
2 the 2036 document. Let me double-check that.

3 Page 62, 63. The total related
4 substances is 0.2 percent.

5 Q And what does it say on this document?

6 A 0.6. Again, that may be --

7 Q Row 33, you're saying?

8 A Yes.

9 Q Okay.

10 A I didn't cross-check to this bigger
11 spreadsheet, which is maybe where that number came
12 from. So that's -- yeah. So the .6 is on here
13 (Indicating).

14 Q Okay. So we should change that number,
15 too, from .6 -- do we know which one is correct?
16 Whether it's 2036 or 2053?

17 A Well, it's -- I think -- this is a
18 summary spreadsheet. So I -- I think it's probably
19 better to rely on the Certificate of Analysis.

20 Q Okay. So you're saying, this value, I
21 should change from .6 to .2?

22 A Yes.

23 Q Do you want to look on the screen?

24 Okay. Shall I do that?

25 Any other changes?

1 A Yes. I also found errors on entry 43,
2 UT15-030401.

3 Q Okay.

4 A And --

5 Q Okay. What should the value be in your
6 view?

7 A On the 2053 document, it has .5.

8 Q Okay.

9 A And on the Certificate of Analysis, it's
10 .6.

11 Q Okay. Shall we change that one to .6?
12 Row 43? By the way, so far, all these errors are
13 due to taking numbers from 2053 instead of 2036; is
14 that right?

15 A That seems to be the case.

16 Q Is that change that I made, is that now
17 correct? If you want to look up at the screen.

18 A The assay purity is 100.1 instead of
19 100.3.

20 Q For 43? Let me check -- verify with you
21 making that change. Is it correct now?

22 A Yes.

23 Q Okay.

24 A And entry 55, UT-15031201 -- the Assay
25 Purity is 100.5, and it says 100.4.

1 Q Okay. So do you want to do this change,
2 or do you want me to do it?

3 A You operate the computer.

4 Q Okay. So that's row 55? If you look on
5 the screen with me, can you just verify that I'm
6 making this change correctly?

7 A Yes.

8 Q Okay. Okay. All right. Were there any
9 other changes?

10 A Not -- not that I could find.

11 Q Okay. Now -- so now we've made all those
12 changes to the spreadsheet.

13 Can you verify for me what -- that the
14 average and standard deviation were calculated
15 correctly? We can show you here how that's done.
16 The average.

17 A Right. It says, "██████".

18 Q Do you see up in the calculation section
19 how that's calculated up at the top?

20 A Yeah. It's just summed and averaged in
21 Excel.

22 Q Is that the correct way to do it?

23 A Yeah.

24 Q Okay. Do you have any issues, then, with
25 this calculation now that we've made the corrections

1 you pointed out?

2 A No.

3 Q Okay. So you'd agree with me that the --
4 for the HPLC assay, the value of [REDACTED] for the
5 average is correct?

6 A Appears to be.

7 Q Any qualms or disagreements about it?

8 A No.

9 Q Okay. And just checking the -- just want
10 to make sure I've calculated the standard deviation
11 correctly. You see the calculation formula up
12 there?

13 A Yes.

14 Q Okay. Is that a correct way to calculate
15 the standard deviation in Excel?

16 A I'm not familiar, because I don't do
17 that, so --

18 Q Okay. You haven't used that function,
19 standard deviation, in Excel?

20 A No. I just don't do that in my normal
21 course of work. So --

22 Q Okay. Okay. Any reason to doubt that
23 that's the standard deviation?

24 A No.

25 Q Okay. So now that we've -- now that

1 you've checked every single data point and looked at
2 the calculations, you agree with me that this
3 calculation of the purity is fair and accurate?

4 A The overall purity. But this does not
5 reflect impurity profile.

6 Q Yeah. I understand. I'm just talking
7 about the overall -- the level of purity.

8 A Yes.

9 Q We don't have anything even in this chart
10 about the impurity profile; correct?

11 A That's right.

12 Q Okay. And so it is correct that for the
13 samples from Exhibits 2036 and 2033, the 46 samples,
14 the average level of purity was [REDACTED] percent for the
15 samples made under the Moriarty process?

16 A Yes.

17 Q Okay. That [REDACTED] value, that is
18 consistent with the value that Moriarty reports in
19 his Journal of Organic Chemistry article?

20 A They're the same numbers.

21 Q Turn back to your Declaration. I'd like
22 you to turn to paragraph 63 in there. That's
23 Williams Deposition Exhibit 2. And I think here
24 you're giving an opinion on the meaning of the word
25 "product"; is that right?

1 A Yes. In the context of the '393 patent.

2 Q And you submitted some articles that you
3 wrote where you used the term "product"; is that
4 correct?

5 A Yes.

6 Q Okay. None of those articles are
7 anything to do with treprostinil and everything else
8 in the '393 patent?

9 A No. Different molecules.

10 MR. POLLACK: I'm going to mark as
11 Williams Deposition Exhibit 22 a document attached
12 to Dr. Williams's Declaration that was known as "UT
13 Exhibit 2028."

14 It's an article by Dr. Williams in the
15 Journal of Organic Chemistry entitled, "Synthetic
16 Studies on Et-743, Assembly of the Pentacyclic Core
17 and a Formal Total Synthesis."

18 (Exhibit 22 marked)

19 BY MR. POLLACK:

20 Q Now, this is one of the articles that you
21 rely upon for your use of the term "product";
22 correct?

23 A Yes.

24 Q And I believe the use of the term
25 "product" that you rely on is on the very first page

1 of Williams Deposition Exhibit 22. And it reads:
2 "The scarcity of a natural product from marine
3 sources renders Et-743 an important target for
4 synthesis."

5 Is that the sentence you were relying on?

6 A That's what I quoted in the Declaration.

7 Q And so then what it's referring to --

8 "marine sources," what does that refer to?

9 A So Et-743 comes from a marine tuna kit,
10 and there's a microbial consortium that is a
11 symbiotic host in the tuna kit that biosynthesizes
12 this molecule. So this natural product is the
13 product of a biosynthetic series of chemical
14 reactions.

15 Q Okay. This is, though, a -- this is a
16 product that's produced by a biological source;
17 correct?

18 A Yes.

19 Q All right. It's not a -- it's not a
20 chemical reaction; this is a biological reaction;
21 correct?

22 A They're still reactions, so it's the
23 product of, ultimately, chemical-bond formation. So
24 it's still understood by a person skilled in the art
25 of a product of chemical reactions.

1 Q Okay. But they're distinguishing marine
2 sources from other kinds of sources here; right?

3 You are, actually.

4 A Yes. That because it comes from a marine
5 source, it's very expensive and very difficult to
6 isolate sufficient quantities of this molecule from
7 a natural source for clinical use.

8 Q Right. And what you're proposing in here
9 is, you can create this molecule from a chemical
10 reaction?

11 A Yes. And that's what we did.

12 Q Yeah. So in this article, the word
13 "products" is used a little more broadly than the
14 typical, or your claim, that it's only the product
15 of chemical reaction, isn't that so?

16 A No.

17 Q No? That's not your view?

18 A No.

19 Q No?

20 So here where it distinguishes getting
21 the product from marine sources and instead says
22 that the product can be gotten from chemical
23 sources, that's not distinguishing?

24 A Well, the use of the word "product" is
25 still the result of chemical reactions that produce

1 that molecular entity, whether it be biochemical
2 reactions or laboratory chemical reactions.

3 Q Let me ask you this: A can of tuna
4 fish -- that's a product from chemical reactions,
5 ultimately; right? At least the way you're using
6 it.

7 A No. A can of tuna fish is a much
8 different substance. I wouldn't make the equation
9 between a can of tuna fish and the product of a
10 chemical reaction.

11 Q Okay. But you've heard a can of tuna
12 fish referred to as a "product"; right?

13 A Yeah. They put salt, and oil, and other
14 things in there. You know.

15 Q So that wouldn't be a legitimate use of
16 the word "product" there, would it?

17 A Well, "product" can be used in -- in
18 different contexts; okay? Just like the word
19 "compound" can be used in different contexts in
20 chemistry.

21 Q Okay. But the word "product" is broad
22 enough -- right? -- to encompass all kinds of
23 products?

24 A It depends on the context.

25 Q It can encompass biological products.

1 A As I just said, it depends on the context
2 in which the word's being used. In the context of
3 the '393 patent, it's very clear that the word
4 "product" is the result of chemical reactions.

5 Q You know, I was wondering about that,
6 because you say here in your Declaration -- could
7 you turn to paragraph 30 in your Declaration?

8 A (Complies).

9 Q Now, here, you say, "I have also been
10 informed by counsel that the claims of the '393
11 patent are product-by-process claims."

12 You wrote that; right?

13 A Yes.

14 Q Okay. And in that phrase there where it
15 says, "product-by-process claims," that's not
16 referring to necessarily a chemical reaction; right?
17 That's a legal phrase there.

18 A Yes. But a person skilled in the art,
19 you know, who would want to understand what a
20 product by process is, we're talking about in this
21 case a chemical process. Chemical reactions that
22 produce the product.

23 Q Yes, but this -- well, let's go on in
24 your paragraph.

25 "I have also been informed by counsel

1 that when evaluating the validity of a patent claim,
2 the 'product' -- and "product"'s in quotes; right?

3 A Hmm-hmm.

4 Q This is defining what a product is --
5 right? -- for this purpose?

6 A Yes.

7 Q That's why it's in quotes; right?

8 A Yes.

9 Q Yes.

10 "The product of product-by-process claims
11 must include structural and/or functional
12 differences over the prior art, even if they are not
13 explicitly claimed."

14 I read that correctly?

15 A Yes.

16 Q That's a different definition of
17 "product" than your chemical reaction, isn't it?

18 A No.

19 MS. HASPER: Objection. Mischaracterizes
20 the document.

21 BY MR. POLLACK:

22 Q No? Now, do you see the word "chemical
23 reaction" in that phrase?

24 A No. But it's -- we're still talking
25 about a chemical process. That's what this patent's

1 about.

2 Q But this paragraph's not talking about a
3 chemical process -- paragraph 30?

4 MS. HASPER: Objection. Mischaracterizes
5 the witness's testimony and the document.

6 THE WITNESS: It is, because I'm talking
7 about the claims of the '393 patent are
8 product-by-process claims. So when the word
9 "product" is used in the '393 patent, we're talking
10 about the result of the chemical reactions, the
11 chemical process that's described in the patent and
12 claimed in the patent.

13 BY MR. POLLACK:

14 Q Let me ask you this: Do you know this --
15 do you know that a product-by-process claim is
16 invalidated by a product made by other processes?
17 Did you know that's the law?

18 MS. HASPER: Same objection. Also seeks
19 a legal conclusion.

20 THE WITNESS: I'm not a lawyer.

21 BY MR. POLLACK:

22 Q Did you know that?

23 A I'm not a lawyer, and I'm, you know --

24 Q I'm not asking if you're a lawyer. I'm
25 asking if you know it. If you don't know it, just

1 say you don't know it.

2 MS. HASPER: Same objections.

3 THE WITNESS: Well, when I was instructed
4 by counsel, was that -- and there are many
5 product-by-process patents out there that are valid.
6 I've been involved in other litigation. And if the
7 product over the prior art has structural and
8 functional differences that are unique, then you can
9 still get a product-by-process patent on an already
10 known substance.

11 BY MR. POLLACK:

12 Q Okay. But what I asked you was: Do you
13 understand -- right? -- that a product-by-process
14 claim is invalidated by any product that's the same
15 as the product claimed, regardless of what process
16 is used?

17 Did you know that was the law?

18 MS. HASPER: Same objection. Also asked
19 and answered.

20 THE WITNESS: So, again, my understanding
21 is that if the product of the new process can be
22 shown to have structural and functional differences
23 over the prior art product, it's patentable.

24 BY MR. POLLACK:

25 Q Hmm-hmm. I understand that. I was just

1 asking if you understood this other thing -- okay?
2 -- which is in my question. Listen to my question;
3 okay?

4 My question is: Did you understand that
5 under the law of product-by-process claims, any
6 product, regardless of what process it's made from,
7 will invalidate a product-by-process claim, so long
8 as the products are the same?

9 Did you understand that? Yes or no?

10 MS. HASPER: Same objections.

11 THE WITNESS: Yeah. My understanding is,
12 the products can be shown to be identical. That's
13 not the case here.

14 BY MR. POLLACK:

15 Q Okay. But if the products are identical,
16 regardless of process, it will invalidate the
17 claims; is that fair?

18 MS. HASPER: Same objection.

19 BY MR. POLLACK:

20 Q Is that your understanding?

21 A So I'm not a lawyer, and I'm not going to
22 come to a legal conclusion.

23 Q Yeah. I'm just asking what your
24 understanding is.

25 A I've already told you my understanding.

1 Q What is it?

2 MS. HASPER: Same objection.

3 THE WITNESS: Would you like to reread my
4 answer into the record?

5 BY MR. POLLACK:

6 Q Sir, you need to answer my question.

7 A I did. I already answered it twice.

8 Q No. I'm asking you to answer it now.

9 MS. HASPER: Same objection.

10 THE WITNESS: Okay. My understanding is
11 that a product-by-process patent is valid if the new
12 process produces a product that's structurally and
13 functionally different than the prior art product.
14 That's my understanding.

15 BY MR. POLLACK:

16 Q Okay. I'm asking you, though, about what
17 will invalidate a product-by-process claim; okay?
18 So listen to my question.

19 Is it your understanding that a product
20 that is the same as the product made by the claimed
21 process in the prior art will invalidate the claim,
22 regardless of what process was used to make that
23 product?

24 Is that your understanding?

25 MS. HASPER: Same objection.

1 THE WITNESS: I do understand that.

2 BY MR. POLLACK:

3 Q Okay. And so that -- that's the legal
4 definition of "product" in "product by process";
5 right? What we just discussed?

6 A Wait. Ask me that again. What was that?

7 Q Yeah. That description you just gave,
8 that's a legal definition of "product" in the phrase
9 "product by process"; right?

10 MS. HASPER: Objection. Calls for a
11 legal conclusion.

12 THE WITNESS: And what was the definition
13 again?

14 BY MR. POLLACK:

15 Q Oh, that a prior product will invalidate
16 a product in a product-by-process claim, if it's the
17 same, regardless of which process is used?

18 MS. HASPER: Objection. Calls for a
19 legal conclusion. Mischaracterizes testimony.

20 THE WITNESS: I mean, I've heard that.
21 But, again, my understanding with regard to this
22 matter is that if the product has structural and
23 functional differences over the prior art, the
24 process patent can be valid.

25 ///

1 BY MR. POLLACK:

2 Q Yeah. Okay. But you'd agree with me
3 that legal definition is different than the
4 definition you typically use in your papers and
5 elsewhere; is that correct?

6 MS. HASPER: Same objection.

7 THE WITNESS: The legal definition of the
8 word "product" or --

9 BY MR. POLLACK:

10 Q Yeah, of the word "product."

11 MS. HASPER: Calls for a legal
12 conclusion.

13 THE WITNESS: I think this is very
14 context-dependent again.

15 BY MR. POLLACK:

16 Q Well, when you're using the word
17 "product" -- and I think you told me it's the
18 product of a chemical reaction; right? Is that
19 correct?

20 A Yeah. When I'm -- when I'm doing organic
21 chemistry, and synthesizing molecules and doing
22 reactions, there's a reactant and then a product.
23 And the product is the result of the chemical
24 reactions used to assemble that molecule, the
25 product.

1 Q Right. You don't use that term "product"
2 to refer to: Oh, well, I can have a product that's
3 done by a different chemical reaction -- you
4 wouldn't call that the same product?

5 MS. HASPER: Objection. Mischaracterizes
6 testimony.

7 THE WITNESS: You've now lost me on --
8 I'm really not following you.

9 BY MR. POLLACK:

10 Q If you made a product using a different
11 chemical reaction, would you consider that to be the
12 same product as you used the term "product"?

13 A Your question is not clear to me.

14 Q What's unclear about it?

15 A Well, I just don't understand it. So
16 perhaps you need to ask me a better question.

17 Q Why don't you tell me what you don't
18 understand, sir.

19 A Your question just didn't make sense to
20 me. I didn't follow it.

21 Q Which word didn't you understand?

22 MS. HASPER: Objection. Mischaracterizes
23 the witness's request for clarification.

24 THE WITNESS: You want to read the
25 question back, perhaps?

1 MR. POLLACK: Yes. Why don't you read
2 the question back.

3 THE WITNESS: Since you're apparently not
4 willing to rephrase it so I can understand what
5 you're trying to ask me.

6 (Record read by the reporter as follows:)

7 "QUESTION: If you made a
8 product using a different
9 chemical reaction, would you
10 consider that to be the same
11 product as you used the term
12 'product'?"

13 THE WITNESS: Okay. So my understanding
14 as a chemist is that -- you know, so my laboratory
15 synthesized this marine natural product,
16 Ecteinascidin-743, and another laboratory
17 synthesized the same molecule by a completely
18 different set of reactions.

19 BY MR. POLLACK:

20 Q Okay.

21 A And chemists would be able to draw the
22 structure and say: Oh, the target -- the desired
23 target molecule is this structure.

24 Q Okay.

25 A But we also understand that, because

1 different chemical processes, reactions were used to
2 make those, that the product that my lab got is
3 going to be distinct from the product that another
4 lab gets because of characteristic impurities that
5 come along as a result of the different reactions
6 that were used, the different starting materials,
7 intermediates, and so on, of the two different
8 processes.

9 Q You're saying, if we looked at another
10 paper by one of your colleagues making the same
11 chemical, they would describe that as a different
12 product?

13 A No. Chemists -- you know, in the art,
14 another paper making the same molecule would say:
15 And the final product Ecteinascidin-743 was purified
16 by blah, blah, blah.

17 They wouldn't call it a different name.
18 They'd say, you know: The product Et-743.

19 But inside the understanding is that you
20 know that because a different type of chemistry,
21 different types of reactions were used, that the
22 impurities that come necessarily with any --
23 anything in chemistry -- there's no such thing as
24 100.0 percent pure anything -- okay -- in chemistry.
25 Everything has some impurities.

1 And so in chemical synthesis, there are
2 going to be signature impurities that come as like a
3 fingerprint -- a unique fingerprint of that process
4 that was used to make that particular molecular
5 entity; okay.

6 So even though two papers may say the
7 same phrase, you know, "The product Et-743," "The
8 product Et-743," that does not mean they're exactly
9 the same, because they were made differently, and
10 their impurities would be made differently.

11 THE VIDEOGRAPHER: Counsel, three minutes
12 to go on this media.

13 MR. POLLACK: Oh, three minutes? Why
14 don't we take a break.

15 THE VIDEOGRAPHER: This ends Media No. 3
16 in the deposition of Robert M. Williams, Ph.D.
17 we're off the record. The time is 5:16 P.M.

18 (Off the record)

19 THE VIDEOGRAPHER: This begins Media
20 No. 4 in the deposition of Robert M. Williams, Ph.D.
21 We're back on the record. The time is 5:24 P.M.

22 BY MR. POLLACK:

23 Q Go back to your Declaration, Exhibit 2.
24 If you could turn to page 13, paragraph 34. There,
25 you record Dr. Winkler's opinion about a person of

1 ordinary skill in the art?

2 A Yes.

3 Q Okay. I don't know if you were told
4 this, but the other expert for United Therapeutics,
5 Dr. Ruffolo -- he believed that a higher level of
6 ordinary skill in the art would be more appropriate.
7 If you like, I can show you his deposition or just
8 read to you what he said?

9 A A higher level than --

10 Q Than Dr. Winkler.

11 A Than Dr. Winkler's?

12 Q Yes. Do you agree?

13 A Well, I don't recall what his --
14 Dr. Ruffolo's definition was.

15 Q Let me tell you his definition. If you
16 want to see his deposition, I can give you that as
17 well.

18 A His deposition or his Declaration?

19 Q His deposition. This was in his
20 deposition.

21 Did you read his deposition?

22 A No.

23 Q Okay. Would you like to see the
24 deposition, or would you like to just hear it from
25 me and let me know if you agree with what he said?

1 A Okay. You can go ahead and read it.

2 Q Okay. He said that he considers the
3 patent to be a complex chemistry, and he would have
4 changed what Dr. Winkler wrote to be a Ph.D., he
5 would not -- he would take out the master's degree.
6 And he also said -- so would set the level higher.

7 And he also said that the number of years
8 of experience -- he would add several years of
9 experience in the pharmaceutical industry on top of
10 the Ph.D.

11 I was just wondering if you agreed with
12 that or had a different opinion?

13 A Well, it sounds substantially very
14 similar to both Dr. Winkler and my definition.
15 Dr. Winkler says, a master's degree, or a Ph.D.
16 degree, or closely related field.

17 Q Hmm-hmm.

18 A Alternatively, a person of ordinary skill
19 would include an individual with a bachelor's
20 degree, and at least five years of practical
21 experience, medicinal or organic chemistry.

22 And my opinion wouldn't change if I
23 adopted Dr. Winkler's or Dr. Ruffolo's that you just
24 read to me. And I think the one I said was also
25 very appropriate.

1 Q Okay. I mean, do you agree with
2 Dr. Ruffolo that it should be set higher; it
3 shouldn't include the master's or the bachelor's?

4 A I don't necessarily agree, because I also
5 said, alternatively, the POSA may have had a lesser
6 degree in one of those fields with correspondingly
7 more experience.

8 Q Okay.

9 A So I also allowed for less than a
10 doctorate.

11 Q Okay.

12 A So I think we're all more or less in the
13 same level of skill.

14 Q All right. I only ask you because
15 Dr. Ruffolo seemed very concerned about this; that
16 the level was too low, and I was wondering if you
17 agreed or not?

18 A Perhaps he misunderstood what Dr. Winkler
19 wrote.

20 Q Okay. I'd like to have you pull out,
21 again, the Phares reference.

22 MS. HASPER: Counsel, can you remind us
23 what number that was?

24 MR. POLLACK: I will. The Phares
25 reference which used to be called "Exhibit 1005" is

1 now Williams Deposition Exhibit 16.

2 BY MR. POLLACK:

3 Q And while you're searching for that, can
4 you also find Williams Deposition Exhibit 12, the
5 Moriarty reference.

6 Do you have -- do you have Deposition
7 Exhibits 12 and 16 in front of you?

8 A I do.

9 Q Okay. So the Phares reference, that was
10 published in 2005; is that right?

11 A Yeah, 27 January 2005.

12 Q Okay. And the Moriarty reference,
13 Deposition Exhibit 12, it was published in 2004;
14 correct?

15 A Yes.

16 Q Okay. So am I right that at the time
17 that the Phares reference was published, a person of
18 ordinary skill in the art would have been familiar
19 with the Moriarty reference?

20 A Yes. It was already published.

21 Q And am I right that at that time in 2005,
22 it was understood that the Moriarty reference was
23 the best way at that time to make treprostinil; is
24 that fair?

25 A Yes. I think that's correct. I would

1 agree.

2 Q Okay. So a person of ordinary skill in
3 the art in 2005 reading the Phares reference, that
4 person would know the best way to make treprostini
5 is the Moriarty method, Exhibit 12; right? Is that
6 fair?

7 A I think that's fair.

8 Q Okay. So a person of ordinary skill in
9 the art, if they wanted to make treprostini
10 diethanolamine salt in 2005, following the Phares
11 method, their best way of doing that would have been
12 to follow Moriarty Deposition Exhibit 12; is that
13 fair?

14 A Well, it's interesting that the Phares
15 reference doesn't reference Moriarty.

16 Q Okay. That's not what I asked you.
17 Would a person of ordinary skill in the
18 art, familiar with Exhibit 12 and Exhibit 16 --
19 would they follow the Moriarty reference? Would
20 that be the best way to do it?

21 A Well, it was certainly in the literature.
22 The Phares reference actually references two other
23 ways to make treprostini that are significantly
24 inferior in my opinion.

25 Q Inferior to Moriarty, even?

1 A Yes.

2 Q Yes. And a person of ordinary skill in
3 the art would have known in 2005 that those other
4 methods were inferior to Moriarty; is that fair?

5 A I guess -- we're assuming that the person
6 of ordinary skill had done a detailed analysis of
7 all the different ones.

8 Q Yes?

9 A And that's the end of my sentence.

10 Q Oh, okay.

11 Well, I mean, did people who were, you
12 know, doing research on treprostinil at that time,
13 do you think they would have read a paper in the
14 Journal of Organic Chemistry?

15 A Sure. It's a very well-known journal.

16 Q It's one of the most prestigious; right?

17 A Yes.

18 Q I mean, you have grad student; right?
19 When you tell 'em to go out and synthesize stuff,
20 they do a basic literature research; right?

21 A Sure.

22 Q You don't think would have missed this
23 article in the Journal of Organic Chemistry; right?

24 A No.

25 Q Okay. So a person of ordinary skill in

1 the art -- they're similar to graduate students or
2 some of the other people you've taught; correct?

3 MS. HASPER: Objection. Mischaracterizes
4 testimony.

5 BY MR. POLLACK:

6 Q Is that fair?

7 A What was the question again, please?

8 Q Your graduate students or some of the
9 other students you've taught, they have a level
10 similar to a person of ordinary skill in the art; is
11 that fair?

12 MS. HASPER: Objection. Mischaracterizes
13 testimony.

14 THE WITNESS: I guess it depends on what
15 year graduate student. First-year graduate
16 students, I would consider to be below the level of
17 ordinary skill. And a 5th- or 6th-year graduate
18 student would probably meet the minimum bar. They
19 don't have a Ph.D. yet.

20 BY MR. POLLACK:

21 Q Let's take one of those 5th-, 6th-year
22 graduate students. You would expect them if you
23 assigned them to make treprostinil, they would find
24 the Moriarty reference; right?

25 A It's easy to find.

1 Q And you would assume that they would
2 follow this Moriarty reference the best way to make
3 treprostinil if you asked them to make treprostinil
4 diethanolamine salt in 2005; right?

5 MS. HASPER: Objection.

6 THE WITNESS: Well, I would certainly
7 want to go over all the options in the literature
8 before I started spending time in chemical grant
9 money on them to do that.

10 BY MR. POLLACK:

11 Q Okay. Right. But what method would you
12 have advised in 2005 to your graduate students?

13 A What? If I -- if I --

14 MS. HASPER: Objection.

15 THE WITNESS: -- needed to make
16 treprostinil in 2005?

17 BY MR. POLLACK:

18 Q Yes.

19 A I certainly would have picked Moriarty
20 paper.

21 Q Yeah. And would you say that your 5th-,
22 6th-year graduate students, they'd be somewhat
23 capable of making that conclusion, as well, that
24 they would use the Moriarty paper?

25 A Possibly.

1 Q Possibly?

2 At least the ones who are actually
3 getting their Ph.D.s, would they be able to get the
4 Moriarty paper?

5 MS. HASPER: Objection.

6 THE WITNESS: You never know what a
7 graduate student is going to come up with, as their
8 favorite way of doing something.

9 BY MR. POLLACK:

10 Q But, you know, on average, a typical
11 person of ordinary skill in the art, typical
12 graduate student, they would have found the Moriarty
13 paper and used that technique to make treprostiniil
14 in 2005?

15 MS. HASPER: Objection.

16 THE WITNESS: It was in the literature.
17 It wasn't buried in some obscure journal. So, sure,
18 it was available.

19 BY MR. POLLACK:

20 Q That was a "yes" to my question, I think?

21 A Yes.

22 Q Okay. I want to talk a little bit about
23 the Kawakami reference. You recall that reference;
24 right?

25 A Yes.

1 Q Why don't we mark the Kawakami reference.

2 THE REPORTER: 23.

3 MR. POLLACK: I'd like to mark two
4 exhibits. Exhibit 23 is going to be the original
5 Kawakami reference in Japanese, just so you can
6 check the figures. That's what's known as
7 "Exhibit 1006" in the proceeding.

8 (Exhibit 23 marked)

9 MR. POLLACK: And Exhibit 1007 is an
10 English translation of the Kawakami reference.

11 THE REPORTER: And that's Exhibit 24.

12 MR. POLLACK: 24. Yes. And that's
13 Exhibit 24.

14 (Exhibit 24 marked)

15 MS. HASPER: And is what you've handed me
16 26 -- 23 or 24?

17 MR. POLLACK: That's 24. And the
18 Japanese is 23.

19 BY MR. POLLACK:

20 Q And Exhibits 23 and 24 are the Kawakami
21 reference discussed in your Declaration?

22 A Yes.

23 Q Okay. And then I'm going to mark as
24 Exhibit 25, a pair of drawings that we made of the
25 compound in the Kawakami reference -- the preferred

1 compound, and treprostinil. I just want you to
2 review them and make sure the drawings are okay.

3 MR. POLLACK: This will be Exhibit 25.

4 (Exhibit 25 marked)

5 BY MR. POLLACK:

6 Q So feel free to use, you know, Moriarty
7 or any other reference you like and the Kawakami
8 reference.

9 And can you verify for me that these are
10 fair and accurate drawings of treprostinil and
11 Kawakami.

12 A (Examining documents) Well, treprostinil
13 is definitely correct.

14 Q Okay.

15 A The structural rendering you have for
16 Kawakami does not show the stereochemistry of the
17 bicyclic portion.

18 Q Okay. But other than that, is it
19 correct?

20 A Yes. That's one of the two geometrical
21 isomers described in Kawakami.

22 Q Okay. And other than I didn't show on
23 here that the ring is below the page -- the upper
24 five-member ring-- this is a correct drawing of the
25 structure of the Kawakami compound?

1 A Yes.

2 Q Okay. So earlier, you and I were
3 discussing the meaning of the term "product." Do
4 you recall that discussion?

5 A Yes.

6 Q Okay. And I think we were talking about
7 how other chemists use the term "product." Do you
8 remember that?

9 A Yes.

10 Q Okay. And you said: Well, you know,
11 chemists might make a product by a different process
12 from yours -- from let's say the product you made in
13 your exhibit. And in their papers, they would say:
14 Oh, yes. We made the product Ecteinascidin --
15 right?

16 A Ecteinascidin.

17 Q They might say that they made the product
18 Ecteinascidin-743, but they may have used a
19 different process; is that right?

20 A Yes.

21 Q Okay. So in chemists' ordinary use of
22 the term "product," is it fair to say that when
23 they're using it in papers and other places, they
24 often don't point out that the impurities or other
25 things are different, because the process was

1 different in using the term "product"?

2 A I don't agree with what you said.

3 Q Why not?

4 A Because chemists use the word "product"
5 in two different contexts, routinely.

6 Q Okay.

7 A There's a molecular structural context;
8 okay? So if I said to one of my students, "Show me
9 the product of this reaction on my blackboard."

10 And they'd write a structure like
11 Ecteinascidin-743; okay?

12 Q Okay.

13 A And if I said, "Bring me a sample of the
14 product that you just made in the lab," they would
15 bring me a bottle, a flask, a vial of a real-world
16 substance that, hopefully, contains mostly what we
17 were trying to make, and it would also have its
18 characteristic impurities.

19 So there's the molecular structural
20 context, and then there's the real-world substance
21 context of the word "product." And chemists know
22 what you're talking about when you use the word
23 "product" in those two different contexts.

24 Q Okay. Let me ask you: In the '393
25 patent, do you see any place where the '393 patent

1 says: I'm going to define the word "product" for
2 this patent?

3 Do you see that anywhere in there?

4 A I don't recall it being defined, other
5 than its plain, ordinary meaning as it's understood,
6 as I just explained.

7 Q Did you see anything in the prosecution
8 history where the term "product" was defined?

9 A I don't recall. Prosecution history is
10 huge. I don't remember everything in there.

11 Q As you sit here now, you don't recall --

12 A I don't recall if that was -- that came
13 up.

14 Q If it's okay, we're going to take a break
15 for a couple minutes.

16 A Okay.

17 THE VIDEOGRAPHER: We're off the record.
18 The time is 5:42 P.M.

19 (Off the record)

20 THE VIDEOGRAPHER: We are back on the
21 record. The time is 6:04 P.M.

22 BY MR. POLLACK:

23 Q Dr. Williams, since the deposition
24 started today, have you had any discussions with
25 counsel regarding, you know, the substance of this

1 case, or this deposition, or anything about
2 treprostiniil or about any redirect testimony with --
3 with counsel?

4 A No.

5 MR. POLLACK: All right. Other than
6 that, no further questions. Thank you for your
7 time.

8

9 EXAMINATION

10 BY MS. HASPER:

11 Q All right. On redirect, Dr. Williams,
12 you noted earlier today when looking at some of the
13 exhibits that were introduced by Mr. Pollack an
14 error in Appendix B of your report; is that correct?

15 A Yes.

16 Q And have you previously asked counsel to
17 correct this error and create updated versions of
18 Appendix B?

19 A Yes. We did that this morning.

20 Q Yes. And I'm going to hand what I
21 guess --

22 THE REPORTER: 26.

23 MS. HASPER: I'm going to hand to be
24 marked as Exhibit 26 a corrected version of both
25 Appendix B and the summary chart table from

1 paragraph 94 of Dr. Williams's report.

2 (Exhibit 26 marked)

3 BY MS. HASPER:

4 Q Dr. Williams, if you take a look at this
5 for a moment, is this the corrected version of
6 Appendix B and the summary chart from paragraph 94
7 of your Declaration that you instructed counsel to
8 prepare and approved before this deposition?

9 A (Examining document) Sorry. I'm just
10 checking against my -- yes. This is the correct --
11 the corrected one.

12 Q And just for the record, the difference
13 between Appendix B in this document and Appendix B,
14 as it appears with your report, is the omission of
15 batch or sample [REDACTED]; is that correct?

16 A That's correct.

17 Q And that slightly changes the averages on
18 both the -- for a few of the values on both the
19 chart in Appendix B and the summary chart in
20 paragraph 94 of your Declaration; is that correct?

21 A Yes.

22 Q And can you just note what those changes
23 are and we can just look at the summary chart from
24 paragraph 94 so you can note what the changes are.

25 A Okay. So these are the '393 patent

1 process impurities one, two, three -- fourth column
2 from the left, the number changed from 0.0642 to
3 0.0643.

4 And three more columns over, the ethyl
5 ester changed from 0.1207 to 0.1208. And then the
6 total related substances changed from 0.2936 to
7 0.2944.

8 Q Thank you, Dr. Williams.

9 And just to confirm, for both Appendix B
10 and Appendix A, those were created using all of the
11 batches or samples of treprostinil that you were
12 able to find?

13 A Yes.

14 Q And there was no selection or additional
15 searching for particular type of batches that you're
16 aware of?

17 MR. POLLACK: Objection. Leading.

18 THE WITNESS: No.

19 BY MS. HASPER:

20 Q If you can please get back out the
21 development report that was previously marked as
22 Exhibit 11.

23 A I have it.

24 Q And if you can also get out in front of
25 you the '393 patent. And that was previously marked

1 as Exhibit 3 to your deposition.

2 A Okay. I have it.

3 Q Okay.

4 MR. POLLACK: Doctor, just give me one
5 second.

6 MS. HASPER: Gonna dig for your own
7 copies?

8 MR. POLLACK: Yeah.

9 MS. HASPER: All right.

10 BY MS. HASPER:

11 Q If you could just look at the face of the
12 '393 patent.

13 I'm sorry. I'm wrong. I wanted you to
14 get out the '117 patent. My apologies. And that
15 was what was previously marked as Exhibit 4.

16 A I have it.

17 Q Now, are you aware, from your own history
18 having patents, that a patent may claim priority to
19 earlier filed applications or -- or be the utility
20 or provisional applications?

21 A Yes.

22 MR. POLLACK: Objection to form. Lack of
23 foundation.

24 BY MS. HASPER:

25 Q And do you see on the first page of the

1 '117 patent the section that's -- that's titled,
2 "Related U.S. Application Data"?

3 A Yes.

4 Q And do you see that that lists a number
5 of patent -- previous patents or applications of
6 which the application which matured into the '117
7 patent is a divisional, or continuation -- or a
8 continuation in part?

9 A Yes. I see that.

10 Q Do you see that the earliest date listed
11 there is for an application No. 08-957736 filed on
12 October 24th, 1997, now abandoned?

13 A Yes, I see that.

14 Q Okay. Can you turn in Exhibit 11 to
15 page 25.

16 Now, earlier today, Mr. Pollack asked you
17 to look at the dates of manufacture for some of the
18 lots that were included in Appendix A of your
19 report, including starting with lot LRX97J01 that is
20 listed on this page. Do you see that lot?

21 A Yes.

22 Q And do you see the date of manufacture on
23 that lot?

24 A October 1997.

25 Q Yeah. Now, earlier today, Mr. Pollack

1 asked you whether or not that lot or any of the lots
2 listed to its right on this chart could have been
3 made using the Moriarty process, based on the
4 publication date of the Moriarty article in 2004 or
5 its submission date in 2003. Do you recall is that?

6 A I do recall that.

7 MR. POLLACK: Objection to form.
8 Mischaracterizes.

9 BY MS. HASPER:

10 Q Looking now at the priority information
11 for the '117 patent and the dates listed therein
12 under your related U.S. application data and looking
13 at the manufacturing dates for these lots, do you
14 believe that these lots could have been made using
15 the Moriarty process?

16 MR. POLLACK: Objection. Cause of
17 action.

18 THE WITNESS: Yes. So that -- I was
19 actually very confused by that, because counsel
20 represented to me that the development batches were
21 made by Moriarty. And I, of course, accepted that
22 as being correct.

23 And so I got confused by the -- I forgot
24 about this earlier application. So indeed, those
25 lots could have -- I believe, were made by the

1 Moriarty process.

2 BY MS. HASPER:

3 Q And I'll just follow up on one point, you
4 know that previously -- and you can still see it
5 here on this document above -- that the manufacturer
6 for those is either Steroids or SynQuest and the
7 subscript 5 notes that Steroids is a company that is
8 now known as SynQuest. Do you see that?

9 A Yes.

10 Q And you also know that Steroids, or
11 SynQuest, to your knowledge, was a contract
12 manufacturer for United Therapeutics; is that
13 correct?

14 MR. POLLACK: Objection. Leading.

15 THE WITNESS: Yes. That's my
16 understanding.

17 BY MS. HASPER:

18 Q Okay.

19 A Actually, I remember that clearly now
20 from the previous trial.

21 Q Do you remember anything else about
22 Steroids, or SynQuest, and their relationship to
23 either United Therapeutics or Dr. Moriarty?

24 A I don't recall the relationship off the
25 top of my head.

1 Q Okay. Do you know what Dr. Moriarty's
2 relationship to Steroids or SynQuest was?

3 MR. POLLACK: Objection to form. Lack of
4 foundation.

5 THE WITNESS: I'm trying to remember.

6 Getting back to the -- I seem to remember
7 that Dr. Moriarty was either a consultant and/or a
8 founder of Steroids.

9 BY MS. HASPER:

10 Q So it's your belief that Dr. Moriarty was
11 associated with Steroids, Ltd.?

12 MR. POLLACK: Objection. Leading and
13 mischaracterizes.

14 THE WITNESS: My vague recollection tells
15 me that that's -- that there was such a
16 relationship, as I recall.

17 BY MS. HASPER:

18 Q Okay. Thank you. I don't want to test
19 your memory too much. I just want to see what you
20 did recall.

21 If you can look at a couple pages earlier
22 in this same document to page 22 of Moriarty
23 Deposition Exhibit 11.

24 A Page 22 numbered at the bottom?

25 Q Yes. The number where it says, "P. 22,"

1 just sort of off-center at the bottom.

2 A Yeah. Got it.

3 Q Do you see the section here that is
4 headed, "Total Related Substances"?

5 A Yes.

6 Q And do you see where underneath that says
7 that, "Total related substances in the drug
8 substance is based on the sum of 1AU90, 2AU90,
9 970W86, 3AU90, UT15 methyl ester, UT15 ethyl ester,
10 750W93, 751W93, and total unidentified impurities."

11 Did I read that correctly?

12 A Yes.

13 Q Does that comport with your understanding
14 of what total related substances indicates in the
15 batch records and other documents that you have
16 reviewed for this case?

17 MR. POLLACK: Objection. Leading.

18 THE WITNESS: Yes. And that's exactly
19 what I said when counsel asked me about what my
20 understanding of total related substances was. I
21 said it was the known impurities which are listed,
22 and the total unidentified impurities.

23 BY MS. HASPER:

24 Q Okay. Thank you. You can put away this
25 document.

1 Now, if you can get out the '393 patent
2 that's Williams Deposition Exhibit 3 and the Phares
3 publication. That's Williams Deposition Exhibit 16.

4 A Okay. So the '393 and Phares?

5 Q Yes.

6 A Okay.

7 Q In Phares, if you will open to page --
8 it's 42 of the exhibit, but as we noted earlier,
9 it's page 40 of the document. So the bottom-most
10 numbering is page 42, but there's also a number 40
11 in the middle of the page.

12 A Yes.

13 Q This is a scheme that you were discussing
14 earlier with Mr. Pollack; is that correct?

15 A Yes.

16 Q Can you open up the '393 patent to claim
17 9 from the second to last page of the claims at
18 columns 19 through 20.

19 A I'm there.

20 Q Now, if you'll look at claim 9, step (a).
21 Step (a) -- am I correct in reading, "It requires
22 calculating a compound of formula 5 with an
23 alkylating agent to produce a compound of formula
24 6"; is that correct?

25 MR. POLLACK: Objection. Leading.

1 THE WITNESS: Yes. That's correct.

2 BY MS. HASPER:

3 Q And then in column 20, it depicts the
4 structures for both compound 5 and compound 6; is
5 that correct?

6 MR. POLLACK: Objection. Leading.

7 THE WITNESS: Yes. That's correct.

8 BY MS. HASPER:

9 Q Now, looking at the structures in the
10 scheme on page 42 of Phares -- that's 42 of the
11 deposition exhibit -- you indicated earlier today --
12 please confirm if this is correct -- that structure
13 11-B, where an R is H, is the enantiomer of
14 structure 5; is that correct?

15 MR. POLLACK: Objection to form.
16 Leading.

17 THE WITNESS: Yes. I believe that's
18 correct.

19 BY MS. HASPER:

20 Q And looking at step (1) below, the first
21 step -- step (1), small (i), reacting that
22 enantiomer of formula 5 as indicated below, how
23 would you describe that step?

24 A So compound 11-B is treated with
25 chloroacetonitrile -- that's CL, CH₂, CN in step (1)

1 under (i) and potassium carbonate.

2 Q And would you characterize that as an
3 alkylation step?

4 MR. POLLACK: Objection. Leading.

5 THE WITNESS: Yes. That's an alkylation
6 of the phenolic oxygen atom with chloroacetonitrile
7 to form the methyl nitrile product.

8 BY MS. HASPER:

9 Q And step (a) of the patent requires the
10 use, specifically, of formula 5 to produce a
11 compound of formula 6; is that correct?

12 MR. POLLACK: Objection. Leading.

13 THE WITNESS: Yes.

14 BY MS. HASPER:

15 Q Is formula 5 the same as compound 11-B?

16 A No.

17 Q How are they different?

18 A They're enantiomers.

19 Q Okay. And if you react compound 11-B as
20 indicated in step (1)(i), do you produce compound 6?

21 A No.

22 Q What do you produce?

23 A The enantiomer of compound 6.

24 Q And so just to make sure I understand
25 what you're saying, performing step (1) sub --

1 small (i) on compound 11-B differs from step (a) of
2 claim 9 in that it involves the enantiomers of the
3 compounds required by step (a); is that correct?

4 MR. POLLACK: Objection. Leading.

5 THE WITNESS: That's correct.

6 BY MS. HASPER:

7 Q Now, step (b) of compound -- of claim 9,
8 I'm going to read it and just confirm that I'm
9 reading this correctly -- "requires hydrolyzing the
10 product of formula 6 of step (a) with a base"; is
11 that correct?

12 MR. POLLACK: Objection. Leading.

13 THE WITNESS: That's what it says.

14 BY MS. HASPER:

15 Q And what is the relationship between
16 the -- oh, sorry. Let me first say this: So then
17 step (1), sub 2, of the process in Phares, how would
18 you describe that reaction?

19 A That's the hydrolysis of the nitrile
20 functional group to the potassium carboxylate.

21 Q And that's performed -- well, what is the
22 starting material for that particular step?

23 A That would be the enantiomer of structure
24 6 in column 20 of claim 9.

25 Q So step (1), small (ii), differs from

1 step (b) of claim 9 of the patent in that it is
2 using the enantiomer of formula 6, rather than
3 formula 6; is that correct?

4 MR. POLLACK: Objection. Leading.
5 Counsel, would you like to take his chair
6 instead or --

7 MS. HASPER: I don't appreciate your
8 sass. I was -- I've listened to you ask questions
9 all day. And I certainly don't appreciate you when
10 you completely, inappropriately call leading
11 objections when I'm asking him to confirm that I've
12 read something correctly from a document that is in
13 front of us all.

14 MR. POLLACK: That's not what you asked
15 now.

16 MS. HASPER: No.

17 MR. POLLACK: And you're asking leading
18 questions, and you are on redirect.

19 BY MS. HASPER:

20 Q Would you like to answer the question, or
21 would you like it repeated after this interruption?

22 A I want to be sure I'm answering the right
23 question. Could the question be repeated?

24 MS. HASPER: Would the court reporter,
25 perhaps, read it back.

1 (Record read by the reporter as follows:)

2 "QUESTION: "So step (1),
3 small (ii), differs from
4 step (b) of claim 9 of the
5 patent in that it is using the
6 enantiomer of formula 6, rather
7 than formula 6; is that
8 correct?"

9 MR. POLLACK: And the objection is
10 "Leading."

11 THE WITNESS: That's correct.

12 BY MS. HASPER:

13 Q In your opinion, does step (1) -- let me
14 start over.

15 In your opinion, what is the relationship
16 between step (1) as recited on page 42 of
17 Exhibit 11, the Phares patent -- sorry, Exhibit 16,
18 the Phares patent -- to steps (b) and (a) in claim 9
19 of the '393 patent?

20 A So what's happening in step (1) is (i) is
21 the alkylation of the benzindine triol structure 5,
22 but it's the enantiomer of structure 5 with
23 chloroacetonitrile, which is the alkylating agent.
24 And that produces, in the case of the Phares
25 document, the enantiomer of structure 6, that's

1 depicted at column 20, line 15 or so.

2 And then the next step of transformation
3 (1) under (ii) is a potassium hydroxide methanol
4 hydrolysis of nitrile functional group to give
5 initially the potassium carboxylate which on workup
6 would give the enantiomer of treprostinil, which is
7 shown as structure 2 in the Phares document.

8 Q So is it your understanding that
9 steps (a) and (b) of the -- of claim 9 of the '393
10 patent and step (1) of the synthesis on this page of
11 the Phares reference are the same or different?

12 A They're different because we're using a
13 different optical isomer -- nonsuperimposable mirror
14 image of what is required by claim 9.

15 Q And ultimately, does one get the same
16 product or a different product if one follows
17 steps (a) and (b) of claim 9 versus step (1) of the
18 scheme on this page of the Phares patent?

19 MR. POLLACK: Objection. Leading.

20 THE WITNESS: One necessarily gets a
21 different product. It's the nonsuperimposable
22 mirror image of treprostinil. So you get a
23 different product.

24 BY MS. HASPER:

25 Q Thank you.

1 A Nonbiologically active compound.

2 Q Thank you very much for your time today,
3 Dr. Williams. If Mr. Pollack has any additional
4 questions --

5

6 FURTHER EXAMINATION

7 BY MR. POLLACK:

8 Q I do. I have some recross for you.
9 I'd like you to pull out Deposition
10 Exhibit 4. That's the Moriarty patent.

11 I think you indicated to your counsel
12 that you had some knowledge of how the patent
13 continuation system worked; is that right?

14 That's what you --

15 A Yes. Yes.

16 Q Okay. If you look where it says, "62" --
17 you see where I'm looking?

18 A On the face page, line 62 -- 62. Yeah.

19 Q Okay. Well, let me go a little above
20 that. The application that led to the Moriarty
21 patent, you see it was filed on July 1st, 2002? Do
22 you see that?

23 A Yes.

24 Q Okay. That's long after the dates in,
25 you know, the process development document,

1 Exhibit -- I think it was 11; right? 2002 is long
2 after the 1998 and 1999 dates we were looking at; is
3 that right?

4 A I don't know if I characterize it as
5 "long after." It's a few -- couple, four years.

6 Q Fair enough.

7 And do you see the -- it says, "The early
8 application is depending on" -- something called a
9 "division." You see that? It's a division of
10 another application?

11 Do you know what that means?

12 MS. HASPER: Objection. Seeks a legal
13 conclusion.

14 THE WITNESS: I'm not a lawyer, so I
15 don't know the correct technical definition of a
16 "divisional application."

17 BY MR. POLLACK:

18 Q Okay. Do you have any understanding of
19 what a divisional application is?

20 A Well, I know that you can file a patent
21 application and then file additional versions
22 thereof after that. And I think some of those are
23 sometimes called "continuation in parts" or
24 "divisionals." But, again, I don't know the
25 technical differences between these.

1 Q Okay. Have you ever heard that a
2 divisional is a kind of application which is filed
3 for an invention which is different than the one
4 claims in the prior application?

5 Did you ever hear that before, and that's
6 why it's called a "divisional"?

7 A Yeah. I -- I don't know.

8 Q Okay. That's news to you? That a
9 divisional is for a different invention than what's
10 in the prior applications? You've never heard that
11 before?

12 A Yeah. I'm not a patent expert.

13 Q Okay.

14 A I don't know the technical metes and
15 bounds of what that means.

16 Q Sure. And if we go from that one, the
17 next one -- that divisional, by the way, ended up in
18 a patent. You see that? 6,441,245?

19 A Yes.

20 Q Okay. Did you look at that patent in
21 forming your opinion?

22 A I do remember the '245 patent from the
23 Sandoz litigation, but I haven't looked at it
24 recently. But I've certainly looked at the '245
25 patent before.

1 Q Okay. What's in the '245 patent?

2 A I don't remember.

3 Q You don't remember.

4 Did it claim treprostinil?

5 A I don't remember.

6 Q You see after that, it says that patent
7 is a continuation in part of a prior application
8 that was filed in 2000. Do you see that?

9 A Yes.

10 Q Okay. Do you know what a "continuation
11 in part" is?

12 MS. HASPER: Objection. Seeks a legal
13 conclusion.

14 THE WITNESS: I don't know the technical
15 legal definition of "continuation in part."

16 BY MR. POLLACK:

17 Q I understand. But do you have any
18 understanding of what a continuation in part is?

19 A Well, there's a relationship to the
20 preceding application. And I don't know, again,
21 what is allowable, and what makes it, you know,
22 completely separate invention. So --

23 Q Okay. I know you have a number of
24 patents; right?

25 A Yes.

1 Q Did some of them involve continuations in
2 part?

3 A Yes, I believe so.

4 Q Okay. And you were made aware of when
5 those continuations in part were filed that what
6 that meant was additional material was added to the
7 specification of the patent. Did they tell you
8 that?

9 A That rings a bell. But, again, I leave
10 this all up to the tech-transfer office at the
11 university.

12 Q Okay. So as you sit here now, do you
13 know whether any of the material from the
14 application filed in 1997 is relevant to the
15 Moriarty process and claims that we've been
16 discussing today?

17 A I believe there is relevant material.

18 Q Okay.

19 A I don't -- you know, I don't have the
20 document in front of me.

21 Q Okay.

22 A I'd be happy to look at it.

23 Q Okay. But as you sit here now, or, you
24 know, you've formed your opinion, do you know
25 whether this 1997 document has the synthesis of the

1 Moriarty process in the document?

2 A You know, I simply just don't know.

3 Q Okay. And I'd like to turn back to the
4 exhibit your counsel gave you, Exhibit 26. It's
5 this corrected version.

6 A Yes.

7 Q Okay. We were looking at -- I'm looking
8 at that version. I see you still list total related
9 substances at .9545 even on this corrected version
10 in the new Exhibit 26. Do you see that?

11 A Yes.

12 Q Okay. Having looked at the data we saw
13 today and the averages that we saw today, showing,
14 you know, an average total related substances for
15 the 46 Moriarty samples of point -- approximately
16 .3, do you still think that this Exhibit 26 doesn't
17 need to be corrected to reflect .3 for the Moriarty
18 samples?

19 A No.

20 Q So you still want to stand by including
21 ten cherry-picked samples from the other exhibit
22 that you added?

23 MS. HASPER: Objection. Mischaracterizes
24 the document. Mischaracterizes testimony.

25 THE WITNESS: Yeah. I would not --

1 again, I would not characterize those ten
2 development batches as cherry-picked because by the
3 same token, the development batches for the '393
4 process patches were also included. So I stick by
5 that the comparison was done fairly. And I'm not
6 about to change anything, other than the numerical
7 corrections due to the typographical error.

8 BY MR. POLLACK:

9 Q Now, the development batches you were
10 referring to, if would you turn to -- in Exhibit 26,
11 this exhibit that we were just looking at -- did you
12 put it away?

13 A This one (indicating)?

14 Q Okay.

15 So the development batches you were
16 referring to, that's -- those are the one, two,
17 three, four -- five batches that came from
18 Exhibit 2005? Is that what you were referring to?

19 A Yes.

20 Q Okay. And you're saying: Well, it's
21 totally fair for me to add five batches to a sum of
22 157 samples.

23 MS. HASPER: Objection. Mischaracterizes
24 the document.

25 BY MR. POLLACK:

1 Q Right? That's what you did; right?

2 MS. HASPER: Objection. Mischaracterizes
3 the document and mischaracterizes the testimony.

4 BY MR. POLLACK:

5 Q How many samples in total are in
6 Appendix B?

7 A I believe it's 121.

8 Q I'm sorry. 121.

9 So there were 116 samples that weren't
10 development batches?

11 MS. HASPER: Objection. Beyond the scope
12 of Cross.

13 THE WITNESS: That's -- that's -- the
14 information I had, if there were more development
15 batches available, I would have put those in. I
16 didn't eliminate anything deliberately.

17 And I would just simply say that the '393
18 process, you're starting off with a better process.
19 So the development batches are -- were better
20 because you're starting with a superior process to
21 begin with.

22 So I didn't eliminate development
23 batches. If they -- had they been more of them, I
24 would have factored them in.

25 BY MR. POLLACK:

1 Q Sure. I'm not saying you did eliminate
2 development batches.

3 I'm saying you added development batches
4 to the other appendix to bring the number down,
5 isn't that right?

6 MS. HASPER: Objection. Mischaracterizes
7 the document. Mischaracterizes testimony. Asked
8 and answered. Beyond the scope of cross and
9 argumentative by this point.

10 THE WITNESS: No.

11 BY MR. POLLACK:

12 Q No. But you're saying it's fair to add
13 only 5 samples to 116 here, that that's a fair
14 comparison with what you did in Appendix A?

15 MS. HASPER: Same objection. Beyond the
16 scope of Cross. Argumentative. Mischaracterizes
17 the document. Mischaracterizes the testimony.

18 THE WITNESS: I worked with everything
19 that I was able to find.

20 BY MR. POLLACK:

21 Q Well, you didn't find anything; right?
22 Counsel gave you all these -- all this information.

23 MS. HASPER: Objection.

24 BY MR. POLLACK:

25 Q Isn't that right?

1 MS. HASPER: Same objections.

2 THE WITNESS: Yes.

3 BY MR. POLLACK:

4 Q Okay.

5 A But I asked if there was any -- I asked
6 several times: Is there anything else?

7 And they said: This is all we could
8 find.

9 So they -- they got from UTC everything
10 that was available, to my knowledge. So --

11 Q All right. You didn't do any
12 investigation to see if that was really true,
13 though, did you?

14 MS. HASPER: Same objection.

15 THE WITNESS: I didn't do any further
16 investigation, no.

17 MR. POLLACK: No further questions.

18 MS. HASPER: None for me.

19 THE REPORTER: I have nothing.

20 (Laughter)

21 THE VIDEOGRAPHER: This ends the
22 deposition of Robert M. Williams, Ph.D.

23 Total number of media used was four.

24 We're off the record. The time is

25 6:40 P.M.

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(The deposition concluded at 6:40 P.M.)

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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.

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DEPOSITION ERRATA SHEET

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Robert M. Williams, Ph.D.

Dated

1 STATE OF CALIFORNIA)

2)

3 COUNTY OF SAN DIEGO)

4

5

6 I, Harry A. Palter, a Certified Shorthand
7 Reporter of the State of California, do hereby certify:

8 That prior to being examined, the witness in
9 the foregoing proceedings was by me duly sworn to
10 testify to the truth, the whole truth, and nothing but
11 the truth;

12 That said proceedings were taken before me at
13 the time and place therein set forth and were taken down
14 by me in shorthand and thereafter transcribed into
15 typewriting under my direction and supervision;

16 I further certify that I am neither counsel
17 for, nor related to, any party to said proceedings, nor
18 in any way interested in the outcome thereof.

19 In witness whereof, I have hereunto
20 subscribed my name.

21 Dated: 8.30.2016

22

23

24

.....
HARRY ALAN PALTER
25 CSR No. 7708

Exhibits			
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PATENT OWNER
UNITED THERAPEUTICS CORPORATION

IPR2016-00006
U.S. Patent No. 8,497,393
November 29, 2016

UT Ex. 2061
SteadyMed v. United Therapeutics
IPR2016-00006

Petitioner Bears the Burden of Proving Invalidity

- “In an inter partes review, the burden of persuasion is on the petitioner to prove ‘unpatentability by a preponderance of the evidence,’ 35 U.S.C. § 316(e), and that burden never shifts to the patentee.”
 - *In re Magnum Oil Tools International, Inc.* (Fed. Cir. 2016), citing *Dynamic Drinkware*, 800 F.3d at 1378; Paper No. 48.
- “[T]he petitioner continues to bear the burden of proving unpatentability after institution, and must do so by a preponderance of the evidence at trial.”
 - *In re Magnum Oil Tools International, Inc.* (Fed. Cir. 2016); Paper No. 48.
- “[T]he Board has an obligation to assess the question anew after trial based on the totality of the record.”
 - *Id.*

Prior Art at Issue

- The only prior art treprostinil examples in this IPR are (a) the single example in Moriarty 2004 of treprostinil acid (Ex. 1004, p. 13) and (b) the single example in Phares WO 2005/007081 of diethanolamine salt of treprostinil, form B (Ex. 1005, pp. 87-88).
- Kawakami and Ege do not disclose treprostinil or any prostacyclin derivative and do not disclose how to purify such compounds specifically.
- To the extent Petitioner's evidence shifts burden of production, Patent Owner need only present sufficient evidence to rebut that evidence relied upon by Petitioner.

Claim Construction in an IPR Analysis

- “While it is true that, as a general rule, the words of a patent claim are to be given their plain, ordinary and accustomed meaning to one of ordinary skill in the relevant art, *Toro Co. v. White Consol. Indus., Inc.*, 199 F.3d 1295, 1299 (Fed. Cir. 1999), a court must nevertheless examine the remaining intrinsic evidence to determine whether the patentee has set forth an explicit definition of a term contrary to its ordinary meaning, has disclaimed subject matter, or has otherwise limited the scope of the claims.”
 - *Day Intern., Inc. v. Reeves Brothers, Inc.*, 260 F.3d 1343, 1349 (Fed. Cir. 2001) (emphasis added) (PO Resp. at pp. 13-14).
- The Federal Circuit in *SafeTCare Mfg* incorporated limitations into claim construction where the specification repeatedly indicated that the invention operated by “pushing (as opposed to pulling) forces,” and then characterized the “pushing forces” as “an important feature of the present invention.”
 - *SafeTCare Mfg., Inc. v. Tele-Made, Inc.*, 497 F.3d 1262, 1269-70 (Fed. Cir. 2007)(PO Resp. at p. 14).

Proper Claim Construction Requires Consideration of Impurities Present In The Product

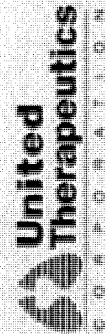
Example 6
Comparison of the Former Process and a Working Example of the Process According to the Present Invention

Step No.	Steps	Former Process (Batch size: 500 g)	Working example of the present invention (Batch size: 5 kg)
38	Brine wash	N/A	
39	Sodium sulfate	N/A	
40	Filter	N/A	
41	Evaporation	N/A	
42	Crude drying on tray	1 or 3 days	
43	Ethanol & water for cryst.	5.1 L + 5.1 L	
44	Crystallization in	20-L rotavap	
45	Temperature of crystallization	2 h rt., fridge	
46	Filtration	Buchner funnel	Aureo
47	Washing	20% (10 L) cooled ethanol-water	20% ethanol
48	Drying before oven	Buchner funnel (20 h)	Aureo
49	Oven drying	Tray (no)	Tray
50	Vacuum	15 hours, 55° C.	6-15 h
51	UT-15 yield weight	<-0.095 mPA	<\$ Top
52	% yield from trial	~535 g	~1,100
53	Purity	~91%	~89%
		~99.0%	99.9%

-continued

Example 6 in the '393 Patent specification indicates the purity of a working example of the invention is 99.9% whereas purity of former Moriarty product was ~99.0%

• Ex. 1001, 17:step 53. (PO Resp. at p. 16)



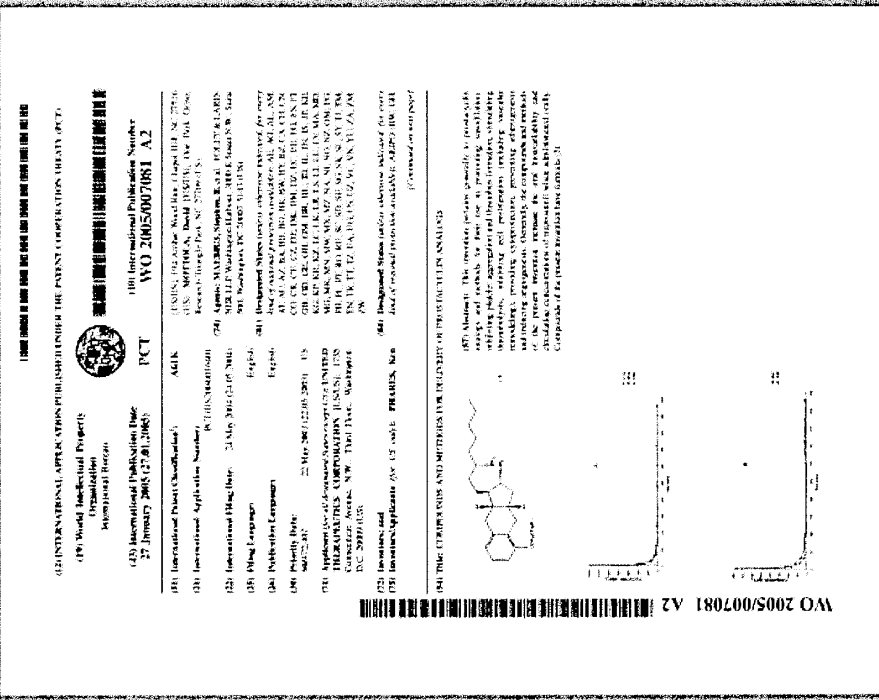
Proper Claim Construction Requires Consideration of Impurities Present In The Product

- Prosecution history clarified that impurity profiles were important to the claimed invention
 - “[e]ach of treprostinil as the free acid and treprostinil diethanolamine prepared according to the process specified in claim 1 or 10 . . . is physically different from treprostinil prepared according to the process of ‘Moriarty’ due to differences in their impurity profiles.”
 - Ex. 1002 at 344. (emphasis added) (PO Resp. at p. 16)
 - UTC thereafter filed the Walsh Declaration, which demonstrated that the claimed product had a different impurity profile and higher purity than a representative batch of Moriarty’s product.
 - Ex. 1002 at 347-349. (PO Resp. at p. 16)
 - Claims allowed within eight days of the submission of Walsh’s Declaration demonstrating differences in impurities.
 - *Id.* at 354.

Proper Claim Construction Requires Consideration of Impurities Present In The Product

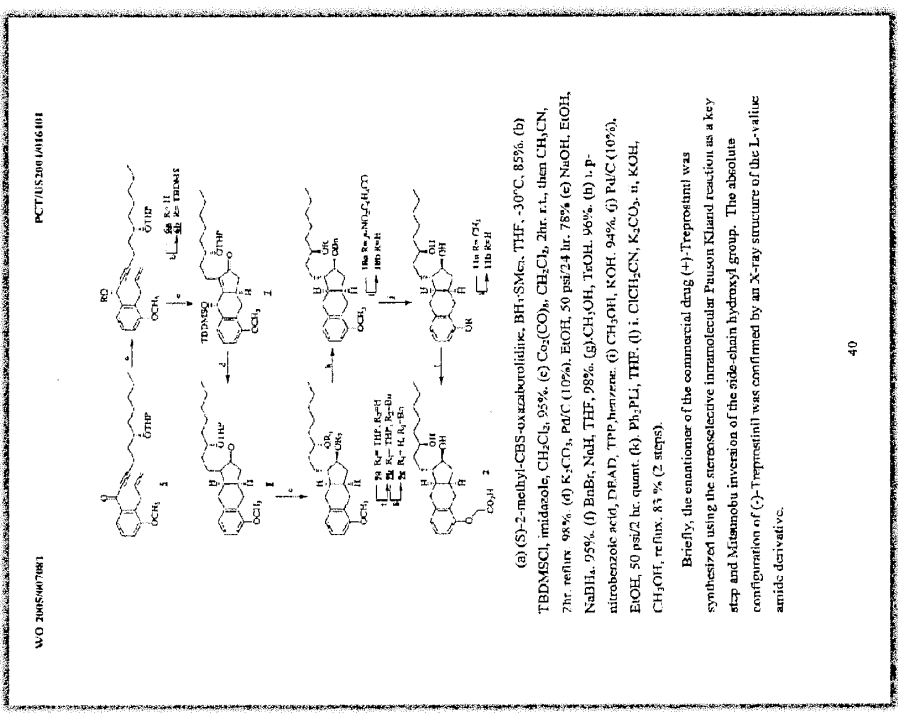
- The '393 patent specifically distinguishes the purification limitation [eliminating purification after step (a) as required in claims 8 & 16] over the prior art. Ex. 1001, Example 6. Moriarty expressly discloses that the compound of formula (VI) from step (a) is purified.
 - Ex. 2020 at ¶104; PO Resp. at p. 32.
- No evidence from Petitioner of the impact of eliminating column purification step from Moriarty 2004 publication; the only direct comparative evidence in the record for claims 8 and 16 is Ex. 6 in '393 patent.
 - Ex. 2020 at ¶104; PO Resp. at p. 32.

Phares Does Not Anticipate Any '393 Patent Claim



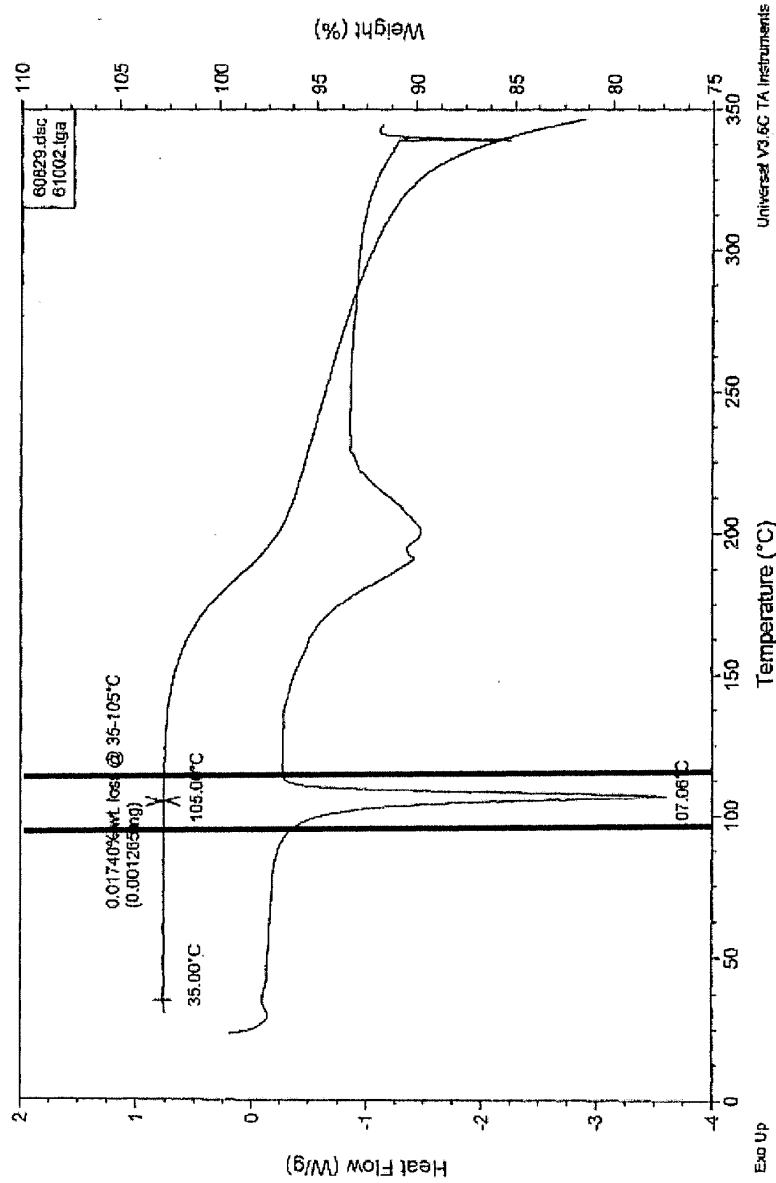
- Phares was disclosed on the face of the '393 patent
- Phares fails to disclose any detailed synthesis of treprostlinol
- Phares fails to disclose any impurity or impurity profile for treprostlinol or treprostlinol diethanolamine
- Phares fails to disclose any purity level for treprostlinol diethanolamine

Synthesis Disclosed In Phares Is Not For Treprostinil



- Dr. Williams confirmed the synthesis in Phares is for the enantiomer of treprostinil, a different product.
 - Ex. 2059, 264:13-265:18; 265:20-23; Ex. 2020 ¶179
- Phares fails to disclose the source of treprostinil used in single step example making treprostinil diethanolamine.
 - Ex. 1005, p. 24; Ex. 2020, ¶179.
- Only reference to treprostinil synthesis in Phares is to early syntheses resulting in impure substances.
 - Ex. 1005, p. 9; Ex. 2020, ¶178.

Phares Fails to Disclose Purity of Treprostinil Diethanolamine



- Dr. Williams confirmed broad approximate 10 degree melting point range from Phares indicated a less pure substance. Ex. 2020, ¶176.

Phares Form B Diethanolamine Salt Example Is Not the Same as the '393 Patent Product

Williams' Declaration

Melting point range is "broad" (¶ 76)

Rogers' Declaration

Melting Point range is "narrow" (¶ 87)

Cites to Marti reference (Ex. 2031) (¶ 76) *NO SUPPORT*

Conclusion: Cannot determine purity from melting point range of Phares (¶ 76)

Conclusion: Phares at least as pure as '393 (¶ 88)

Phares Does Not Anticipate Any Claim of the '393 Patent

- Petitioner's expert Dr. Rogers acknowledges Phares form B has a different melting point range than the '393 patent products and "[a]ny difference in their measured melting point, Ts, is due to differing levels of impurities."
 - Ex. 1022, ¶172 and 82
- Phares form B sample made for polymorph screen by a very different process that converts to form B from form A, it is not clear where the specific batch of form B used for analysis came from, and is not a large scale batch.
- Petitioner has failed to show the Phares product is the same as the products disclosed in the '393 patent.
 - Ex. 2020, ¶73; PO Resp., p. 25.
 - PO Resp. at pp. 22-26.



Winkler Improperly Compared Purity Levels

- “When purity is determined by comparison of a sample to a reference standard such as assay purity, one cannot directly compare the purity values of two samples in any meaningful way unless each value was achieved by comparison to the same reference standard. Neither the Walsh Declaration nor Moriarty identifies a specific reference standard.” (emphasis supplied)
 - Ex. 2034, pp. 28-29; Ex. 2035, pp. 5-8; Ex. 2020, ¶ 88; PO Resp., pp. 2, 29
- Moriarty 2004 purity of “99.7%” cannot be compared to Walsh, ‘393 data or any FDA data in the record.
 - Ex. 1004, p. 13

Winkler Improperly Compared Purity Levels

- Winkler mistakenly thought that an “assay” purity in the ‘393 patent represented HPLC error rate rather than a relative purity level compared to a reference standard, which gave rise to his further misunderstanding about the Walsh Declaration, the ‘393 specification, & Moriarty purity measurements.
 - Ex. 1001, col. 13, l. 2; Ex. 2020 ¶¶ 89-93; PO Resp. at pp. 29-30
- Winkler later acknowledged that assay purity determinations over 100% and FDA purity measurement limits are valid; however, the Institution Decision was based on Winkler’s erroneous initial purity conclusions.
 - PO Response at 3; Ex. 2051 at 64:7-9; Paper No. 12 at pp. 8, 17, 19, 48

Winkler Improperly Compared Purity Levels

- Dr. Williams: “the level of detection for measuring impurities in these treprostinil samples was somewhere between 0 and 0.05%, not something in excess of 0.4% as Dr. Winkler erroneously concludes” (emphasis supplied).
 - Ex. 2020, at ¶192; PO Resp. at p. 3
- Dr. Ruffolo: the Certificates of Analysis purity data presented in the Walsh, Ruffolo and Williams Dec.’s is the same data required by FDA in its purity specification for treprostinil and relied upon by UT to comply with FDA’s requirements .
 - Ex. 2022 at ¶132; Ex. 2020 at ¶194; PO Resp. at pp. 3-4

Petitioner Bears the Burden of Proving Invalidity

- Institution Decision was based on Winkler's erroneous initial purity conclusions (Paper No. 12 at pp. 8, 17, 19, & 48)
- '393 comparative data, FDA data submitted in this IPR & Walsh's Declaration should all be credited over Winkler's debunked Declaration/misunderstanding of purity
- When Winkler's mistaken testimony about purity levels is removed, Petitioner has not carried its threshold burden

Significant Differences Exist Between Batches Made by the '393 Patent and Moriarty Processes

Moriarty Process Impurities (Average Percent Detected)							Total Related Substance
1AU90	2AU90	3AU90	750W93	751W93	97W86	ethyl ester	methyl ester
0.0473	0.0407	0.2545	0.1646	0.1025	0.0405	0.0889	0.1028
'393 Patent Process Impurities (Average Percent Detected)							0.9545
1AU90	2AU90	3AU90	750W93	751W93	97W86	ethyl ester	methyl ester
0.0004	0.0004	0.0455	0.0643	0.0488	0	0.1208	0.005
							0.2944

- Dr. Williams analyzed over 170 batches of treprostinil and treprostinil diethanolamine made by either the Moriarty process or the '393 patent process to analyze impurities and total related substances

• Ex. 2020, ¶194-98

Significant Differences Exist Between Batches Made by the '393 Patent and Moriarty Processes

Moriarty Process Impurities (Average Percent Detected)									
	1AU90	2AU90	3AU90	750W93	751W93	97W86	ethyl ester	methyl ester	Total Related Substance
	0.0473	0.0407	0.2545	0.1646	0.1025	0.0405	0.0889	0.1028	0.9545
'393 Patent Process Impurities (Average Percent Detected)									
	1AU90	2AU90	3AU90	750W93	751W93	97W86	ethyl ester	methyl ester	Total Related Substance
	0.0004	0.0004	0.0455	0.0643	0.0488	0	0.1208	0.005	0.2944

• Greater than 100 fold reduction in 1AU90 and 2AU90 impurities

• Ex. 2020, ¶¶94-98

Significant Differences Exist Between Batches Made by the '393 Patent and Moriarty Processes

Moriarty Process Impurities (Average Percent Detected)									
1AU90	2AU90	3AU90	750W93	751W93	97W86	ethyl ester	methyl ester	Total Related Substance	
0.0473	0.0407	0.2545	0.1646	0.1025	0.0405	0.0889	0.1028	0.9545	
'393 Patent Process Impurities (Average Percent Detected)									
1AU90	2AU90	3AU90	750W93	751W93	97W86	ethyl ester	methyl ester	Total Related Substance	
0.0004	0.0004	0.0455	0.0643	0.0488	0	0.1208	0.005	0.2944	

- Twenty fold reduction in methyl ester impurity

- Ex. 2020, ¶¶94-98

Significant Differences Exist Between Batches Made by the '393 Patent and Moriarty Processes

Moriarty Process Impurities (Average Percent Detected)									
	2AU90	3AU90	750W93	751W93	97W86	ethyl ester	methyl ester	Total Related Substance	
1AU90	0.0407	0.2545	0.1646	0.1025	0.0405	0.0889	0.1028	0.9545	
'393 Patent Process Impurities (Average Percent Detected)									
	2AU90	3AU90	750W93	751W93	97W86	ethyl ester	methyl ester	Total Related Substance	
1AU90	0.0004	0.0455	0.0643	0.0488	0	0.1208	0.005	0.2944	

- Significant reductions in 750W93, 751W93, and 3AU90 impurities
- 97W86 impurity eliminated in '393 patent process

• Ex. 2020, ¶¶94-98

Significant Differences Exist Between Batches Made by the '393 Patent and Moriarty Processes

Moriarty Process Impurities (Average Percent Detected)

1AU90	2AU90	3AU90	750W93	751W93	97W86	ethyl ester	methyl ester	Total Related Substance
0.0473	0.0407	0.2545	0.1646	0.1025	0.0405	0.0889	0.1028	0.9545

'393 Patent Process Impurities (Average Percent Detected)

1AU90	2AU90	3AU90	750W93	751W93	97W86	ethyl ester	methyl ester	Total Related Substance
0.0004	0.0004	0.0455	0.0643	0.0488	0	0.1208	0.005	0.2944

• Overall reduction in impurities by approximately 0.7%

• Ex. 2020, ¶¶94-98

Significant Differences Exist Between Batches Made by the '393 Patent and Moriarty Processes

Moriarty Process Impurities (Average Percent Detected)									
	1AU90	2AU90	3AU90	750W93	751W93	97W86	ethyl ester	methyl ester	Total Related Substance
	0.0473	0.0407	0.2545	0.1646	0.1025	0.0405	0.0889	0.1028	0.9545
'393 Patent Process Impurities (Average Percent Detected)									
	1AU90	2AU90	3AU90	750W93	751W93	97W86	ethyl ester	methyl ester	Total Related Substance
	0.0004	0.0004	0.0455	0.0643	0.0488	0	0.1208	0.005	0.2944

- Ethyl ester actually increased in '393 patent demonstrating another difference between the '393 and Moriarty batches

• Ex. 2020, ¶¶94-98

'393 Product Has Higher Ethyl Ester Impurities Than Moriarty

- Dr. Williams also found that ethyl ester unexpectedly increased in the '393 product of the batches he reviewed compared to the Moriarty batches he reviewed
 - Ex. 2020, ¶¶94-98; PO Resp. at p. 10
- This point is not challenged by Petitioner
- '393 product is different regardless of claim construction due to higher impurity level of ethyl ester compared to Moriarty

Petitioner Challenges Averages But Ignores Other Evidence Supporting Williams Declaration

- “Looking past the average data, it is also worth noting that, out of all the batches of trestatinil product made by the ’393 patent process which I reviewed, 1AU90 was only detected in a single batch (01A07001) and 2AU90 was also only detected in a single batch (01A07003), and both impurities were only detected at a level of 0.05% or less. Furthermore, batches 01A07001 and 01A07003 were both identified as ‘optimization batches’ (as distinguished from commercial batches).” (emphasis supplied).
 - Ex. 2020 at ¶ 97, PO Resp. at p. 4
- Dr. Williams relied on these individual impurity values and trends, not just calculated averages to support his conclusion that the products are different.

Petitioner Challenges Averages But Ignores Other Evidence Supporting Williams Declaration

- “the averages presented in the Process Optimization Report still show significant differences between ‘393 trestoninil products and the Moriarty trestoninil products. Specifically, Table 2 of the Process Optimization Report shows that on average 97W86 was detectable in these 96 batches, and that these 96 batches contained higher average levels of 3AU90, 750W93, 751W93, and total impurities as compared to the averages for the ‘393 trestoninil product. Ex. 2005 at 7; Appendix B.” (emphasis supplied).
- These 96 batches relied upon by Williams were not used in the other average calculations criticized by Petitioner for including development batches.

• UT Ex. 2005, at 7; Ex. 2020 at footnote 1



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Petitioner Objects To Admissibility Of Certain Moriarty Batches But Filed No Motion To Exclude Them

- Petitioner’s Reply objects to relevance of certain Moriarty batches, but yet Petitioner filed no Motion to Exclude as to this evidence.
 - Paper No. 52, p. 7.
- However, Petitioner also objected to relevance of the Moriarty batches in its evidentiary objections, in response to which Patent Owner supplemented the record with authenticating Declarations.
 - Ex. 2052; Paper No. 43, p. 11.
- Petitioner cannot maintain its position on lack of relevance after objecting and then failing to move to exclude, depriving Patent Owner of its right to rely on timely served supplemental evidence.





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Additional Comparative Data in Dr. Williams Declaration Stands Unchallenged By Petitioner and Confirms Dr. Williams Conclusions

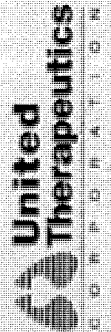
Table 2. RELEASE TESTING DATA RANGE FOR UT-15 (TREPRESTINIL) API
SUMMARY 2000 TO 2006 FOR CHICAGO SITE
BATCH SIZE 350 GRAMS TO 1 KILOGRAM
NUMBER OF BATCHES: 96

TEST	SPECIFICATION	MINIMUM	MAXIMUM	AVERAGE
Specific Rotation	Not less than +42.0° and not more than +49.0° at 589 nm and 25 °C.	+43.3°	+47.7°	+45.8°
Residue on Ignition	Not more than 0.2%, w/w	0.0 % w/w	0.2%, w/w	0.0%, w/w
Water (Karl Fischer)	Not more than 2.0%, w/w	0.1 % w/w	1.8%, w/w	0.4%, w/w
Residual Solvents by Gas Chromatography				
• Ethyl Acetate	Not more than 0.5%, w/w	ND	<0.1 %	<0.1%
• Ethanol	Not more than 0.5%, w/w	0.0 %	0.2 %	0.1%
• Acetic Acid	Not more than 0.5%, w/w	ND	0.2 %	<0.1%
• Methanol	Not more than 0.1%, w/w	ND	<0.1 %	<0.1%
Melting Range	Not less than 120.0 °C and not more than 126.0 °C	120.1 °C	125.2 °C	Low:121.6 °C High:122.7 °C
Heavy Metals	Not more than 0.002%	Not more than 0.002%	Not more than 0.002%	Not more than 0.002%
Assay (HPLC)	Not less than 97.0% and not more than 101.0%, w/w, on the volatiles-free basis	98.9 % w/w	100.3 % w/w	99.3 % w/w
Impurities				
• 1AU90	Not more than 0.4%	ND	0.2 %	<0.05 %
• 2AU90	Not more than 0.1%	ND	<0.05 %	<0.05 %
• 97W86	Not more than 0.2%	ND	0.07 %	<0.05 %
• 3AU90	Not more than 1.0%	0.09 %	0.4 %	0.2 %
• UT-15 methyl ester	Not more than 0.2%	ND	0.1%	<0.05 %
• 98W86	Not more than 0.5%	ND	<0.05 %	<0.05 %
• UT-15 ethyl ester	Not more than 0.5%	<0.05 %	0.4 %	0.1 %
• 750W93	Not more than 0.5%	<0.05 %	0.2 %	0.1 %
• 751W93	Not more than 0.1% AUC each	<0.05 %	0.3%	0.07 %
• Unidentified	Not more than 0.1% AUC each	ND	0.6% (Total)	0.05 %
Total Related Substances	Not more than 3.0%	0.3 %	0.8 %	0.5 %

w/w = weight/weight; ND = not detected; AUC = area under the curve.

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• Ex. 2005 at 7; Ex. 2020 at FN 1.



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Additional Comparative Data in Dr. Williams Declaration Stands Unchallenged By Petitioner and Confirms Dr. Williams Conclusions

- The averages of impurities presented in the Process Optimization Report analyzing 96 Moriarty batches also show significant differences between '393 treprostinil products and the Moriarty treprostinil products.
 - Ex. 2005 at 7; Ex. 2020 at FN 1.
- These 96 batches contained higher average levels of 3AU90, 750W93, 751W93, and total impurities as compared to the averages for the '393 treprostinil product and lower overall average impurities.
 - Ex. 2005 at 7; Ex. 2020 at FN 1.

FDA Expressed a Long-Felt Need For Each Individual Known Impurity To Be Minimized

- Each of the known impurities are “sources of potential adverse toxicities to patients. Impurities, therefore, can only add to the risk assessments, which are often unknown, made by regulatory agencies in the evaluation of new drug products.”
 - Ex. 2040 at 3-4 and 5-8; Ex. 2022 at ¶ 36; PO Resp. at p. 7.
- Even trace impurities can pose serious health risks.
 - Ex. 2022 at ¶ 40; PO Resp. at p. 12.
- To FDA, a product is different if it presents a reduced risk profile due to reduced amounts of individual known impurities, even if there is currently no known adverse effect in patients attributable to those impurities.
 - Ex. 2022 at ¶ 36; PO Resp. at pp. 7-8.

The '393 Patent Met the Long-Felt Need of Improved Purity

- Patent Owner requested and FDA approved a higher purity specification to reflect the treprostinil product resulting from Patent Owner's switch to the '393 patent steps.
 - Ex. 2006, 2003; PO Resp. at p. 12.
- “[W]hile FDA approval is not determinative of nonobviousness, it can be relevant in evaluating the objective indicia of nonobviousness.”
 - *Knoll Pharm. Co., Inc. v. Teva Pharm. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004); PO Resp. at p. 48.

The '393 Patent Met the Long-Felt Need of Improved Purity

- FDA initially rejected UT's requested purity specification change, leading to resubmission with additional evidence.
 - Ex. 2006 at 1; Ex. 2022 at ¶ 66; PO Resp. at pp. 12 and 48.
- “any change in the synthesis or manufacture of the drug substance that may affect its impurity profile and/or the physical, chemical, or biological properties of a drug is considered a major change.”
 - Ex. 2050 at 17. (emphasis added); Ex. 2022 at ¶72; PO Resp. at p. 12.
- “Because the FDA allowed the drug specification for purity to be changed to reflect the higher level of purity, from a lower level of 97% to 98%, around means of 99% to 100%, respectfully, resulting from the '393 patent process, it is clear that the FDA considered this to represent a major/significant change.”
 - Ex. 2022 at ¶72; PO Resp. at p. 12.

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FDA's Drug Purity Specifications Are Rigorously Analyzed & Commercially Important

- Purity data must be prepared according to detailed FDA guidelines.
 - Ex. 2022, ¶53, citing: Ex. 2006 p. 6, Ex. 2044 pp. 34-35, and Ex. 2035 pp. 8-11
- UT's data had to meet these requirements.
 - Ex. 2022 ¶ 57
- If a Certificate of Analysis for a batch does not meet the FDA's purity specification in any aspect, it cannot be sold for use by patients.
 - Ex. 2022 ¶ 32; PO Resp. p. 12

'393 Patent Product Is Structurally Different Regardless Of Batch-To-Batch Variability In Starting Material

- Petitioner has not established that any specific batch of Moriarty treprostinil is not physically changed by performing step (c), and all the evidence suggests that it is.
- Petitioner presents no test data of its own.
- The FDA agreed that the evidence presented by the Patent Owner in this IPR warranted a change in purity specification.

• PO Resp. at p. 12

• PO Resp. at p. 12; Ex. 2006 at 4-6; Ex. 2022 at ¶¶66-72.



The '393 Patent Product Is Structurally Different Regardless Of Batch-To-Batch Variability In Starting Material

- “The chemical manufacturing steps have not changed during the transfer to [supplier A] and [supplier B] from the process used by UT in Chicago to prepare benzindene triol.”
 - Ex. 2006 at 3.
- “There is a release specification for benzindene triol that must be achieved for each lot of benzindene triol before it is released for use by UT to prepare treprostinil. This is the same specification that was used by United Therapeutics in our Chicago facility.”
 - *Id.*
- “In all lots [of benzindene triol from suppliers A, B, C, and D], the total unidentified impurity level (%AUC) decreased from triol [step (a)] to UT-15C intermediate [step (c)].”
 - *Id.*

Winkler Fundamentally Misunderstood Certain Purity Measurements

- The level of detection for measuring impurities in these treprostinil samples was somewhere between 0 and 0.05%, not something in excess of 0.4% as Dr. Winkler erroneously concluded.
 - Ex. 2020 at ¶192; PO Resp. at p. 3.
- The Certificates of Analysis purity data presented in the declarations of Drs. Walsh and Williams is the same data required by FDA in its purity specification for treprostinil and relied upon by UT to comply with FDA's requirements
 - Ex. 2022 at ¶132; Ex. 2020 at ¶194; PO Resp. at pp. 3-4.
- Walsh's Declaration should be credited over Winkler's debunked Declaration/misunderstanding of purity
 - Petitioner did not depose Dr. Walsh, a further reason to credit Dr. Walsh's Declaration over Dr. Winkler



Petitioner's Expert Dr. Winkler Fundamentally Misunderstood Certain Purity Measurements

- Dr. Winkler mistakenly thought that an “assay” purity in the ‘393 patent represented HPLC error rate rather than a relative purity level compared to a reference standard, which gave rise to his further misunderstanding about the Walsh Declaration, the ‘393 specification, & Moriarty purity measurements.
- Winkler later acknowledged that assay purity determinations over 100% and FDA purity measurement limits are valid, however, the Institution Decision was based on Dr. Winkler’s erroneous initial purity conclusions.

• Ex. 2020 at ¶¶ 89-93; PO Resp. at pp. 29-30.

• PO Response at 3; see also Ex. 2051 at 64:7-9; Paper No. 12 at pp. 8, 17, 19, & 48.



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Claims 6, 10, 15, 21, & 22 Are Not Obvious

- Only instituted ground for claims 6, 10, 15, 21, and 22 is obviousness based on Moriarty, Phares, Kawakami & Ege
 - Institution Decision at 37.
- “the absence of a known or obvious process for making the claimed compounds overcomes any presumption that the compounds are obvious based on close relationships between their structures and those of prior art compounds.”
 - *In re Hoeksema*, 399 F.2d 269, 274 (C.C.P.A. 1968); PO Response at p. 45.
- Petitioner fails to provide any motivation or reason a POSA would look to Kawakami or Ege to purify treprostinil or any related prostacyclin.

- PO Resp. at pp. 34-44.

No Reasonable Expectation To Further Purify Moriarty By Combining Phares, Ege, & Kawakami

- Petitioner contradicts itself by asserting that Moriarty is already as pure as the '393 product, but yet a POSA would be motivated to apply further purification efforts to Moriarty based on Phares, Ege & Kawakami.
 - Compare Petitioner Reply at 4-6 and 19-20.
- Kawakami relates to use of a different salt to purify a different impurity present in a much larger amount (at least 22.8%) in a different compound
 - PO Response at pp. 39-44.
- A POSA would have no reason to turn to Kawakami or Ege given these differences.
 - Ex. 2020 at ¶ 106, PO Response at p. 37.

A POSA Would Not Turn to Kawakami

- Kawakami uses a different salt to remove a different sort of impurity from a different structure.
- a POSA would have no reason to combine the teachings of Kawakami with Moriarty and Phares in the particular manner of the asserted grounds in the Petition, or a reasonable expectation of success of achieving a more pure treprostinil product by such a combination.

• Ex. 2020 ¶1114; PO Resp. at p. 41.

(15) Japanese Patent Office (JP) (11) Unexamined Patent Application (Kokusai) No.	
(12) Unexamined Patent Gazette (A)	56-122328
International Office Registration No.	7114-AC
Date of Publication	September 21, 1981
Classifications	
Symbol	7114-AC
A-61K	317-06
C-07C	317-06
Request for Examination: Non-prior art	Number of Claims: 2
	Total of 4 pages (in original)
(54) Title of the Invention:	CRYSTALLINE AMINE SALT OF METHANOPROSTACYCLIN DERIVATIVE, MANUFACTURING METHOD THEREOF, AND PURIFYING METHOD THEREOF
(61) App. No.	55-25726
(62) Date of Filing:	February 29, 1980
(71) Inventor:	Kawakami, Hajime Takanashi-shi, Hyogo-ken 2-chome, 14-ban, 7-go
(72) Inventor:	Ogata, Shiro Osaka-shi, Higashi-ku, Higashinari 1-chome, 5-ban, 3-506-go
(73) Inventor:	Suzie, Akihito Toyonaka-shi, Senrihigashinocho, 2-chome, 10-ban, 1-116-go
(73) Inventor:	Katube, Susumono Toyonaka-shi, Machigayama-cho, 10-20
(71) Applicant:	Sunimono Chemical Co., Ltd. Osaka-shi, Higashi-ku, Kitabata, 5-chome, 15-banchi
(74) Agent:	Katuya Kinura, Patent Attorney
1. Title of the Invention	CRYSTALLINE AMINE SALT OF METHANOPROSTACYCLIN DERIVATIVE, MANUFACTURING METHOD THEREOF, AND PURIFYING METHOD THEREOF
	Page 1

Kawakami Teaches Away From Claim 15

- Petition selectively uses Kawakami only for teaching regenerating the acid after salt formation, while ignoring the fact that it suggests using a different salt than what is taught by Phares for the purpose of purifying a much less pure starting material.

- PO Resp. at p. 41.

(15) Japanese Patent Office (JP)	(11) Unexamined Patent Application (Kokai) No.	56-122328
(12) Unexamined Patent Gazette (A)	56-122328	
Classification Symbol	International Publication No.	7:13-C
(31) Int. Cl. ⁷	International Registration No.	7:13-C
C07C 59/26		7:13-C
51/25		7:13-C
A61K 31/55		7:13-C
C07C 177/00		7:13-C
Request for Examination, Not yet submitted	Number of Claims: 2	Total of pages (including abstract)

(54) Title of the Invention:	CRYSTALLINE AMINE SALT OF METHANOPROSTACYCLIN DERIVATIVE, MANUFACTURING METHOD THEREOF, AND PURIFYING METHOD THEREOF
(21) Application No.:	55-25726
(22) Date of Filing:	February 29, 1980
(72) Inventor:	Kawakami, Hajime
(72) Inventor:	Tokorozaki-shi, Ryugasaki-ku, 2-chome, 14-ban, 7-go
(72) Inventor:	Otao, Kenichi
(72) Inventor:	Osaka-shi, Higashi-yaodogawa-ku, Higashitawara 1-chome, 5-ban, 3-590-go
(72) Inventor:	Suzie, Akihiko
(72) Inventor:	Toyonaka-shi, Senchogagaohashi, 2-chome, 10-ban, 1-116-go
(72) Inventor:	Katoh, Sumitomo
(72) Inventor:	Toyonaka-shi, Maehigashiyama eho, 10-20
(71) Applicant:	Sunimino Chemical Co., Ltd.
(74) Agent:	Osaka-shi, Higashi-ku, Kitahama, 5-chome, 15-banchi Katsuya Kanoura, Patent Attorney

SPECIFICATION

1. Title of the Invention
CRYSTALLINE AMINE SALT OF METHANOPROSTACYCLIN DERIVATIVE, MANUFACTURING METHOD THEREOF, AND PURIFYING METHOD THEREOF

JP 56 122328 1

Page 1

Petitioner Mischaracterizes Dr. Williams Testimony Regarding Batch Analysis

- Petitioner alleged that Williams did not know if 10 data points in his analysis were produced under the Moriarty process.
 - Petitioner's Reply pp. 2 & 6.
- Dr. Williams clarified on redirect that they “were made by the Moriarty process.”
 - Ex. 2059, 254-256.

Petitioner Mischaracterizes Dr. Williams Testimony Regarding Batch Analysis

- Petitioner also falsely alleged that the Moriarty batches were “cherry-picked” by including developmental batches with poor results.
 - Petitioner’s Reply pp. 2 & 6.
- Dr. Williams clarified that he relied on Dr. Aristoff’s selection of Moriarty batches from a separate case, *United Therapeutics v. Sandoz*.
- Those same batches were previously used to show how good the Moriarty batches were compared to a previous method.

Petitioner Mischaracterizes Dr. Williams Testimony Regarding Batch Analysis

- *In United Therapeutics v. Sandoz, Inc.*, the Court ruled that the same Moriarty batches used by Dr. Williams had fewer amounts of impurities and a lower amount of total related substances over batches made by the prior art.
 - 2014 WL 4259153, C.A. Nos. 12–CV–01617, 13–CV–316 (D.N.J. August, 29, 2014).
- Dr. Williams also clarified that developmental batches for both the Moriarty and '393 patent process were used in his analysis.
 - Ex. 2059, 101:21-102:13.

Petitioner Mischaracterizes Dr. Williams Testimony Regarding Batch Analysis

- Petitioner also alleged that Dr. Williams “had no explanation for why he included 10 development batches... for his analysis of Moriarty batches, but only 5 development batches... for his analysis of ‘393-Patent batches’”.
 - Petitioner’s Reply p. 7.
- But Dr. Williams actually testified that “these were all the batches we could find records for”.
 - Ex. 2059, 94:25- 95:9

Petitioner Mischaracterizes Dr. Williams Testimony Regarding Batch Analysis

- Dr. Williams’ testimony stated only that calculation was correct, not that it was a “a fair analysis” as claimed in Petitioner’s reply.
 - Ex. 2059 p. 219; Petitioner’s Reply p. 2
- Petitioner also alleged that Dr. Williams testimony suggested that Steadymed’s calculation of 99.7% “should be relied upon.” Dr. Williams merely confirmed that calculation was correct using Steadymed’s selected numbers.
 - Petitioner’s Reply pp. 2-3;

Petitioner Mischaracterizes Dr. Williams Testimony Regarding Batch Analysis

- Petitioner also alleged that Dr. Williams did not perform calculations on data in Appendices A and B of his declaration, “having relied solely on counsel’s work”. Dr. Williams actually testified that he “checked the calculation” performed by counsel.
- Petitioner’s Reply pp. 8-9; Ex. 2059, 102:12-20

Petitioner Mischaracterizes Dr. Williams Testimony Regarding Batch Analysis

- Petitioner also alleged that the free acid is *less pure* than the diethanoleamine salt, and not more pure as UT represented to the FDA in Exhibit 2006. Dr. Williams could not provide an explanation for this discrepancy, which contradicts the Walsh Declaration. Dr. Williams stated that this wasn't something he considered in forming his opinion, and that he'd need more time to consider it; he simply wasn't able to provide an immediate explanation.

- Petitioner's Reply p. 12; Ex. 2059, 199:6-18; Ex. 2059, 198:1-199:5, 199:19-21

Petitioner Mischaracterizes Dr. Williams Testimony Regarding Batch Analysis

- Petitioner also alleged that Dr. Williams concedes that the process in Phares for making treprostinil's (-)-enantiomer carries out the same alkylation step (a) and hydrolysis step (b) in the '393 Patent's claims, thus disclosing these steps for treprostinil. Dr. Williams stated on redirect that it was, in fact, a different step because in Phares you're using and producing the enantiomers, not the specified structures.

- Petitioner's Reply p. 13; Ex. 2059, 264:15-265:23

Petitioner Grossly Mischaracterizes Dr. Williams Testimony Regarding Batch Analysis

- Petitioner also alleged that Dr. Williams, who is “not a polymorph expert,” contends nevertheless that the melting point of two samples of the same polymorph (crystal form) cannot be compared to determine their relative purities. Dr. Williams’ Declaration states that, when different solvents and crystallization conditions are used, you can’t directly compare melting points to determine purities, not that melting points can’t ever be compared to determine purity, and he reiterated this point at his deposition.

- Petitioner’s Reply p. 14; Ex. 2059, 158:17-18; 156:25-157:2; 159:6-160:12; Ex. 2020 ¶ 75

Petitioner Mischaracterizes Dr. Williams Testimony Regarding Batch Analysis

- Petitioner also alleged that, as admitted by Dr. Williams, melting point is one of the most common ways to identify different polymorphs; but the cited portion of Dr. Williams' transcript actually says "Q. Well, why do you think they do that? Why do you think they append a melting point to each polymorph? [Objection] THE WITNESS: Well, certainly, that's a physical characteristic of an individual solid form."

- Petitioner's Reply p. 14; Ex. 2059, 158:20-25



Petitioner Mischaracterizes Dr. Williams Testimony Regarding Batch Analysis

- Petitioner also alleged that Dr. Williams concedes that the same tereprostinil diethanolamine salt polymorph—Form B—is presented in the Phares reference and '393 Patent; while Dr. Williams conceded they were both “called” polymorph B, he said he couldn’t “be 100 percent certain” they were the same crystal form because the melting points differed.

- Petitioner’s Reply P. 15; Ex. 2059, 168:6-11, 168:12-169:2

Petitioner Mischaracterizes Dr. Williams Testimony Regarding Batch Analysis

- Petitioner also alleged that while Dr. Williams relies on his “personal experience” observing different melting points for crystals made with different solvents, he conceded that he knew of no literature to support his opinion; Dr. Williams does base it on his own experience but in the cited testimony states, regarding literature references, “I’m sure I could find it if I was asked to”.

- Petitioner’s Reply p. 15; Ex. 2059, 184:22-185:2, 184-185:2

Petitioner Mischaracterizes Dr. Williams Testimony Regarding Batch Analysis

- Petitioner also alleged that Dr. Williams conceded that the one article he relied upon in his declaration, Ex. 2030, in fact describes different crystal forms having different melting points, and not the same crystal form having different melting points; but Dr. Williams' testimony was actually the opposite: "I'm not sure I can come to that conclusion. And what I did cite from this article is that the conclusion, which I quoted in my Declaration, and it's also based on my experience of crystallizing the same compound on different days from different solvents under slightly different conditions, you can get a different melting point. And it depends on the scale and lots of things."

- Petitioner's Reply p. 15; Ex. 2059, 180:9-25, 181:17-182:13



Petitioner Mischaracterizes Dr. Williams Testimony Regarding Batch Analysis

- Petitioner also alleged that it is now confirmed that UT's Moriarty purity varies by at least 0.6%, and indeed, Dr. Williams conceded he had no reason to disagree with this 0.6% value; but directly before the cited portion, Dr. Williams said that he was “not familiar” with the standard deviation function in Excel because he doesn’t use it “in [his] normal course of work.”

- Petitioner’s Reply P. 16; Ex. 2059, 218:22-24, 218:15-21

Petitioner Mischaracterizes Dr. Williams Testimony Regarding Batch Analysis

- Petitioner also alleged that Dr. Williams' own example of "product" in his own writing—Ex. 2028—uses "product" to mean a product created by nature, and not by a chemical reaction, when it refers to "the natural product from marine sources." But Dr. Williams testimony actually was:

"Q. . . All right. It's not a -- it's not a chemical reaction; this is a biological reaction; correct? A. . . They're still reactions, so it's the product of, ultimately, chemical-bond formation. . . So it's still understood by a person skilled in the art of a product of chemical reactions."

- Petitioner's Reply p. 22; Ex. 2020, ¶ 63; Ex. 2059, 221:19-25

IPR2016-00006
Patent 8,497,393

CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of Exhibit 2061 was served on November 23, 2016 via email to the counsel of record for the Petitioner at the following address: Steadymed-IPR@dlapiper.com.

Date: November 23, 2016

/Stephen B. Maebius/
Stephen B. Maebius
Registration No. 35,264
Counsel for Patent Owner

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

STEADYMED LTD.,
Petitioner,

v.

UNITED THERAPEUTICS CORPORATION,
Patent Owner.

Case IPR2016-00006
Patent 8,497,393 B2

Before LORA M. GREEN, JONI Y. CHANG, and
JACQUELINE T. HARLOW, *Administrative Patent Judges*.

HARLOW, *Administrative Patent Judge*.

DECISION
Redacted Institution of *Inter Partes* Review
37 C.F.R. § 42.108

I. INTRODUCTION

Petitioner, SteadyMed LTD (“SteadyMed”), filed a Petition requesting an *inter partes* review of claims 1–22 of U.S. Patent No. 8,497,393 B2 (Ex. 1001, “the ’393 patent”). Paper 1 (“Pet.”). Patent Owner, United Therapeutics Corporation (“UTC”), filed a Preliminary Response on January 14, 2016. Paper 10¹ (“Prelim. Resp.”). We have jurisdiction under 35 U.S.C. § 314, which provides that an *inter partes* review may not be instituted unless the information presented in the petition “shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition.”

For the reasons set forth below, we institute an *inter partes* review of claims 1–22 of the ’393 patent.

A. Related Matters

The ’393 patent is asserted in: *United Therapeutics Corp. v. Sandoz, Inc.*, No. 14-cv-05499 (D.N.J.); *United Therapeutics Corp. v. Teva Pharmaceuticals U.S.A., Inc.*, No. 14-cv-05498 (D.N.J.); and *United Therapeutics Corp. v. Watson Laboratories, Inc.*, No. 15-cv-05723 (D.N.J). Pet. 1. SteadyMed is not party to the above identified litigations. *Id.*

¹ Paper 10 is the Unredacted Preliminary Response. Paper 8, filed concurrently with Paper 10, is a redacted version of the Preliminary Response.

B. The '393 Patent

The '393 patent, titled “Process to Prepare Treprostinil, the Active Ingredient in Remodulin®,” issued July 30, 2013, from U.S. Patent Application No. 13/548,446 (“the '446 application”) (Ex. 1002), filed July 13, 2012. Ex. 1001, [54], [45], [21], [22]. The '446 application is a continuation of U.S. Patent Application No. 12/334,731 (“the '731 application”) (Ex. 1002), filed on December 15, 2008, now issued as U.S. Patent No. 8,242,305 (“the '305 patent”). Ex. 1001, [63]. The '393 patent claims priority to U.S. Provisional Patent Application No. 61/014,232 (Ex. 2008), filed December 17, 2007. Ex. 1001, [60].

The '393 patent recites 22 product-by-process claims for prostacyclin derivatives, including treprostinil.² *Id.* at 17:51–21:16; Pet. 5; Prelim. Resp. 3. The process disclosed by the '393 patent takes advantage of carbon treatment and salt formation steps to remove impurities, eliminating the need for purification by column chromatography. *Id.* at 17:29–32; *see also id.* at 5:41–45 (“purification by column chromatography is eliminated . . . [T]he salt formation is a much easier operation than column chromatography.”).

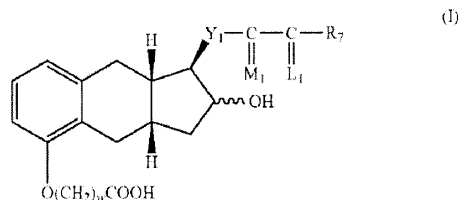
² The '305 patent, which issued from the parent to the application for the '393 patent, recites claims to a process for the preparation of prostacyclin derivatives comprising steps similar to those set forth in the product-by-process claims of the '393 patent. *Compare* Ex. 1001, 17:51–21:16, *with* Ex. 2007, 17:39–24:3.

The process for forming prostacyclin derivatives described in the '393 patent includes four steps: (a) alkylating a prostacyclin derivative to form an alkylated prostacyclin derivative; (b) hydrolyzing the alkylated prostacyclin derivative with a base to form a prostacyclin acid; (c) contacting the prostacyclin acid with a base to form a prostacyclin carboxylate salt; and (d) optionally reacting the prostacyclin carboxylate salt formed in (c) with an acid to form the desired compound, or pharmaceutically acceptable salt thereof. *Id.* at 1:65–3:19.

C. Illustrative Claim

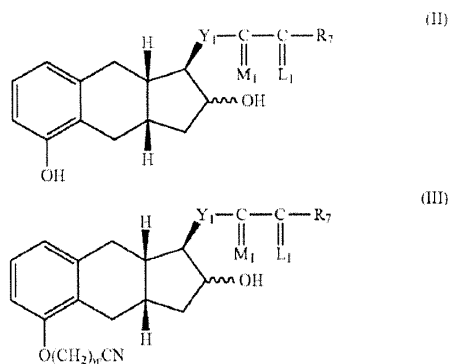
Each of the challenged claims is a product-by-process claim. Of the challenged claims, claims 1 and 9 are independent. Claim 1, reproduced below, is illustrative of the claimed subject matter.

1. A product comprising a compound of formula I



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

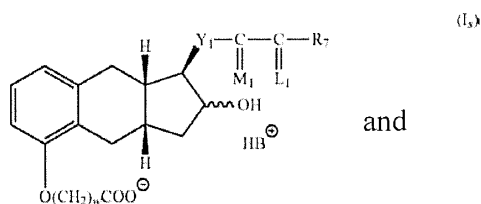
a) alkylating a compound of structure II with an alkylating agent to produce a compound of formula III,



wherein [recitation of Markush groups for the specified structures],

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

c) contacting the product of step (h)³ with a base B to form a salt of formula I_s.



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

³ We note that the reference to “step (h),” rather than “step (b),” in claim 1 is an apparent typographical error. *See* Ex. 1001, 3:66–67 (“(c) contacting the product of step (b) with a base B to form a salt of formula IV_s”); *see also* Pet. 25; Ex. 1009 ¶ 51.

Ex. 1001, 17:51–19:29. Claim 9 is drawn to a product comprising a specific treprostinil compound within the genus set forth in claim 1, and made by the process recited in claim 1. *Id.* at 19:48–20:46.

D. Prior Art Relied Upon

SteadyMed relies upon the following prior art references (Pet. 4–6):

Phares	WO 2005/007081 A2	Jan. 27, 2005	(Ex. 1005)
Kawakami	JP 56-122328A	Sept. 25, 1981	(Ex. 1006 ⁴)

Moriarty et al., *The Intramolecular Asymmetric Pauson-Khand Cyclization as a Novel and General Stereoselective Route to Benzindene Prostacyclins: Synthesis of UT-15 (Treprostinil)*, 69 J. Org. Chem. 1890–1902 (2004) (“Moriarty”) (Ex. 1004); and

Seyhan N. Ege, ORGANIC CHEMISTRY 543–547 (2d ed. 1989) (“Ege”) (Ex. 1008).

E. Asserted Grounds of Unpatentability

SteadyMed asserts the following grounds of unpatentability (Pet. 3–4):

Claims	Basis	Reference(s)
1–5, 7–9, 11–14, and 16–20	§ 102(b)	Phares
1–5, 7–9, 11–14, and 16–20	§ 103(a)	Moriarty and Phares or Kawakami
6, 10, 15, 21, and 22	§ 103(a)	Moriarty, Phares, Kawakami, and Ege

⁴ SteadyMed submitted a certified English translation of Kawakami as Ex. 1007. As discussed in Part II.F below, UTC argues the admissibility of this translation.

II. ANALYSIS

A. 35 U.S.C. § 325(d)

UTC urges the exercise of our discretion under 35 U.S.C. § 325(d) to deny some or all of the grounds of unpatentability presented by SteadyMed because the same, or substantially similar issues were addressed during prosecution. Prelim. Resp. 25–26. UTC states that the Patent Office considered Moriarty alone, and in combination with Phares, during prosecution of the '393 patent. *Id.* at 8–10, 26. UTC also reports that Phares was considered alone, and in combination with Moriarty, during prosecution of U.S. Patent Application No. 13/910,583 (“the '583 application”) (Ex. 2010) filed June 5, 2013, which is a continuation of the '446 application. *Id.* at 11–14.

Regarding the patentability of claims 6, 15, 21, and 22, in particular, UTC asserts that Ege “is nothing more than a first-year organic chemistry textbook,” and that SteadyMed “relies on nothing more than conclusory statements in three paragraphs of the [Declaration of Jeffery D. Winkler]” to support its unpatentability arguments. *Id.* at 26. UTC therefore contends that SteadyMed “has provided no evidence of probative value that is any different than what was already before the Patent Office during prosecution.” *Id.* at 26–27.

Although it is within our discretion to “reject the petition or request because, the same or substantially the same prior art or arguments previously were presented to the Office” pursuant to 35 U.S.C. § 325(d), we decline to do so here.

We note that during prosecution of the '446 application, which issued as the '393 patent, the Examiner rejected the claims as anticipated by Moriarty, but subsequently withdrew that rejection, without elaboration, in response to a declaration filed by David A. Walsh (“Walsh Declaration”) (Ex. 1002, 346–350), one of the named inventors of the '393 patent, and the Executive Vice President of Chemical Research and Development at UTC. Ex. 1002, 344, 346–360. Although Phares is listed as a cited reference on the face of the '393 patent (Ex. 1001, [56]), we observe that the Examiner neither relied on, nor otherwise discussed Phares during prosecution of the '446 application (Ex. 1002, 295–296, 327–330, 359). In addition, neither Ege nor Kawakami was considered during prosecution of the '446 application. *Id.* at 235–359. The grounds of unpatentability asserted in the instant Petition likewise differ from the rejections entered by the Examiner during prosecution of the '731 application, the parent to the '446 application. *See* Ex. 1002, 122–124.

Moreover, as discussed in detail in Part II.B below, the Declaration of Jeffrey D. Winkler (“Winkler Declaration”) (Ex. 1009), submitted in support of SteadyMed’s Petition, calls into question Dr. Walsh’s conclusion that treprostinil prepared according to the process claimed in the '393 patent is “physically different from treprostinil prepared according to the process of ‘Moriarty’” (Ex. 1002, 347 (¶ 6)). Ex. 1009 ¶¶ 63–71. In addition, as set forth in Part II.F, we disagree with UTC’s characterization of Dr. Winkler’s testimony as conclusory. *See, e.g.*, Ex. 1009 ¶¶ 80–90.

We, therefore, decline to exercise our discretion to deny the Petition pursuant to 35 U.S.C. § 325(d). *See Nestle USA, Inc. v. Steuben Foods, Inc.*, Case IPR2014-01235, slip op. at 7 (PTAB Dec. 22, 2014) (Paper 12) (“[W]e conclude that Petitioner’s arguments regarding the unpatentability of claims 18–20, which include arguments relating to Biewendt and a combination of references previously not considered and supported by a declaration previously not considered, are persuasive. . .”); *Merial Ltd., v. Virbac*, Case IPR2014-01279, slip op. at 9 (PTAB Jan. 22, 2015) (Paper 13) (noting the different burdens of proof and evidentiary standards applicable to *ex parte* examination and *inter partes review* proceedings).

B. Claim Construction

In an *inter partes* review, claim terms in an unexpired patent are given their broadest reasonable interpretation in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b); *see also In re Cuozzo Speed Techs., LLC*, 793 F.3d 1268, 1278–79 (Fed. Cir. 2015) (“Congress implicitly approved the broadest reasonable interpretation standard in enacting the AIA,” and “the standard was properly adopted by PTO regulation.”), *cert. granted sub nom. Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 890 (2016) (mem.). Under this standard, we may take into account definitions or other explanations provided in the written description of the specification. *In re Morris*, 127 F.3d 1048, 1054 (Fed. Cir. 1997). Any special definition for a claim term must be set forth in the specification with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d

1475, 1480 (Fed. Cir. 1994). Only those terms that are in controversy need be construed, and only to the extent necessary to resolve the controversy. *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999).

“Product” / “A product comprising a compound [of/having] formula [I/IV] . . . or a pharmaceutically acceptable salt thereof”

Independent claims 1 and 9 recite the phrase “[a] product comprising a compound [of/having] formula [I/IV] . . . or a pharmaceutically acceptable salt thereof . . .” Ex. 1001, 19:48–20:46. In addition, each challenged dependent claim recites the term “product.” *Id.* at 17:51–21:16. Because the parties advance similar arguments pertaining to the construction of these terms, we address these terms together.

SteadyMed asserts that the phrase “[a] product comprising a compound [of/having] formula [I/IV] . . . or a pharmaceutically acceptable salt thereof” should be interpreted to mean “a chemical composition that includes, but is not limited to, a compound of Formula I, or a pharmaceutically acceptable salt thereof, and that may also include other non-mentioned substances (including impurities), additives, or carriers, without limitation as to the types or relative amounts thereof.” Pet. 11. SteadyMed contends that because independent claims 1 and 9 recite “[a] product comprising,” the claim term “product” should be construed to include “the treprostinil compound along with other substances (including impurities),” i.e., a “chemical composition.” *Id.* at 11.

UTC counters that “[a] product comprising a compound [of/having] formula [I/IV] . . . or a pharmaceutically acceptable salt thereof” should be interpreted as “a substance resulting from a chemical reaction constituted primarily of formula I/IV or a pharmaceutically acceptable salt thereof.”

Prelim. Resp. 21. As an initial matter, UTC notes that SteadyMed’s proposed construction refers only to Formula I, and asserts that SteadyMed “inexplicably read[s] Formula IV out of the term entirely.” *Id.* at 22.

UTC further argues that the claims and Specification of the ’393 patent use “product” to refer to a substance resulting from a chemical reaction. *Id.* at 17. UTC also contends that the prosecution history for the ’393 patent supports its proposed construction because “during prosecution, the Patent Owner and Examiner explicitly discussed the ‘product’ of the claims as a real world substance that results from employing a specific chemical process, as differentiated from the substance obtained from employing a different chemical process.” *Id.* at 18–19. UTC points to chemistry textbooks as buttressing its position that a skilled artisan would understand the claim term “product” as referring to “a substance resulting from a chemical reaction.” *Id.* at 19. UTC further reasons that “the ‘product’ claimed in a product-by-process claim is necessarily a substance that results from the process specified in that claim” (*id.*), and that SteadyMed’s proposed construction “contradicts this inherent limitation of the claims” (*id.* at 22).

On this record, and for purposes of this decision, we interpret the phrase “[a] product comprising a compound [of/having] formula [I/IV] or a

pharmaceutically acceptable salt thereof,” to mean “a product including, but not limited to, a compound [of/having] formula [I/IV] or a pharmaceutically acceptable salt thereof.”

The claim term “product,” as it is used in the ’393 patent, does not require construction because the claimed “product” is defined by the limitations recited in the challenged claims. This is evidenced by independent claims 1 and 9, which recite “[a] product comprising . . . ,” and go on to define the essential elements of the claimed product. The transitional term “‘comprising’ is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim.” *Genentech, Inc. v. Chiron Corp.*, 112 F.3d 495, 501 (Fed. Cir. 1997); *see also* Ex. 1001, 4:23–25 (defining “comprising” as “including, but not limited to”). Thus, the open-ended structure of the challenged claims forecloses limitation of the term “product” beyond that achieved by the recited claim elements.

Indeed, neither UTC nor SteadyMed identifies any disclosure in the ’393 patent or its prosecution history that necessitates a contrary understanding of the term “product.” For example, the portions of the Specification to which UTC points comport with an understanding of “product” as being defined only by the recited claim elements. *See* Ex. 1001, 5:45–46, 7:16–20, 17:37–40. Furthermore, far from disavowing or otherwise limiting claim scope, the portions of the prosecution history identified by UTC are consistent with an understanding that the claimed “product” is defined solely by the recited claim elements. *See* Ex. 1002,

315, 328–329, 346–350. We similarly are unpersuaded that the chemistry textbook glossaries to which UTC points (Exs. 2011, 2012, 2014) provide a basis for narrowly interpreting “product” to require that the product result from a chemical reaction.

Regarding the larger claim phrase “[a] product comprising a compound [of/having] formula [I/IV] . . . or a pharmaceutically acceptable salt thereof,” as explained above, we determine that the embedded claim term “comprising” means “including, but not limited to.” *See Genentech*, 112 F.3d at 501; *see also* Ex. 1001, 4:23–25. Accordingly, we reject UTC’s proposal that claims 1 and 9 be read to require a product “*constituted primarily of* formula I/IV or a pharmaceutically acceptable salt thereof.” Prelim. Resp. 21 (emphasis added).

“[A/the] process comprising”

SteadyMed argues that the claim phrase “[a/the] process comprising,” which appears in independent claims 1 and 9, should be interpreted as “a process that includes, but is not limited to, the recited process steps, and may include, without limitation, any other non-recited steps.” Pet. 12. UTC counters that this claim phrase should be construed to mean “a/the process including but not limited to.” Prelim. Resp. 23–24. For the reasons set forth above, we agree with UTC that these claim phrases should be interpreted to mean “a/the process including, but not limited to.”

Product-by-Process Claims

Each of the challenged claims is a product-by-process claim. Ex. 1001, 17:51–21:16; Pet. 5; Prelim. Resp. 3. The general rule when determining patentability of a product-by-process claim is to “focus . . . on the product and not on the process of making it.” *Amgen, Inc. v. Hoffmann-La Roche Ltd.*, 580 F.3d 1340, 1369 (Fed. Cir. 2009). This general rule embodies the long-standing principle that “an old product is not patentable even if it is made by a new process.” *Id.* at 1370. An exception applies when process steps recited in the claim impart “structural and functional differences” to the claimed product. *Greenliant Sys., Inc. v. Xicor LLC*, 692 F.3d 1261, 1267–1268 (Fed. Cir. 2012). If the exception applies, the structural and functional differences conveyed by the recited process steps “‘are relevant as evidence of no anticipation’ although they ‘are not explicitly part of the claim.’” *Id.* at 1268 (citing *Amgen*, 580 F.3d at 1370).

SteadyMed contends that the challenged claims do not yield a treprostinil product having structural or functional differences as compared to treprostinil products produced by prior art methods. Pet. 19–22. Specifically, SteadyMed asserts that the Walsh Declaration, relied on by UTC during prosecution as evidencing differences in the treprostinil products of the ’393 patent and Moriarty, fails to demonstrate any functional or structural differences between the instantly claimed and prior art treprostinil products. *Id.* SteadyMed relies on the Winkler Declaration (Ex. 1009) to support its position. *Id.*

UTC acknowledges that “at the time of the ’393 patent, there existed at least three prior art methods” for making treprostinil. Prelim. Resp. 33. Relying on the Walsh Declaration, UTC asserts that the process steps recited in independent claims 1 and 9 are entitled to patentable weight because they yield a “physically different and improved final product with significantly reduced overall impurities and a distinct and unexpected impurity profile” as compared to treprostinil produced using prior art methods. *Id.* at 3.

The Walsh Declaration compares the impurity profile of treprostinil free acid “prepared according to the process of ‘Moriarty’” to the impurity profiles of treprostinil free acid and treprostinil diethanolamine “prepared according to the process specified in claim 1 or [9]” of the ’393 patent.⁵ Ex. 1002, 347–348 (¶ 6). Dr. Walsh concludes that the treprostinil free acid and treprostinil diethanolamine prepared according to the process of claims 1 and 9 is physically different from the treprostinil diethanolamine prepared according to the process of Moriarty “at least because neither of [the ’393 patent products] contains a detectable amount of any of benzindene triol, treprostinil methyl ester, 1AU90 treprostinil stereoisomer and 2AU90 treprostinil stereoisomer, each of which were present in detectable amounts in treprostinil produced according to the process of ‘Moriarty’.” *Id.* at 349 (¶ 8). In addition, Dr. Walsh provides “data obtained from representative Certificates of Analysis” indicating that treprostinil free acid “prepared

⁵ Issued claim 9 of the ’393 patent is identified as claim 10 in the Walsh Declaration, and other documents in the prosecution history in the ’393 patent.

according to ‘Moriarty’” is 99.4% pure, while the treprostinil free acid and treprostinil diethanolamine “prepared according to the process specified in claim 1 or [9]” are 99.8% pure and 99.9% pure, respectively. *Id.* at 347–348 (¶ 6).

SteadyMed disputes Dr. Walsh’s contention that there are physical differences between the treprostinil products of the ’393 patent and prior art. Pet. 19–22; *see also* Ex. 1009 ¶¶ 63–71. As an initial matter, SteadyMed points out that the 99.7% treprostinil purity reported by Moriarty (Ex. 1004, 13) is higher than the 99.5% purity recited in claims 2 and 10 of the ’393 patent, the only challenged claims that recite a purity level. Pet. 20; *see also* Ex. 1009 ¶ 65. In addition, Dr. Winkler testifies that the limited sample set, consisting of “*only two specific batches* of treprostinil” (Ex. 1009 ¶ 66), and absence of any disclosure concerning the reaction conditions, reagents, and solvents used in carrying out the process of claims 1 and 9 of the ’393 patent (*id.* ¶ 67), undermine the veracity of Dr. Walsh’s conclusion regarding the purity of these products. *Id.* ¶¶ 66–67. SteadyMed also observes that the statement in the Specification of the ’393 patent that in one embodiment the purity of treprostinil is “at least 90.0%, 95.0%, 99.0%, 99.5%” (Ex. 1001, 8:66–67), supports the conclusion that the 99.8% purity purportedly achieved by Dr. Walsh “is based on a particular set of process steps that are not claimed and which must have been found after the filing date.” Pet. 20.

Dr. Winkler additionally testifies that the alleged differences in purity between the treprostinil batches described by Dr. Walsh are attributable to

experimental error. *Id.* ¶¶ 68–70. Dr. Winkler testifies that “the literature on [High Performance Liquid Chromatography’s (“HPLC’s”)] precision indicates that the ‘RSD’ or ‘relative standard deviation’ for a typical instrument is about 1%. (Ex. 1017).” *Id.* ¶ 70. Dr. Winkler further observes that “[i]n the present case, we can estimate the precision of the equipment the inventors actually used, since the inventors found that Example 4’s Batch 1 had an HPLC Assay of 100.4%, which is obviously greater than the 100% value theoretically achievable. (Ex. 1001, col. 13, lines 50-65).” *Id.* Dr. Winkler, thus, concludes that “[t]his deviation between experimental and theoretical shows that the instrument can have variations of at least 0.4%, which is greater than the differences in purity that the inventors offered to support their contention regarding greater purity over the prior art.” *Id.* On this record, we credit Dr. Winkler’s testimony, as it is consistent with the disclosures of the prior art and the disclosure of the ’393 patent itself.

UTC does not challenge SteadyMed’s arguments concerning the shortcomings of the Walsh Declaration. Rather, UTC points to correspondence with, and reports submitted to, the Food and Drug Administration (“FDA”) relating to the acceptance of a supplemental new drug application for treprostinil. Prelim. Resp. 36–38. UTC contends that these reports show that “the purity of the treprostinil improved close to 100%” for treprostinil prepared as described in claims 1 and 9 of the ’393 patent as opposed to the prior process implemented by UTC. Prelim. Resp. 38; *see also* Ex. 2006, 3–4.

On the record before us, and for purposes of this decision, we conclude that the process steps recited in the challenged claims do not impart structural or functional differences to the claimed product.

As an initial matter, we observe that the challenged product-by-process claims are drawn to “[a] product comprising a compound” of either formula I or formula IV, or a pharmaceutically acceptable salt of the recited formula. Ex. 1001, 17:51–19:29, 19:48–20:46). “‘Comprising’ is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim.” *Genentech*, 112 F.3d at 501. Thus, a product comprising a particular compound must contain that compound, but may additionally include other substances, such as impurities. On this record, therefore, it is unclear how claims 1, 3–9, and 11–22, which claim a product comprising a particular compound, but do not recite limitations concerning the purity profile of that product, could be restricted to a product including the claimed compound, but also having a particular purity profile. In addition, although claims 2 and 10 require a purity of at least 99.5% (Ex. 1001, 19:29–30, 20:47–48), these claims similarly are drawn to a product comprising a compound, and do not specify the type of impurities that may be present in the compound or restrict the amount of any particular impurity that may be present, so long as the product remains at least 99.5% pure.

Furthermore, the evidence presently before us, including UTC’s own testing results, suggests that inter-batch variability in impurity profiles,

experimental error in impurity measuring equipment, and variations in reagents, solvents, and reaction conditions, rather than the instantly recited process steps, account for any purported improvements in purity reported by UTC. We observe that UTC offers no explanation for the variation between the 99.7% purity reported by Moriarty, and the 99.4% purity Dr. Walsh obtained for treprostinil purportedly prepared according to the process described by Moriarty. Neither does UTC offer reasoning for crediting Dr. Walsh's results over those reported by Moriarty himself. Similarly, UTC neglects Dr. Winker's assessment of the experimental error present, but unaccounted for, in the impurity measurements reported in the Walsh Declaration, and fails to account for the absence of any disclosure regarding the experimental protocols followed by Dr. Walsh, such as the reaction conditions, or the solvents or reagents used, in synthesizing treprostinil according to Moriarty or the '393 patent.

Moreover, the Process Optimization Report (Ex. 2005) proffered by UTC supports the conclusion that the process steps recited in the '393 patent do not produce a treprostinil product that differs, either structurally or functionally, from that produced using prior art methods.

The Process Optimization Report discloses the impurity analyses for five batches of treprostinil identified by UTC as having been prepared using the process recited in the '393 patent. Ex. 2005, 4–6; *see also* Prelim. Resp. 36 (“Ex. 2005 is a Process Optimization Report that provides results

for batches resulting from step (d) of claims 1 and 10 in the '393 patent,⁶ which was performed on specific batches of the diethanolamine salt intermediate produced by steps (a)-(c) [REDACTED].”⁷ The Process Optimization Report states that the purity of these batches, as determined by HPLC analysis, ranged from [REDACTED] to [REDACTED].⁷ Ex. 2005, 6. Additionally, the Process Optimization Report indicates that each of the following impurities were detected by HPLC analysis in one or more of the above referenced treprostinil batches: [REDACTED]
[REDACTED]
[REDACTED]. *Id.*

We also observe that although UTC sought, and obtained from the FDA, modification of the specification for the HPLC assay for treprostinil to require a purity range of 98%–102%, rather than 97%–101%, [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED] Ex. 2006, 3–4, 6; Ex. 2003. Notably, UTC’s specification for treprostinil produced according to the '393 patent permits

⁶ We note that UTC likely intended to reference independent claim 9 of the '393 patent, rather than dependent claim 10; however our analysis is equally applicable to claim 9 or claim 10.

⁷ The reported batch purity values were [REDACTED] for an average purity of [REDACTED] Ex. 2005, 6.

each of the following impurities: [REDACTED]

[REDACTED]
[REDACTED]. Ex. 2006, 6. The analysis of treprostinil purportedly prepared according to the process of Moriarty, set forth in the Walsh Declaration, reveals that each of the impurities detected in Moriarty treprostinil was present in an amount [REDACTED]

[REDACTED] *Compare*
Ex.1002, 347, *with* Ex. 2006, 6.

Accordingly, on the record before us, and for purposes of this decision, we conclude that the process steps recited in the challenged claims of '393 patent do not impart structural or functional differences to the claimed product as compared to prior art processes, and therefore, that these process steps do not patentably limit the claimed product. We note, however, that the factual dispute between the parties concerning the existence of any structural or functional differences between treprostinil products produced according to the process recited in the '393 patent and prior art processes, as well as arguments addressing our concerns regarding the relevance of the impurity profile of a product obtained by the recited process to the patentability of claims drawn to a product *comprising* a compound, are appropriate for further development at trial.

C. Principles of Law

To establish anticipation, each and every element in a claim, arranged as recited in the claim, must be found in a single prior art reference. *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369 (Fed. Cir. 2008).

“A reference anticipates a claim if it discloses the claimed invention ‘such that a skilled artisan could take its teachings in combination with his own knowledge of the particular art and be in possession of the invention.’” *In re Graves*, 69 F.3d 1147, 1152 (Fed. Cir. 1995) (emphasis omitted) (quoting *In re LeGrice*, 301 F.2d 929, 936 (CCPA 1962)).

A patent claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the claimed subject matter and the prior art are such that the subject matter, as a whole, would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

When a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability. For the same reason, if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the

same way, using the technique is obvious unless its actual application is beyond his or her skill. *Sakraida* [*v. Ag Pro, Inc.*, 425 U.S. 273 (1976)] and *Anderson's-Black Rock* [*v. Pavement Salvage Co.*, 396 U.S. 57 (1969)] are illustrative—a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions.

KSR, 550 U.S. at 417.

The level of ordinary skill in the art is reflected by the prior art of record. See *Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001); *In re GPAC Inc.*, 57 F.3d 1573, 1579 (Fed. Cir. 1995); *In re Oelrich*, 579 F.2d 86, 91 (CCPA 1978).

*D. Anticipation Grounds of Unpatentability
Based on Phares*

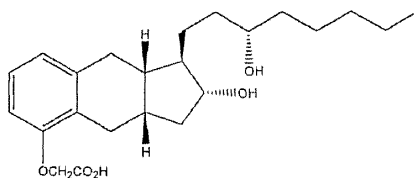
SteadyMed asserts that claims 1–5, 7–9, 11–14, and 16–20 are unpatentable under § 102(b) as anticipated by Phares. Pet. 22–37. Claims 2–5, 7, 8, and 19 depend directly from claim 1, and claims 11–14, 16–18, and 20 depend, directly or indirectly, from claim 9. In support of its assertion, SteadyMed provides detailed explanations as to how Phares discloses each claim limitation (*id.*), and relies upon the Winkler Declaration (Ex. 1009) to support its positions.

UTC counters that the treprostinil product of Phares is physically different from that produced by the process disclosed in the '393 patent, and, therefore, that the process steps disclosed in the claims of the '393 patent are limiting for purposes of the patentability determination. Prelim. Resp. 33–36. UTC also argues that SteadyMed improperly engages in picking and choosing among distinct embodiments in Phares to piece together an

anticipation argument as to the recited process steps. *Id.* at 29–31. UTC further asserts that explicit disclosure of certain claimed process steps is absent from SteadyMed’s anticipation analysis, and that SteadyMed fails to show that those limitations are inherently disclosed by Phares. *Id.* at 31–36.

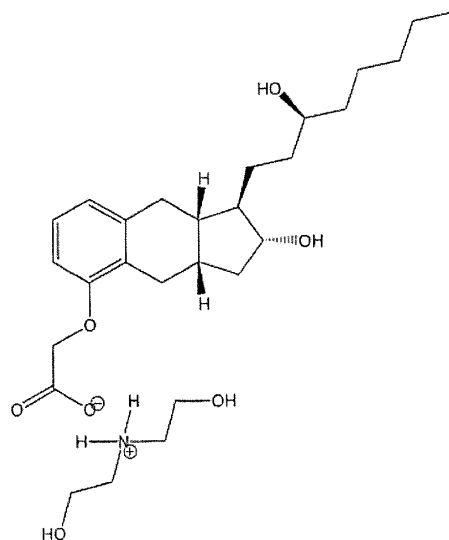
Phares

Phares describes “compounds and methods for inducing prostacyclin-like effects in a subject or patient,” including treprostinil and derivatives thereof. Ex. 1005, 10. The chemical structure of treprostinil disclosed by Phares, on page 10 of Exhibit 1005, is reproduced below:



Id. Phares explains that “[t]reprostinil is a chemically stable analog of prostacyclin, and as such is a potent vasodilator and inhibitor of platelet aggregation.” *Id.*

Phares further discloses that “[a] preferred embodiment of the present invention is the diethanolamine salt of treprostinil. . . . A particularly preferred embodiment of the present invention is form B of treprostinil diethanolamine.” *Id.* at 11. The structure of the diethanolamine salt of treprostinil described by Phares, on page 99 of Exhibit 1005, is reproduced below:

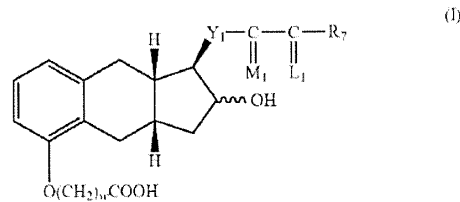


Id. at 99 (claim 49). Phares reports that form B of the diethanolamine salt of treprostiril “appears to be a crystalline material which melts at 107°C.” *Id.* at 91.

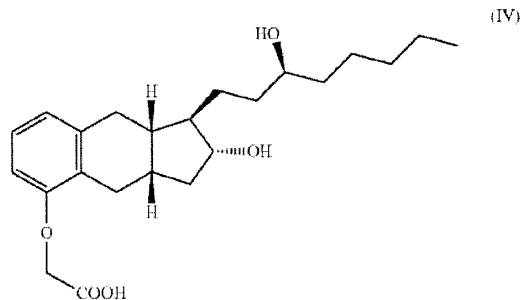
Phares describes the synthesis of (-)-treprostiril, the enantiomer of treprostiril. Ex. 1005, 41–42. Phares explains that “[e]nantimers of these compounds . . . can be synthesized using reagents and synthons of enantiomeric chirality of the above reagents.” *Id.* at 41. In particular, Phares teaches that “the enantiomer of the commercial drug (+)-Treprostiril was synthesized using the stereoselective intramolecular Pauson Khand reaction as a key step and Mitsunobu inversion of the side-chain hydroxyl group.” *Id.* at 42. Phares discloses the following reaction procedure: “i. ClCH₂CN, K₂CO₃. ii, KOH, CH₃OH, reflux. 83 % (2 steps).” *Id.*

A product comprising a compound [of/having] formula [I/IV] . . . or a pharmaceutically acceptable salt thereof

Claim 1 of the '393 patent recites “[a] product comprising a compound of formula I



or a pharmaceutically acceptable salt thereof,” and sets forth a series of process steps for obtaining the claimed product. Claim 9 recites “[a] product comprising a compound having formula IV



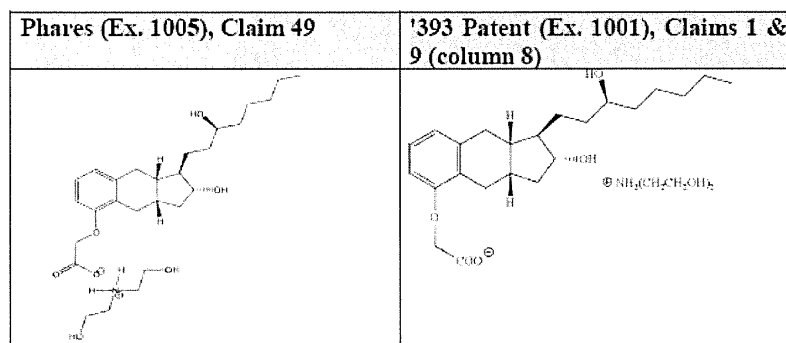
or a pharmaceutically acceptable salt thereof,” and includes the same process steps for obtaining the claimed product as recited in claim 1. Claim 9 is identical to claim 1, except that it is drawn to a product comprising the specific treprostinil compound, a species of the genus of claim 1.

Accordingly, we address these claims together.

SteadyMed contends that “Phares discloses in its Claim 49 the identical, pharmaceutically acceptable treprostinil diethanolamine salt” claimed in the '393 patent. Pet. 26; *see also* Ex. 1005, 24, 85–93, 99

(claim 49); Ex. 1009 ¶¶ 50–53. In support of SteadyMed’s position, Dr. Winkler testifies that “[o]ther than a change in formatting, the two structures [for treprostiniol diethanolamine salt] from Phares and the ’393 Patent are identical.” Ex. 1009 ¶ 53.

Paragraph 52 of the Winkler Declaration depicts a side-by-side comparison of the chemical structures disclosed in claim 49 of Phares, and column 8, lines 50–63 of the ’393 patent, reproduced below:



Id. ¶ 52. As shown in the figure from paragraph 52 of the Winkler Declaration, the treprostiniol diethanolamine salt disclosed by Phares is structurally identical to that disclosed in the ’393 patent.

As set forth in Part II.B above, SteadyMed, relying on the Winkler Declaration, further asserts that the process disclosed in claims 1 and 9 of the ’393 patent does not result in a treprostiniol product that is physically different or unique from treprostiniol produced by prior art methods. Pet. 19–22; *see also* Ex. 1009 ¶¶ 63–71. In support of this position, Dr. Winkler testifies that “[i]n both the ’393 Patent and Phares (Ex. 1005), treprostiniol diethanolamine salt Form B is made Phares further discloses a melting point of 107° C (Ex. 1005, p. 91 & Fig. 21) for the Form B salt.”

Ex. 1009 ¶ 59; *see also* Ex. 1005, 90–93; Pet. 27. Dr. Winkler also testifies that Phares discloses the same procedure as is claimed in the '393 patent, but describes this procedure in reference to the synthesis of the enantiomer of treprostinil. Ex. 1009 ¶¶ 55–57; Ex. 1005, 41–42; Pet. 25–26. Dr. Winkler thus concludes that in “making the most stable crystal form (Form B) and preparing a product that melts at a higher temperature higher than that described in the '393 Patent, Phares necessarily discloses a salt of at least equal purity to the salt in the '393 Patent.” Ex. 1009 ¶ 62; *see also id.* ¶ 60 (citing Ex. 1018, 6); Pet. 27–28.

SteadyMed also contends that Phares anticipates the process steps recited in claim 1. Pet. 24–28; Ex. 1005, 24, 41–42, 85–93, 99 (claim 49); Ex. 1009 ¶¶ 44–71.

UTC does not dispute Phares' disclosure of a treprostinil product; rather, as previewed in relation to its claim construction arguments above, UTC contends that the treprostinil product of Phares is “physically different” from that claimed in the '393 patent, and, therefore, not anticipatory. Prelim. Resp. 33–36. UTC argues that as Phares does not disclose which treprostinil starting material is used, it “cannot inherently anticipate the final treprostinil product of the '393 patent because each method would result in a distinct impurity profile.” Prelim. Resp. 34. Referring to the Walsh Declaration, UTC further asserts that “even if the Moriarty treprostinil was used for Phares, Petitioner has failed to provide any evidence that the final Phares treprostinil product would necessarily be the same as the products claimed in the '393 patent.” *Id.* UTC also asserts that SteadyMed's reliance

on the melting point of the treprostinil product of Phares as a proxy for purity is misplaced because “melting point does not disclose any specific impurity level and instead may demonstrate a different form, or polymorph, of treprostinil diethanolamine altogether.” *Id.* at 35.

UTC additionally argues that Phares does not disclose the same process for generating treprostinil as recited in claims 1 and 9, and that SteadyMed improperly “cobble together disclosure from four disparate portions of Phares covering multiple distinct embodiments” to arrive at the claimed invention. Prelim. Resp. 27. Further, UTC asserts that even if SteadyMed were permitted to pick and choose steps from various embodiments of Phares, SteadyMed nevertheless must rely on inherency to prove anticipation because “Phares lacks express disclosure of certain claim elements.” *Id.* at 28.

The present record supports SteadyMed’s contention that the treprostinil diethanolamine salt taught by Phares is identical in structure to the pharmaceutically acceptable treprostinil diethanolamine salt recited in claims 1 and 9. Pet. 24; *see also* Ex. 1005, 24, 99 (claim 49); Ex. 1009 ¶¶ 52–53. Dr. Winkler testifies that the process for producing treprostinil disclosed by Phares yields the same form (Form B) of treprostinil diethanolamine salt as the process of the ’393 patent, and that the treprostinil diethanolamine salt of Phares is at least equal in purity to the treprostinil product of the ’393 patent. Ex. 1009 ¶¶ 59–62. Dr. Winkler further testifies that Phares discloses the same process for synthesizing treprostinil as the

'393 patent. Ex. 1009 ¶¶ 55–57, 62; Ex. 1005, 41–42; Pet. 25–26. On this record, we credit Dr. Winkler's testimony.

We are not persuaded by UTC's arguments concerning the possibility that treprostinil produced according to Phares might have a different impurity profile than that produced according to the process disclosed in the '393 patent. First, for the reasons set forth in Part II.B above, it is unclear on this record how the use of the transitional phrase "comprising" excludes any impurities that may possibly be produced by the process of Phares. In addition, the present record supports a finding that the impurity profiles for treprostinil diethanolamine salt prepared as described by Phares and that prepared according to the '393 patent are the same. As explained above, Dr. Winkler's testimony regarding the form and melting point of Phares' treprostinil product, is consistent with the conclusion that the products of Phares and the '393 patent are the same.

Furthermore, we note that, as explained in Parts II.A and II.B above, the inter-batch variability in treprostinil impurity profiles, experimental error inherent in impurity measurements, and the variety and extent of impurities permitted in UTC's specification for the manufacture of treprostinil according to the process of the '393 patent, which remained unchanged when UTC migrated from a prior art process to the process of the '393 patent, support the conclusion that the process steps recited in claims 1 and 9 of the '393 patent do not impart any structural or functional differences over prior art treprostinil products.

Accordingly, given the evidence before us in this record, we conclude that SteadyMed has established adequately for purposes of this decision that Phares teaches the treprostinil diethanolamine salt product recited in claims 1 and 9. Because we determine, on the record before us, and for purposes of this decision, that the process steps recited in claims 1 and 9 do not impart structural or functional differences to the claimed treprostinil product and are therefore not limiting, we do not address the parties' contentions concerning Phares' anticipation of the recited process steps.

Conclusion

UTC has not raised any additional arguments with regard to the dependent claims other than those addressed above. We have reviewed SteadyMed's evidence, arguments, and claim charts, and conclude that SteadyMed has sufficiently demonstrated that the dependent claims are also anticipated by Phares. Thus, for the foregoing reasons, we conclude that SteadyMed has shown a reasonable likelihood of prevailing on its assertions that claims 1–5, 7–9, 11–14, and 16–20 are anticipated by Phares.

*E. Obviousness Grounds of Unpatentability
Based on Moriarty and Phares*

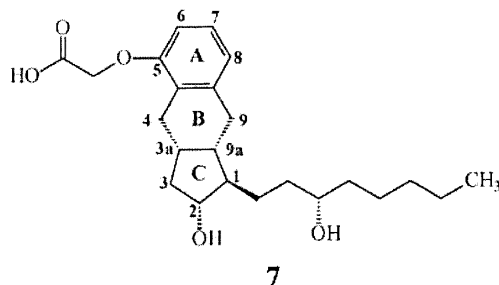
SteadyMed asserts that claims 1–5, 7–9, 11–14, and 16–20 are unpatentable under § 103(a) as obvious in view of Moriarty and Phares. Pet. 37–52. Claims 2–5, 7, 8, and 19 depend directly from claim 1, and claims 11–14, 16–18, and 20 depend, directly or indirectly, from claim 9. In support of its assertion, SteadyMed provides detailed explanations as to how

the combination of Moriarty and Phares discloses each claim limitation (*id.*), and relies upon the Winkler Declaration (Ex. 1009) to support its positions.

UTC counters that “Phares fails to disclose the synthetic route or purity of the claimed treprostinil product. Moriarty adds nothing to cure these deficiencies.” Prelim. Resp. 43. UTC asserts that the process described in the '393 patent “unexpectedly reduced the impurity level in the claimed treprostinil product even more” than Moriarty, and reiterates its position that treprostinil produced according to the process of the '393 patent has “a superior purity profile compared to the prior art.” *Id.* at 44.

Moriarty

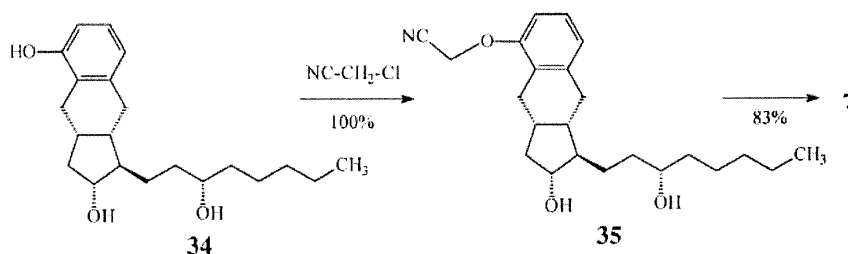
Moriarty describes the synthesis of treprostinil “via the stereoselective intramolecular Pauson-Khand cyclization.” Ex. 1004, 1. Formula 7 of Moriarty is reproduced below:



Id. at 3. Formula 7 of Moriarty depicts the chemical structure of treprostinil.

Id.

An excerpt of Scheme 4 of Moriarty is reproduced below:



Id. at 6. The excerpted portion of Scheme 4 of Moriarty illustrates the alkylation Formula 34 to yield Formula 35, and subsequent hydrolysis of Formula 35 with a base (followed by acidification) to yield Formula 7, treprostinil. Ex. 1004, 6, 13.

A product comprising a compound [of/having] formula [I/IV] . . . or a pharmaceutically acceptable salt thereof

SteadyMed contends that Moriarty and Phares respectively disclose treprostinil acid and treprostinil diethanolamine salt, as recited in claims 1 and 9 of the '393 patent. Pet. 22–23, 24, 33, 39, 48; *see also* Ex. 1004, 6, 13; Ex. 1005, 24, 99 (claim 49); Ex. 1009 ¶¶ 74, 76. Furthermore, Dr. Winkler testifies that the combination of Moriarty and Phares “discloses the same process steps and same product of the '393 Patent. For the same reasons discussed above regarding Phares, the purity of the combinations would be of at least equal purity to that claimed in the '393 Patent.” Ex. 1009 ¶ 76.

SteadyMed asserts that Moriarty discloses steps (a) and (b) of claims 1 and 9, and that Phares discloses step (c) of these claims. Pet. 43; *see also* Ex. 1004, 6, 13; Ex. 1005, 24; Ex. 1009 ¶ 74. Dr. Winkler testifies

that a relevant skilled artisan would have recognized that the treprostini acid produced in Moriarty could be purified by contacting it with a base as described by Phares. Ex. 1009 ¶ 74. In addition, as discussed in Part II.D above, Dr. Winkler testifies that Phares “details the same Claim 1 and 9 steps (a) or (b) as were used to make treprostini in the ’117 Patent and Moriarty reference, but applies them to make (-)-treprostini, the enantiomer of (+)- treprostini (Ex. 1005, p. 42).” *Id.* ¶55. Dr. Winkler further testifies that a relevant skilled artisan would have had “more than a reasonable expectation of success that the reaction of treprostini with diethanolamine would be successful” because “Phares (Ex. 1005, p. 24, p. 99, Claim 49) performed the same reaction and it was successful.” Ex. 1009 ¶ 80.

UTC reasserts the arguments described above concerning the purity of treprostini produced according to the process disclosed in the ’393 patent. UTC acknowledges that Moriarty itself was an improvement over the prior art, but contends that “the ’393 patent unexpectedly reduced the impurity level in the claimed treprostini product even more.” Prelim. Resp. 44. Specifically, UTC contends that “performing step (c) on a product that resulted from steps (a) and (b) provided a product with reduced impurities.” *Id.* UTC also reiterates its arguments concerning the Walsh Declaration, and highlights the purported differences in the impurity profile of treprostini produced according to Moriarty compared to that produced according to the ’393 patent.

The present record supports SteadyMed’s contention that the treprostini diethanolamine salt disclosed by the combination of Moriarty

and Phares is identical in structure to the pharmaceutically acceptable treprostinil diethanolamine salt recited in claims 1 and 9. Pet. 41–42; *see also* Ex. 1004, 6, 13; Ex. 1005, 24, 99 (claim 49); Ex. 1009 ¶ 76.

First, as explained in Part II.B above, the present record does not support the conclusion that claims drawn to “[a] product comprising a compound . . .” can be distinguished from prior art products on the basis of differences in the impurity profiles of those products.

Moreover, as explained in detail in Parts II.A, II.B, and II.D above, we determine that the present record supports the contention that the treprostinil product of Moriarty and Phares is the same as that produced according to the steps recited in claims 1 and 9 of ’393 patent.

As discussed in Part II.B, the Walsh Declaration fails to disclose the protocols followed in producing the Moriarty and ’393 patent treprostinil samples analyzed, and fails to account for the experimental error in Dr. Walsh’s impurity measurements. In addition, the inter-batch variability in the types and amounts of impurities observed in treprostinil prepared according to the ’393 patent, and the fact that the treprostinil Dr. Walsh prepared according to Moriarty satisfies the FDA purity specification for treprostinil prepared per the ’393 patent, lends further support to the conclusion that no structural or functional differences exist between treprostinil produced according to Moriarty, and that produced according to the ’393 patent.

Similarly, as discussed in Part II.D, the present record supports a finding that the impurity profile of treprostinil diethanolamine salt prepared

as described by Moriarty in combination with Phares is the same as that prepared according to the '393 patent. Dr. Winkler's testimony regarding the form and melting point of Phares' treprostinil product (Ex. 1009 ¶¶ 59–60, 62), as well as his testimony regarding the disclosure by Phares of the same synthesis process as described by Moriarty (Ex. 1009 ¶¶ 55–57), is consistent with the conclusion that treprostinil diethanolamine generated by reacting Formula 7 of Moriarty with a base, as disclosed by Phares, to form a salt of Formula 7 would result in a treprostinil diethanolamine salt of at least equal purity to that disclosed in the '393 patent.

Accordingly, given the evidence before us in this record, we conclude that SteadyMed has established adequately for purposes of this decision that the combination of Moriarty and Phares renders obvious the treprostinil diethanolamine salt product recited in claims 1 and 9. Because we determine, on the record before us, and for purposes of institution, that the process steps recited in claims 1 and 9 do not impart structural or functional differences to the claimed treprostinil product and are therefore not limiting, we need not address the parties' contentions concerning the obviousness of the recited process steps.

Conclusion

UTC has not raised any additional arguments with regard to the dependent claims other than those addressed above. We have reviewed SteadyMed's evidence, arguments, and claim charts, and conclude that SteadyMed has sufficiently demonstrated that the dependent claims are also rendered obvious by the combination of Moriarty and Phares. Thus, for the

foregoing reasons, we conclude that SteadyMed has shown a reasonable likelihood of prevailing on its assertions that claims 1–5, 7–9, 11–14, and 16–20 are obvious in view of Moriarty and Phares.

*F. Obviousness Grounds of Unpatentability
Based on Moriarty, Phares, Kawakami, and Ege*

SteadyMed asserts that claims 6, 10, 15, 21, and 22 are unpatentable under § 103(a) as obvious in view of Moriarty, Phares or Kawakami, and Ege. Pet. 37–52. Although SteadyMed nominally identifies this ground of unpatentability as being over “Moriarty (Ex. 1004) with Phares (Ex. 1005) or Kawakami (Exs. 1006 & 1007) and in further combination with Ege (Ex. 1008)” (Pet. 53 (emphasis omitted)), as discussed below, SteadyMed explicitly relies on Kawakami in arguing unpatentability in view of Moriarty, Phares, and Ege. Accordingly, we understand SteadyMed’s stated ground of unpatentability as relying on the combination of Moriarty, Phares, Kawakami, and Ege. Claims 6, 21, and 22 depend, directly or indirectly, from claim 1, and claims 10 and 15 depend directly from claim 9. In support of its assertion, SteadyMed provides detailed explanations as to how the combination of Moriarty, Ege, Phares, and Kawakami discloses each claim limitation (*id.*), and relies upon the Winkler Declaration (Ex. 1009) to support its positions.

UTC contends that Kawakami should not be considered as evidence of unpatentability because the declaration certifying the accuracy of the translation is deficient. Prelim. Resp. 38–39. UTC also asserts that Ege is merely a generic introductory chemistry text, and irrelevant to the

'393 patent. *Id.* at 47. UTC further argues that SteadyMed has not identified a rationale for, or expectation of success in, combining either Moriarty, Phares, and Ege, or Moriarty, Kawakami, and Ege. *Id.* In addition, UTC contends that SteadyMed improperly asserts that the cited combination would inherently result in the claimed product. *Id.* at 54.

Kawakami

Kawakami describes “a crystalline dicyclohexylamine salt of a methanoprostacyclin derivative, a manufacturing method thereof, and a purifying method thereof.” Ex. 1007, 3. Kawakami discloses obtaining a dicyclohexylamine salt by “mixing a methanoprostacyclin derivative [I] . . . with dicyclohexylamine in an appropriate solvent.” Ex. 1007, 5–6. Kawakami explains that “[t]he dicyclohexylamine salt of the methanoprostacyclin derivative [I] thus obtained generally has fairly high purity, and the purity can be further improved by recrystallization as needed with the use of an appropriate solvent.” *Id.* at 6.

Kawakami further teaches that “[t]he dicyclohexylamine salt obtained by the present invention can be easily reverted to a free methanoprostacyclin derivative [I] by conventional methods, and the resulting methanoprostacyclin derivative exhibits excellent crystallinity compared with substances not purified according to the present invention.” *Id.*

Ege

Ege is an organic chemistry textbook. Ex. 1008, 1. Ege discloses:

Carboxylic acids that have low solubility in water, such as benzoic acid, are converted to water-soluble salts by reaction

with aqueous base. Protonation of the carboxylate anion by a strong acid regenerates the water-insoluble acid. These properties of carboxylic acids are useful in separating them from reaction mixtures containing neutral and basic compounds.

Id. at 8 (reference omitted).

Compliance with 37 C.F.R. § 42.63(b)

Kawakami is a Japanese patent application. Ex. 1006. SteadyMed submitted an English translation of Kawakami (Ex. 1007), as well as an affidavit certifying that translation (Ex. 1011) with its Petition.

UTC nevertheless contends that Kawakami should not be considered as evidence of unpatentability because the President of the translation service, rather than the individual who prepared the translation, executed the certification affidavit. Prelim. Resp. 38–39. UTC asserts that certification affidavit is objectionable because the affiant lacks personal knowledge of the relevant facts, the accuracy of the translation cannot be determined, and the translator is shielded from cross-examination. *Id.* at 39.

In view of the record before us, and for purposes of this decision, we decline UTC's invitation to disregard Kawakami. No credible prejudice to UTC has been called to our attention, and none is apparent. An English translation of Kawakami was available to UTC in time to prepare its Preliminary Response.⁸ Furthermore, UTC has not identified any error in

⁸ It does not appear that UTC has served objections on SteadyMed concerning the adequacy of the English translation of Kawakami or the certifying affidavit.

the translation that would call into question its authenticity. Regarding UTC's contention that the accuracy of the translation cannot be determined absent a certification affidavit from the translator himself, we note that the commission of an independent translation would confirm the veracity of the translation submitted by SteadyMed. We also observe that even if the individual personally responsible for generating the English translation of Kawakami had submitted a certification affidavit, UTC would not have had the opportunity to cross-examine him prior to the submission of its Preliminary Response.

Accordingly, on the record before us, and for purposes of this decision, we decline UTC's request that we disregard Kawakami. We observe, however, that the adequacy of the Kawakami translation and certification affidavit may be subject to further challenge during trial.⁹

Rationale to Combine Prior Art Teachings

Building on the rationale for combining Moriarty and Phares discussed in Part II.E above, SteadyMed contends that a relevant skilled

⁹ Pursuant to 37 C.F.R. § 42.64(b)(1), "[a]ny objection to evidence submitted during a preliminary proceeding must be served within ten business days of the institution of the trial. . . . The objection must identify the grounds for the objection with sufficient particularity to allow correction in the form of supplemental evidence." "The party relying on evidence to which an objection is timely served may respond to the objection by serving supplemental evidence within ten business days of service of the objection." 37 C.F.R. § 42.64(b)(2). Furthermore, "[a] motion to exclude evidence must be filed to preserve any objection. . . . The motion may be filed without prior authorization from the Board." 37 C.F.R. § 42.64(c)

artisan would add further purification steps from Kawakami and Ege because Kawakami “discloses that the dicyclohexylamine salt of a methanoprostacyclin derivative ‘can be easily reverted to the free methanoprostacyclin derivative by *conventional methods*,’” and that the “fairly high purity” of the salt obtained “can be further improved by recrystallization as needed with the use of an appropriate solvent.” Pet. 53; *see also* Ex. 1007, 6; Ex. 1009 ¶ 83. Dr. Winkler testifies that, as evidenced by Ege, a relevant skilled artisan “would understand that one such conventional method for converting the dicyclohexylamine salt of a methanoprostacyclin derivative to the free methanoprostacyclin derivative, or converting the treprostinil diethanolamine salt to treprostinil (*i.e.*, the free acid) is by treating the salt with a strong acid such as HCl or H₂SO₄.” Ex. 1009 ¶ 84; *see also* Pet. 53–54.

Dr. Winkler elaborates on this rationale for combining the cited references, testifying that a relevant skilled artisan

would want to form the treprostinil diethanolamine salt, purify it, and then convert it back to its free form (*i.e.*, treprostinil) in order to obtain excellent crystallinity and increased purity. And Ege (Ex. 1008, p. 8) teaches that one such method for obtaining the free form of treprostinil or any carboxylic acid would be by treatment of the carboxylate salt with a strong acid.

Ex. 1009 ¶ 88; *see also* Ex. 1008, 8; Pet. 54.

UTC does not address the combination of Moriarty, Ege, Phares, and Kawakami. Instead, UTC addresses Moriarty, Ege, and Phares as one combination, and Moriarty, Ege, and Kawakami as an alternative combination. Prelim. Resp. 46–47.

As an initial matter, UTC asserts that Ege is irrelevant to the '393 patent because it does not discuss prostacyclin derivatives or pharmaceutical synthesis. *Id.* at 47. UTC argues that Ege in fact “would teach away or discourage the use of salt formation for purifying a mixture of compounds that includes other carboxylic-acid containing compounds as impurities.” *Id.* at 48.

Regarding the combination of Moriarty, Ege, and Phares, UTC contends that “even though Phares discloses forming a salt from treprostinil free acid, and Ege generally discusses that carboxylate salt formation was known in the art, there would have been no motivation or expectation of success in using these teachings on the already-formed free acid disclosed in Moriarty.” Prelim. Resp. 50. Pertaining to the combination of Moriarty, Ege, and Kawakami, UTC asserts that SteadyMed “fails to establish that a [relevant skilled artisan] would reasonably expect the teachings of Kawakami to extend to the products in Moriarty.” *Id.* at 52.

UTC also argues that Dr. Winkler’s testimony regarding the reasons a relevant skilled artisan would want to form treprostinil diethanolamine salt, and treat it with a strong acid to convert it back to its free form (treprostinil) is improperly conclusory. *Id.* at 50, 52.

On the record before us, and for purposes of this decision, we agree that SteadyMed has sufficiently demonstrated that a relevant skilled artisan would have had reason to include the carboxylate salt formation and regeneration of the neutral carboxylic acid with the syntheses of Moriarty and Phares based on the teachings of Kawakami and Ege.

We recognize, but do not find persuasive, UTC's position that Ege is irrelevant to the synthesis of prostacyclin derivatives, and that it teaches away from the use of salt formation for purifying a mixture of compounds that includes other carboxylic-acid containing compounds as impurities. First, we observe that SteadyMed relies on Ege not for any teachings specific to prostacyclin derivative synthesis, but rather, to support the contention that the addition of a strong acid to a carboxylate salt to regenerate the neutral carboxylic acid is a conventional purification technique in organic chemistry. Pet. 53–55; Ex. 1009 ¶¶ 86, 88. In particular, Dr. Winkler testifies that the “addition of a strong acid to a carboxylate salt to regenerate the neutral carboxylic acid is a common reaction in organic chemistry and this process is well within the skill of one of ordinary skill in the art (indeed, a process that I teach to my organic chemistry students)” (Ex. 1009 ¶ 85), and that Ege, an introductory organic chemistry text, “discloses that sodium benzoate (i.e., a carboxylate salt) can be converted back to benzoic acid (i.e., a carboxylic acid) by treatment with the acid HCl” (*id.* ¶ 86). On this record, we credit Dr. Winkler's testimony, as it is consistent with the prior art.

Second, we note that even crediting UTC's position that the use of salt formation would not be effective for purifying treprostinil from its stereoisomers (Prelim. Resp. 47–48), the present record suggests that it would be effective for removing other impurities (Pet. 53–55; Ex. 1009 ¶¶ 86, 88). Moreover, as explained below, the present record, including Kawakami, indicates that treprostinil diethanolamine salt formation followed

by regeneration of treprostinil using a strong acid is an effective purification step. Pet. 53–55; *see also* Ex. 1007, 6; Ex. 1008, 8; Ex. 1009 ¶¶ 82–90.

Additionally, we agree with SteadyMed that a relevant skilled artisan would have had reason to combine Moriarty, Phares, Kawakami, and Ege. Pet. 53–55; Ex. 1009 ¶¶ 82–90. For example, Dr. Winkler testifies that a relevant skilled artisan would want to include a carboxylate salt formation and regeneration of the neutral carboxylic acid as described by Ege with the syntheses of Moriarty and Phares because Kawakami teaches that “the dicyclohexylamine salt obtained by the present invention can be easily reverted to a free methanoprostacyclin derivative [I] by conventional methods, and the resulting methanoprostacyclin derivative exhibits excellent crystallinity compared with substances not purified according to the present invention.” Ex. 1009 ¶ 86; *see also* Ex. 1007, 6; Pet. 53–55. Dr. Winkler additionally testifies that a skilled artisan would be motivated to form treprostinil diethanolamine salt, and treat it with a strong acid to “obtain excellent crystallinity and increased purity” of the final treprostinil product (Ex. 1009 ¶ 88), and that a skilled artisan would have a reasonable expectation of success in performing such reaction because it is “a common reaction in organic chemistry and this process is well within the skill of one of ordinary skill in the art” (*id.* ¶ 90).

On this record, we credit Dr. Winkler’s testimony, as it is consistent with the prior art. Moreover, we disagree with UTC that Dr. Winkler’s testimony is improperly conclusory. Rather, as illustrated by the excerpts of his testimony referenced above, Dr. Winkler supports his opinions with

reference to the cited art, as well as his experience as a chemist and chemistry professor.

Accordingly, on the record before us, we agree that SteadyMed has sufficiently demonstrated that one of ordinary skill in the art would have included the carboxylate salt formation and regeneration of the neutral carboxylic acid of Ege with the syntheses of Moriarty and Phares based on Kawakami's disclosure that the conversion of salts of prostacyclin derivatives to their free forms by conventional methods increases purity of the final product. *See KSR*, 550 U.S. at 417 (“[I]f a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill.”).

Claims 6, 15, and 21

Claims 6, 15, and 21 each recite the product of either claim 1 or claim 9, subject to additional process steps. For example, claim 6 recites “[t]he product of claim 1, wherein the acid in step (d) is HCl or H₂SO₄.” Ex. 1001, 19:39–40. Claim 15 similarly recites “[t]he product of claim 9, wherein the acid in step (d) is HCl.” *Id.* at 20:59–60. Claim 21 simply recites “[t]he product of claim 1, wherein step (d) is performed.” *Id.* at 21:13.

The present record supports SteadyMed's contention that claims 6, 15, and 21 would have been obvious in view of Moriarty, Ege, Phares, and

Kawakami. Pet. 53–56; Ex. 1009 ¶¶ 82–90. For example, Dr. Winkler testifies that

the combination of Moriarty (Ex. 1004) and Phares (Ex. 1005) (or Kawakami, Exs. 1006 & 1007) and Ege (Ex. 1008) would disclose . . . treprostinil of at least equal purity to that claimed in the '393 Patent, since the combination of these references discloses the same product and same process of Claims 1 and 9.

Ex. 1009 ¶ 89; *see also* Pet. 54. In addition, as explained above, Dr. Winkler testifies that a skilled artisan would have made the cited combination, with an expectation of success, in order to obtain a treprostinil product of improved purity. Ex. 1009 ¶¶ 88–90; Pet. 54–55. On this record, we credit Dr. Winkler's testimony.

UTC does not offer evidence or argument to suggest that the additional process steps recited in claims 6, 15, and 21 impart structural or functional differences to the claimed product beyond that discussed above in Parts II.B, II.D, and II.E. Rather, UTC contends that SteadyMed has not asserted that the products of claims 6, 15, and 21 would have been obvious in view of the cited art. Prelim. Resp. 54. UTC frames SteadyMed's position as an argument that the recited process steps would have been obvious, and would have inherently resulted in the claimed product. *Id.*

We do not find UTC's contentions persuasive. We observe that claims 6, 15, and 21 differ from their respective independent claims only in that they require the performance of optional step (d) from claims 1 and 9, and in the case of claims 6 and 15, specify the acid to be used in carrying out that process step. Ex. 1001, 19:39–40, 20:59–60. As set forth in detail in Parts II.A, II.B, II.D, and II.E, on the record before us, and for purposes of

this decision, we conclude that the process steps recited in the challenged claims, including step (d), do not impart structural or functional differences over prior art treprostinil products.

Furthermore, we disagree with UTC's characterization of SteadyMed's obviousness argument. We note, for example, that under the general rule for the interpretation of product-by-process claims, which we determine applies here, the products of claims 1, 6, and 21 are interpreted to be the same, namely, the product of claim 1. Likewise, the same analysis applies for the products of claims 9 and 15.

Accordingly, given the evidence before us in this record, we conclude that SteadyMed has established adequately for purposes of this decision that the combination of Ege, Phares, and Kawakami renders obvious the treprostinil products of claims 6, 15, and 21. Because we determine, on the record before us, and for purposes of institution, that the process steps recited in claims 6, 15, and 21 do not impart structural or functional differences to the claimed treprostinil product, we do not address the parties' contentions concerning the obviousness of the recited process steps.

Claim 10

Claim 10 recites "[t]he product of claim 9, wherein the purity of product of step (d) is at least 99.5%." Ex. 1001, 20:47–48. The present record supports SteadyMed's contention that claim 10 is obvious in view of Moriarty, Ege, Phares, and Kawakami. Pet. 55–56; *see also* Ex. 1009 ¶¶ 82–90. As detailed in Parts II.B, II.D, and II.E, the present record supports SteadyMed's position that Moriarty discloses treprostinil free acid having a

purity of 99.7% (Pet. 20; *see also* Ex. 1004, 13; Ex. 1009 ¶ 65), and Phares discloses treprostinil diethanolamine salt of the same form and at least the same purity as that claimed in the '393 patent (Pet. 27–28; Ex. 1005, 88–93; Ex. 1009 ¶¶ 59–62). The present record further supports SteadyMed's contention that even if Dr. Walsh's impurity measurements are credited, the 0.1% difference between the purity of the sample prepared according to Moriarty, and claim 10 is within the expected level experimental error for impurity measurements, and the degree of inter-batch variability in impurity content is such that Dr. Walsh's results are insufficient to support a conclusion of nonobviousness. Pet. 19–22; *see also* Ex. 1009 ¶¶ 63–71.

UTC does not offer evidence or argument to suggest that the additional process step recited in claim 10 imparts structural or functional differences to the claimed product beyond that discussed above in Parts II.A, II.B, II.D, and II.E. Neither does UTC present any additional argument regarding the recited purity requirement beyond those already addressed above. UTC does reassert its position, discussed with regard to claims 6, 15, and 21, that SteadyMed has not asserted that the product of claim 10 would have been obvious in view of the cited art. Prelim. Resp. 54. For the reasons set forth above, however, we do not find this contention persuasive.

Accordingly, given the evidence before us in this record, we conclude that SteadyMed has established adequately for purposes of this decision that the combination of Ege, Phares, and Kawakami renders obvious the treprostinil product of claim 10. Because we determine, on the record before us, and for purposes of institution, that the process steps recited in claim 10

do not impart structural or functional differences to the claimed treprostinil product, we do not address the parties' contentions concerning the obviousness of the recited process steps at this time.

Claim 22

Claim 22 recites “[t]he product of claim 21, wherein the product comprises a pharmaceutically acceptable salt formed from the product of step (d).” Ex. 1001, 21:14–16. The present record supports SteadyMed’s contention that claim 22 is obvious in view of Moriarty, Ege, Phares, and Kawakami. Pet. 56–57; *see also* Ex. 1009 ¶¶ 82–90. As discussed above in Parts II.D and II.E, the present record supports SteadyMed’s position that the cited combination renders obvious a pharmaceutically acceptable treprostinil salt.

UTC does not offer evidence or argument to suggest that the additional process step recited in claim 22 imparts structural or functional differences to the claimed product beyond that discussed above in Parts II.A, II.B, II.D, and II.E. Neither does UTC present any additional argument regarding the recited purity requirement beyond those already addressed above. UTC does reassert its position, discussed with regard to claims 6, 15, and 21, that SteadyMed has not asserted that the product of claim 22 would have been obvious in view of the cited art. Prelim. Resp. 54. For the reasons set forth above, however, we do not find this contention persuasive.

Accordingly, given the evidence before us in this record, we conclude that SteadyMed has established adequately for purposes of this decision that the combination of Ege, Phares, and Kawakami renders obvious the

treprostinil products of claim 22. Because we determine, on the record before us, and for purposes of institution, that the process steps recited in claims 22 do not impart structural or functional differences to the claimed treprostinil product, we do not address the parties' contentions concerning the obviousness of the recited process steps at this time.

Conclusion

For the foregoing reasons, we conclude that SteadyMed has shown a reasonable likelihood of prevailing on its assertions that claims 6, 10, 15, 21, and 22 are obvious in view of Moriarty, Ege, Phares, and Kawakami.

G. Secondary Considerations of Non-Obviousness

UTC contends that objective indicia of non-obviousness, such as purported evidence of long-felt but unmet need, unexpected results, commercial success, and copying support the patentability of the challenged claims of the '393 patent. Prelim. Resp. 55–58.

We conclude that the evidence of secondary considerations currently of record is not sufficient, at this point in the proceeding, to support UTC's contention. As an initial matter, we observe that "secondary considerations are better considered in the context of a trial when the ultimate determination of obviousness is made." *Crocs, Inc. v. Polliwalks, Inc.*, Case IPR2014-00424, slip op. 16 (PTAB Aug. 20, 2014) (Paper 8). In addition, we note that UTC's contentions regarding long-felt need and unexpected results are predicated on UTC's claim that treprostinil made according to the process described in the '393 patent has fewer impurities than treprostinil produced by other methods. However, as explained in Parts II.B, II.D, and

II.E above, the present record does not support that contention. We also observe that UTC does not offer evidence of a nexus between the claimed invention and its commercial success. For example, UTC does not offer evidence concerning its relative share of the market for treprostinil products, or demonstrating that its revenues or market share increased after it began manufacturing treprostinil according to the process described in the '393 patent. Finally, we note that the mere existence of litigation concerning the '393 patent alone is insufficient to establish copying. *See Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1325 (Fed. Cir. 2004) (“Not every competing product that arguably fails within the scope of a patent is evidence of copying. Otherwise every infringement suit would automatically confirm the nonobviousness of the patent.”).

H. Other Asserted Grounds of Unpatentability

SteadyMed also asserts the following ground of unpatentability:

Claims	Basis	Reference(s)
1–5, 7–9, 11–14, and 16–20	§ 103(a)	Moriarty and Kawakami

In light of the grounds specifically discussed above, on the basis of which we institute review, we exercise our discretion and decline to consider these other grounds asserted in the Petition. *See* 37 C.F.R. § 42.108(a). We observe that SteadyMed presents the above ground of unpatentability and the obviousness of claims 1–5, 7–9, 11–14, and 16–20 in view of Moriarty and Phares, a ground on which we institute review, in the alternative.

III. CONCLUSION

For the foregoing reasons, we determine that the information presented in the Petition establishes that there is a reasonable likelihood that SteadyMed would prevail in challenging claims 1–22 of the '393 patent. At this juncture, we have not made a final determination with respect to the patentability of the challenged claims, nor with respect to claim construction.

IV. ORDER

For the foregoing reasons, it is

ORDERED that pursuant to 35 U.S.C. § 314(a), an *inter partes* review is hereby instituted for the following grounds of unpatentability:

Claims	Basis	Reference(s)
1–5, 7–9, 11–14, and 16–20	§ 102(b)	Phares
1–5, 7–9, 11–14, and 16–20	§ 103(a)	Moriarty and Phares
6, 10, 15, 21, and 22	§ 103(a)	Moriarty, Phares, Kawakami, and Ege

FURTHER ORDERED that no other ground of unpatentability asserted in the Petition is authorized for this *inter partes* review; and

FURTHER ORDERED that pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial; the trial will commence on the entry date of this decision.

IPR2016-00006
Patent 8,497,393 B2

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Hitesh Batra et al.
Assignee: UNITED THERAPEUTICS CORPORATION
Title: PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE
INGREDIENT IN REMODULIN®
Appl. Number: 14/849,981
Filed: 9/10/2015
Examiner: Yevgeny Valenrod
Group Art Unit: 1672

**THIRD PARTY SUBMISSION UNDER 37 CFR § 1.501
OF PATENT OWNER WRITTEN CLAIM SCOPE STATEMENTS**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450
ATTENTION: Director, Technology Center 1600 (1672)

Dear Commissioner:

The undersigned hereby submits six public documents (collectively, "Documents 1-6"), which are patent owner written claim scope statements and additional information of relevance to the examination of the above-identified patent application (the "Batra Application") assigned to United Therapeutics Corp. ("Patent Owner"), in accordance with 37 C.F.R. § 1.501(a)(2). This submission includes the requisite forum and proceeding in which patent owner filed each statement, the specific papers submitted in that proceeding that contain the statements, and how each statement submitted is a statement concerning the scope of any claim in the patent.

The submitted documents are written statements of the patent owner and applicant United Therapeutics Corporation in a separate proceeding before the Office—*SteadyMed Ltd. v. United Therapeutics Corp.*, IPR No. 2016-000006—in which patent owner took a position on the scope of claims in the related parent patent, U.S. Patent No. 8,497,393, or they are documents, pleadings, or evidence from IPR No. 2016-000006 that address these written statements. All documents, where necessary, are submitted in redacted form.

The undersigned submits that he and she are not individuals who have a duty to disclose information with respect to the above-identified application under 37 C.F.R. § 1.56.

I. The forum and proceeding in which patent owner filed each statement.

All six documents being submitted are from the following proceeding: *SteadyMed Ltd. v. United Therapeutics Corp.*, IPR No. 2016-000006, instituted on April 8, 2016. These documents complete the record regarding Patent Owner's statements regarding claim construction in the parallel IPR2016-000006 regarding the '393 Parent Patent, and related to the claim construction of the pending claims in the Batra Application.

II. Patent owner written claim scope statements, and documents, pleadings, or evidence being submitted.

The list of documents being submitted and enclosed herewith includes the following Documents 1-6, in accordance with 37 C.F.R. § 1.501(a)(2):

Document 1 — Patent Owner Redacted Response in IPR2016-000006, Paper No. 35, concerning claim construction in parent patent U.S. Patent No. 8,497,393.

Document 2 — Declaration of Robert M. Williams, Ph.D. in Support of Patent Owner Response to Petition (Redacted), in IPR2016-000006, Ex. 2020, concerning claim construction in parent patent U.S. Patent No. 8,497,393.

Document 3 — Petitioner's Redacted Reply in IPR2016-000006, Paper No. 52 (September 27, 2016), concerning claim construction in parent patent U.S. Patent No. 8,497,393.

Document 4 — Redacted Deposition Transcript of Dr. Robert M. Williams, Ph.D., Exhibit 2059 in IPR2016-000006.

Document 5 — Redacted Deposition Transcript of Dr. Robert R. Ruffolo, Jr., Ph.D., Exhibit 2058 in IPR2016-000006.

Document 6 — "Spreadsheet of 46 batches from Exs. 2053 and 2036," Exhibit 1021 (Redacting 2 values from Ex. 2053 not publicly disclosed) in IPR2016-000006.

III. How each document submitted is a statement concerning the scope of any claim in the patent.

A concise explanation of the relevance of each of Documents 1-6 is provided below, in accordance with 37 C.F.R. § 1.501(b)(1).

Document 1

Document 1, the Patent Owner Redacted Response in IPR2016-000006, Paper No. 35, concerns claim construction in parent patent U.S. Patent No. 8,497,393 (the "'393 Parent Patent"). The document addresses the meaning of the claim terms "product" in product-by-process claims, and the interpretation of the scope of product-by-process claims. The claims in the Batra Application are product-by-process claims.

Document 1 also makes statements regarding how purity affects the claim construction of the claims in the '393 Parent Patent, which are relevant to the same question of the scope of the current claims in the Batra Application.

Document 2

Document 2, the Declaration of Robert M. Williams, Ph.D. in Support of Patent Owner Response to Petition (Redacted), in IPR2016-000006, Ex. 2020, concerns claim construction in the '393 Parent Patent. It agrees with and reiterates the statements regarding claim construction found in Document 1, the Patent Owner Redacted Response in IPR2016-000006, Paper No. 35, and is relevant for the same reasons.

Document 3

Document 3, the Petitioner's Redacted Reply in IPR2016-000006, Paper No. 52, makes statements opposing the claim constructions proposed by Patent Owner in the '393 Parent Patent, which are relevant to the same question of the scope of the current claims in the Batra Application. Document 3 completes the record regarding Patent Owner's statements regarding claim construction in the parallel IPR2016-000006 regarding the '393 Parent Patent.

Document 3 proves that the statements regarding purity of the prior art Moriarty and Phares treprostinil and treprostinil diethanolamine salt and the scope of the claims made in Documents 1 and 2 are false, and that data provided by the Patent Owner to support the scope of the claims and the prior art were distorted by cherry picking questionable data points and adding them to the analysis to lower the average purity value of the prior art. *See especially* Document 3 at pp. 2-3, 4-9. A corrected analysis of the data, approved by Patent Owner's own Declarant Robert M. Williams, shows that the correct purity value for the prior art is the same as for the claimed invention in the '393 Parent Patent, *see especially id.* at pp. 8-9, which is the

same scope as the claims now presented in the Batra Application, and shows that the claim construction of the terms "pharmaceutical composition" and "comprising" in the Batra Application proposed by the Applicant and Patent Owner is meaningless. *See especially* Document 3 at pp. 9-10.

Document 3 addresses and completes Patent Owner and Applicant's statements regarding the meaning of the terms "pharmaceutical composition" and "comprising" in the Batra Application that was proposed by Patent Owner. Document 3 proves that there are no fixed set of impurities associated with the product-by-process claims in the Batra Application, but that the set of impurities is a moving target that varies from batch to batch. *See especially* Document 3 at p. 11. And Document 3 shows that the scope of the terms "pharmaceutical composition" and "comprising" in the Batra Application cannot be fixed by much better than $\pm 2\%$, in contradiction with Patent Owner and Applicant's claim construction arguments in the Batra Application. *See especially* Document 3 at 15-17. Thus, Patent Owner's statements regarding claim construction in the Batra Application are contradicted by Document 3.

Document 4

Document 4 is the Deposition Transcript of Dr. Robert M. Williams, Ph.D., Exhibit 2059 in IPR2016-000006. Dr. Williams is Patent Owner and Applicant's Declarant in the Batra Application, and makes statements in his Declaration regarding the construction of product-by-process claims. This deposition addresses the statements made by Dr. Williams in his Declaration, and shows that these statements were based on his being misled by Applicant's counsel into believing a calculation that he did not perform supported Applicant's claim construction. *See especially* Ex. 2059, 79:3-10, 81:2-13, 82:1-11, 103:24-104:20, 112:24-114:2. These statements addresses the claim construction of the product-by-process claims at issue in both the Batra Application and the '393 Parent Patent. It shows that the construction of product-by-process claims advocated by Patent Owner and Applicant in the Batra Application should be ignored, and that the prior art purity was the same as in the claimed invention. *See especially* Ex. 2059, 217:11-219:20.

Document 4 also shows that certain data relied upon by Patent Owner and Applicant to support its arguments for the construction of the claims in the Batra Application were cherry-picked to reduce the average purity values of treprostinil made in accordance with the Moriarty

prior art, and which define the scope of the claims and the terms "pharmaceutical composition" and "comprising" in the Batra Application. *See especially* Ex. 2059, 112:20-113:20, 270:15-271:6. Moreover, it shows that the scope of the terms "pharmaceutical composition" and "comprising" in the Batra Application cannot be fixed by much better than $\pm 2\%$, in contradiction with Patent Owner and Applicant's claim construction arguments in the Batra Application. *See especially* Ex. 2059, 133:134:24-135:4.

Document 5

Document 5 is the Deposition Transcript of Dr. Robert R. Ruffolo, Jr., Ph.D., Exhibit 2058 in IPR2016-000006. Dr. Ruffolo is Patent Owner and Applicant's Declarant in the Batra Application, and makes statements in his Declaration regarding the construction of product-by-process claims. This deposition addresses the statements made by Dr. Ruffolo in his Declaration, and shows that these statements contradict Patent Owner and Applicant's assertion regarding claim construction of product-by-process claims, including whether such claims are structurally and functionally unique. *See especially* Ex. 2058, 159:20-161:7, 179:23-180:17, 217:11-218:5. These statements address the claim construction of the product-by-process claims at issue in both the Batra Application and the '393 Parent Patent. It shows that the construction of product-by-process claims advocated by Patent Owner and Applicant in the Batra Application should be ignored, because contrary to the Patent Owner's statement during the Batra Patent Application's prosecution, the patent's specification does not even mention or characterize what impurities are present in treprostinil, which Patent Owner maintains as a trade secret to this day. *See especially* Ex. 2058, 234:16-235:12, 93:19-94:24, 233:5-12. It also contradicts Patent Owner's claim construction arguments regarding structural and functional differences, since Dr. Ruffolo testified that there were no such functional differences. *See especially* Ex. 2058, 159:20-161:7, 257:22-258:9.

Document 5 (Ex. 2058) also contradicts Patent Owner's construction of "pharmaceutical composition" and "comprising" in the Batra Application because contrary to Patent Owner's arguments, the impurities are not uniquely associated with the claims of the Batra Application. Document 5 proves that there are no fixed set of impurities associated with the product-by-process claims in the Batra Application, but that the set of impurities is a moving target that varies with the solvents used, and whether intermediate products were purified. *See especially*

Ex. 2058, 239:8-241:14. Thus, Patent Owner's statements regarding claim construction in the Batra Application are contradicted by Document 5.

Document 6

Document 6, a "Spreadsheet of 46 batches from Exs. 2053 and 2036," Exhibit 1021 in IPR2016-000006, proves that the statements made in Documents 1 and 2 regarding claim construction and the scope of the claims were false. Document 6 compiles all batches shown to be made by the Moriarty process and demonstrates that the average purity of Moriarty products was the same as in the claimed invention. Patent Owner's own Declarant Robert M. Williams testified that the calculation in Exhibit 1021 was performed correctly.

Date: October 21, 2016

Respectfully submitted,

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CERTIFICATE OF SERVICE

The undersigned certifies that a copy of the attached THIRD PARTY SUBMISSION UNDER 37 CFR § 1.501 OF PATENT OWNER WRITTEN CLAIM SCOPE STATEMENTS was served by FIRST CLASS MAIL to the following:

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

STEADYMED LTD.,

Petitioner,

v.

UNITED THERAPEUTICS CORPORATION,

Patent Owner.

Case IPR2016-00006
Patent 8,497,393

Patent Owner Response to Petition

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I. INTRODUCTION

United Therapeutics Corporation (“UTC”) submits this Response in accordance with 35 U.S.C. § 316(a)(8) and 37 C.F.R. § 42.120, responding to the instituted grounds of the Petition for *Inter Partes* Review filed by SteadyMed Ltd. (“SteadyMed”) challenging claims 1-22 of U.S. Patent No. 8,497,393 (“the ’393 patent”). The Declaration of Dr. Williams (“Ex. 2020”) and of Dr. Ruffolo (“Ex. 2022”) are filed herewith in support of the Response (Ex. 2020 and Ex. 2022, respectively). The Board should conclude that SteadyMed has failed to prove by a preponderance of the evidence that the instituted claims are unpatentable, as required under 35 U.S.C. § 316(e).

II. SUMMARY OF THE ARGUMENT

SteadyMed’s anticipation and obviousness arguments are flawed for two fundamental reasons. First, SteadyMed’s arguments rely on Moriarty (Moriarty *et al.*, J. Org. Chem. 2004, 1890-1902; Ex. 1004) and Phares (International Publication No. WO 2005/007081; Ex. 1005), but neither reference discloses the same highly pure treprostinil or treprostinil diethanolamine product claimed by the ’393 patent when properly construed, let alone the same synthesis recited in the instituted claims. In fact, the Office considered both references during prosecution of the ’393 patent, and the Office construed the claims of the ’393 patent in a way that distinguished the product of the ’393 patent specifically from the Moriarty

product. Moreover, a person of ordinary skill in the art (“POSA”) would not look to either Ege (Seyhan N. Ege, Organic Chemistry 543-547 (2d ed. 1989) (Ex. 1008) or Kawakami (JP 56-122328A) (Ex. 1007) as neither reference is relevant to further purification of the complex treprostinil carboxylic acid structure that is at issue in the ’393 patent, and a POSA would have no reasonable expectation of success in combining these references with either Moriarty or Phares.

Second, SteadyMed’s anticipation and obviousness arguments are flawed because they misunderstand, both the error associated with such measurements and the difference between “assay purity” against a standard and measurements of purity that directly measure the level of impurities. As explained in the Williams and Ruffolo Declarations, this misunderstanding resulted in Petitioner’s incorrect assertion that there are inconsistencies between the purity values recited in the ’393 specification, the Walsh Declaration, and the Moriarty prior art. Ex. 2020 at ¶¶88-89; Ex. 2022 at ¶¶73-74. Dr. Williams notes that the ’393 patent itself expressly refers to assay purity values as “HPLC (assay)” values whenever it uses such measurements, as opposed to other purity values based on measuring amount of impurities. Ex. 2020 at ¶89. Dr. Ruffolo further explains that FDA drug approval system rests on precise measurements of individual impurities that make up a purity “specification” for a drug, which can be reliably determined within the detection limits of HPLC measurements. Ex. 2022 at ¶¶32-35 and 44-50. Dr.

Ruffolo also specifically notes that it is routine to have assay purity values above 100% because it is a relative value measurement. Ex. 2022 at ¶53.

SteadyMed's purported expert, Dr. Winkler, confirmed this misunderstanding. Dr. Winkler acknowledged at his deposition that FDA's purity specification of less than 0.1% for the impurity 2AU90 indicates that precise measurements of impurities are possible: "I would think that the error in the measurement for 2AU90 would be, should be less than 0.1 percent." Ex. 2051 at 64:7-9. Dr. Winkler further acknowledged that he did not know how the treprostinil purity specification adopted by FDA could change from 101% to 102% and stated that he viewed purity levels above 100% as errors: "I think the thing that I am able to conclude from the data that is on page 6 of this, of this letter [Ex. 2006] is that the error in the HPLC assay could be as high as 1 percent in the first column and by my analysis could be as high as 2 percent in the second column." Ex. 2051 at 86:15-21; 24-25; 87:2-9. As Dr. Williams explained, Dr. Winkler's conclusions on this point appear "to arise from Dr. Winkler's fundamental misunderstanding of how assay purity values are calculated." Ex. 2020 at ¶¶90-92; *see also* Ex. 2022 at ¶¶74. Moreover, Dr. Winkler admitted he did not know what the actual error was associated with the measurements submitted in the Walsh declaration. Ex. 2051 at 62:16-25; 63:2-14. Because Dr. Winkler does not understand the basic differences in types of purity measurements and their related

errors that are used in the '393 patent, discussed in the Walsh Declaration, and which form the basis for FDA's regulation of drug product manufacturing, his declaration should not be credited.

Moreover, the Williams Declaration establishes that there are measurable structural differences between the average impurity profiles of the Moriarty product and the claimed product based on data obtained from 175 batches. Ex. 2020 ¶¶94-99, Appendices A-B; see also Ex. 2005, Ex. 2036, Ex. 2037, Ex. 2052, Ex. 2053. The average impurity profiles show that Moriarty process and the '393 process produce two physically distinct products that contain different total and specific impurities. *Id.* Specifically, the claimed product essentially lacks certain impurities found in the Moriarty product, such as [REDACTED], and [REDACTED]. Ex.2020 at ¶¶96-97. The claimed product also contains much smaller amounts of other impurities that are found in the Moriarty product, such as [REDACTED], [REDACTED]. *Id.* at ¶96.

Furthermore, based on the same 175 batches, the average purity of the '393 product is [REDACTED] greater than the average purity of the Moriarty product, thereby corroborating that the Moriarty process and the '393 process produces two physically distinct products that contain measurable and significant structural differences. *Id.* at ¶98.

Finally, the initial claim construction of the preamble “a product... comprising” urged by SteadyMed and adopted by the Board would violate the canon that patent claims may not be construed to encompass material that was clearly disavowed in order to obtain allowance of claims. Even under the broadest reasonable interpretation standard, the Board has found in its own cases that the prosecution history may limit the plain meaning of a limitation in a claim, which otherwise is presumed to apply. The '393 claims were allowed after submission of the Walsh Declaration, which established the differences between the '393 products and the Moriarty product. This disavowal of the Moriarty subject matter is further reinforced by additional intrinsic evidence. The '393 patent includes a side-by-side comparison in Example 6 to show the difference between the Moriarty product and the '393 product and repeatedly references higher purity and different impurity profile compared to Moriarty. In the face of this disavowal, it is improper to construe “a product ...comprising” to allow the impurities “without limitation,” as such a construction would encompass the impurity profile of Moriarty.

In addition, the Williams Declaration explains why Phares cannot anticipate the claimed products because of the particular conditions used to prepare the Phares product for polymorph screening and because of the uncertain provenance of starting treprostinil used to make the diethanolamine salt.

As to instituted grounds 2 and 3, Dr. Williams also explains why the references in the instituted obviousness grounds would not have been combined in the asserted manner due to lack of motivation and the failure of the references to provide an expectation of success for achieving the purity level and impurity profile of the '393 patent in the specific case of treprostinil. Kawakami teaches away from the selection of diethanolamine, the salt specifically claimed in claims 14 and 18. Lastly, secondary considerations of long-felt need and unexpected results would rebut any case of obviousness as to grounds 2 and 3.

In view of the foregoing, SteadyMed has not met its burden of proving the unpatentability of claims 1-22 by a preponderance of the evidence, as required under 35 U.S.C. § 316(e).

III. STRUCTURAL/FUNCTIONAL DIFFERENCES OF THE CLAIMED PRODUCTS OVER THE CITED ART

The combined Declarations of Dr. Williams and Dr. Ruffolo establish that the '393 product has a different impurity profile than the Moriarty product, and in fact, that the '393 product has higher average purity. These differences matter. FDA uses both overall purity and levels of individual impurities (“purity specification”) as a basis to regulate the manufacturing of pharmaceuticals. Batches that fall outside of the purity specification cannot be sold or used to treat

patients. Thus, differences in purity and impurity profile are not merely academic, but critical to the successful manufacture of a clinical product.

A. The Importance of Purity in Pharmaceuticals

As noted by the '393 patent itself, "because Treprostinil, and other prostacyclin derivatives are of great importance from a medicinal point of view, a need exists for an efficient process to synthesize these compounds on a large scale suitable for commercial production." Ex. 1001, col. 1:57-61. The invention therefore "provides for a process that is more economical, safer, faster, greener, easier to operate, and provides higher purity." *Id.*, col. 5:47-50. As the treprostinil product is a drug product subject to the rules of FDA, the reduction of impurities is of great importance in the drug. Drug purity is defined by FDA as "relative freedom from extraneous matter in the finished product, whether or not harmful to the recipient or deleterious to the product." See, Ex. 2022 at ¶33; see also 21 C.F.R. §600.3 (r) (2015). The purity of a drug is of such importance to FDA that the purity level of a drug substance must appear in the drug product specification, which is a collection of data about the drug required by FDA. See, Ex. 2022 at ¶¶32-34. "Regulatory agencies have also sought to increase levels of purity, and consequently decrease levels of impurities, in order to provide to the maximum extent possible, the highest level of safety to patients." *Id.* at ¶36. This is due to

the fact that even trace amounts of impurities can sometime pose serious health concerns.

For example, the drug penicillin is one of the best known and extensively studied examples of trace impurities that can cause serious, life-threatening adverse events. *Id.* at ¶62. While penicillin is safe and effective for most people, it can cause serious allergic reactions resulting in anaphylaxis and death. *Id.* Because the amount of trace impurity of penicillin needed to cause an allergic reaction is so low, FDA has mandated the production of penicillin active pharmaceutical ingredient (API) and finished product to be made in buildings entirely separate from buildings that manufacture other APIs or finished drug product. *Id.*, *see also* FDA Guidance for Industry, Non-Penicillin Beta-Lactam Drugs: A CGMP Framework for Preventing Cross-Contamination, (2013) (Ex. 2047) at 1-6. The same is true for the drug cephalosporin. Ex. 2022 at ¶63; *see also* Ex. 2047 at 1-6.

Additionally, human insulin is another example. For many years, human insulin was derived from pig pancreases, but then it became possible to produce human insulin in the bacteria *E. coli* using large bioreactors. Ex. 2022 at ¶64. Even though the human insulin derived from *E. coli* was highly pure, it contained very small trace amounts of *E. coli*, a very dangerous bacteria causing reactions (directly from the trace amounts of bacteria, and not due to infection) in some people even in trace amounts. *Id.* As a result, the product needed to be even more

highly purified to further minimize or eliminate the trace bacterial contaminants.

Id. These examples highlight the importance of drug purity in pharmaceutical formulations and the potential risks to patients between two products that differ in their impurity profile and purity. By having a different impurity profile and overall purity, two products are structurally and functionally different.

B. The '393 Product Has A Different Impurity Profile and a Higher Purity Than Moriarty

As detailed in Dr. Williams' Declaration and supporting exhibits, comparing the average impurity profiles for the '393 product and the Moriarty product using data obtained from over 175 batches reveals measurable structural differences, as the two processes produce physically different products which contain different total and specific amounts of impurities. Ex. 2020 ¶¶94-99 and Appendices A-B; *see also* Ex. 2005, Ex. 2036, Ex. 2037, Ex. 2052, Ex. 2053. The batch reports show that the Moriarty product and the claimed product exhibit different impurity profiles and that the claimed product has a higher average purity than Moriarty's product. *Id.*

Moriarty Process Impurities (Average Percent Detected)								
1AU90	2AU90	3AU90	750W93	751W93	97W86	ethyl ester	methyl ester	Total Related Substance
0.0473	0.0407	0.2545	0.1646	0.1025	0.0405	0.0889	0.1028	0.9545
'393 patent Process Impurities (Average Percent Detected)								

In total, the '393 product has [REDACTED] times fewer impurities than the Moriarty product.¹ Ex. 2020 ¶¶94-95. Additionally, certain specific impurities found in the prior art Moriarty product are essentially eliminated in the '393 product, as the '393 product does not contain detectable amounts of the impurity [REDACTED], and none of the commercial batches of the '393 product contain detectable amounts of [REDACTED] or [REDACTED]. Ex. 2020 ¶¶94, 96-97. Other impurities, including [REDACTED], [REDACTED], [REDACTED], and [REDACTED], are also greatly [REDACTED] in the '393 product as compared to the Moriarty product, while the level of the [REDACTED] impurity is slightly [REDACTED] in the '393 product. Ex. 2020 ¶96. These substantial differences between the impurity profiles of the '393 product and the Moriarty product constitute structural differences between the claimed product and the prior art.

Furthermore, the average purity based on data from over 175 batches is higher for the '393 product than that of Moriarty. As shown above, the average purity of a Moriarty batch was 99.05% while the average purity of a '393 batch

¹ Moriarty Total Related Substances: 0.9545; '393 patent Process Total Related Substances: [REDACTED]

was [REDACTED]. Ex. 2020 ¶¶94-99. This is a marked improvement in overall purity. Moreover, the purity analyzed in these batches – the total related substances – is exactly the same type of analysis Dr. Walsh referred to in his declaration when referring to purity of the '393 patent process versus that of the Moriarty process. Thus, this analysis is consistent with how the inventor interpreted the purity of the '393 patent. And this analysis also persuaded the Office to allow the claims.

The Institution Decision cited to the Walsh Declaration for revealing “that each of the impurities detected in [the tested batch of] Moriarty treprostinil was present in an amount below that identified as acceptable in UTC’s own specification for treprostinil produced according to the process disclosed in the ‘393 patent.” Paper 12 at 20-21. First, the above data shows that the average amount of each impurity and the average purity is different between Moriarty treprostinil and the '393 product. Second, whether an isolated batch of Moriarty treprostinil does or does not satisfy the new FDA purity specification is not relevant to patentability. The question for patentability is whether or not a given batch of *starting* Moriarty treprostinil (steps a and b of the '393 independent claims) will be physically changed when step (c) is performed *on that batch*. The above averages show that it does change, as do the large scale synthesis examples 4-6 in the '393 patent. While Moriarty treprostinil may show inter-batch variation in overall purity and impurity profiles, the data of record establishes that

performing step (c) *on a given starting batch* of Moriarty treprostinil will lead to a higher purity and a different impurity profile in the end product. Petitioner has not established that any specific batch of Moriarty treprostinil is not physically changed by performing step (c), and all the evidence suggests that it is.

C. The Differences In Impurity Profile And Average Purity Between The '393 Product And Moriarty Are Functionally Important

The higher purity of the claimed product resulted in FDA approving a new assay purity for the treprostinil drug as noted in the January 2009 letter submitted to FDA by UTC. Ex. 2006 at 4-6; Ex. 2022 at ¶¶66-68; Ex. 2020 at ¶91. Furthermore, this change constitutes a “major” change according to the classification system for manufacturing changes used by FDA. Ex. 2022 at ¶¶70-72. FDA requires continuous testing of pharmaceutical batches to ensure that they fall within the established purity specification. Ex. 2022 at ¶¶32-40. If a given batch falls outside the established purity specification, then it will be rejected by FDA and cannot be sold for patient use. *Id.* at ¶32. FDA is so concerned about purity of pharmaceuticals that it requires companies to test for very tiny amounts of individual known impurities carried over into the final product based on the manufacturing process. *Id.* at ¶¶32-40. Thus, the change in the '393 product is commercially important and has real-world value.

IV. CLAIM CONSTRUCTION

In the Decision on Institution (Paper 28), the preliminary claim construction construes “[a] product comprising a compound [of/having] formula [I/IV] or a pharmaceutically acceptable salt thereof” and “product” in an unreasonably broad manner. The Board is not bound by that preliminary construction based on an incomplete record. *See e.g., The Scotts Co., LLC v. Encap, LLC*, IPR2013-00110, Paper 79 (PTAB June 24, 2014) (overturning preliminary claim construction in final written opinion) (Ex. 2024). On the fuller record now available to it, the Board should adopt UTC’s construction of the disputed terms.

A. **Intrinsic Evidence Can Override The Presumption That “Comprising” Creates An “Open” Claim Construction**

The claims at issue in an IPR must be given their broadest reasonable interpretation (BRI) in light of the specification, but the Board must still interpret claim terms according to established principles. The transition phrase “comprising” is only *presumed* to be an “open” phrase. *Crystal Semiconductor Corp. v. TriTech Microelectronics Int’l, Inc.*, 246 F.3d 1336, 1348 (Fed. Cir. 2001) (“In the parlance of patent law, the transition ‘comprising’ creates a presumption that the recited elements are only a part of the device, that the claim does not exclude additional, unrecited elements.”). “While it is true that, as a general rule, the words of a patent claim are to be given their plain, ordinary and accustomed

meaning to one of ordinary skill in the relevant art, *Toro Co. v. White Consol. Indus., Inc.*, 199 F.3d 1295, 1299 (Fed. Cir. 1999), a court must nevertheless examine the remaining intrinsic evidence to determine whether the patentee has set forth an explicit definition of a term contrary to its ordinary meaning, has disclaimed subject matter, or has otherwise limited the scope of the claims.” *Day Intern., Inc. v. Reeves Brothers, Inc.*, 260 F.3d 1343, 1349 (Fed. Cir. 2001).

The intrinsic record, both the specification and the prosecution history, must be reviewed to determine if there are limits to terms in the claims that would otherwise be given their presumptive plain meanings. Prosecution history “limits the interpretation of claims so as to exclude any interpretation that may have been disclaimed or disavowed during prosecution in order to obtain claim allowance.” *Standard Oil Co. v. American Cyanamid Co.*, 774 F.2d 448, 452 (Fed. Cir. 1985). Similarly, the specification may contain repeated statements distinguishing the prior art that limit the claims. *SafeTCare Mfg., Inc. v. Tele-Made, Inc.*, 497 F.3d 1262, 1269-70 (Fed. Cir. 2007) (finding disclaimer where the specification repeatedly indicated that the invention operated by “pushing (as opposed to pulling) forces,” and then characterized the “pushing forces” as “an important feature of the present invention”).

Under the BRI standard, the Board should take into account both the specification and the prosecution history because the patent examiner and the

applicant have already worked together to determine the scope of the claimed invention. *See In re Buszard*, 504 F.3d 1364, 1366-67 (Fed. Cir. 2007) (“The patent examiner and the applicant, in the give and take of rejection and response, work toward defining the metes and bounds of the invention to be patented.”); *In re Zletz*, 893 F.2d 319, 321 (Fed. Cir. 1989) (“When the applicant states the meaning that the claim terms are intended to have, the claims are examined with that meaning, in order to achieve a complete exploration of the applicant's invention and its relation to the prior art.”).

The Board has followed these principles of claim construction in other IPR proceedings. *See, e.g., The Scotts Co., LLC v. Encap, LLC*, IPR2013-00110, Ex. 2024 at 14-16. In *Scotts*, the Board changed its preliminary claim construction of “being in a solid state at time of coating” because the Board found that the patent owner had disavowed claim scope during prosecution in order to overcome a specific prior art reference. Ex. 2024 at 15. The Board relied on statements made in Examiner Interview Summaries which confirmed that claim amendments and arguments presented overcame the prior art. *Id.*; *see also* Prosecution History of U.S. Patent No. 6,209,259 (Ex. 2025). As another example, the Board recently construed a phrase to exclude trace amounts of a substance based on statements made during prosecution distinguishing prior art containing trace amounts of the substance. *Daicel Corp. v. Celanese Int’l Corp.*, IPR2015-00171, Paper 86 at 41

(PTAB June 23, 2016). Thus, the BRI cannot be divorced from the intrinsic evidence, including the prosecution history. Such a construction is not reasonable.

B. The Distinct Impurity Profile And Higher Purity Of the '393 Patent Product Were Clearly Considered Part of the Claimed Product During Prosecution

As explained during prosecution, “[e]ach of treprostiniil as the free acid and treprostiniil diethanolamine prepared according to the process specified in claim 1 or 10 . . . is physically different from treprostiniil prepared according to the process of ‘Moriarty’ due to differences in their impurity profiles.” Ex. 1002 at 344. In fact, the Examiner required UTC to provide evidence in declaration form showing that the product of claims 1 and 10 was different than Moriarty’s product. *Id.* at 328. In response, UTC filed the Walsh Declaration, which demonstrated that the claimed product had a different impurity profile and higher purity than Moriarty’s product. *Id.* at 347-349. It was upon these statements and evidence that Moriarty was overcome, and shortly thereafter the Examiner issued a Notice of Allowance. *Id.* at 354-360.

In addition, the ‘393 specification repeatedly refers to the differences of the ‘393 product compared to Moriarty. The entirety of Example 6 in the ‘393 specification is a large scale, side-by-side comparison between Moriarty and the ‘393 product, which shows a purity of 99.0% for Moriarty and 99.9% for the ‘393 product. Ex. 1001, 17:step 53. At the end of this example, the ‘393 specification

further states that “impurities carried over from intermediate steps (i.e., alkylation of triol and hydrolysis of benzindene nitrile) are removed during the carbon treatment and salt formation step” (Ex. 1001, 17:29-32), which are the same differences (higher purity and different impurity profile) that UTC relied upon in the Walsh Declaration during prosecution as noted above.

These statements by UTC demonstrate that the claimed “product” must have an impurity profile conferred by its process steps. *See Purdue Pharma L.P. v. Endo Pharms. Ins.*, 438 F.3d 1123, 1136 (Fed. Cir. 2006); *see also Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 997 (Fed. Cir. 2006) (statements made during prosecution history that distinguished the claimed invention from the prior art constituted a prosecution disclaimer); *see also United Therapeutics Corp. v. Sandoz, Inc.*, 2014 WL 4259153, *54-56 (D.N.J. Aug 29, 2014) (finding compounds made by different processes resulted in different impurity profiles meaning they were structurally different).

D. The Plain Meaning Of “Product” In The Context Of The ’393 Product-By-Process Claims Requires The Characteristics Conferred By The Process Steps Be Present

The term “product” in the context of the ’393 patent should be construed as “a substance resulting from a chemical reaction.” This is consistent with the ’393 patent itself (Ex. 1001 at col. 3, lines 3, 4, 65, and 66; col. 5, line 45; col. 6, lines 65 and 66; and col. 7, line 17), as well as the understanding of a POSA and the

generally accepted definition in chemistry. Ex. 2020 at ¶¶60-62. Additionally, Dr. Williams and Dr. Winkler both use the term product to refer to the result of a chemical reaction in their own work. Id. at ¶¶63-65; *see also* Ex. 2031 at 155:2-11 (“the product of a chemical reaction would be essentially all of the substances that result from the treatment of a particular reactant with a particular set of reagents.”). To construe the term “product” as “a chemical composition” is too broad and improperly disregards a significant portion of the intrinsic record. As described above, a product is the result of a chemical reaction and has its own impurity profile depending upon how it is made. “A chemical composition” could be anything and is in no way limiting to what the term “product” actually means. Ex. 2020 at ¶¶66-68.

V. GROUND 1: PHARES FAILS TO EXPLICITLY OR INHERENTLY DISCLOSE EACH AND EVERY LIMITATION OF CLAIMS 1-5, 7-9, 11-14 OR 16-20

The Board instituted Ground 1 based on the conclusion that Phares teaches the treprostini diethanolamine salt product recited in claims 1 and 9, and that the recited process steps of the claims do not impart structural or functional differences over Phares’ treprostini diethanolamine salt. As discussed below, SteadyMed has failed to establish anticipation based on Phares.

A. SteadyMed Cannot Pick and Choose From Unrelated Portions of Phares to Establish Anticipation

In attempting to show anticipation, SteadyMed cites four different portions of Phares, Ex. 1005, as teaching the combined elements of claims 1 and 9.

However, SteadyMed selectively ignores other portions in the Phares disclosure that suggest the four disparate portions of Phares should not be cobbled together to a single allegedly anticipatory embodiment. Petition at 22-24 and 33-34.

The portions of Phares cited by SteadyMed each relate to distinct subject matter, and Phares provides no description that would lead to the combination of these separate disclosures. Ex. 2020 at ¶¶79-84. Phares' only disclosure of steps (a) and (b) is directed to the enantiomer (-)-treprostinil, which are not the same as the synthesis for treprostinil. Ex. 2020 at ¶¶79-81. In fact, the intermediate products disclosed in the enantiomer synthesis as well as several reagents are different than the synthesis of treprostinil. *Id.* at ¶81. In contrast, Phares' separate alleged disclosure of step (c) is silent as to how the starting treprostinil acid was prepared. Ex. 1005 at 85. Thus, there is no reason set forth in Phares to combine the single teaching of steps (a) and (b) directed to one enantiomer with the other teachings of step (c), which are all directed to the other enantiomer. Ex. 2020 at ¶¶79-81.

Despite the alleged disclosure in Phares' that enantiomers of the disclosed compounds can be prepared using the proper chiral reagents, Phares itself teaches that treprostinil can be prepared in other ways that do not include steps (a) and (b), including the processes disclosed in US Patent Nos. 4,306,075 (Ex. 2032) and 5,153,222 (Ex. 2033). Ex. 1005 at 11; Ex. 2020 at ¶78. Thus, a POSA would reasonably conclude that the diethanolamine salts of Phares were prepared based on other disclosed methods that do not require steps (a) and (b). Ex. 2020 at ¶78. If the diethanolamine salts of Phares were prepared differently than the recited process steps, nothing in Phares establishes that the diethanolamine salts are necessarily the claimed product.

B. The Proper Construction of a “product comprising a compound [of/having] formula [I/IV] or a pharmaceutically acceptable salt thereof” Precludes A Finding That Phares Anticipates the Present Claims

The Board's institution of Ground 1 was partly based on its preliminary finding that “comprising” does not exclude impurities that may possibly be produced by the process of Phares and that the impurity profile of Phares' diethanolamine salt is identical to that of the claimed product. *See* Paper 12 at 30. However, such a finding does not take into consideration the reasonable construction of “product comprising a compound [of/having] formula [I/IV] or a

pharmaceutically acceptable salt thereof,” which is set forth in this Response and supported by the record now before the Board.

As discussed above in Section IV, both the specification and the prosecution history of the '393 patent distinguish the claimed product from prior art treprostinil products based on its higher purity and different impurity profile, which is achieved through the recited process steps. Thus, to prevail on Ground 1, SteadyMed must show that the Phares' diethanolamine salt necessarily possesses an impurity profile that is distinct from that of the Moriarty product and with higher purity.

Steadymed simply assumes that the diethanolamine salt discussed by Dr. Winkler is prepared from Moriarty treprostinil and does not acknowledge that the source of treprostinil would impact both the overall purity and impurity profile of the resulting salt. As exemplified in the '393 patent, the claimed process provides an improved treprostinil product due to its superior purity. As evidenced by the Williams Declaration and the batch record data, the claimed product has an average purity of [REDACTED] and a distinct impurity profile from Moriarty's product. Ex. 2020 at ¶¶94-99. Importantly, SteadyMed has failed to show that, at a minimum, the Phares' diethanolamine salt possesses an impurity profile that is distinct from that of the Moriarty product and contains fewer overall impurities than the Moriarty product. Nor has SteadyMed shown that the Phares'

diethanolamine salt has a higher purity than the Moriarty product. Indeed, SteadyMed's only argument regarding the purity of Phares' diethanolamine salt is based on the theory that the higher melting point of Phares' diethanolamine salt necessarily means that it must be at least equal in purity to that of the exemplified batches in the '393 patent. *See* Petition at 27-28. However, for the reasons noted below, that is an incorrect conclusion based on the evidence now in the record.

C. The Higher Melting Point of Phares' Diethanolamine Salt Does Not Necessarily Mean That it is of Higher Purity Than the Diethanolamine Salts of the '393 Patent

The Board relied on incorrect statements in the Winkler Declaration alleging that Phares' diethanolamine salt must be more or at least equally pure as the claimed product solely because the former has a higher melting point. Paper 12 at 28-29. However, melting point is just one factor in assessing a compound's purity and is not necessarily a reliable metric of purity. This is especially applicable to Phares because only one melting point value was obtained in a sample for a polymorph screen. A POSA would not rely upon a single melting point value, absent any other impurity information, to determine the purity of a substance made under unspecified conditions. Ex. 2020 ¶76. Indeed, the "higher" melting point of Phares' diethanolamine salt could be indicative of the inclusion of impurities or the result of the use of different solvent systems for the crystal forms. *Id.* Accordingly,

the purity of a compound cannot be assessed based solely on its melting point value.

Moreover, even if the melting point could be relied upon, the data cited by Dr. Winkler does not indicate a product of high purity. To the contrary, Fig. 21 of Phares “shows a broad melting peak with a range of close to 10 degrees which is indicative of a lower purity substance.” Ex. 2020 ¶76; *see also*, Marti, E., *Purity determination by differential scanning calorimetry*, *Thermochimica Acta*, 5(1972) 173-220 at 214 (“The melting of diphenyl is extremely sharp because of the purity level; on the other hand, the melting region of phenacetin-benzamide is rather broad.”) (Ex. 2031).

Additionally, Phares discloses several different conditions for preparing Polymorph A of the diethanolamine salt and that Polymorph A is required to make Polymorph B. Ex. 2020 at ¶73. The '393 patent does not indicate that making Polymorph A first is required. *Id.* Phares also indicates many conditions used to make Polymorph A and Polymorph B, but it is not clear what conditions were specifically used for the sample analyzed in Figure 21 that Dr. Winkler relies upon. *Id.* at ¶¶73-74. It is well known that the use of different solvent systems in forming different crystal forms can have a significant effect on the melting point of a substance, as well as other characteristics, including purity, and a higher melting point does not always mean a higher purity. *Id.* at ¶¶75-76; *see also* R. Adhiyaman,

et.al., *Crystal modification of dipyridamole using different solvents and crystallization conditions*, Int'l J. Pharm.321 (2006) 27-34 at 33 (“Adhiyaman”) (“In conclusion, it can be said that the crystallization conditions and medium used have major effect on dipyridamole crystals habit modification under ambient conditions. The crystals showed significant changes in the shape, size, melting points, dissolution rate, XRD patterns and DSC curves.”) (Ex. 2030).

Dr. Williams, therefore, has concluded that “[i]t is known in the art that sample size, rate of heating, the recrystallization solvent(s) used, and the conditions under which the crystalline sample was obtained can significantly affect the DSC data. Dr. Winkler’s conclusion based on this single vague and incompletely described DSC data is not scientifically sound.” *Id.* at ¶76.

Thus, nothing in Phares establishes that the disclosed diethanolamine salt is at least of equal purity to the diethanolamine salts of the '393 patent. With respect to claim 2 of the '393 patent specifically, nothing in Phares discloses a purity of at least 99.5%. Ex. 2020 at ¶82. For this additional reason, Phares cannot anticipate claim 2.

D. Phares Fails To Disclose the Claimed Process for Making Treprostinil or Any Purity or Impurity Profile for Treprostinil Diethanolamine

SteadyMed has failed to establish that Phares’ diethanolamine salt (Form B) is the claimed product.

First, as Dr. Williams notes, the samples of trestatinil diethanolamine disclosed in Phares were “made for a polymorph screen, not large scale batches.” Ex. 2020 ¶73. Accordingly, “the samples of polymorph B described in Phares are prepared in a completely different way under different conditions than those described in the ’393 patent.” Ex. 2020 ¶75. Specifically, Phares discloses first preparing polymorph A by any one of a variety of methods and then preparing polymorph B from some sample of polymorph A. In contrast, the ’393 patent makes no mention of first forming polymorph A. Ex. 2020 ¶¶73-74. Additionally, Phares describes reaction conditions for making the polymorph samples that are not described anywhere in the ’393 patent. *Id.* In particular, the reaction conditions disclosed for the sample of polymorph B characterized by Phares, heated slurries of form A in 1,4-dioxane and toluene, are not described anywhere in the ’393 patent. *Id.* It is well-known that the use of different reaction conditions, including different solvents, can significantly affect the characteristics of a given crystal form. Ex. 2020 ¶75. As a result, the diethanolamine salt disclosed in Phares cannot be directly compared to the diethanolamine salt disclosed in the ’393 patent.

Second, the Williams Declaration clearly establishes that the claimed product has an average purity of [REDACTED], thus giving it a superior purity and distinct impurity profile over that of the prior art trestatinil products. Ex. 2020 ¶¶94-99. The purity of the claimed product provides a structural difference from the prior art

treprostinil, as evidenced by the differences in the average impurity profiles for the Moriarty product and the '393 product. *Id.*, Ex. 2036, Ex. 2037. Indeed, the higher purity of the claimed product resulted in FDA approving a new purity specification for the treprostinil drug as noted in the January 2009 letter submitted to FDA by UTC. Ex. 2006 at 4-6; Ex. 2022 at ¶¶70-72; Ex. 2020 at ¶91.

The impurity profile of the *starting* treprostinil acid used to prepare the Phares diethanolamine salt is crucial to assess whether the diethanolamine salt is the same as the claimed product, *i.e.*, whether the impurity profile of the diethanolamine salt in Phares is identical to that of the claimed product. Ex. 2020 ¶¶76-78. However, nowhere does Phares disclose the process of preparing the treprostinil acid used to prepare the diethanolamine salt. As acknowledged in both Phares and the '393 patent, several different processes can produce treprostinil acid. *See, e.g.*, Ex. 1005 at 11; *see also*, Ex. 2020 ¶78. Each known process can produce a treprostinil acid with a unique impurity profile. Ex. 2020 ¶78. Because Phares does not disclose the process of preparing the starting treprostinil acid for the diethanolamine salt, the impurity profile of the diethanolamine salt cannot be established. Without knowing the impurity profile and level of purity of Phares' diethanolamine salt, SteadyMed cannot show that it is necessarily identical to the claimed product or has equal purity to the claimed product.

Consequently, SteadyMed has not carried its burden on Ground 1.

VI. GROUND 2: MORIARTY AND PHARES FAIL TO RENDER OBVIOUS CLAIMS 1-5, 7-9, 11-14, OR 16-20

Moriarty does not teach salt formation and regeneration of the free acid. SteadyMed attempts to cure this deficiency in Moriarty by citing Phares for allegedly teaching step (c). However, Moriarty teaches three distinct methods of preparing the treprostinil free acid. Nothing in Moriarty directs a POSA to select one specific process over the three disclosed for purposes of further modification by adding a salt formation step. Furthermore, SteadyMed fails to recognize that the performance of step (c) after steps (a) and (b) unexpectedly results in a product with an improved average purity over that of the prior art. Indeed, the Williams Declaration demonstrates that, out of 122 samples, the claimed product has an average purity of greater than [REDACTED]. Ex. 2020 at ¶¶94-95 and Appendices A-B.

As discussed above, the claimed product is structurally different from Moriarty's product because the claimed product has a distinct impurity profile, including a marked reduction in several specific impurities, and a higher average purity relative to Moriarty's product. Ex. 2020 at ¶¶94-99 and Appendices A-B. This evidence shows that, in the recited combination, performing step (c) in conjunction with steps (a) and (b) of the present claims produces a treprostinil product that is significantly improved over that of the prior art. Ex. 2020 at ¶¶48-49, 70.

Moreover, Moriarty's product cannot render obvious the claimed product because during prosecution of the '393 patent, UTC overcame a rejection based upon Moriarty by providing evidence of representative sample impurity profiles, showing the physical difference between the product of the '393 patent and the Moriarty product. Ex. 1002 at p. 347. Phares does not cure this deficiency because, as noted above, nothing in Phares establishes that the diethanolamine salt either 1) has an impurity profile similar to the claimed product or 2) has an overall purity at least equal to the claimed product.

In particular, it would not have been obvious to use the salt formation step of Phares to decrease amounts of at least [REDACTED] and [REDACTED], which are stereoisomers of treprostinil, and accordingly, are acidic rather than neutral or basic. Ex. 2020 at ¶102. Thus, when subject to salt-forming conditions, a POSA would expect that any undesired stereoisomer of treprostinil would be included in the final salt product because the stereoisomer would also be converted to the corresponding salt under such salt-forming conditions. A POSA has no reasonable expectation of success in removing any undesired treprostinil stereoisomer impurities by salt formation and subsequent regeneration of the free acid. *Id.* Instead, a POSA would expect the salt formation and subsequent regeneration to produce a final product with the same initial amount of stereoisomer impurities before the salt formation step. *Id.* Yet these impurities are each detected in only a single optimization batch

of the '393 product, and in none of the commercial batches. Even taking these optimization batches into consideration, this represents a greater than 100-fold reduction as compared to the Moriarty product. *Id.* at ¶¶94-96.

Additionally, as described above, there is no basis for comparing the “purity” in Moriarty with the purity described in the Walsh Declaration. *Id.* at ¶88. Walsh’s Declaration makes clear that purity in terms of the '393 patent is assessed by looking to the total related substances of a batch. *Id.* at ¶¶88-89. The Moriarty reference, while not specifying a reference standard, does refer to a comparison to an authentic sample. *Id.* As a result, it is not clear what method was used to determine the purity in Moriarty and therefore a direct comparison of the value reported in Moriarty cannot be made to the '393 patent.

Moreover, Dr. Winkler fundamentally misunderstands the error associated with various purity measurements used in the Walsh Declaration, the '393 patent, the prior art, and FDA. Dr. Winkler states in his declaration that:

even a difference of 0.4% as discussed below, between the claimed processes of the '393 Patent and the prior art, such as Moriarty (Ex. 1004), would be attributable to experimental error, and thus the claimed degree of purity under the claimed processes of the '393 Patent presents no distinction from the prior art.

Ex. 1009 at ¶69.

He goes on to state that “HPLC’s precision indicates that the ‘RSD’ or ‘relative standard deviation’ for a typical instrument is about 1%.” *Id.* at ¶70.

This is wrong for several reasons. First, during his deposition, Dr. Winkler admitted he did not know what the actual error in the measurement was for the data submitted in the Walsh Declaration during prosecution of the ’393 patent. Ex. 2051 at 62:16-25; 63:2-14.² While he did not know the error associated with the measurements made in the data submitted with the Walsh Declaration, he did admit that “the error in the measurement for the [REDACTED] [treprostinil impurity] would be, should be less than .1 percent,” and in general, “[t]he error should be less than the maximum number reported, that’s correct, for the measurement of the materials described here.” Ex. 2051 at 63:25-64:4; 64:7-16. By his own admission, the error associated with the measurement of impurities in treprostinil batch records such as those submitted in Walsh’s Declaration are therefore far less than the alleged error of 1% or 0.4% he stated in his declaration.

² Indeed, Dr Winkler admitted he was not familiar with FDA guidelines regarding impurity profiles for a drug, did not know what is required in order to change a drug specification, and was not familiar with published guidances from FDA regarding changes to new drug applications or abbreviated new drug applications. Ex. 2051 at 19:3-24.

In contrast, FDA requires that impurity determinations must be measured at or below 0.05% for drugs such as treprostinil. *See*, Ex. 2022 at ¶47; Ex. 2020 at ¶92. As Dr. Ruffolo explains, impurities in drug substances such as treprostinil that are administered in dosages less than 2 grams per day require that impurities be reported if they are present at a level less than or equal to 0.05%. *See, e.g.*, Ex. 2022 at ¶¶44-47; *see also* ICH Impurities in New Drug Substances Q3A(R2) monograph at 5-11 (Ex. 2038). “As a result of these thresholds, by definition, the limit of detection for impurities (and therefore total related substances) must be at least as low as 0.05%.” Ex. 2022 at ¶50.

Furthermore, the '393 patent is directed to an improved and more pure treprostinil product. *See, e.g.*, Ex. 1001, 17:27-40. Given that Moriarty discloses the use of column chromatography for purification, a POSA would not be motivated to create the salt form in Phares, as Phares does not disclose any benefit or increased purity as a result of using the diethanolamine salt. Ex. 2020 at ¶101. “In fact, Phares does not allege that the diethanolamine salt is superior in any way to the treprostinil product of Moriarty and instead identifies other earlier treprostinil disclosures as a means to create the treprostinil used to form the diethanolamine salt.” *Id.* A POSA would not have a reasonable expectation of success by using salt formation as a purification step separate from or in addition to the column chromatography of Moriarty, as Phares does not disclose any alleged

benefit to forming the salt and a POSA would have no expectation that only certain acidic and neutral impurities would be reduced or completely eliminated while others remained. *Id.* at ¶102. Thus, the combination of Moriarty and Phares cannot render obvious claims 1-5, 7-9, 11-14, or 16-20.

Similarly, as described above, there is no basis to compare the purity disclosed in Moriarty to the measurements obtained in the '393 patent or those obtained by Dr. Walsh in his declaration, and therefore, claim 2 would also not be rendered obvious by the combination of Phares and Moriarty for this additional reason. *Id.* at ¶103.

Claims 8 and 16 also require the additional limitation that the formula (VI) compound of step (a) is not purified. In fact, the '393 patent specifically distinguishes this limitation over the prior art. Ex. 1001, Example 6. Moriarty expressly discloses that the compound of formula (VI) from step (a) is purified. Ex. 2020 at ¶104. Phares does not disclose any synthesis for treprostinil and, even in the abbreviated synthesis of the enantiomer, no details of purification are disclosed. *Id.* Thus, claims 8 and 16 are not rendered obvious by the combination of Phares and Moriarty for this additional reason. Process advantages should be considered as secondary considerations to rebut obviousness, even if the process steps or advantages are not considered in the initial determination of whether there is *prima*

facie obviousness (where the products are compared regardless of how they are made).

Consequently, SteadyMed has not carried its burden on Ground 2.

VII. GROUND 3: MORIARTY, PHARES, KAWAKAMI, AND EĞE FAIL TO RENDER OBVIOUS CLAIMS 6, 10, 15, 21, AND 22

A. The Product of Claims 6, 15, and 21 Are Different Than the Prior Art Treprostinil Products

The Board concluded that the process steps of claims 6, 15, and 21, including step (d), do not impart structural or functional differences over prior art treprostinil products. Paper 12 at 46-47.

Based on the evidentiary record now before the Board, and in view of the reasons set forth in Section III, above, the free acid substance formed by step (d) of claims 6, 10, 15, 21 and 22 is structurally different from the prior art treprostinil products in Phares and Moriarty. The evidentiary record shows that the free acid substance of claims 6, 10, 15, 21 and 22 contains a distinct impurity profile and a higher average purity over the treprostinil free acid of Moriarty, and thus is structurally different. Further, Phares' diethanolamine salt of treprostinil is structurally and functionally distinct from the free acid substance formed by step (d) of claims 6, 15 and 21.

1. The '393 Patent Product is Structurally and Functionally Distinct from Moriarty's Product

As explained in the Williams Declaration and discussed above, the free acid substances of claims 6, 10, 15, 21 and 22 are structurally distinct from Moriarty's product because the formation of the salt in step (c) leads to a product that has a distinct and improved impurity profile. *See* Sections III, VI, *supra*. Additionally, the average purity of the product of claim 21 is about [REDACTED] greater than that of Moriarty. Ex. 2020 ¶¶94-99 and Appendices A-B. Indeed, as evidenced by Dr. Ruffolo's Declaration, a [REDACTED] difference in average purity for a highly potent drug, such as treprostinil is a very significant difference. *See, e.g.*, Ex. 2022 at ¶70.

B. There Is No Motivation For A POSA To Combine Moriarty and Phares with Ege and Kawakami

In the Institution Decision, the Board determined "on the record before us, and for purposes of institution, that the process steps recited in claims 6, 15, and 21 do not impart structural or functional differences to the claimed treprostinil product, we do not address the parties' contentions concerning the obviousness of the recited process steps." Paper 12 at 47. However, the fuller record now indicates that the claimed treprostinil product is structurally and/or functionally different from Moriarty's treprostinil free acid and Phares' treprostinil diethanolamine salt. Thus, the recited process steps must now be considered.

Similarly, the board credited Dr. Winkler's opinion regarding the combination of Kawakami and Ege with Moriarty and Phares. Paper at 42. Dr. Winkler, however, too easily dismisses the complexity and difficulty associated with further purifying a drug substance as complex as treprostinil. Dr. Winkler attempts to portray the chemistry involved in the '393 patent as "nothing more than basic organic chemistry techniques – in my view 'organic chemistry 101'" in an effort to minimize the significant invention of the '393 patent. Ex.1009 at ¶3. Yet, Dr. Winkler contradicts himself by defining a POSA as having "a master's degree or Ph.D. in medicinal or organic chemistry, or a closely related field. Alternatively a person of ordinary skill would include a bachelor's degree and at least five years of practical experience in medicinal or organic chemistry." *Id.* at ¶14. Indeed, Dr. Winkler goes on to testify that to understand the science and chemistry of the patent, you would need that level of skill in the art. Ex. 2051 at 29:12-16. As a result, a POSA would not look to an undergraduate textbook like Ege, for example, to figure out improved purification techniques for a complex drug substance such as treprostinil.

1. There Is No Motivation to Follow the Carboxylate Salt Formation With Regeneration of the Carboxylic Acid

The Board credited Dr. Winkler's opinion regarding the combination of Kawakami and Ege with Moriarty and Phares. Paper 12 at 42. Dr. Winkler,

however, too easily dismisses the complexity and difficulty associated with further purifying a drug substance as complex as treprostinil. After first referencing “organic chemistry 101” to minimize the significance of the ’393 patent (Ex. 1009 at ¶3), Dr. Winkler contradicts himself by defining a POSA as having “a master’s degree or Ph.D. in medicinal or organic chemistry, or a closely related field. Alternatively a person of ordinary skill would include a bachelor’s degree and at least five years of practical experience in medicinal or organic chemistry.” *Id.* at ¶14. At his deposition, Dr. Winkler conceded that, to understand the science and chemistry of the ’393 patent, you would need this higher level of skill in the art. Ex. 2051 at 29:12-16. As a result, a POSA would not look to an undergraduate textbook like Ege, for example, to figure out improved purification techniques for a complex drug substance such as treprostinil.

As explained previously, the claimed free-acid compounds, including treprostinil, produced by the processes of claims 6, 10, 15, and 21 provide a new product that induced FDA to adopt a new purity standard for treprostinil free acid due to the excellent purity of the final product. Furthermore, UTC demonstrated that treprostinil free acid made by the claimed methods provides a compound that lacks or reduces the levels of the impurities found in the free acid treprostinil of the Moriarty process.

Neither Phares nor Ege provide a reason that a POSA would include a “carboxylate salt formation and regeneration of the neutral carboxylic acid” step. *See* Petition, p. 54. Phares merely discloses forming a salt from treprostinil free acid of undisclosed origin. *See* Section V.E., *supra*. There is no suggestion that this salt should then be converted *back* to the free acid (*e.g.*, there is no suggestion of using the salt formation as a purification method). “Given that the purification techniques disclosed in Moriarty include chromatography and recrystallization after many years of research to optimize the process of making treprostinil, a POSA would not have been motivated to use a salt purification technique disclosed in an undergraduate chemistry textbook. More importantly, a POSA would not have had a reasonable expectation of success in further purifying the treprostinil product of Moriarty by using such a technique. To the extent a POSA was motivated to further purify treprostinil, a POSA would have focused on the known impurities and investigated methods of removing those.” Ex. 2020 at ¶106. Indeed, stereoisomers were known impurities in treprostinil. *Id.* Ege, however, simply discloses that “carboxylic acids that have low solubility in water, such as benzoic acid, are converted to water-soluble salts by reaction with aqueous base. Protonation of the carboxylate anion by a strong acid regenerates the water-insoluble acid. These properties of carboxylic acids are useful in separating them from reaction mixtures containing neutral and basic compounds.” *Id.* at ¶107.

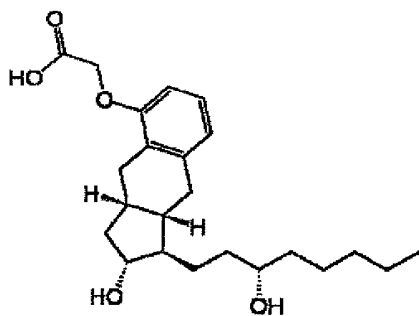
Indeed, the only example given in Ege is of benzoic acid – a very simple aromatic acid that is quite different from the structure of treprostinil, as it has no chiral centers and therefore no stereoisomeric impurities. *Id.* at ¶108. Given that Ege only predicts the removal of neutral and basic compounds by a salt purification step followed by acidification and only describes a simple non-chiral carboxylic acid, a POSA would have no motivation to look to Ege for purification and no reasonable expectation of success given that many of the impurities in treprostinil are acidic stereoisomers. *Id.* at ¶¶108-109.

As discussed above, the average impurities found in samples of the Moriarty product include three different stereoisomers of treprostinil free acid. Ege suggests that a “carboxylate salt formation and regeneration of the neutral carboxylic acid” step would not remove these compounds from the product. Thus, a POSA would have understood Moriarty, Phares, and Ege to suggest simply making the treprostinil free acid product of Moriarty, and not undergoing the additional time and expense of a “carboxylate salt formation and regeneration of the neutral carboxylic acid” step because Ege actually teaches away from the usefulness of this step when impurities include acidic stereoisomers are present because a POSA would have to ignore Ege’s teaching that these types of impurities could not be removed by carboxylate salt formation. *See* Ex. 2020 ¶¶107-109; *see also United States v. Adams*, 383 U.S. 39, 42-43 (1966).

The Institution Decision cites *KSR* for the proposition that “a technique has been used to improve one device, and a POSA would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill.” Paper 12 at 45. However, the simple application of this proposition regarding devices (a predictable art) should not be applied to an unpredictable field, such as the chemical arts, without truly examining whether the technique would improve *similar compounds* in the *same way*. See, e.g., *In re Fisher*, 427 F.2d 833, 839 (C.C.P.A., 1970)(contrasting “predictable factors, such as mechanical or electrical elements” from “unpredictable factors, such as most chemical reactions”); see also, *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008).

For example, Kawakami teaches purification of a methanoprostacyclin derivative by forming the dicyclohexyl amine salt and then regenerating the free acid to achieve a “fairly high” purity. Analogizing to the language cited from *KSR*, a POSA must have recognized that the “technique” of salt formation followed by regeneration of the free acid would improve *similar compounds* in the *same way*.

However, as can be seen by the below comparison, the structures of treprostinil and the methanoprostacyclin derivative of Kawakami are structurally very different – they are not *similar compounds/devices*.



Treprostinil



methanoprostacyclin compound in Kawakami

First, the methanoprostacyclin compound in Kawakami is a two-fused-ring structure, while treprostinil is a three-fused-ring structure. Ex. 2020 at ¶112.

Second, Kawakami does not actually disclose a purification method for separating diastereomers, but instead one for separating E and Z isomers. Ex. 2020 ¶¶112-113.

Indeed, Kawakami teaches that the starting material does not vary at each chiral center other than the alkene double bond. *Id.* In other words, Kawakami discloses a mixture of two compounds: (1) the E-isomer of a stereoisomerically pure compound and (2) the Z-isomer of a stereoisomerically pure compound. *Id.* at ¶113. Treprostinil contains no mixture of E and Z isomers because it does not contain a carbon-carbon double bond that is capable of forming E and Z isomers. Indeed, the use of a specific salt to isolate a specific E/Z isomer does not reasonably suggest that salt formation of a much more complex compound with

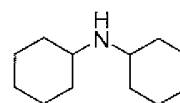
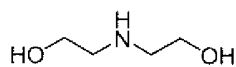
multiple chiral centers such as treprostinil could be isolated from entirely different impurities and then converted back to the free acid form. *Id.*

Thus, the purification of treprostinil from its stereoisomers and related impurities is quite different from the purification of the methanoprostacyclin derivative from its structural isomer – the compositions are not improved in the *same way*.

As a result of these differences, “a POSA would not have looked to Kawakami (or Ege) if they were looking for additional purification techniques for treprostinil because neither reference discloses how to remove stereoisomeric impurities.” *Id.* at ¶112.

2. Kawakami Would Have Motivated One of Ordinary Skill In The Art To Select A Dicyclohexyl Amine Salt, Teaching Away From The Diethanolamine Salt of Claims 14 and 18

Not only are there structural differences between treprostinil and the “methanoprostacyclin compound” in Kawakami, but the counter-ion used to prepare the salt is structurally different. *Id.* at ¶114. Specifically, Kawakami teaches preparing the dicyclohexyl amine salt, whereas particular claims of the '393 patent require use of the diethanolamine salt.



Diethanolamine

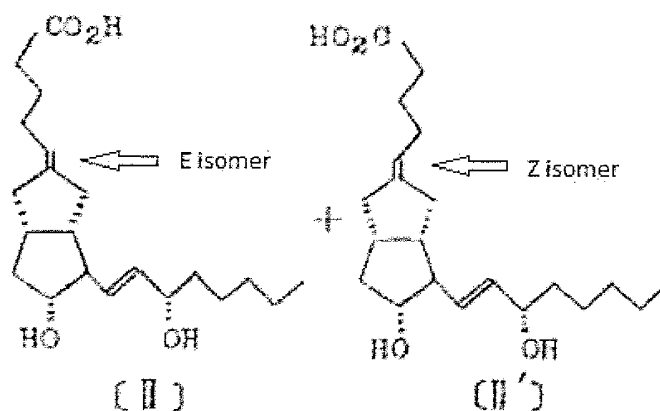
dicyclohexyl amine

Because Kawakami uses a different salt to remove a different sort of impurity from a different structure, a POSA would have no reason to combine the teachings of Kawakami with Moriarty and Phares in the particular manner of the asserted grounds in the Petition, or a reasonable expectation of success of achieving a more pure treprostinil product by such a combination. Ex. 2020 ¶¶114. For this reason, claims 14 and 18 are separately patentable.

3. Kawakami Does Not Provide A Reasonable Expectation Of Success That Treprostinil Products Could Be Further Purified Because Different Impurities Are Targeted

The purification of treprostinil from its stereoisomers and related impurities is quite different from the purification of the methanoprostacyclin derivative from its structural isomer, and thus, Kawakami provides no reasonable expectation of success. Ex. 2020 ¶¶112-114

To illustrate this point further, Kawakami is directed to purifying E- and Z-isomers of methanoprostacyclin compound from one another. In order for the E- and Z-isomers to exist, the “prostacyclin compound” must have an alkene. For example, Kawakami discusses separating a mixture of the following compounds:



Treprostinil, on the other hand, contains no mixture of E/Z isomers. In fact, it cannot because it does not contain an alkene capable of E/Z isomerization. SteadyMed has failed to provide a factual basis as to how or why the separation of E/Z isomers of an alkene would provide a motivation to combine or reasonable expectation of success in a compound not containing an alkene capable of E/Z isomerization, such as treprostinil. As explained in the Williams Declaration, the use of a specific salt to isolate a specific E/Z isomer does not reasonably suggest that salt formation of an entirely different compound, such as treprostinil, could be isolated from entirely different impurities, such as stereoisomers and related impurities. Ex. 2020 ¶¶112-114.

Furthermore, the Kawakami reference would have provided no motivation or rationale to attempt to remove the trace impurities of the Moriarty treprostinil free acid through the process of salt formation followed by conversion back to the

free acid. Indeed, Kawakami was concerned with isolating a particular isomer from a 7:2 E/Z isomeric mixture. Ex. 1007 at 4. In other words, the composition in Kawakami contained, at most, a purity of 77.8% prior to the salt formation step. Kawakami provides a crude purification of the desired E-isomer through a particular salt formation, and suggests that not all impurities were removed by formation of a salt and conversion back to the free acid. *Id.* at 5 (“purity can be further improved by recrystallization”). Nothing in the reference suggests that a substance as pure as the Moriarty treprostinil free acid (a substance with about 99.4% assay purity) – a substance that had already been “further improved” by recrystallization (*see* Ex. 1004 at 13, right column) – would be improved by formation of a salt and conversion back to the free acid. Ex. 2020 ¶¶113-114.

Thus, even if formation of a salt and conversion back to the free acid was known in the art, it would not have rendered the present claims obvious without some motivation and expectation of success in its use on the Moriarty treprostinil free acid. To put it another way, there would have been no reason to incur additional time and expense to form a salt of the valuable, relatively pure Moriarty treprostinil free acid only to then convert it back to the free acid, even though the addition would have been technologically possible. *In re Omeprazole Patent Litigation*, 536 F.3d 1361 (Fed. Cir. 2008).

4. Any “Close” Structural Similarity of the Moriarty Free Acid Does Not Render the Claims Obvious

As explained above, the claimed substance is structurally different from Moriarty’s treprostinil free acid because the claimed substance has an improved and different impurity profile. Even if the Board views an improvement in impurity profile of, e.g., [REDACTED], as a close relationship between the substances of the present claims and of Moriarty, there is no obviousness because there was not a known or obvious process for making the claimed free acid substance. *See In re Hoeksema*, 399 F.2d 269, 274 (C.C.P.A. 1968)(“the absence of a known or obvious process for making the claimed compounds overcomes any presumption that the compounds are obvious based on close relationships between their structures and those of prior art compounds”). For the reasons set forth in the previous sections, conducting a salt-formation purification step on the known treprostinil free acid of Moriarty would not have been obvious, so the mere existence of a “close relationship” in the products cannot be used to deny patentability.

5. Additional Claim Limitations Are Not Disclosed by the Cited Prior Art

In addition to the reasons above, certain dependent claims would also not have been obvious in light of the combination of Phares, Moriarty, Ege, and Kawakami. Claim 6 requires the acid in step (d) to be either HCl or H₂SO₄ and

claim 15 requires the acid to be HCl. Similarly, claim 21 requires step (d) is performed. Phares, Moriarty, and Kawakami all do not disclose the use of either HCl or H₂SO₄ and do not disclose converting a carboxylic acid salt back to its salt form using an acid. Ex. 2020 at ¶115. “Ege cites HCl as an example in the conversion of benzoic acid, but as described above, a POSA would not have looked to Ege to further purify a complex carboxylic acid such as treprostinil from its stereoisomers and other impurities and would have no reasonable expectation of success by using HCl based on this disclosure.” *Id.* In addition to the reasons above, claims 6, 15, and 21 would not be obvious in light of any combination of the cited prior art.

Like claim 2, claim 10 requires that the product be 99.5% pure and that step (d) be performed. The only purity limitation disclosed in any cited prior art reference is in Moriarty and, as explained above, that purity cannot be directly compared to the purity recited by the claims. Similarly, Moriarty does not perform steps (c) or (d). *Id.* at ¶116. A POSA would have no motivation to look to Phares, Kawakami or Ege to improve the purity to at least 99.5% and, given that none of these references disclose a purity amount, would have no reasonable expectation of success in achieving that purity. *Id.* Finally, claim 22 requires an extra step of forming a pharmaceutically acceptable salt from the product of step (d). SteadyMed and Dr. Winkler cite no evidence whatsoever for this additional step.

“In fact, none of the references cited even suggest converting a carboxylic acid to a salt form, then regenerating the carboxylic acid, then forming a pharmaceutically acceptable salt from that.” *Id.* at ¶117. For this additional reason, claim 22 is not obvious in light of the combination of Phares, Moriarty, Kawakami, or Ege.

Consequently, SteadyMed has not carried its burden on Ground 3.

VIII. SECONDARY CONSIDERATIONS REBUT ANY POSSIBLE CASE OF OBVIOUSNESS

SteadyMed has not established a *prima facie* case of obviousness. Thus, UTC is not obligated to provide evidence of objective indicia of non-obviousness. Nonetheless, objective indicia of non-obviousness confirm that the claims of the '393 patent would not have been obvious and, in fact, represent a surprising solution to the problem of minimizing impurities and providing a safer and purer treprostinil product.

A. Long-Felt Unmet Need

At the time of the invention, there was a long-felt need to have a more efficient synthesis to produce treprostinil in a more pure form and in a cost-effective manner. *See generally*, Ex. 2022 at ¶¶31, 65. Treprostinil has five chiral centers resulting in 32 possible diastereomers, so the potential for diastereomeric impurities is high; only the treprostinil stereoisomer has the desired pharmaceutical effect. Ex. 2013, at pp. 11, ll. 18-25, pp. 15, ll. 1-pp. 16, ll. 8, pp. 19, ll. 14-25.

Treprostinil is also a very potent drug so any diastereomeric impurities would also potentially be potent. *Id.*; Ex. 2022 at ¶54. Specifically, the FDA as a matter of course seeks to minimize all impurities in drug substances and particularly in highly potent drug substances such as treprostinil. Ex. 2022 at ¶¶ 31, 54. The reduction and removal of several types of impurities met the long-felt need expressed by the FDA to minimize impurities as much as possible. *Id.* at ¶¶ 31, 75. Additionally, because the '393 patent product was so successful, it resulted in a change in the drug specification submitted to FDA. *Id.* at ¶¶66-67. The change indicated that the assay purity of the new drug substance made by the '393 patent process increased in purity from an assay range of ██████████ to ██████████ ██████████ - a full ██████████ increase in assay purity. *Id.* at ¶ 70. The range of assay values of ██████████ as well as the amount above 100% does not indicate an error associated with the measurement, but just the acceptable value of this measurement approved by the FDA. *Id.* at ¶¶ 69-70. The fact that UTC submitted a ██████████ increase in assay purity to FDA is considered a "major" change by FDA. *Id.* at ¶ 72. *See Knoll Pharm. Co., Inc. v. Teva. Pharm. USA, Inc.*, 367 F.3d 1381, 1385 (Fed.Cir. 2004) (while FDA approval is not determinative of nonobviousness, it can be relevant in evaluating the objective indicia of nonobviousness). In fact, even a change as small as 0.1% of impurities can have an impact on a drug substance. *See, e.g., id.* at ¶¶ 32, 45. Given that FDA consistently wants drug substances to have fewer

impurities and in less amounts, the '393 patent invention met that need by further reducing and removing certain specific impurities and by increasing the overall assay purity of the drug substance.

B. Unexpected Results

The results of the claimed inventions in the '393 were unexpected. The use of a salt form of treprostinil to further purify the treprostinil acid in a cheaper and better way than the previously used methods of purification was an unexpected result. Moreover, it was unexpected that the salt purification step reduced not only diastereomeric impurities, but also certain non-acidic impurities as well. *See, supra*, Section XI.B.1; Ex. 2020 ¶¶94-97, 102, 108-109. Indeed, Ege itself predicted that a salt formation followed by regeneration using an acid would remove only basic and neutral impurities. *Id.* at ¶107. The unpredictability of this result is supported by the fact that the salt purification step did not reduce all non-acidic impurities; in fact, the '393 product has slightly increased levels of one such impurity, [REDACTED]. Ex. 2020 ¶96. Thus, a person of skill in the art would not have expected the results of the '393 patent to be so successful at reducing the levels of so many impurities.

IX. Conclusion

For the foregoing reasons, the Board should hold that SteadyMed has failed to carry its burden attacking the patentability of the instituted claims because none

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of the prior art cited by SteadyMed anticipates or renders obvious any claim of the
'393 patent.

Respectfully submitted,

Date: July 6, 2016

/Stephen B. Maebius/
Stephen B. Maebius
Reg. No. 35,264

CERTIFICATE OF COMPLIANCE

This Paper contains 11,230 words according to the word processing program in which it was created, excluding the portions exempted by 37 C.F.R.

¶42.24(a)(1). Accordingly, this Paper complies with the requirements of 37 C.F.R.

§ 42.24(b)(1).

Date: July 6, 2016

Signature: /Stephen B. Maebius/
Stephen B. Maebius

CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of the foregoing Patent Owner Response and accompanying exhibits was served on counsel of record for Petitioner on July 6, 2016 by filing through the Board's PRPS system and by delivering a copy via email to Stuart Pollack and Lisa Haile (the counsel of record for the Petitioner) at the following address:

Steadymed-IPR@dlapiper.com

Date: July 6, 2016

Signature: /Stephen B. Maebius/
Stephen B. Maebius

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

STEADYMED LTD.,

Petitioner,

v.

UNITED THERAPEUTICS CORPORATION,

Patent Owner.

Case IPR2016-00006
Patent 8,497,393

**DECLARATION OF ROBERT M. WILLIAMS, Ph.D., IN SUPPORT OF
PATENT OWNER RESPONSE TO PETITION**

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I have been retained by the law firm of Wilson Sonsini Goodrich & Rosati (“WSGR”) as an expert consultant to United Therapeutics Corporation (“UTC”) in connection with the above-identified matter to provide expert testimony concerning U.S. Patent No. 8,497,393 (“the ‘393 Patent”, Ex. 1001) by Batra *et al.*, entitled “Process to prepare Treprostinil, the active ingredient in Remodulin,” issued on July 30, 2013. At the request of Counsel for UTC, I hereby submit this expert declaration.

I. Qualifications and Background

A. Education and Experience

1. I am a tenured University Distinguished Professor of Chemistry at Colorado State University (CSU). I currently serve as the Director for the Colorado Center for Drug Discovery. I also served as co-Director (Experimental Therapeutics) for the Infectious Diseases Supercluster Initiative and also served as co-Director for the Cancer Supercluster Initiative at CSU. My *curriculum vitae* is attached hereto as Exhibit A (Ex. 2021).

2. I received a B.A. in Chemistry from Syracuse University in 1975, and did laboratory research in the field of synthetic organic chemistry under the guidance of the recent Nobel Laureate Professor Ei-ichi Negishi. In 1979, I received both a Master’s degree and Ph.D. degree in Organic Chemistry from the Massachusetts Institute of Technology (MIT) under the direction of Professor William H. Rastetter. Upon graduating from MIT, I spent one year (1979-80) as a postdoctoral fellow at Harvard University in the laboratories of the Nobel Laureate, the late Professor Robert B. Woodward, whose laboratory was subsequently managed by Professor Yoshito Kishi.

3. Subsequent to my fellowship at Harvard, I served as an Assistant Professor at Colorado State University from 1980–84. I was tenured and promoted early, to the rank of

Associate Professor in 1985, and in 1988, I was promoted to the rank of Full Professor. In 2002, I was named a University Distinguished Professor, which is my current position. University Distinguished Professor is the highest academic rank at Colorado State University, and there are a maximum of twelve University Distinguished Professors at any given time out of a faculty of 1,200. This is a lifetime appointment until retirement, whereupon Emeritus status is granted. In addition to my positions at Colorado State University, I was a Visiting Professor of Chemistry at Harvard University from 1994–95, at which time I was sponsored by Professor Stuart L. Schreiber and taught a sophomore organic chemistry course for pre-medical students, Chem 17. I was also a Visiting Professor of Chemistry at the University of California at Berkeley in 1990 and worked in the laboratory of Professor Peter G. Schultz.

4. I have extensive experience in the field of synthetic organic chemistry and medicinal chemistry with an emphasis on biologically active compounds including anti-tumor agents, heterocycles, antibiotics, anti-fungal agents, anti-viral agents, immunomodulators, amino acids, peptides and alkaloids, among many other classes of biologically active organic substances. My organic chemistry research interests include the total synthesis of novel natural and synthetic products, heterocyclic chemistry, asymmetric synthesis, synthetic methodology, process chemistry, and reaction mechanisms. I have extensive experience in the synthesis, chemistry, conformational analysis, biochemical activity, and biological activity of a range of organic compounds.

5. My research laboratory at Colorado State University has worked extensively on the chemistry and biology of numerous drugs over my career, including Quinocarcin (Quinocarmycin citrate), Tetrazomine, Bioxalomycin, Ecteinascidin 743 (Yondelis® or trabectedin), Renieramycin, Cribrostatin-4, Jorumycin, the Mitomycins, FR900482, FK973,

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FK317, FK228 (Romidepsin), Largazole, Stephacidins A and B, Avrainvillamide, Spirotryprostatins, TMC-95A/B, Rottlerin, and Antimycin, amongst many others.

6. I have been the Principal Investigator on numerous research grants from Federal agencies, such as the National Institutes of Health (NIH) and the National Science Foundation (NSF) as well as from various Foundations, and corporations to synthesize biologically active compounds on both small laboratory scale as well as larger industrial scales.

7. I held a funded research collaboration with the Infectious Diseases Research Institute (IDRI), in Seattle, Washington, to develop several novel adjuvants for the treatment and prevention of autoimmune diseases, infectious diseases and cancer (2010).

8. From 1991-1993, I held a research grant from Symphony Pharmaceuticals, located in Philadelphia, Pennsylvania, to prepare anti-HIV drugs based on inhibition of the HIV protease. I supervised a graduate student who prepared several very potent peptide isosteres that exhibited in vitro activity against HIV.

9. I have taught undergraduate and graduate courses in organic chemistry, organic synthesis, biosynthesis, biological chemistry, drug design, and the synthesis of natural products. I have also lectured at numerous professional conferences, universities, and in corporate R&D laboratories in those areas.

10. I am a Scientific Founder, Acting President, and Chair of the Scientific Advisory Board of Cetya Therapeutics, a company that is developing several drugs, including drugs for the treatment of various cancers, multiple myeloma, autoimmune diseases, and hemoglobinopathies. I also direct all of the process scale synthesis optimization and drug formulation studies being conducted on Cetya's HDAC inhibitors. This includes injectable formulations as well as oral formulations. Specifically, I directed and supervised post-doctoral researchers in my laboratory

(on behalf of Cetya Therapeutics) to formulate the poorly water-soluble drug Largazole, including a myriad of synthetic analogs of Largazole prepared in my laboratory, as a polysorbate-80/ethanol co-solvent excipient system. This formulation has been used in animal studies for obtaining critical dose-escalation and pharmacokinetic data. I have also specifically directed and supervised the formulation of Largazole and related analogs in various PEG-based (polyethylene glycol) excipient systems. This work is currently being conducted in collaboration with oncologist Dr. Douglas Thamm of the Colorado State University Animal Cancer Center, pharmacologist Dr. Dan Gustafson of the Colorado State University Animal Cancer Center, Dr. Kimberly Stegmaier of the Dana-Farber Cancer Institute/Harvard Medical School and Dr. James E. Bradner of the Dana-Farber Cancer Institute/Harvard Medical School. The animal studies commenced in 2010, and the drug formulation studies are being conducted in my laboratory at Colorado State University under my direction.

11. I was a Scientific Founder, Member of the Scientific Advisory Board, and Member of the Corporate Board of Directors for Xcyte Therapies, a company devoted to developing *ex vivo* T-cell therapies for treating cancer, autoimmune, and infectious diseases, including HIV. As a Scientific Founder and Member of the Board of Directors of Xcyte Therapies, I was deeply involved in writing the patents and developing formulation strategies for both topical and injectable drugs based on FK228 (Romidepsin).

12. As a Scientific Founder and Acting Vice-President of Discovery Chemistry of HemaQuest Pharmaceuticals (Seattle, Washington), I have directed the pre-clinical and clinical synthesis, scale-up and formulation studies of several of the companies' drugs. These include both water-soluble drugs and hydrophobic, poorly water-soluble drugs for therapeutic applications in both cancer and hemoglobinopathies. I directed both the medicinal chemistry

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efforts as well as the pre-process optimization work for potential industrial-scale syntheses of our lead drug candidates.

13. In addition, I am a Scientific Founder and member of the Scientific Advisory Board of Sapiientia Therapeutics, located in Philadelphia, Pennsylvania. I am the acting Director of the Medicinal Chemistry, Process Chemistry and Drug Formulation efforts of this company to develop novel small-molecule inhibitors of protein kinase C-delta for autoimmune diseases, cancer and scleroderma. My laboratory has synthesized the first lead compounds, which are protein kinase C-delta (PKC- Δ) inhibitors and are water-insoluble substances. Under my direction we have engaged in early scale-up and route optimization for our leading drug candidates.

14. As a chemist with expertise in structure-activity studies and synthesis of biologically active agents, I have been retained to consult for a number of pharmaceutical and biopharmaceutical companies for both drug discovery and process research applications over the past thirty years. I consulted for Ajinomoto Co., Japan from 2002-2014 in the general area of process chemistry in the manufacture of amino acids, their derivatives, pharmaceutical intermediates and peptide synthesis. I served as a consultant for Cubist Pharmaceutical Company (2000-03) in the general field of antibacterial agents. I consulted for NewBiotics, Inc. (2001-02) in the general fields of anti-infective agents and anti-cancer agents. I consulted for Hoffman-La Roche, Inc. (1989-92) in the field of cephalosporin-fluoroquinolone dual-action antibacterial agents, as well as on a project concerned with inhibitors of diaminopimelic acid (DAP) biosynthesis as potential antibacterial agents. I consulted for W.R. Grace (1985-90) in the area of specialty chemicals and pharmaceutical intermediates process manufacturing and process development. I was a Scientific Founder, Member of the Scientific Advisory Board,

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Consultant and sub-contractor for Microcide Pharmaceutical Co. (Microcide) in their drug discovery and early process research efforts. Microcide was a biopharmaceutical company devoted to developing antibacterial agents against a range of drug-resistant bacterial and fungal infectious diseases. In addition, I have consulted for EPIX Medical, G. D. Searle, Nutrasweet, and Boehringer-Ingelheim, among others. The consulting work I performed for Nutrasweet (1990-1991), was concerned with large-scale manufacturing process chemistry for Aspartame.

15. I was a co-organizer of a special Symposium on process chemistry at The International Chemical Congress of Pacific Basin Societies, PacifiChem 2015 (December 15-18, Honolulu, Hawaii) entitled: "*New Horizon of Process Chemistry by Scalable Reactions and Technology.*"

16. I have directed the research activities of more than sixty PhD students and eighty post-doctoral fellows; most of my former co-workers have gone on to successful careers in the pharmaceutical industry in both process research and medicinal chemistry.

17. I have delivered numerous named and plenary lectures at Universities, corporations, and scientific societies on the synthesis, chemistry, biology, and mechanism of action of numerous classes of therapeutic agents, as detailed in my *curriculum vitae* attached hereto as Exhibit A.

18. I have published more than 315 scientific research articles, authored numerous chapters in books, and have written a well-known textbook on the synthesis of optically active amino acids. I have particular expertise in the large-scale industrial synthesis of amino acids and their derivatives. I am also a named inventor on seventeen issued U.S. patents and published patent applications. My publications and patents are listed on my CV, provided in Exhibit 2021.

19. I currently serve on the Editorial board for *Chemistry & Biology*. I have served as Editor for the *Organic Chemistry Series* published by Pergamon Press and Elsevier (1997-2012), and *Mini Reviews in Organic Chemistry* (Bentham Science). I have also served as an editor for several other journals in the past, including *Tetrahedron: Asymmetry*, *Tetrahedron Publications*, *Amino Acids*, and the *Journal of the American Chemical Society*.

20. I am a member of the American Chemical Society, the Japan Antibiotics Research Association, the International Society of Heterocyclic Chemistry, and the American Association for the Advancement of Science. I am a Member of the University of Colorado Cancer Center, located in Aurora, Colorado. I have served as organizer or co-organizer of numerous scientific meetings and symposia, and served as the Vice President of the International Society of Heterocyclic Chemistry, Chairing the 2003 International Congress of Heterocyclic Chemistry.

21. I serve on the Scientific Advisory Board of Arch Therapeutics, located in Boston, Massachusetts, that is developing self-assembling peptides for wound healing and surgical closure.

22. I have also served on the Scientific Advisory Boards for a number of other companies. I currently serve on the External Advisory Committee for the Puerto Rico Alliance for the Advancement of Biomedical Research Excellence. I was a Scientific Founder, Director of Chemistry, and member of the Scientific Advisory Board for HemaQuest Pharmaceuticals. I was a Founding Scientist and Member of the Scientific Advisory Board of Microcide Pharmaceuticals from 1993 to 1998.

23. I have expertise in drug formulation for injectable, topical and oral medications. I have directed research programs, both through my academic laboratory at Colorado State University as well as through my various consulting engagements and as a research director

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and/or consultant for companies developing medicines for numerous therapeutic indications. I have consulted on many aspects of pharmaceutical drug discovery, development, formulation, and manufacturing. This includes basic discovery and optimization, early process research, large-scale manufacturing, and drug formulation.

24. I have served as a consultant for a number of companies for both drug discovery and process research applications, including, for example, W.R. Grace Company (1985-1990, fine chemicals synthesis); Symphony Pharmaceuticals (1991-1993, anti-HIV drugs); G.D. Searle Co. (1988-1990, memory and learning enhancement agents based on NMDA receptor antagonists); Nutrasweet Co. (1990-1991, artificial sweeteners); EPIX Medical (1993-1997, MRI imaging and contrast agents); Hoffman-La Roche, Inc. (1989-1992, cephalosporin-fluoroquinolone dual-action antibacterial agents); Boehringer-Ingelheim Pharmaceuticals (1992-1993, antiviral agents); Cubist Pharmaceutical Company (2000-2003, macrocyclic peptide antibacterial agents); NewBiotics, Inc. (2001-2002, anti-infective agents and anti-cancer agents); Microcide Pharmaceutical Co. (1993-1998, analogs of macrocyclic anti-fungal agents related to echinocandin, cephalosporins, and quinolones); Xcyte Therapies (1996-2006, T-cell activation); Ajinomoto Co, Japan (2002-2014, amino acids, peptides, and other specialty chemicals); HemaQuest Pharmaceuticals (2006-2014, short chain fatty acids for treating hemoglobinopathies); Sapientia Therapeutics (2012-present, small-molecule inhibitors of protein kinase C-delta); Arch Therapeutics (2010-present, self-assembling peptides for wound healing); and most recently, Cetya Therapeutics (2012-present, histone deacetylase inhibitors as therapeutic agents for treating cancers, multiple myeloma, autoimmune diseases, and hemoglobinopathies).

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25. Under my direction, my laboratory developed the technology for the asymmetric synthesis of amino acids in 1985 that was commercialized by Aldrich Chemical Co. in 1988. My laboratory devised several large-scale (multi-kilogram) process routes for the manufacture of the so-called "Williams Lactone" that has been sold by Sigma-Aldrich Chemical Company since 1988. Early manufacturing was conducted in China by several of my former co-workers at the Chengdu Institute of Organic Chemistry.

26. I have been awarded numerous prizes and awards including the NIH Research Career Development Award (1984-89), the Eli Lilly Young Investigator Award (1986), the Merck, Sharp & Dohme Academic Development Award (1991), an award from the Japanese Society for the Promotion of Science Fellowship (1999), the Arthur C. Cope Scholar Award sponsored by The American Chemical Society (2002), the Multiple Myeloma Research Foundation Senior Award (2010), the ACS Ernest Guenther Award in the Chemistry of Natural Products sponsored by Givoudan and The American Chemical Society (2011), an award from the Japanese Society for the Promotion of Science Long-term Fellowship (2012-2013), and the Organic Synthesis Award from the local Rocky Mountain section of the American Chemical Society (2012).

27. I have testified numerous times as an expert witness in process chemistry patent litigation in the following matters: Great Lakes Chemical *versus* Archimica SPA. Civil Action No. 99-728-JJF; Ranbaxy Laboratories *versus* Abbott Laboratories. Case No. 04 C 8078; Lundbeck *versus* Infosint. 06 Civ. 2869 (LAK); United Therapeutics Corp. *versus* Sandoz, Inc. C.A. Nos.: 12-1617 (PGS)(LHG) and 13-316 (PGS) (LHG); Gilead Sciences, Inc. and Emory University *versus* Cipla, Limited. Civil Action No.: 1:12-cv-06350-RJS; United Therapeutics

Corp. *versus* Teva Pharmaceuticals, USA, Inc. C.A. No.: 3:14-cv-05498 (PGS)(LHG); United Therapeutics Corp. *versus* Sandoz, Inc. C.A. No.: 3:14-cv-05499 (PGS)(LHG).

B. Materials Considered

28. In forming my opinions in this report, I have relied upon my professional experience and personal knowledge. I have also reviewed a number of documents in this case including all documents cited by the SteadyMed and UTC as well as the materials I have cited in this declaration. In this report, I have provided representative citations to exemplary documents that I have relied upon in reaching my opinions. If I am provided additional information or documents in this proceeding, I may offer further opinions regarding the additional information.

II. Legal Standards Provided By Counsel

29. I have been informed by Counsel that, during an *inter partes* review (IPR), a petitioner must prove invalidity by a preponderance of the evidence. Accordingly, I understand that the burden is on a petitioner to prove invalidity, rather than a patent owner to prove validity. I have been informed by Counsel that because each claim defines a separate invention, the validity of each claim in a patent is addressed independently of the validity of the other claims in that patent.

30. I have also been informed by Counsel that the claims of the '393 patent are "product-by-process" claims. I have also been informed by Counsel that when evaluating the validity of a patent claim, the "product" of product-by-process claims must include structural and/or functional differences over the prior art, even if they are not explicitly claimed.

A. The Person of Ordinary Skill in the Art

31. I have been informed by Counsel that a patent is to be interpreted from the perspective of a hypothetical person referred to as the person of ordinary skill in the art ("POSA")

to which the patent pertains. I am further informed that a determination of the level of ordinary skill is based on, among other things, the type of problems encountered in the art, prior art solutions to those problems, rapidity with which innovations are made, sophistication of the art, and the educational level of active workers in the field. I have been informed that in any particular case, every factor may not be present, and one or more factors may predominate. I understand the person of ordinary skill in the art is presumed to know all prior art that is reasonably relevant to the subject matter of the claimed invention.

32. I understand from Counsel that the validity of a patent claim must be assessed from the perspective of a POSA at the time of the invention.

33. Given the complexity of the chemistry involved in the '393 patent, it is my opinion that a POSA with respect to the patent-in-suit would have had, at the time of the claimed invention, a doctorate degree in chemistry, pharmaceuticals, pharmaceutical sciences, medicine, or a related discipline. Alternatively, the POSA may have had a lesser degree in one of those fields, with correspondingly more experience. To the extent necessary, a POSA may have collaborated with others of skill in the art, such that the individual and/or team collectively would have had experience in synthesizing and analyzing complex organic compounds. It is my understanding that a patent is to be interpreted from the perspective of a person of ordinary skill in the art at the time of the patent's priority date.

34. I understand that SteadyMed's expert Dr. Winkler has opined that a POSA would have "a master's degree or a Ph.D. in medicinal or organic chemistry, or a closely related field. Alternatively, a person of ordinary skill would include an individual with a bachelor's degree and at least five years of practical experience in medicinal or organic chemistry." Ex. 1009 at ¶14.

35. All of my opinions regarding validity contained in this report are expressed from the view of a POSA at the time of the priority date of the '393 patent. These opinions apply equally whether my definition of a POSA or Dr. Winkler's is applied.

B. Anticipation

36. I understand from Counsel that anticipation requires that each and every element of a claim is set forth in a single prior art reference, and that these elements are arranged or combined in that reference in the same way as recited by the claim. I further understand from Counsel that if there is any difference between the prior art reference and the claimed invention, there is no anticipation by that reference. Further, I understand that there is no anticipation if the elements disclosed in a prior art reference must be combined with the knowledge of one skilled in the art to achieve the subject matter of the claim. I understand that for a prior art reference to be anticipatory, it must enable a POSA to make or practice the invention without undue experimentation.

37. I also understand from Counsel that if the single prior art reference is missing a claimed feature, the reference may inherently anticipate if that missing feature is necessarily present in the single prior art reference.

38. I also understand from Counsel that if there are structural or functional differences in the product of the product by process claims of the invention from the product of the prior art that arise from the process in which it was made, those differences may be evidence of no anticipation even if those differences are not explicitly claimed.

C. Obviousness

39. I understand from Counsel that obviousness requires that a POSA would have been able to arrive at the claimed invention by modifying a single prior art reference or by

combining two or more prior art references. I also understand from Counsel that obviousness analysis must be conducted from the point of view of a POSA at the time of the invention, and that it is improper to employ hindsight or consider the inventors' own path to the invention as proof of obviousness.

40. Counsel has also informed me that obviousness requires that a POSA would have had a reasonable expectation of success in achieving the claimed invention.

41. I understand from Counsel that four factual issues are relevant to obviousness analysis: the scope and content of the prior art; the level of ordinary skill in the field of the art at the time of the invention; the differences between the claimed invention and the prior art; and various objective indicia of non-obviousness.

42. I understand from Counsel that, in addition to considering the prior art, certain objective indicia may also provide evidence that a claimed invention is not obvious. I am informed by Counsel that these objective indicia, which are also referred to as secondary considerations, may include factors such as commercial success, unexpected results, the resolution of long-felt but previously unmet needs, skepticism by others prior to achieving the invention, failure of others to achieve the invention, praise from others for the invention, and copying by others.

43. I understand from Counsel that, like anticipation, if there are structural or functional differences in the product of the product by process claims of the invention from the product of the prior art that arise from the process in which it was made, those differences may be evidence of non-obviousness even if those differences are not explicitly claimed.

III. Summary of Opinions

44. It is my opinion that the term “product” as it is used in the claims of the ’393 patent should be construed using UTC’s construction: “a substance resulting from a chemical reaction.”

45. It is my opinion that the term “[a] product comprising a compound of formula I/IV or a pharmaceutically acceptable salt thereof” as it is used in the claims of the ’393 patent should be construed using UTC’s construction: “a substance resulting from a chemical reaction constituted primarily of formula I/IV or a pharmaceutically acceptable salt thereof.”

46. It is also my opinion that none of the claims of the ’393 patent are anticipated by or rendered obvious by the prior art.

47. My opinions and the bases for them are based on information that I know, that I have reviewed, and that I am currently aware exists. I reserve the right to supplement or amend my opinions in light of any additional evidence, testimony, or other information that may be provided to me after the date of this declaration. Additionally, I may use the cited materials to assist me in preparing demonstratives such as graphics and animations if I am asked to testify.

IV. The ’393 Patent

48. The ’393 patent is directed to an improved treprostinil product and improved process for making the product. I understand from Counsel that the priority date for the ’393 patent is December 17, 2007.

49. The synthesis of treprostinil is complex as several improvements resulting in improved products are disclosed in the ’393 patent itself. The structure of treprostinil has five chiral centers (stereogenic centers) resulting in 32 possible stereoisomers of treprostinil.

50. The '393 patent has two independent claims: Claims 1 and 9. Claim 1 requires “a product comprising a compound of formula I...or a pharmaceutically acceptable salt thereof,” in which formula I can be several structures including treprostinil. Claim 9 requires “[a] product comprising a compound having formula IV...or a pharmaceutically acceptable salt thereof,” in which is the structure of treprostinil. Both Claims 1 and 9 then specify that the product is prepared by a process comprising (a) alkylating a compound of Formula II or V [a benzindene triol structure] with an alkylating agent to produce a compound of Formula III or VI [a benzindene nitrile intermediate], (b) hydrolyzing the product of formula III or VI of step (a) with a base, (c) contacting the product of step (b) with a base B to form a salt of Formula Is or IVs [indicating a salt form of treprostinil with an HB+ counterion], and (d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula I or IV. Dependent Claim 7 further identifies the specific structure of Formula I of the product of Claim 1 as treprostinil. Because the other possible structures of Claim 1 are not at issue here, I will consider these Claims 1, 7, and 9 together in my analysis. Likewise, I will consider the following dependent claims together that have similar claim limitations.

51. Dependent Claims 2 and 10 provide a further purity limitation. Claim 2 further requires “[t]he product of claim 1 wherein the purity of compound of formula I in said product is at least 99.5%.” Similarly, Claim 10 requires “[t]he product of claim 9, wherein the purity of product of step (d) is at least 99.5%.” Thus, step (d) must be performed in claim 10, but both of these claims require a purity of at least 99.5%.

52. Dependent Claims 3 and 11 provide a further limitation on what alkylating agent may be used. Claim 3 requires the alkylating agent be $\text{Cl}(\text{CH}_2)_w\text{CN}$, $\text{Br}(\text{CH}_2)_w\text{CN}$, or $\text{I}(\text{CH}_2)_w\text{CN}$. Claim 11 requires the alkylating agent be $\text{Cl}(\text{CH}_2)_w\text{CN}$.

53. Dependent Claims 4 and 12 specify what base may be used in step (b). Claim 4 requires the base in step (b) to be KOH or NaOH and Claim 12 requires the base to be KOH.

54. Dependent Claims 5, 13, 14, 17 and 18 specify what the base B in step (c) may be selected from certain specific bases. Claims 5, 13, and 17 limit base B to the group consisting of ammonia, N-methylglucamine, procaine, tromethamine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine. Claims 14 and 18 specify that the base B is diethanolamine.

55. Dependent Claims 6 and 15 specify what acid is used in step (d). Claim 6 specifies the acid is HCl or H₂SO₄. Claim 15 specifies the acid is HCl.

56. Dependent Claims 8 and 16 specify that the process does not include purifying the compound of formula III or VI produced in step (a).

57. Dependent Claims 19 and 20 depend on Claims 1 and 9, respectively. Each dependent claim further specifies the base in step (b) is KOH or NaOH and the base in step (c) is selected from the same group specified in Claims 5, 13, and 17.

58. Claim 21 depends on Claim 1 and requires that step (d) is performed. Claim 22 depends on Claim 21 and further requires that the product comprises a pharmaceutically acceptable salt formed from the product of step (d).

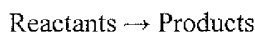
V. Claim Construction

59. I understand from Counsel that different claim constructions for certain terms used in the claims of the '393 patent have been proposed by SteadyMed and UTC, and that the U.S. Patent and Trademark Office ("PTO") has entered a preliminary claim construction for certain terms.

60. I agree with UTC's construction of the term "product" as "a substance resulting from a chemical reaction" which is consistent with the plain and ordinary meaning of the term.

61. In the chemical context, "product" generally refers to the real world outcome or result of a reaction:

Generalized Chemical Reaction



I agree with UTC that the '393 patent itself distinguishes "product" to identify it as what comes at the end of a chemical process or chemical reaction. Prelim. Resp. at pp.17-18.

62. I also agree with the consistent definitions given by the several textbooks cited by UTC all referring to "product" as the result of a chemical reaction. *Id.* at 19.

63. In fact, I have used the term "product" consistently in my own publications to refer to the real world result of a chemical reaction. *See, e.g.,* Williams, et.al., *Asymmetric, Stereocontrolled Total Synthesis of Paraherquamide A*, J. Am. Chem. Soc. 2003, 125, 12172-178. ("However, the reaction was very slow and gave the desired cyclization product 64 in only 25% yield, accompanied by products from competing pathways.") (Ex. 2026); Williams, et.al., *Stereocontrolled Total Synthesis of (+)-Paraherquamide B*, J. Am. Chem. Soc. 1996, 118, 557-579 ("Compound 66 was refluxed in benzene with 20 equiv of sodium hydride, resulting in a very clean and high yielding cyclization reaction furnishing the desired product 68 in 93% yield.") (Ex. 2027); Williams, et.al., *Synthetic Studies on Et-743. Assembly of the Pentacyclic Core and a Formal Total Synthesis*, J. Org. Chem. 73.24 (2008): 9594-9600. ("The scarcity of the natural product from marine sources renders Et-743 an important target for synthesis.") (Ex. 2028).

64. Dr. Winkler also uses the term “product” as the result of a chemical reaction in his own publications and confirmed that understanding during his deposition. *See, e.g.*, Winkler, J., et.al., *A Pauson-Khand Approach to the Synthesis of Ingenol*, *Org. Lett.*, 2005, 8, 1489-1491 at Abstract (“Pauson-Khand cyclization of dioxanone photoadduct 21 leads to the formation of a single product in good yield.”) (Ex. 2029); *see also* Ex. 2051 at 155:12-157:3.

65. Specifically, Dr. Winkler confirmed that “the product of a chemical reaction would be essentially all of the substances that result from the treatment of a particular reactant with a particular set of reagents.” Ex. 2051 at 155:2-11. This is consistent with UTC’s definition as well as how Dr. Walsh interpreted the product in his Declaration submitted during prosecution of the ’393 Patent. Ex. 1002 at 346-347 (showing the products containing certain other substances as impurities).

66. I disagree with the PTO’s preliminary construction and SteadyMed’s construction of “product” as “a chemical composition.” I believe that this proposed definition is too broad and does not accurately describe the term as it is customarily used in the art and in the context of how it is defined in the ’393 patent. In the chemical context, there can be no “product” if there is no corresponding reaction, process, or synthesis that it refers to. A “chemical composition” could be used to describe the starting materials, solvents, reagents, catalysts, and even the glassware used during a chemical reaction as there is no limitation on SteadyMed’s construction of the term “product” on how it relates to the chemical reaction at issue.

67. In the ’393 patent and each of the references I describe above, the word “product” is exclusively used to describe a substance resulting from a chemical reaction, and it is not used to describe any and all “chemical compositions.”

68. SteadyMed's construction is therefore inconsistent with the understanding of a POSA and inconsistent with the '393 patent specification regarding the term "product" because "a chemical composition" is not an accurate and specific definition of the term.

69. For the reasons I previously described regarding the term "product", a POSA would understand the plain and ordinary meaning of the claim term "A product comprising a compound of formula I/IV or a pharmaceutically acceptable salt thereof," as UTC's construction: "a substance resulting from a chemical reaction constituted primarily of formula I/IV or a pharmaceutically acceptable salt thereof." This definition is consistent with how a POSA would understand the term and is consistent with its plain and ordinary meaning.

70. I disagree with the PTO's preliminary construction and SteadyMed's construction of "[a] product comprising a compound of formula I/IV or a pharmaceutically acceptable salt thereof" as "a chemical composition that includes, but is not limited to, a compound of Formula I, or a pharmaceutically acceptable salt thereof, and that may also include other non-mentioned substances (including impurities), additives, or carriers, without limitation as to the types of or relative amounts thereof." I believe that this proposed definition is too broad and does not accurately describe the term. The entirety of the '393 patent is directed to an improved product with lower amounts of impurities and therefore the product includes its own impurity profile which provides a high level of purity and does not indiscriminately include other substances and impurities "without limitation as to the types of or relative amounts thereof."

VI. Phares Does Not Anticipate Claims 1-5, 7-9, 11-14, or 16-20 of the '393 Patent

71. I have reviewed Dr. Winkler's opinions alleging that Phares (Ex. 1005) inherently anticipates Claims, 1-5, 7-9, 11-14, and 16-20. I have also reviewed the Institution Decision in which the Board credited Dr. Winkler's opinion regarding this lack of physical differences

between the treprostinil products of the '393 patent and Phares. Paper 12 at 23-31. I disagree. Additionally, the Board credited Dr. Winkler's opinion that Phares discloses the same process for synthesizing treprostinil as the '393 patent. Paper 12 at 29-30. This is not true. Because no synthesis of treprostinil is disclosed in Phares, the diethanolamine salt described would have an unknown impurity profile and therefore cannot anticipate any claim of the '393 patent.

A. The Product Disclosed in Phares is Physically Different Than the Products Disclosed in the '393 Patent Claims

72. In order for Phares to anticipate any claim of the '393 patent, Phares must disclose every claim limitation of the product. Phares does not disclose the same product as claimed in the '393 patent.

73. Contrary to Dr. Winkler's opinion, the polymorph form and purity of the treprostinil diethanolamine salt is not the same as that claimed in the '393 patent. Specifically, Phares discloses samples made for a polymorph screen, not large scale batches. *See, e.g.*, Ex. 1005 at 85-86. In fact Phares notes several different conditions to form polymorph A including preparation using fast evaporation, slow evaporation, freeze drying, heating, and slow cooling in a variety of solvent systems including water and ethanol; water, toluene, and tetrahydrofuran. *Id.* Once polymorph A is prepared, Phares then further states that polymorph form B must be made from polymorph A, listing several conditions under which polymorph B is prepared. *Id.* Phares further notes that the polymorph B sample that was used for characterization was made from heated slurries of form A in 1,4-dioxane and toluene. *Id.* at 87. In fact, it is not clear which sample of polymorph form A was further used to create the characterized sample of polymorph B that Dr. Winkler discusses. Ex. 1009 at ¶¶58-61.

74. The '393 patent does not discuss that polymorph A must be formed first. *See, e.g.*, Ex. 1001 at col. 12-13 and 15. The '393 patent also does not describe the use of 1,4 dioxane or toluene and only describes forming the diethanolamine salt followed by cooling and filtering the salt with ethyl acetate and ethanol, and then drying. *Id.* Thus, the treprostinil diethanolamine salt formed in Phares required an extra step to first form polymorph A, under different reaction conditions with different solvents.

75. It is well-known that the use of different solvent systems in forming different crystal forms can have a significant effect on the melting point of a substance as well as other characteristics including purity. *See, e.g.*, R. Adhiyaman, et.al., *Crystal modification of dipyridamole using different solvents and crystallization conditions*, Int'l J. Pharm.321, 2006, 27-34 at 33 (“Adhiyaman”) (“In conclusion, it can be said that the crystallization conditions and medium used have major effect on dipyridamole crystals habit modification under ambient conditions. The crystals showed significant changes in the shape, size, melting points, dissolution rate, XRD patterns and DSC curves.”) (Ex. 2030). Given that the samples of polymorph B described in Phares are prepared in a completely different way under different conditions than those described in the '393 patent, their melting points and other analytical data cannot be directly compared.

76. Furthermore, the only data that Dr. Winkler relies upon to conclude that the polymorph B sample of treprostinil diethanolamine salt in Phares has a “higher purity than the '393 product” is that the recorded melting point was higher in one sample than the melting point of the diethanolamine salt sample of the '393 patent. Ex. 1009 at ¶¶ 59-60. This is incorrect for several reasons. First, as mentioned above, the different solvents and conditions used to form the salt can greatly affect the melting point – which is the only purported evidence

that Dr. Winkler cites for purity. Second, there is absolutely no actual purity data disclosed in Phares for the diethanolamine salt or treprostinil free acid and a POSA would not have concluded based on a single melting point example of polymorph B prepared under unknown conditions (e.g., recrystallization solvent and recrystallization conditions are not identified) would be of a higher purity than the known purity of the '393 patent. Third, even if the diethanolamine salt samples were prepared under the same work-up and purification conditions, a higher melting point does not mean that the substance must be of a higher purity. *See*, Ex. 2030 at Fig. 5 showing modified crystals in several different solvents had a higher melting point than the pure dipyrindamole). Fourth, the DSC curve cited by Dr. Winkler in Fig. 21 of Phares (Ex. 1009 at ¶59) shows a broad melting peak with a range of close to 10 degrees which is indicative of a lower purity substance. *See*, Marti, E., *Purity determination by differential scanning calorimetry*, *Thermochimica Acta*, 5(1972) 173-220 at 214 (“The melting of diphenyl is extremely sharp because of the purity level; on the other hand, the melting region of phenacetin-benzamide is rather broad.”) (Ex. 2031). Additionally, the DSC data provided does not describe the sample size, the rate of temperature increase as a function of time and does not compare this with an authentic standard of known purity melted under identical conditions. It is known in the art that sample size, rate of heating, the recrystallization solvent(s) used, and the conditions under which the crystalline sample was obtained can significantly affect the DSC data. Dr. Winkler’s conclusion based on this single vague and incompletely described DSC data is not scientifically sound.

77. Dr. Winkler also points to the brief description of the formation of the treprostinil diethanolamine salt (Ex. 1009 at ¶¶50-54), but that description does not indicate what treprostinil free acid was used to make it. While the Board agreed with Dr. Winkler regarding the similarity

of the products of Phares and the '393 patent, the source of the treprostinil used to make treprostinil diethanolamine is very important and would greatly affect the impurity profile and other analytical characteristics, including DSC, of the sample.

78. In fact, Phares itself describes several references that could be used to make treprostinil, but does not identify which one, if any, was used to make the sample for the treprostinil diethanolamine salt. *See, e.g.*, Ex. 1005 at 9 (“Compounds of the present invention can also be provided by modifying the compounds found in U.S. Patent Nos. 4,306,075 (“the '075 patent”, Ex. 2032) and 5,153,222 (“the '222 patent”, Ex. 2033) in like manner.”). The '075 patent, for example, discloses a very different and less pure treprostinil product than that of Moriarty (Ex. 1004). *See, e.g.*, Ex. 1004 at 1892-93. Thus, without knowing the source of the treprostinil used in Phares to make the treprostinil diethanolamine salt, the resulting product could have a very different purity and impurity profile and would necessarily have a distinct impurity profile if it were made by a different process than that disclosed in the '393 patent.

B. Phares Does Not Disclose Several Other Claim Limitations

79. Dr. Winkler alleges that Phares discloses the same synthesis to make treprostinil diethanolamine as the synthesis described in the '393 patent and the Board credited his opinion on this point. *See*, Ex. 1009 at ¶¶51-57; Paper 12 at 29-30. I disagree. First, there is no description whatsoever in Phares of how to make treprostinil free acid. Instead, Dr. Winkler points to the synthesis of the enantiomer of treprostinil ((-) treprostinil) which is a completely different synthesis for a different stereoisomer. Ex. 1009 at ¶57. Winkler alleges that because certain steps are used in forming the enantiomer, those steps are inherently disclosed for use with treprostinil. Ex. 1009 at ¶¶56-57.

80. I understand the Board decision did not address the additional limitations of independent Claims 1 and 9 nor the dependent claim limitations in its anticipation analysis because “the process steps recited in claims 1 and 9 do not impart structural or functional differences to the claimed treprostinil product.” Paper 12 at 31. I disagree with this assertion. Even if Phares used the synthesis of Moriarty to make treprostinil, there are significant differences between the product of Moriarty and the product of the '393 patent. *See*, Section VII(A) below. Because the products are different, the process differences are relevant to the anticipation analysis.

81. The synthesis for the enantiomer of treprostinil disclosed in Phares, however, is different than the synthesis of treprostinil disclosed in the '393 patent. First, contrary to Dr. Winkler's claims, the earlier part of the synthesis used in Phares to make the enantiomer is not the same synthesis disclosed in Moriarty. Specifically, the Moriarty reference obviously does not describe the synthesis of the enantiomer of treprostinil, but also does not include the Mitsunobu inversion step described by Phares wherein the stereochemistry of the secondary alcohol moiety has to be chemically reversed. Ex. 1005 at 40. In fact, because (S)-2-methyl-CBS-oxazaborolidine is used on structure 5, the resulting structures 6-11 are diastereoisomers of the intermediates used in the synthesis of the '393 patent. As a result, intermediate products of formulas (II) and (III) of Claim 1 and intermediate products of formulas (V) and (VI) of Claim 9 of the '393 patent are not disclosed in Phares. Thus, because steps (a) – (c) of *every claim* of the patent requires these products, Phares cannot anticipate any claim of the '393 patent.

82. Second, Claim 2 requires a specific purity of 99.5%. As I discussed above, there are no specific purity measurements disclosed in Phares and a single broad melting point determination with a large melting point range does not provide evidence that the purity of the

treprostini diethanolamine sample is at least 99.5%. *See*, Section VI(A) above. For this additional reason, Phares does not anticipate Claim 2. The purity of that sample was not calculated from the DSC data as no control to an authentic standard of known purity was performed or reported.

83. SteadyMed claims that because the synthesis of the enantiomer of treprostini in Phares does not describe a purification step, that the claim limitation of Claims 8 and 16 that the process does not include purifying the compound of Formula III (or VI) produced in step (a) is satisfied. That is not correct. In fact, Phares does not disclose any specific details of those steps whatsoever. Indeed, if the same synthesis from Moriarty was used as Dr. Winkler suggests, purification at step (a) is specifically described in that reference. Ex. 1004 at 1901-1902. Regardless of what synthesis was used, however, the fact remains that compounds of Formula III and VI do not appear in Phares as described above.

84. Under my interpretation of the highly pure product described in each of the claims of the '393 patent, Phares does not anticipate Claims 1-5, 7-9, 11-14, or 16-20 because it does not disclose the highly-pure product of the '393 patent, the synthesis of treprostini, nor compounds of structures (II) and (III) from independent Claim 1 or structures (V) and (VI) from independent Claim 9, which are required by all of the claims.

VII. None of the Claims of the '393 patent Are Rendered Obvious by the Prior Art

85. I understand that the Board cited additional grounds for unpatentability including obviousness based on the combination of Moriarty and Phares and obviousness based on the combination of Moriarty, Phares, Kawakami (Ex. 1007), and Ege (Ex. 1008). I disagree that any claim of the '393 patent is rendered obvious by any combination of these references.

A. The Product of the '393 Patent Is Structurally Different Than the Product of the Prior Art

86. In his declaration, Dr. Winkler expresses his opinion that “the '393 patent processes do not result in a physically different or unique product than that disclosed in the prior art.” Ex. 1009 at ¶71. I am aware that, in the Institution Decision, the Board credited Dr. Winkler’s opinion regarding this lack of physical differences between the treprostinil products of the '393 patent and the prior art. Paper 12 at 16-17. I disagree with Dr. Winkler’s opinion for at least the following reasons.

87. Dr. Winkler appears to base his opinion on a comparison between the '393 patent process batches identified in the declaration submitted by Dr. David Walsh, one of the inventors of the '393 patent, during prosecution (Walsh Declaration), and a single prior art process batch identified in a particular prior art publication by Moriarty . Ex. 1009 at ¶¶63-71. However, Dr. Winkler’s comparison suffers from several critical flaws.

88. First, and most fundamentally, there is no basis for comparing the “purity” reported in Moriarty with the purity discussed in the Walsh Declaration. When purity is determined by comparison of a sample to a reference standard such as assay purity (*see, e.g.*, ICH Guidance For Industry: Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients (2001) (“Q7A”) at 28-29 (Ex. 2034); see also Reviewer Guidance: Validation of Chromatographic Methods (1994) (“Reviewer Guidance”) at 5-8) (Ex. 2035), one cannot directly compare the purity values of two samples in any meaningful way unless each value was achieved by comparison to the same reference standard. Neither the Walsh Declaration nor Moriarty identifies a specific reference standard. While Moriarty notes that the

treprostinil product obtained was compared to an authentic sample of UT-15, there is no mention of any such comparison in the Walsh Declaration.

89. Instead, with respect to the Walsh Declaration, purity must be understood not with respect to any reference standard, but with respect to the amount of total impurities reported as detected in each of the sample batches. The term “purity” must also be understood with respect to the amount of total impurities detected in the context of the ’393 patent itself; wherever assay purity is referred to, the ’393 patent specifies that the number indicated refers to “HPLC (Assay).” For each of the representative batches discussed in the Walsh Declaration, impurity data is presented in the same way, and thus the purity of these samples can properly be compared to each other; the same cannot necessarily be said of the sample data reported in Moriarty.

90. Second, Dr. Winkler concludes from Example 4 of the ’393 patent that the instrumentation used to measure purity “can have variations of at least 0.4%,” and thus any detected difference less than that can be attributed to experimental error. Ex. 1009 at ¶¶69-70. Dr. Winkler bases his estimate of experimental error on the statement “that Example 4’s Batch 1 had an HPLC Assay of 100.4%, which is obviously greater than the 100% value theoretically achievable.” Ex. 1009 at ¶70. This is unsupported and appears to arise from Dr. Winkler’s fundamental misunderstanding of how assay purity values are calculated. HPLC assay values are calculated with respect to a reference standard; thus, any time that the sample you are measuring has a greater purity than the reference standard, the assay value will exceed 100%. As such, it is incorrect to conclude that an assay value of 100.4% must indicate an error of at least 0.4%. Dr. Winkler’s conclusion on this point is therefore fundamentally flawed.

91. This explains why the assay value for drug specification submitted to the FDA changed from a range of [REDACTED] to [REDACTED]. See, Ex. 2003 at 6. This change was not due to

an increase in impurities, but because the purity of the product using the '393 patent process improved (as compared to the already-established reference standard) thus moving the acceptability range to a higher purity specification. *Id.* The letter notes that the scope of the range remained unchanged which simply indicates the acceptability criteria was increased, and does not index an error rate or limit of detection. Indeed, the change to the specification is further evidence that the product of the '393 patent is physically different than the product of Moriarty.

92. Indeed, Dr. Winkler's conclusion is contradicted by the impurity data actually measured for the treprostinil product made by both the '393 patent process and the prior art process according to Moriarty. For both processes, impurities are reported with specific numbers unless the amount detected fell below 0.05%; in cases where some amount of an impurity less than 0.05% was detected, it was reported as simply "less than 0.05%" or "< 0.05%." This means that the level of detection for measuring impurities in these treprostinil samples was somewhere between 0 and 0.05%, not something in excess of 0.4% as Dr. Winkler erroneously concludes.

93. Third, as Dr. Winkler himself points out, there is the possibility for "significant batch-to-batch variations in the impurity profile of each batch of treprostinil." Dr. Walsh stated that the data presented in his declaration came from representative samples of each synthetic process. Ex. 1002 at 346-347. However, there is no such indication that the purity data reported in Moriarty comes from a representative sample of the prior art process. Due to the possibility of batch-to-batch variations, if a small number of batches are to be used as the basis for comparison, it is critical that those batches be representative of their respective products and processes. Thus while one could reasonably rely on a comparison between the representative batches presented in

the Walsh Declaration, one could not reasonably add the batch discussed in Moriarty to that comparison. It is exactly this scientifically unsound comparison to Moriarty upon which Dr. Winkler bases his opinion.

94. Ideally, to avoid the risk of batch-to-batch variations unintentionally biasing the data, a comparison should be made between the average impurities detected in treprostini products made by the '393 patent process and treprostini products made by the prior art process. To this end, I have prepared a chart containing impurity data for 56 samples of treprostini product as produced by the prior art process according to Moriarty through 2004 (the date of the publication), attached as Appendix A to this declaration¹, and another chart containing impurity data for 122 samples of treprostini product as produced by the '393 patent processes, attached as Appendix B to this declaration. I have prepared these charts using impurity data from release testing of samples of the respective treprostini products that were produced by or for UTC for the purposes of obtaining regulatory approval and/or commercial sale. See Appendix A, Appendix B; Ex. 2005; Ex. 2036; Ex. 2037; Ex. 2052; Ex. 2053. As the purpose of these charts is to calculate the average impurities – both specific and total – found in the treprostini products of each process, I have necessarily assigned a value of zero where the level of impurities was

¹ I am aware that UTC's Process Optimization Report for treprostini prepared according to the '393 process included Table 2, which provided average impurity data for 96 batches of treprostini made according to the prior art process. UT Ex. 2005, at 7. However, Table 2 does not provide exact values for four of the eight impurities under consideration, [REDACTED] and does not identify the underlying batch data. *Id.* As such, I have prepared my own chart using data on 56 treprostini samples made by the prior art method and have based my analysis, including my calculations of average for total and individual impurities, upon this chart. While I believe my chart allows for a more precise comparison between Moriarty treprostini products and '393 treprostini products, the averages presented in the Process Optimization Report still show significant differences between '393 treprostini products and the Moriarty treprostini products. Specifically, Table 2 of the Process Optimization Report shows that on average [REDACTED] was detectable in these 96 batches, and that these 96 batches contained higher average levels of [REDACTED], and total impurities as compared to the averages for the '393 treprostini product. Ex. 2005 at 7; Appendix B.

reported as “ND” (Not Detected), and a value of 0.05 where the level of impurities was reported as being less than 0.05%. From these data, I have found the following average impurity levels:

Moriarty Process Impurities (Average Percent Detected)								
1AU90	2AU90	3AU90	750W93	751W93	97W86	ethyl ester	methyl ester	Total Related Substance
0.0473	0.0407	0.2545	0.1646	0.1025	0.0405	0.0889	0.1028	0.9545
'393 patent Process Impurities (Average Percent Detected)								

95. These averages make clear that the '393 patent process does result in a treprostinil product that is physically different from the prior art treprostinil product. In terms of total volume of impurities, the Moriarty process resulted in [REDACTED] times the amount of impurities that is achieved with the '393 patent process.

96. The products from the two processes also differ significantly with respect to the individual impurities in each product's impurity profile. Notably, the '393 patent process produces a treprostinil product that does not contain any detectable amounts of [REDACTED]. Additionally, the '393 patent process produces a treprostinil product that, on average, contains only [REDACTED] each of [REDACTED] and [REDACTED] and only [REDACTED] of [REDACTED]; as compared to the Moriarty process, this represents greater than a [REDACTED] reduction in each of the [REDACTED] and [REDACTED] impurities and a [REDACTED] reduction in the [REDACTED] impurity. The '393 patent process also produces a treprostinil product that, on average, has significantly reduced amounts of several other identified impurities; as compared to the average of the Moriarty process, the '393 patent process produces a treprostinil product with less than [REDACTED] the amount of [REDACTED], approximately [REDACTED] the amount of [REDACTED], and approximately [REDACTED] the amount of [REDACTED].

[REDACTED]. Conversely, the '393 patent process produces a treprostinil product which actually contains slightly more [REDACTED] impurity than was detected in the treprostinil product of the Moriarty process.

97. Looking past the average data, it is also worth noting that, out of all the batches of treprostinil product made by the '393 patent process which I reviewed, [REDACTED] was only detected in a single batch ([REDACTED]) and [REDACTED] was also only detected in a single batch ([REDACTED]), and both impurities were only detected at a level of 0.05% or less. Furthermore, batches [REDACTED] and [REDACTED] were both identified as "optimization batches" (as distinguished from commercial batches) and thus are not properly representative of treprostinil products made by the '393 patent process.

98. From these data, it is clear that the treprostinil product produced by the '393 patent process has a markedly different impurity profile than the treprostinil product of the Moriarty prior art process, and as such is physically distinct from the prior art product. Moreover, it could not have been obvious that employing the process of the '393 patent would result in a reduction of impurities as compared to the Moriarty process. Indeed, the '393 patent process actually results in an [REDACTED] in one detected impurity, [REDACTED]. Furthermore, it is also clear that the treprostinil product produced by the '393 patent process has a higher average purity than the Moriarty product. The treprostinil product of the '393 patent has an average purity of [REDACTED] while the Moriarty product has an average purity of 99.05%. Thus, the treprostinil product of the '393 patent has an average purity that is [REDACTED] higher than that of Moriarty's.

99. Therefore, it is my opinion that the treprostinil product produced by the process used in the '393 patent Claims 1 and 9 is physically different than the treprostinil product produced by Moriarty.

B. Claims 1-5, 7-9, 11-14, and 16-20 Are Not Rendered Obvious by the Combination of Moriarty and Phares

100. As described above, the product of Moriarty is physically different than the product of the '393 patent process. Even if the Moriarty synthesis was used to make treprostinil, a POSA would not have been motivated to make the diethanolamine salt identified in Phares.

101. Specifically, the '393 patent notes that the salt formation step results in an improved and more pure treprostinil product. Given that Moriarty discloses the use of column chromatography for purification, a POSA would not have been motivated to create the salt form in Phares as Phares does not disclose any benefit or increased purity as a result of using the diethanolamine salt. In fact, Phares does not allege that the diethanolamine salt is superior in any way to the treprostinil product of Moriarty and instead identifies other earlier treprostinil disclosures as a means to create the treprostinil used to form the diethanolamine salt. *See*, Section VI(A) above.

102. Additionally, a POSA would not have had a reasonable expectation of success in making the higher purity treprostinil product claimed in the '393 patent by the use of a salt formation step. As identified above, the impurities of treprostinil include [REDACTED] ([REDACTED]), [REDACTED] ([REDACTED]), the [REDACTED] starting material ([REDACTED]), and the [REDACTED]. As described above, the '393 patent process essentially eliminated the [REDACTED] impurities [REDACTED], and [REDACTED] impurity [REDACTED], but did not eliminate another [REDACTED] which likely has the same [REDACTED] as the other

stereoisomers. Similarly, the [REDACTED] impurity increased while the [REDACTED] impurity decreased. A POSA would have expected that all of the stereoisomers would remain as salt impurities, but that is not the case. Instead, the impurity profile of the '393 patent process yields an unexpected result by removing [REDACTED] while [REDACTED] impurity and [REDACTED] another. A POSA could not have predicted this outcome based on the salt formation described in Phares.

103. Regarding Claim 2, neither Moriarty nor Phares discloses treprostinil or treprostinil diethanolamine at a purity of 99.5%. As described above, Phares does not disclose any purity measurement (see Section VI above) and the purity measurement identified in Moriarty does not identify how the measurement was taken (see Section VII(A) above). Regardless of the purity identified in Moriarty, a further analysis of all batches made by the Moriarty process up to the time of the reference itself reveals an average purity of [REDACTED] while the average purity of the '393 patent batches is [REDACTED]. Given that the error rate must be below 0.05% for these measurements (see Section VII(A) above), the '393 patent process batches are significantly better in terms of overall purity. For this additional reason, Claim 2 is not rendered obvious by the combination of Moriarty and Phares.

104. Regarding Claims 8 and 16, Phares does not disclose any synthesis for treprostinil and therefore cannot disclose whether purification was needed for step (a). (*See*, Section VI(B) above). As previously described, Moriarty specifically discloses that purification is performed at step (a). See Section VII(B) above). In fact and most significantly, the '393 patent itself identifies that as a distinguishing feature over the prior art. *See, e.g.*, Ex. 1001 at Example 6. For this additional reason, Claims 8 and 16 are not rendered obvious by the combination of Moriarty and Phares.

C. Claims 6, 10, 15, 21, and 22 Are Not Rendered Obvious by the Combination of Moriarty, Phares, Kawakami, and Ege

105. Each of Claims 6, 10, 14, 21, and 22 require the additional step (d) of independent Claims 1 and 9 which is to react the salt formed in step (c) with an acid to form the compound of formula I or IV (treprostinil). Claim 22 further requires a pharmaceutically acceptable salt formed from the product of step (d). Step (d) is not disclosed in any way in Moriarty, Phares, Kawakami, or Ege. Additionally, it is my opinion that it would not have been obvious to combine these references to arrive at the claimed inventions of Claims 6, 10, 15, 21, or 22.

106. First, there is no teaching or suggestion to perform step (d) in either Moriarty or Phares and similarly no reference to reverting back to treprostinil free acid from any treprostinil salt. Given that the purification techniques disclosed in Moriarty include chromatography and recrystallization after many years of research to optimize the process of making treprostinil, a POSA would not have been motivated to use a salt purification technique disclosed in an undergraduate chemistry textbook. More importantly, a POSA would not have had a reasonable expectation of success in further purifying the treprostinil product of Moriarty by using such a technique. To the extent a POSA was motivated to further purify treprostinil, a POSA would have focused on the known impurities and investigated methods of removing those. At the time of the invention, it was known that the formation of diastereomers occurred in the formation of treprostinil. *See*, Ex. 1004 at 1897-99. Thus, a POSA would have focused on how to remove those types of impurities.

107. Ege simply discloses that “carboxylic acids that have low solubility in water, such as benzoic acid, are converted to water-soluble salts by reaction with aqueous base. Protonation of the carboxylate anion by a strong acid regenerates the water-insoluble acid. These properties

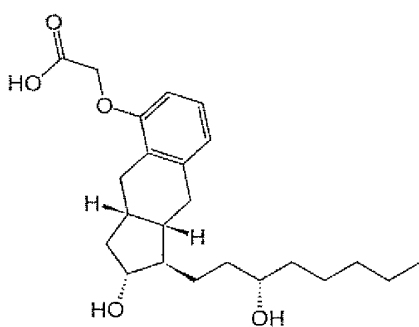
of carboxylic acids are useful in separating them from reaction mixtures containing neutral and basic compounds.” Ex. 1008 at 8. This disclosure, however, would not have provided a POSA with a motivation to make the treprostinil free acid disclosed in Moriarty, convert that to the salt form of Phares, then convert the salt form back to the free acid.

108. First, Ege does not provide any detail regarding how this reaction could be applied to more complex carboxylic acids or if it even could be applied. Specifically, the only carboxylic acid referenced in Ege as an example is benzoic acid, a very simple aromatic acid, which is structurally very different from treprostinil acid. Indeed, benzoic acid has no chiral centers and therefore no stereoisomers and there is no suggestion in Ege that this step could be used in purifying more complex carboxylic acids such as treprostinil which have stereoisomeric impurities. Second, Ege specifically notes that “these properties of carboxylic acids are useful in separating them from reaction mixtures containing neutral and basic compounds,” therefore Ege would not apply to purifying carboxylic acids with stereoisomeric impurities because each stereoisomer would necessarily be an acidic impurity. As described above, the impurities that are removed from the ’393 patent product include some, but not all acidic impurities and some but not all neutral impurities. *See*, Section VII(B) above. For these reasons a POSA would not have been motivated to combine Ege with either Moriarty or Phares and would not have had a reasonable expectation of success in further purifying treprostinil using the acid reformation step described in Ege.

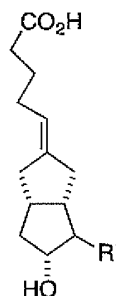
109. Indeed, given that Ege predicts that only neutral and basic impurities would be removed, the actual average impurity profile for the ’393 patent product is an unexpected result given that some but not all neutral impurities are removed as well as some but not all acidic impurities. *See*, Section VII(B) above.

110. Kawakami similarly does not provide any motivation for combining with either Phares or Moriarty and a POSA would not have had a reasonable expectation of success in preparing the products of Claims 6, 10, 15, 21, or 22 by combining these references.

111. Kawakami discloses the purification of a methanoprostacyclin derivative by forming the dicyclohexyl amine salt then regenerating the free acid to achieve a “fairly high” purity. Ex. 1007 at 6. Treprostinil and methanoprostacyclin, however, are very different structures:



Treprostinil



methanoprostacyclin compound in Kawakami

112. As shown here, the methanoprostacyclin compound in Kawakami is a two-fused ring structure which is different than the three-fused ring structure of treprostinil that also includes an aromatic ring absent in the Kawakami methanoprostacyclin. These differences matter because a POSA would not have looked to Kawakami (or Ege) if they were looking for additional purification techniques for treprostinil because neither reference discloses how to remove stereoisomeric impurities.

113. Instead, Kawakami provides a purification method for separating E and Z isomers of a starting material that is otherwise free of impurities, and not diastereomers that result from the various chiral centers that treprostinil was known to have as impurities. In fact, treprostinil

contains no mixture of E and Z isomers because it does not contain a carbon-carbon double bond that is capable of forming E and Z isomers. Indeed, the use of a specific salt to isolate a specific E/Z isomer does not reasonably suggest that salt formation of a much more complex compound with multiple chiral centers such as treprostinil could be isolated from entirely different impurities and then converted back to the free acid form. In fact, nothing in Kawakami suggests that this method could be used for a substance that was already fairly pure such as the treprostinil disclosed in Moriarty.

114. Similarly, Kawakami uses a dicyclohexylamine salt and does not use a diethanolamine salt, nor any salt counterion disclosed in the '393 patent. A POSA would have had no reason to combine the synthesis of Moriarty, use the salt only disclosed by Phares, and convert back to the free acid based on the teaching of Kawakami because Kawakami uses a different salt to separate a different structure from different types of impurities. Even if a POSA did combine these references in this way, a POSA would not have had a reasonable expectation of success in forming a more pure treprostinil product because Kawakami does not provide any information regarding the high level of purity required by the '393 patent and does not describe the separation of the types of stereoisomeric impurities known to be present in the treprostinil product. Dr. Winkler's obviousness analysis using these combinations is flawed and suffers from hindsight analysis.

115. Claim 6 requires the acid in step (d) be either HCl or H₂SO₄ and Claim 15 requires the acid to be HCl. Claim 21 requires that step (d) is performed. Phares, Moriarty, and Kawakami all do not disclose the use of either HCl or H₂SO₄ in converting a salt back to a carboxylic acid of any kind. Ege cites HCl as an example in the conversion of benzoic acid, but as described above, a POSA would not have looked to Ege to further purify a complex

carboxylic acid such as treprostinil from its stereoisomers and other impurities and would have no reasonable expectation of success by using HCl based on this disclosure. For this additional reason, Claims 6 and 15 would not have been rendered obvious by any combination of Phares, Moriarty, Kawakami or Ege. Similarly, given the deficiencies described above regarding Ege and Kawakami, Claim 21 would not have been rendered obvious by any combination of Phares, Moriarty, Ege, or Kawakami.

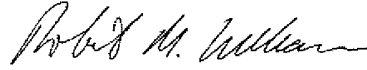
116. Claim 10 requires that step (d) is performed and further requires the product to be at least 99.5% pure. The only purity limitation disclosed in any of the cited prior art references is to Moriarty in which neither step (c) or (d) is performed. There is absolutely no other disclosure of a purity of at least 99.5% in any other cited prior art reference. A POSA looking to improve the purity of treprostinil above that level would have had no reason to look to Phares, Kawakami, or Ege and based on their disclosures, would have had no reasonable expectation of success in making a treprostinil product with that level of purity as it simply is not present in the prior art allegedly disclosing step (d).

117. Claim 22 depends on Claim 21 and further requires a pharmaceutically acceptable salt be formed from the product of step (d). Dr. Winkler cites no evidence for this additional step in the prior art. In fact, none of the references cited even suggest converting a carboxylic acid to a salt form, then regenerating the carboxylic acid, then forming a pharmaceutically acceptable salt from that. It is my opinion that there is no evidence in the prior art supporting the additional claim limitation of Claim 22 and therefore no combination of Moriarty, Phares, Kawakami, or Ege would render this claim obvious.

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I declare under penalty of perjury that the foregoing is true and correct.

Date: July 6, 2016



Robert M. Williams, Ph.D.

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APPENDIX A

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		Impurities (Percent Detected)							Data Source	
		2AU90	3AU90	750W93	751W93	97W86	ethyl ester	methyl ester	Total Related Substances	
0.3	0.3	0.4	0.4	1.2	0.7	0.1	0	0.7	5.4	Ex. 2052, pp. 25-27
0.4	0.07	0.5	0.5	0.1	0.09	0.2	0	0.3	4.4	Ex. 2052, pp. 25-27
0.4	0.1	1	1	0.1	0.06	0.2	0	0.3	4.8	Ex. 2052, pp. 25-27
0.2	0.07	0.4	0.4	0.6	0.3	0	0	1.2	3.6	Ex. 2052, pp. 25-27
0.2	0.07	0.4	0.4	0.6	0.4	0.05	0	0.8	3.8	Ex. 2052, pp. 25-27
0.3	0.06	0.4	0.4	0.8	0.4	0	0	0.8	3.5	Ex. 2052, pp. 25-27
0.1	0.06	0.3	0.3	0.4	0.2	0	0	0.1	1.6	Ex. 2052, pp. 25-27
0.5	0.05	0	0	0.2	0.1	0.05	0.1	0.05	0.4	Ex. 2052, pp. 28-30
0.5	0.05	0.2	0.2	0.1	0.1	0	0	0.05	0.7	Ex. 2052, pp. 28-30
0.5	0.05	1.1	1.1	0.3	0.2	0.6	0.6	0.05	2.8	Ex. 2052, pp. 28-30
0.5	0.05	0	0	0.5	0.3	0	0.1	0.06	1.0	Ex. 2052, pp. 28-30; Ex. 2036, pp. 2-3
0	0.05	0.1	0.1	0.06	0.05	0	0	0.05	0.2	Ex. 2053, p. 19; Ex. 2036, pp. 88-89
0	0.05	0.2	0.2	0.07	0.05	0	0	0.05	0.4	Ex. 2053, p. 19; Ex. 2036, pp. 91-92
0	0.05	0.1	0.1	0.1	0.07	0	0	0.05	0.3	Ex. 2053, p. 19; Ex. 2036, pp. 94-95
0	0.05	0.2	0.2	0.2	0.09	0	0	0.05	0.6	Ex. 2053, p. 19; Ex. 2036, pp. 100-101
0	0.05	0.3	0.3	0.05	0.05	0	0.05	0.05	0.05	Ex. 2053, p. 19; Ex. 2036, pp. 33-34
0	0.05	0.2	0.2	0.1	0.06	0	0.05	0.05	0.5	Ex. 2053, p. 19; Ex. 2036, pp. 97-98

0.05	0.05	0.2	0.09	0.06	0	0.05	0.05	0.05	0.4	Ex. 2053, p. 19; Ex. 2036, pp. 35-36
0	0.05	0.2	0.09	0.05	0.05	0	0	0.4	Ex. 2053, p. 19; Ex. 2036, pp. 37-38	
0	0.05	0.2	0.09	0.05	0.05	0	0.05	0.4	Ex. 2053, p. 19; Ex. 2036, pp. 39-40	
0.2	0.05	0.3	0.4	0.2	0.08	0.05	0.05	1.5	Ex. 2053, p. 19; Ex. 2036, pp. 41-42	
0	0.05	0.3	0.09	0.05	0.05	0.05	0	0.5	Ex. 2053, p. 19; Ex. 2036, pp. 43-44	
0.5	0	0.2	0.05	0.05	0.05	0.08	0	0.3	Ex. 2053, p. 19; Ex. 2036, pp. 45-46	
0	0	0.2	0.1	0.05	0.05	0	0	0.3	Ex. 2053, p. 19; Ex. 2036, pp. 47-48	
0	0.05	0.1	0.2	0.1	0.05	0.2	0	0.6	Ex. 2053, p. 20; Ex. 2036, pp. 60-61	
0.5	0.05	0.2	0.05	0.05	0	0.05	0.05	0.2	Ex. 2053, p. 20; Ex. 2036, pp. 50-52	
0.5	0.05	0.2	0.1	0.06	0	0.07	0.05	0.4	Ex. 2053, p. 20; Ex. 2036, pp. 52-53	
0	0.05	0.2	0.1	0.08	0.07	0.09	0	0.6	Ex. 2053, p. 20; Ex. 2036, pp. 54-55	
0	0.05	0.2	0.05	0.05	0	0.1	0	0.4	Ex. 2053, p. 20; Ex. 2036, pp. 56-57	
0	0.05	0.3	0.08	0.05	0.05	0.1	0	0.6	Ex. 2053, p. 20; Ex. 2036, pp. 58-59	
0	0.05	0.2	0.05	0.05	0	0.05	0	0.4	Ex. 2053, p. 20	
0	0.05	0.2	0.1	0.1	0	0.1	0	0.4	Ex. 2053, p. 20	
0	0.05	0.1	0.1	0.1	0.05	0.2	0	0.6	Ex. 2053, p. 20; Ex. 2036, pp. 62-63	
0	0	0.05	0.05	0.05	0	0.1	0.05	0.2	Ex. 2053, p. 20; Ex. 2036, pp. 64-65	

0	0.05	0.2	0.05	0.05	0	0.1	0	0.3	Ex. 2053, p. 20; Ex. 2036, pp. 66-67
0	0.05	0.2	0.06	0.05	0	0.1	0	0.4	Ex. 2053, p. 20; Ex. 2036, pp. 68-69
0	0.05	0.2	0.05	0.05	0	0.1	0	0.3	Ex. 2053, p. 20; Ex. 2036, pp. 70-71
0	0	0.4	0.1	0.08	0.05	0.1	0.05	0.8	Ex. 2053, p. 21; Ex. 2036, pp. 72-73
0	0.05	0.3	0.06	0.05	0.05	0.2	0.05	0.6	Ex. 2053, p. 21; Ex. 2036, pp. 74-76
0	0	0.4	0.05	0.05	0	0.1	0.05	0.6	Ex. 2053, p. 21; Ex. 2036, pp. 78-79
0	0	0.2	0.09	0.06	0	0.1	0	0.5	Ex. 2053, p. 21; Ex. 2036, pp. 80-82
0	0	0.1	0.2	0.1	0.07	0.1	0	0.6	Ex. 2053, p. 21; Ex. 2036, pp. 83-85
0	0	0.3	0.06	0.05	0	0.2	0.05	0.5	Ex. 2053, p. 21; Ex. 2036, pp. 31-32
0	0	0.3	0.1	0.07	0	0.1	0.05	0.6	Ex. 2036, pp. 29-30
0	0	0.3	0.1	0.06	0	0.1	0.05	0.6	Ex. 2036, pp. 27-28
0	0	0.3	0.2	0.1	0.05	0.2	0.05	0.9	Ex. 2036, pp. 25-26
0.05	0.05	0.2	0.06	0.05	0.05	0.1	0.05	0.4	Ex. 2036, pp. 23-24
0.05	0.05	0.2	0.05	0.05	0.05	0.09	0.05	0.3	Ex. 2036, pp. 21-22
0.05	0.05	0.2	0.06	0.05	0.05	0.1	0.05	0.4	Ex. 2036, pp. 19-20
0	0	0.2	0.2	0.08	0.05	0.1	0.05	0.6	Ex. 2036, pp. 17-18
0	0	0.2	0.05	0.05	0	0.1	0	0.4	Ex. 2036, pp. 15-16
0	0	0.2	0.1	0.06	0.05	0.2	0.05	0.6	Ex. 2036, pp. 13-14
0	0	0.2	0.05	0.05	0	0.2	0	0.5	Ex. 2036, pp. 11-12
0	0	0.1	0.1	0.06	0.05	0.1	0.05	0.4	Ex. 2036, pp. 8-10
0	0	0.2	0.09	0.05	0	0.1	0.05	0.4	Ex. 2036, pp. 6-7

0	0	0.2	0.07	0.05	0	0.2	0.05	0.5	Ex. 2036, pp. 4-5
73	0.0407	0.2545	0.1646	0.1025	0.0405	0.0889	0.1028	0.9545	
90	2AU90	3AU90	750W93	751W93	97W86	ethyl ester	methyl ester	Total Related Substances	

Impurities reported as not detected ("ND") a value of 0 has been assigned; for impurities reported as <0.05, a value has been assigned.

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APPENDIX B

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reported as not detected ("ND") a value of 0 has been assigned; for impurities reported as <0.05, a value of 0.05 has

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

STEADYMED LTD.

Petitioner,

v.

UNITED THERAPEUTICS CORPORATION

Patent Owner.

Case IPR 2016-00006

Patent No. 8,497,393B2

**PETITIONER'S REPLY TO PATENT OWNER'S RESPONSE TO
PETITION**

37 C.F.R. § 42.23

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Petitioner SteadyMed, Ltd. submits this reply pursuant to 37 C.F.R. § 42.23.

I. SUMMARY OF THE ARGUMENT

As SteadyMed explained in its Petition, purifying by crystallization is taught in undergraduate chemistry courses: it's Organic Chemistry 101. Even Patent Owner United Therapeutics' (UT) expert recognizes this fact:

Q: How long has crystallization been around as a method of purification?

A: I don't know how long it's been around.

Q: Before 2007?

A: Oh, yes.

Q: Did you learn about it when you were in college at the university?

A: Yes, I did. [...]

Q: And when did you go to college?

A: In 1968 I started. In 1968.

...

Q: ... But how far back does doing that process you just described, how far back does that go?

The Witness: Decades.

(Ex. 2058, 175:19-176:22, 179:11-17).

Even though the purification process claimed in the '393 Patent is so trivial an undergraduate student in the late 1960s would know how to do it, UT maintains that a product made by the '393 Patent process is "materially and functionally" distinct from products of the prior art Moriarty (Ex. 1004) and Phares (Ex. 1005) references. UT relies on 175 measurements showing the average purity of products

made by one process included in the '393 Patent's claims is [REDACTED]. (Resp., 34; Ex. 2020, ¶¶ 94-99.) And it relies on measurements alleged to show that one version of the Moriarty process produced an average purity of 99.0%. (Ex. 2020, ¶ 98.) Except that the 99.0% value is a distortion of this data, that required UT, and its attorneys who actually performed this calculation (Ex. 2059, 79:3-10, 81:2-13, 104:14-20), to select 10 data points from another source to lower the purity results (*id.*, 112:22-113:20).

As confirmed by Dr. Williams (*id.*, 218:3-219:16), a fair analysis of the data without the 10 data points shows that the value of [REDACTED], reported in [REDACTED] [REDACTED] itself, is consistent with UT's purity measurements for batches made according to the Moriarty process (Ex. 2059, 219:17-20). Data purporting to show a lower purity, including UT's Walsh Declaration, mischaracterizes the Moriarty process' purity.

UT's expert Dr. Williams initially believed UT's counsel's calculations. But Dr. Williams conceded that: (1) he performed no calculations on this data himself; (2) he only "spot-checked" the data that was selected by counsel; and (3) he "did not know" whether the 10 data points were produced under the Moriarty process. (Ex. 2059, 81:2-13; 82:1-11; 103:24-104:20; 112:24-114:2). Accordingly, no weight should be afforded to his declaration, or UT's reliance on his declaration. Dr. Williams agreed that SteadyMed's calculation of [REDACTED] purity was correctly

performed, and should be relied upon (*id.*, 217:11-219:20). This corrected calculation supported what SteadyMed stated in its Petition: that the [REDACTED] [REDACTED] showed that treprostinil made by Moriarty was of similar purity, and similarly, the particular example of treprostinil diethanolamine salt made by Phares was as pure as the examples in the '393 Patent. This calculation confirms that the '393 Patent claims merit cancellation.

UT relies on these now-discredited differences in purity values to argue there was a "long-felt unmet need" for more pure treprostinil. (Resp., 12, 47-48; Ex. 2022, ¶¶ 70-72). But UT's long-felt-need expert Dr. Ruffolo concedes that the claims are not limited to treprostinil, nor treprostinil salt, but include hundreds of thousands of other compounds, for which UT provides no evidence regarding long-felt need or impurities. (Ex. 2059, 71:17-72:17; Ex. 2058, 234:16-235:17.) Except for those claims that are limited to treprostinil alone (only claims 10 and 15), or treprostinil diethanolamine salt (claims 14 and 17), Dr. Ruffolo is not offering an opinion that there is a long-felt need for any other claims. (Ex. 2058, 109:18-121:23.) And even for the products in claims 10, 14, 15, and 17, Dr. Ruffolo concedes that: (1) the FDA requires only a [REDACTED] purity level, which is *much lower* than any levels produced by the prior art, (Ex. 2058, 159:20-161:7); and, (2) the FDA would allow treprostinil batches produced by the Moriarty process to be sold, (Ex. 2058, 179:23-180:17), since Moriarty products are "highly, highly pure,"(*id.*

217:11-218:5). *See also* (Ex. 2059, 151:2-25).

UT devotes much of its Response to argue that the common patent claim terms "product" and "comprising" were improperly construed by the Board, and should not have their usual legally defined meaning. (Resp., 5, 13-15). UT contends these terms should have special meaning in the '393 Patent, although UT's expert concedes that a plain and ordinary meaning should apply, and that the patent and prosecution history contain no language that redefine these terms. (Ex. 2059, 248:24-249:13.) UT cannot show "clear and unambiguous disclaimer" of the plain meaning of these terms.

II. UT MISCHARACTERIZES ITS OWN DATA.

A. UT's Moriarty Batches Have an Average Purity of ██████████.

In its Response and supporting Williams Declaration (Ex. 2020), UT uses Dr. Williams to present the average purity of treprostinil made by the Moriarty prior-art method, in order to contrast it to the '393 Patent product. Specifically, Dr. Williams relied on 56 batch Certificates of Analysis of treprostinil that were allegedly produced under the Moriarty method (*see* Ex. 2020, Appx. A), and contended that the treprostinil product produced by the '393 Patent process had a higher average purity than the Moriarty product (████████% v. 99.05%), and thus "the treprostinil product of the '393 patent has an average purity that is ██████ higher than that of Moriarty's." (Ex. 2020, ¶ 98; Resp., 4, 34, and 45). But UT's counsel

selected batches to include in its calculation, and cherry-picked 10 batches to drive down the average purity value of the Moriarty product from [REDACTED] to 99.05%. These 10 "development" batches, as UT calls them, come from a separate source, and may not have been produced by the Moriarty method. When instead, the 46 "production" batches made by the Moriarty method, and under the same analytical methods, are examined, the correct conclusion is that the Moriarty method produces the *same product as the product of the '393 Patent*: a product with [REDACTED] purity, just as Moriarty himself reported in his JOC article (Ex. 1004).

Because Dr. Williams and Dr. Ruffolo relied on UT's counsel's incorrect calculation, UT's experts' opinions on differences between the Moriarty product and the '393 Patent product should be disregarded.

1. UT's Data Sources.

UT attaches three exhibits that contain purity information for tadalafil made under the Moriarty method: Exhibits 2036, 2052, and 2053. (Ex. 2020, Appx. A.) Exhibit 2036 is the main source of this data, and contains 44 Certificates of Analysis from either Magellan Laboratories or Cardinal Health for commercial lots of tadalafil. Exhibit 2053 is UT's NDA Annual Report from 2003, which summarizes Certificates of Analysis and purity information from 32 commercial lots, including 30 lots that were already included in Exhibit 2036, plus two additional lots not included in Exhibit 2036. Thus, Exhibits 2036 and 2053 contain

purity data for 46 lots of treprostinil.

Exhibit 2052 is an undated but older document entitled "UT-15 Injection Drug Substance Volume 1.2 Chemistry, Manufacturing and Controls, NDA 21-272," and appears to be a portion of UT's original New Drug Application to sell treprostinil. It contains a summary of purity analyses for 13 lots of treprostinil made by third party companies called "[REDACTED]" "[REDACTED]," and "[REDACTED]" (Ex. 2052, 25-30.) The two [REDACTED] lots, made in 1986, were not included in UT's Appendix A. "These lots were manufactured by [REDACTED] using a slightly different route of synthesis." (*id.*, at 25 n.4.) [REDACTED] was also not included in UT's Appendix A. [REDACTED], "which was deliberately spiked for use in toxicology studies," (*id.*, at 29 n.2) was included by UT, as were "[REDACTED]" [REDACTED], and [REDACTED] [which] were tested and released using different analytical procedures previously submitted," and for which "the listed specifications do not apply ...," (*id.*, at 25 n.3). The 10 samples selected from the 13 samples in Ex. 2052 were manufactured several years before Moriarty's 2004 Journal of Organic Chemistry article (Ex. 1004). As Dr. Williams confirmed, there is no information provided on what method was used to make these lots, other than the fact that the methods used for many of them were similar to methods [REDACTED] used in 1986. These 10 data points have purity values far below the values reported in Exhibits 2036 and 2053.

2. Are the 10 Batches Even Moriarty Samples?

The dates of manufacture and footnotes recorded in Exhibit 2052 associated with UT's 10 cherry-picked samples make it unlikely that they were representative of treprostinil made by the Moriarty process:

Q You don't know the details of how all these lots were made?

A No. I haven't seen the detailed batch records of what went into those lots.

Q Okay. So you don't know whether or not these lots were made by the '393 process, the Moriarty process, the older Aristoff process; is that right?

THE WITNESS: Um, you know, I -- I'd have to investigate further. I don't know.

Q Right. You -- you don't know if any of these are from the Moriarty process? At least not the ones on page 25?

A So the Moriarty paper came out in 2003.

...

A So I don't think it's possible that any of these could have been made by Moriarty process just based on the dates.

(Ex. 2059, 112:20-113:20). While Dr. Williams contends that these 10 samples represent "development" batches included for "fairness" (*id.*, at 81:23-82:7), he had no explanation for why he included 10 development batches out of 56 samples for his analysis of Moriarty batches, but only 5 development batches out of 157 samples for his analysis of '393-Patent batches. (*Id.*, at 270:15-271:6).

3. 46 Known Moriarty Samples Average to [REDACTED].

Once the cherry-picked data points are eliminated, the average purity of the 46 remaining samples increases from 99.05% to [REDACTED]: *the same purity as the product produced by the '393 Patent process.* SteadyMed prepared an Excel spreadsheet containing these 46 data points (Ex. 1021), and had Dr. Williams review every data point and calculation at his deposition to confirm that the [REDACTED] number is correct, and consistent with the number reported in Ex. 1004:

Q: Okay. So now that we've – now that you've checked every single data point and looked at the calculations, you agree with me that this calculation of the purity is fair and accurate?

A: The overall purity. But this does not reflect impurity profile.

Q: Yeah I understand. I'm just talking about the overall – the level of purity.

A: Yes.

[...]

Q: Okay. And so it is correct that for the samples from Exhibits 2036 and 20[5]3, the 46 samples, the average level of purity was [REDACTED] percent for the samples made under the Moriarty process?

A: Yes.

Q: Okay. That [REDACTED] value, that is consistent with the value that [REDACTED]?

A: They're the same numbers.

(Ex. 2059, 218:25-219:20). By contrast with Dr. Williams' careful review of SteadyMed's calculation, Dr. Williams did not perform any calculations on UT's

data in Appendices A and B, having relied solely on counsel's work. (*id.*, 81:2-13; 82:1-11; 103:24-104:20; 112:24-114:2).

When the science is done properly, UT's data proves that Dr. Moriarty's [REDACTED] reported value in Ex. 1004 is correct.

4. Any Difference in "Impurity Profiles" is Meaningless.

UT still argues that the exact identity of the impurities generated by each process in the tiny [REDACTED] set of impurities matters. UT ignores that the '393 Patent claims contain at least hundreds of thousands of compounds (Ex. 2059, 71:17-22), for which none of the impurities have ever been characterized, (*id.*, 72:12-17). And the '393 Patent does not even characterize the impurities of treprostinil (Ex. 2058, 234:16-235:12), which UT maintains as a trade secret requiring a protective order, (Ex. 2058, 93:19-94:24, 233:5-12). As UT's expert Dr. Ruffolo conceded, "I see primarily purities of the parent compound, which is what I believe the invention is related to" and "so I see comparisons between the old process and new process with purities, but – but I don't see, unless I've missed it, I don't see the impurities." (Ex. 2058, 235:6-12.) Secret impurities not identified in the '393 patent for treprostinil, or for hundreds of thousands of other compounds, cannot make the claims patentable.

In any event, neither Dr. Williams nor Dr. Ruffolo opined that the impurity profile of treprostinil mattered:

Q: Do ... any of these particular impurities have deleterious biological consequences? [...]

A: I'm not a clinician, so I don't know.

Q: You don't know?

A: I don't know.

(Ex. 2059, 47:4-13; *see also* Ex. 2058, 257:22-258:9.)

Dr. Ruffolo agrees that both the prior-art and '393 Patent treprostinil are "highly, highly pure." (Ex. 2058, 217:24-218:5.) The FDA only requires [REDACTED] purity for treprostinil, so achieving higher purity is immaterial to the product, (Ex. 2058, 159:20-161:7), and Moriarty-process treprostinil was, and can still be, sold to the public, (Ex. 2058, 179:23-180:17). Where Moriarty and '393-Patent treprostinil have the same purity, as proven by the [REDACTED]-purity level, there are no functional differences between them, as Dr. Williams conceded. (Ex. 2059, 67:2-15.)

B. The Walsh Declaration Is Questionable.

During prosecution of the '393 Patent, UT relied on the Walsh Declaration, and differentiated the '393 Patent product from Moriarty's product by showing a "representative sample" of Moriarty product containing 0.6% impurities, which was contrasted with '393 Patent treprostinil diethanolamine salt and treprostinil having 0.1% and 0.2% impurities, respectively. (Ex. 1002 at 343-350.). As noted by UT, the '393 Patent claims were allowed after submission of the Walsh Declaration. (Resp., 5).

The 46 samples contained in Exhibits 2036 and 2053, and a new exhibit submitted by UT—Exhibit 2006—contradict the Walsh Declaration. As Dr. Winkler observed, the data in the Walsh Declaration was derived from a single sample, and significant batch-to-batch variations in the impurity profile of each batch of treprostinil could affect the results. (Ex. 1009, ¶ 66).

Dr. Winkler's concern is confirmed by UT's results from the 46 batches. For example, Moriarty Batch No. [REDACTED], dated January 25, 2004, and having a purity of [REDACTED] which is the [REDACTED] for these batches, had only [REDACTED] [REDACTED]: [REDACTED]. (Ex. 2036, 5.) According to Dr. Walsh's June 4, 2013 Declaration, "treprostinil as the free acid prepared according to the process specified in claim 1 or 10 of the present application has only three impurities" (Ex. 1002, 348-49.) Moreover, "each of treprostinil as the free acid and treprostinil diethanolamine prepared according to the process specified in claim 1 or 10 of the present application is physically different from treprostinil prepared according to the process of 'Moriarty' at least because neither of them contains a detectable amount of any of benzindene triol, treprostinil methyl ester, 1AU90 treprostinil stereoisomer and 2AU90 treprostinil stereoisomer, each of which were present in detectable amounts in treprostinil produced according to the process of "Moriarty." (Ex. 1002, 349.) Yet Moriarty Batch No. [REDACTED] did not contain detectable amounts of any of these impurities either, proving that

Dr. Walsh could not make his conclusion.

UT told the FDA that treprostinil diethanolamine salt made in accordance with the '393 Patent "[REDACTED] [REDACTED] [REDACTED]." (Ex. 2006, 3-6.) Yet these impurities, supposedly removed by carrying out step (d) in the '393 Patent's claims, are not described in the Walsh Declaration, which instead presents "Impurities ... [Total Related Substances]" as 0.2% for the free acid, and 0.1% for the salt, (Ex. 1002, 348), meaning that the free acid is *less pure* than the diethanolamine salt, and not more pure as UT represented to the FDA in Exhibit 2006. Dr. Williams could not provide an explanation for this discrepancy (Ex. 2059, 199:6-18), which contradicts the Walsh Declaration.

III. DR. WILLIAMS' TESTIMONY CONFIRMS THAT PHARES ANTICIPATES CERTAIN '393 PATENT CLAIMS.

Phares (Ex.1005) makes the same treprostinil diethanolamine salt claimed in every claim of the '393 Patent where optional step (d) is not completed, as explained in SteadyMed's Petition and Dr. Winkler's Declaration (Ex. 1009, ¶¶ 44-71.) UT responds by rejecting the Board's claim construction, discussed later in this Reply, and with three factual arguments: (1) that SteadyMed cannot show that Phares used the Moriarty process, claimed in steps (a) and (b) of the '393 Patent's claims; (2) that SteadyMed cannot show that Phares' treprostinil diethanolamine

Form B salt has the same purity level as the '393 Patent's Form B salt; and (3) that HPLC Assay Analysis can measure purity better than 0.4%, even though Dr. Winkler pointed out that the error in UT's own equipment is at least 0.4%, (Ex. 1009, ¶ 70).

But Dr. Williams concedes that the process in Phares for making treprostinil's (-)-enantiomer carries out the same alkylation step (a) and hydrolysis step (b) in the '393 Patent's claims, thus disclosing these steps for treprostinil. And the attached Declaration of Robin D. Rogers (Ex. 1022), SteadyMed's polymorph expert, explains why the melting point of treprostinil diethanolamine salt Form B can be compared between the '393 Patent and Phares reference, and that the particular sample in Phares had at least the same purity as the '393 Patent's examples. Finally, UT's own data showed that the average purity of Moriarty samples was [REDACTED], proving that batch variation is at least [REDACTED] and UT's representation to the FDA stated that treprostinil purity will be maintained between [REDACTED] [REDACTED], (Ex. 2006), proving a [REDACTED] variability applies to purity measurements.

A. Phares discloses steps(a) and (b) of the '393 Patent.

"Q. Okay. So what we see here is there's an alkylating step (a) and a hydrolyzing step (b) on page 42 of the Phares reference. A. Yes." (Ex. 2059, 190:16-19). On Phares page 42 (Ex. 1005), as Dr. Williams concedes in this testimony, steps (a) and (b) are carried out on the mirror image version of the

compounds described in the '393 Patent claims, and as Dr. Winkler explains, the Phares patent at page 42 states that the enantiomer procedure is the same procedure used to make "the commercial drug (+)-Treprostinil." (Ex. 1009 ¶ 56; Ex. 1005, 42.) Thus, in describing that the process for making both enantiomers uses steps (a) and (b), and explaining that the process for the (-)-enantiomer is merely a variation on the already known (+)-enantiomer process, Phares inherently discloses steps (a) and (b) to create the (+)-enantiomer.

B. Phares' Higher Melting Point Means It is at Least Equally Pure.

Dr. Winkler explained that since the Phares treprostinil diethanolamine salt Form B melted at 107°C, but the same Form B in the '393 Patent melted at around 106.6 °C, the Phares sample was necessarily as pure as the '393 Patent's samples. Dr. Williams, who is "not a polymorph expert," (Ex. 2059, 158:17-18; 156:25-157:2), contends nevertheless that the melting point of two samples of the same polymorph (crystal form) cannot be compared to determine their relative purities. (Ex. 2020 ¶ 75.) According to UT and Dr. Williams, how a polymorph is made, including what solvents are used, can affect its melting point, even if the polymorphs are identical. (Resp., 22-24; Ex. 2020 ¶ 75.)

As set forth in Dr. Rogers' Declaration (Ex. 1022, ¶¶ 49-52) and admitted by Dr. Williams, melting point is one of the most common ways to identify different polymorphs. (Ex. 2059, 158:20-25); *see also* Exs. 1024-1026. Dr. Williams

concedes that in the '393 Patent, treprostinil diethanolamine salt is identified as being Form B based solely on its melting point. (Ex. 2059, 170:24-171:3.) And Dr. Williams concedes that the same treprostinil diethanolamine salt polymorph—Form B—is presented in the Phares reference and '393 Patent. (*Id.*, 168:6-11).

While Dr. Williams relies on his "personal experience" observing different melting points for crystals made with different solvents, he conceded that he knew of no literature to support his opinion. (*Id.*, 184:22-185:2.) Dr. Williams conceded that the one article he relied upon in his declaration, Ex. 2030, in fact describes different crystal forms having different melting points, and not the same crystal form having different melting points. (*Id.*, 180:9-25.)

By contrast, Dr. Rogers' Declaration cites several literature sources explaining that melting point uniquely identifies a polymorph. (Ex. 1022, ¶¶ 49-52). Thus, for the same polymorph, if the melting point differs, it is due to impurities contained in the sample having a lower melting point. (*Id.*, ¶ 64.) Dr. Rogers concludes that Phares' higher melting point is necessarily due to higher or at least identical purity. (*Id.*, ¶ 74.) Moreover, the width of the DSC peak in the Phares reference is very narrow, consistent with a very pure material. (*Id.*, ¶ 84.)

C. HPLC Analysis Has Error Bars Too Large to Distinguish the Tiny Differences in Purity Levels UT Relies Upon.

As Dr. Winkler explained, it is not possible to measure treprostinil purity levels better than 0.4%, as shown by UT's own data. (Ex. 1009, ¶ 70.) Now that UT has

provided multiple certificates of analysis for treprostinil, it is now confirmed that UT's Moriarty purity varies by at least [REDACTED], and indeed, Dr. Williams conceded he had no reason to disagree with this [REDACTED] value. (Ex. 2059, 218:22-24.)

UT's own exhibits confirm that HPLC assay analysis has a wide error range:

" [REDACTED]
[REDACTED]. " (Ex. 2006, 3.) UT's expert Dr. Williams agrees with this statement and that "[REDACTED]
[REDACTED]" refers to the HPLC assay for purity. (Ex. 2059, 133:17-25, 134:24-135:4.)

UT discounts that HPLC assay analysis has a wide error range by suggesting that purity should instead be measured by totaling up "total related substances," which are measurements of particular impurities identified in the HPLC analysis. (Resp., 2-3, 29-30.) But as acknowledged by Dr. Williams, some impurities will not be detected in a total-related-substance analysis (Ex. 2059, 140:5-9.). UT's expert Dr. Ruffolo confirmed that in the '393 Patent, all of the analyses are HPLC analyses of the total treprostinil against a reference standard, and not measurements of total related substances. (Ex. 2058, 153:16-154:7.) And both UT experts acknowledged that the FDA uses HPLC assay analysis to evaluate the overall purity of treprostinil, and to decide whether that treprostinil meets a [REDACTED] purity requirement that would allow it to be sold. (Ex. 2058, 159:20-161:7; Ex.

2059, 150:23-151:25.)

UT criticizes Dr. Winkler, falsely stating that Dr. Winkler does not understand HPLC analysis, and does not know anything about the error in UT's HPLC equipment. (Resp., 3, 30.) Dr. Winkler instead testified that there is no information regarding the error in the amount of "[REDACTED]," an impurity present in UT's treprostinil at about [REDACTED]. (Ex. 2051, 63:3-14.) The error in the [REDACTED] measurement is irrelevant to the error in treprostinil purity, especially where treprostinil purity is a number near [REDACTED] ([REDACTED]), 1000 times larger than the amount of [REDACTED]. Regarding error in HPLC Analysis of treprostinil purity, Dr. Winkler was unequivocal at his deposition:

I think the thing that I am able to conclude from the data that is on page 6 of this, of this letter is that the error in the HPLC assay could be as high as 1 percent in the first column and by my analysis could be as high as 2 percent in the second column.

(Ex. 2051, 88:12-18.)

IV. UT'S EXPERTS CONFIRM THE CLAIMS' OBVIOUSNESS.

A. Moriarty Was Recognized as the Best Method to Make Treprostinil Before the Phares Reference was Published.

UT contends that Phares does not anticipate because it does not disclose the first two steps, steps (a) and (b), which were used in the Moriarty process. As explained above, this contention is wrong. But even if it were true, UT's expert Dr. Williams provided testimony confirming that there was a strong reason to combine

Moriarty with Phares: Moriarty was well-known to be the best way to make treprostinil, and would have been the way Dr. Williams' own graduate students would have made the treprostinil in Phares before turning it into its salt.

First, Dr. Williams confirmed that steps (a) and (b) in the '393 Patent claims were disclosed by the Moriarty patent, Ex. 1003. (Ex. 2059, 53:19-54:7). Second, Dr. Williams confirmed that "a person of ordinary skill in the art in 2005 reading the Phares reference, that person would know that the best way to make treprostinil is the Moriarty method" (*id.*, 240:2-7). And third, he confirmed that "a typical person of ordinary skill in the art, typical graduate student, they would have found the Moriarty paper and used that technique to make treprostinil in 2005." (*Id.*, 244:10-21.) While UT's expert Dr. Ruffolo disagrees with Dr. Winkler regarding the appropriate level of skill, it is Dr. Ruffolo's opinion that the skill level should be higher than Dr. Winkler's, and that a person of ordinary skill should at least have a Ph.D. (Ex. 2058, 52:2-17.) If a graduate student would use Moriarty, then certainly a Ph.D. would do so. Thus, UT's experts essentially confirm that a person of ordinary skill in the art would combine Moriarty with Phares when making Phares' treprostinil salt.

B. UT's Experts Confirm That Crystallization Through A Salt To Purify Is Organic Chemistry 101.

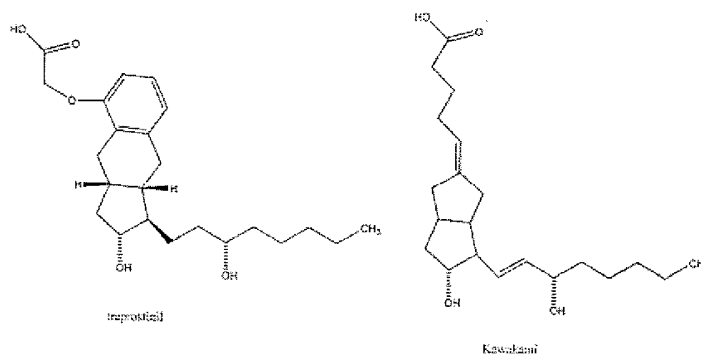
As shown by UT expert Dr. Ruffolo's testimony, *supra*, the process steps (c) and (d), which crystallize a compound as its salt and then convert the salt back to

the acid, have been around for "decades," at least as far back as the late 1960s. (Ex. 2058, 175:19-176:22, 179:11-17.) "[I]f a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 417 (2007). UT cannot claim that using this elementary chemistry technique is nonobvious merely because UT applied it to treprostinil.

UT also argues that the particular impurities found in treprostinil, which are said to be stereoisomers, would not have been removed using crystallization. First, there is no teaching in the '393 Patent or the prior art of record regarding what kinds of impurities are present in treprostinil, or, as conceded by UT's experts, of the hundreds of thousands of other compounds included in the claims. (Ex. 2059, 74:18-25; Ex. 2058, 234:16-235:17.) UT maintains the identity of these impurities as a trade secret, necessitating a Protective Order to cover these proceedings so that information on these impurities is not revealed. UT's secret information regarding these impurities' identity cannot be the basis for why a person of ordinary skill in the art would not use crystallization here.

Second, the Kawakami reference, Ex. 1007, used crystallization to separate stereoisomers, as confirmed by Dr. Winkler under UT's counsel's cross-examination. (Ex. 2051, 203:4-204:20.) UT distinguishes Kawakami on grounds

that it concerns a different prostacyclin, not treprostinil, and offers chemical drawings making Kawakami's prostacyclin look different from treprostinil. (Resp., 40.) But SteadyMed has generated more fair drawings of these two structures, and Dr. Williams confirmed that these drawings accurately depict the structures. (Ex. 2059, 245:23-247:1). These new drawings are submitted as Ex. 1028:



When properly depicted, treprostinil and Kawakami are similar compounds.

Finally, treprostinil can be made in any purity desired, as Dr. Williams admitted, by prior-art purification processes like chromatography, since "you could repurify and purify anything you want by chromatography to 99.99999 percent if you wanted to." (Ex. 2059, 94:8-12). While Dr. Williams contends that would be an impractical approach in large-scale manufacturing, he concedes that the '393 Patent's claims are not limited to large-scale manufacturing. (*Id.*, 187:18-188:3.) Thus, there was no barrier to making treprostinil of any purity, and while doing so by using crystallization is obvious, a product having any desired purity can be made by any method, so purer treprostinil is obvious.

V. THE BOARD CONSTRUED THE CLAIMS CORRECTLY.

UT challenges the Board's construction of the legal terms "comprising" and "product," which is surprising since that the Board generally accepted UT's constructions from UT's Preliminary Response. UT had argued that "comprising" should mean "included but not limited to." (Paper 10, at 23). And the Board agreed. (Paper 12, at 13). Now UT contends that "comprising" should not be given its usual open-ended construction. (Resp., 13.) UT points to the prosecution history as effecting a disclaimer of the usual meaning of "comprising," but "[a] statement in the prosecution history can only amount to disclaimer if the applicant clearly and unambiguously' disavowed claim scope." *Toshiba Corp. v. Imation Corp.*, 681 F. 3d 1358, 1370 (Fed. Cir. 2012). UT points to no statements in the prosecution history regarding the meaning of "comprising," but, argues that since the examiner allowed the claims, he must have construed "comprising" according to UT's non-open construction. (Resp., 16.) If that were a clear and unambiguous disavowal, every Patent Owner could argue that its claims should be construed narrowly enough to make them valid, since the initial examiner allowed them.

UT also objects to the Board's plain and ordinary meaning for the term "product," and contends that "product" should be narrowly construed. But this narrow construction is not supportable, and even UT's expert Dr. Williams conceded that "product" is broadly used in the art, assuming that it is even a term

of art and not a legal term. First, Dr. Williams acknowledged that "chemists use the word 'product' in two different contexts, routinely." (Ex. 2059, 248:4-5.) "Product" can mean in chemistry a product and its impurities, or the molecular structure alone. (*Id.*, 248:13-23.) Second, Dr. Williams conceded that the '393 Patent and prosecution history do not provide definitions for "product." (*Id.*, 248:24-249:13.) Third, Dr. Williams' Declaration recognizes that "product" is a term in patent law relating to "product-by-process" claims, (Ex. 2020, ¶ 30), but does not explain why this legal definition should not apply here. Fourth, Dr. Williams' own example of "product" in his own writing—Ex. 2028—uses "product" to mean a product created by nature, and not by a chemical reaction, when it refers to "the natural product from marine sources." (Ex. 2020, ¶ 63.) And fifth, while Dr. Winkler testified that "product" includes the product of a chemical reaction, he testified that "product" was a broad term that encompassed more. (Ex. 2051, 152:21-154:21.)

It is unclear how UT's claim constructions matter. UT seeks a construction limiting the claims by impurity profile, (Resp., 18), but UT cannot articulate how its proposed constructions for "comprising" and "product" effect this result. There is no record evidence showing that the claimed processes and their products have unique impurity profiles, and the '393 Patent lacks information regarding the impurity profiles of treprostinil or its many salts, or for the thousands of compounds in its claims. (Ex. 2059, 71:17-72:17, 74:18-25; Ex. 2058, 234:16-

235:17.) The impurity profiles are not unique to each claim, but depend on unclaimed elements like what solvents were used, (Ex. 2058, 239:22-241:14), whether the intermediate products were purified, (Ex. 2058, 239:8-20, Ex. 2059, 69:17-71:9), and what bases, acids, or other reactants that the claims allow were used. Product-by-process claims would have no definite scope under UT's analysis.

VI. NO LONG-FELT NEED FOR THESE CLAIMS' PRODUCTS.

While UT suggests there was a long-felt need for these claims' products, its long-felt-need expert Dr. Ruffolo testified otherwise: "there's nothing I can tell you about the long-felt need for those other compounds [of claim 1]," (Ex. 2058, 65:4-13); or of claim 9 (Ex. 2058, 69:20-70:11); or of claims 12, 13, 16, 17, 21, or 22 (Ex. 2058, 110:17-111:9, 114:16-117:3, 118:2-5; 118:23-119:23, 121:5-23); or of any claim that was not limited to treprostinil and treprostinil diethanolamine salt, (Ex. 2058, 68:14-25). Only claims 10, 14, 15, and 17 are limited to treprostinil or its salt.

Regarding treprostinil or its diethanolamine salt, Dr. Ruffolo conceded that he had no idea if FDA had asked for a change in purity, (*id.*, 45:15-22), nor could he identify anyone who expressed a particular desire for greater purity, (*id.*, 130:16-25.) He also recognized that one could usually purify a drug further by running purification procedures repeatedly, (*id.*, 46:9-18), which Dr. Williams confirmed was true for treprostinil, (Ex. 2059, 94:8-12), and proves that there was no need for

the "invention." Dr. Ruffolo also conceded, contrary to UT's arguments, that a change in purity specifications is not a major amendment, (Ex. 2058, 310:5-13), but that the other changes UT applied for—changing starting materials and manufacturing facilities, were major amendments (*id.*, 310:13-18).

Regarding claims 10, 14, 15, and 17, Dr. Ruffolo concedes that: (1) the FDA requires only a [REDACTED] purity level, which is *much lower* than any levels produced by the prior art, (*id.*, 159:20-161:7); (2) the FDA would allow batches of treprostinil produced by the Moriarty process to be sold, (*id.*, 179:23-180:17), since Moriarty products are "highly, highly pure," (*id.*, 217:11-218:5); and (3) there is no clinical difference between the prior-art Moriarty product and the '393 Patent product (*id.* 315:15-23). Thus, the FDA expressed no need for a purer product. Moreover, Dr. Ruffolo does not know if UT's products that he relies upon are covered by these claims. (*Id.*, 292:25-293:2.)

Dr. Ruffolo's opinion relies on Dr. Williams' incorrect calculation showing 99.0% purity, but Dr. Ruffolo concedes he did not review that calculation, nor speak to Dr. Williams, and depends entirely on Dr. Williams. (*Id.*, 262:4-263:5.) Since Dr. Williams now concedes that the correctly performed calculation shows a [REDACTED] purity, (Ex. 2059, 218:3-8), Dr. Ruffolo's opinions should be disregarded.

Date: September 27, 2016

/s/ Stuart E. Pollack /
Stuart E. Pollack, J.D. Ph.D.
Reg. No. 43,862
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Respectfully submitted,

/s/ Lisa A. Haile /
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CERTIFICATE OF WORD COUNT

Pursuant to 37 C.F.R. § 42.24, the undersigned attorney for Petitioner certifies that the document contains 5,599 words in 14-point Times New Roman font, excluding the parts of the document that are exempted by 37 C.F.R. § 42.24(a)(1), according to the word count tool in Microsoft Word.

Date: September 27, 2016

Respectfully submitted,

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CERTIFICATE OF SERVICE

The undersigned certifies that a copy of the attached Petitioner's Reply was served via electronic mail to the following:

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1 UNITED STATES PATENT AND TRADEMARK OFFICE
2 BEFORE THE PATENT TRIAL AND APPEAL BOARD

3
4 STEADYMED LTD.,
5 Petitioner,

6 vs.

7 UNITED THERAPEUTICS
8 CORPORATION,

9 Patent Owner.

10 Case IPR2016-000006 (Patent 8,497,393)

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12
13
14 VIDEOTAPED DEPOSITION OF ROBERT M. WILLIAMS, PH.D.

15
16 Friday, August 26, 2016

17 9:30 a.m.

18
19 12235 El Camino Real

20 San Diego, California

21
22
23 Reported by:

24 Harry Alan Palter

25 CSR No. 7708, Certified LiveNote Reporter
P.1

UT Ex. 2059
SteadyMed v. United Therapeutics
IPR2016-00006

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P.2

UT Ex. 2059
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IPR2016-00006

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UT Ex. 2059
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IPR2016-00006

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BY MS. HASPER

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•—————•
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United Therapeutics EX2006
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ROBERT M. WILLIAMS, PH.D.

SteadyMed Ltd. vs. United Therapeutics Corporation

Friday, August 26, 2016

Harry Alan Palter, CSR No. 7708

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Elisa Dreier Reporting Corp., U.S. Legal Support Company (212)557-5558
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San Diego, California

Friday, August 26, 2016; 9:30 a.m.

THE VIDEOGRAPHER: Good morning. We are on the record. This is the videotaped deposition of Robert M. Williams, Ph.D., in the matter of SteadyMed, Ltd., vs. United Therapeutics Corporation.

This deposition is taking place at 12235 El Camino Real, Suite 200, San Diego, California 92130, on August 26, 2016, at 9:30 A.M.

My name is Kory Ross. I'm the videographer with U.S. Legal Support. Video and audio recording will be taking place unless all counsel agree to go off the record.

Would all present please identify themselves, beginning with the witness.

THE WITNESS: Robert M. Williams.

MR. POLLACK: Stuart E. Pollack, DLA Piper, LLP U.S., on behalf of SteadyMed, Ltd., the petitioner. I'm joined with Maya Choksi from the same law firm.

MS. HASPER: Katherine Hasper of Wilson, Sonsini, Goodrich & Rosati, on behalf of United

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1 Therapeutics and the witness.

2 MR. MAEBIUS: And Steve Maebius from
3 Foley & Lardner on behalf of patent owner.

4 THE VIDEOGRAPHER: Thank you, Counsel.
5 The certified court reporter is Harry
6 Palter.

7 Will you please swear in the witness.
8
9

10 ROBERT M. WILLIAMS, PH.D.,
11 having been duly administered an oath in accordance
12 with the California Code of Civil Procedure
13 Section 2094, was examined and testified as follows:
14
15

16 EXAMINATION

17 BY MR. POLLACK:

18 Q Good morning, Dr. Williams.

19 A Good morning, Counselor.

20 Q Just as a formality to start today, could
21 you state your name for the record and your current
22 position.

23 A Robert M. Williams, university
24 distinguished professor at Colorado State
25 University.

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1 Q Okay. Now, I know you've been deposed
2 before; correct?

3 A Yes.

4 Q How many times have you been deposed?

5 A I don't know the exact number. It's
6 somewhere around 17, 15 -- 16, 17, somewhere in
7 there. I lost count, actually.

8 Q Okay. Were all of those patent cases?

9 A Yes.

10 Q And how many of those cases were for
11 United Therapeutics?

12 A Let me see. Three. I think this would
13 be my third deposition with United Therapeutics.
14 But I'd have to -- I can check -- check. It may be
15 three or four. I don't remember. I think it's for
16 sure three.

17 Q Okay. But you understand all the rules
18 of depositions at this point?

19 A Yes.

20 Q Okay. And there's no reason today that
21 you can't give your best testimony?

22 A No.

23 Q All right.

24 MR. POLLACK: I'm going to mark as

25 Williams Deposition Exhibit 1 the Petitioner's

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1 Notice of Deposition.

2 (Exhibit 1 marked)

3 BY MR. POLLACK:

4 Q And Dr. Williams, are you here today in
5 response to Petitioner's Notice of Deposition of
6 Robert M. Williams, Ph.D.?

7 A Yes, that's my understanding.

8 Q So you've done two other depositions for
9 United Therapeutics. Did both of those cases also
10 involve treprostinil?

11 A Yes.

12 Q And those were two cases in New Jersey
13 involving generic challenges to United Therapeutics
14 Remodulin product?

15 A Yes.

16 Q Do you remember the names of the two
17 defendants in those cases?

18 A Sandoz in the first case, which went to
19 trial, and then Teva.

20 Q Okay. And the type of case is still
21 ongoing?

22 A I believe so.

23 Q Have you submitted an expert report or
24 Declaration in the Teva case?

25 A Yes.

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1 Q And have you -- and you've been deposed
2 already in that Teva case?

3 A Yes.

4 Q Did your expert Declaration or deposition
5 concern the '393 patent at all?

6 A Yes.

7 Q Okay. Did you opine on the validity or
8 invalidity of the '393 patent in that case?

9 A No.

10 Q Okay. What did you opine on?

11 A Claim construction.

12 Q Okay. And what were the issues regarding
13 claim construction in that case?

14 MS. HASPER: Objection. Relevance.

15 THE WITNESS: I don't -- I don't recall
16 off the top of my head.

17 BY MR. POLLACK:

18 Q Okay. Were they similar to the claim
19 construction issues in the current IPR?

20 A I believe there was some overlap, yes.

21 Q Which ones were an overlap?

22 A Again, I'd have to go back and look at my
23 Declaration.

24 Q You don't recall --

25 A It's -- I don't recall exactly.

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1 Q Okay.

2 A I don't want to give an inaccurate
3 answer.

4 Q Absolutely.

5 Do you recall if there was any discussion
6 of the meaning of the term "product" in the '393
7 case with either -- with Teva?

8 MS. HASPER: Objection. Relevance.

9 You may answer to the extent it doesn't
10 reveal privilege.

11 THE WITNESS: Again, my -- I haven't
12 looked at that material for awhile, so I'm hesitant
13 to give an answer right now.

14 BY MR. POLLACK:

15 Q You're not sure?

16 A I'm not 100 percent sure.

17 Q Okay. What about the word "comprising"?
18 Was there any issue about the meaning of the word
19 "comprising" in the '393 case?

20 MS. HASPER: Same objection.

21 THE WITNESS: I'd have to give the same
22 answer. I don't exactly recall.

23 BY MR. POLLACK:

24 Q Well, do you know did you -- whether
25 there was an issue or not, did you make any comments

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UT Ex. 2059

1 or provide any opinions regarding the meaning of the
2 word "comprising" in the Teva case?

3 MS. HASPER: Same objection.

4 THE WITNESS: I didn't hear you,
5 Katherine?

6 MS. HASPER: Same objection.

7 THE WITNESS: And your question again
8 was? Did I give --

9 BY MR. POLLACK:

10 Q Did you give any opinion of any form
11 regarding the meaning of the term "comprising" in
12 the Teva case regardless of what the -- ultimate
13 issue was?

14 A I'd need to refresh my recollection by
15 looking at the Declaration I submitted.

16 Q You don't recall as you sit here?

17 A I don't recall.

18 Q And do you know whether the Declaration
19 you submitted, whether it was -- whether it was
20 stamped "confidential"?

21 A I believe so.

22 MR. POLLACK: Counsel, to the extent it's
23 available, we'd like to get a copy of his
24 Declaration from the Teva case.

25 MS. HASPER: I'll look into it for you.

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1 BY MR. POLLACK:

2 Q And are you also involved in certain
3 other generic challenges to the Remodulin product,
4 also pending the District of New Jersey?

5 A I know that there's a case now that I've
6 been retained for involving Watson Laboratories.

7 Q Any others?

8 MS. HASPER: Objection. Privilege.

9 To the extent that you can answer without
10 revealing attorney-client communications or
11 confidential information, you may do so.

12 THE WITNESS: Not that I'm aware of.

13 BY MR. POLLACK:

14 Q Not that you're aware of? Okay.

15 And in the Watson case, have you
16 submitted any opinions or formed any opinions in
17 that case?

18 A Not yet.

19 Q Not yet? Do you know what the issues are
20 in the Watson case?

21 MS. HASPER: Again, objection.

22 Privilege.

23 I caution the witness not to answer to
24 the extent that doing so would reveal privileged
25 information.

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1 THE WITNESS: That's at a very early
2 stage, so I haven't done any --

3 BY MR. POLLACK:

4 Q You haven't done anything?

5 A No.

6 Q Okay. About how many hours in total have
7 you worked on cases for United Therapeutics at this
8 point?

9 MS. HASPER: Objection.

10 Mr. Pollack, this is -- you're asking
11 about how much time he's spent either on his own
12 with counsel working on --

13 MR. POLLACK: Okay. Stop the speaking
14 objections now; all right?

15 MS. HASPER: I'm trying to explain that
16 you're asking a line of questions which assumes --

17 MR. POLLACK: Okay. Just -- just say
18 your objection.

19 (Indiscernible crosstalk)

20 THE WITNESS: Excuse me, Counselor?

21 BY MR. POLLACK:

22 Q Yes. How many hours have you worked on
23 cases for United Therapeutics?

24 MS. HASPER: Objection. I instruct the
25 witness not to answer to the extent doing so will

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1 reveal privileged information.

2 THE WITNESS: I have no idea.

3 BY MR. POLLACK:

4 Q Well, more than a hundred?

5 MS. HASPER: Objection. Privileged.

6 THE WITNESS: I don't know.

7 MR. POLLACK: Are you instructing him not
8 to answer?

9 MS. HASPER: The objection -- so I'm
10 going to give you a standing instruction to this
11 entire line of questioning, that to the extent
12 Mr. Pollack asks you about privileged information,
13 including your communications with counsel for
14 United Therapeutics, that we request you not answer.

15 MR. POLLACK: I'm not asking about his
16 communications.

17 BY MR. POLLACK:

18 Q About how much income have you received
19 so far from United Therapeutics working on their
20 cases?

21 MS. HASPER: Objection. Relevance.
22 Prejudicial.

23 THE WITNESS: I don't recall.

24 BY MR. POLLACK:

25 Q Over \$100,000?

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UT Ex. 2059
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1 MS. HASPER: Objection. Relevance.
2 Prejudicial.

3 THE WITNESS: I'd have to go look at my
4 invoices.

5 BY MR. POLLACK:

6 Q Over \$50,000?

7 MS. HASPER: Objection. Relevance.
8 Prejudicial.

9 THE WITNESS: Likely.

10 BY MR. POLLACK:

11 Q Likely over 50 -- between 50 and 100? Is
12 that fair?

13 MS. HASPER: Objection. Relevance.
14 Prejudicial.

15 THE WITNESS: I don't know.

16 BY MR. POLLACK:

17 Q It could be over hundred?

18 MS. HASPER: Objection. Relevance.
19 Prejudicial. Asked and answered.

20 BY MR. POLLACK:

21 Q It could be over a hundred thousand
22 dollars?

23 A I'm thinking I'd have to go look.

24 MS. HASPER: Objection. Relevance,
25 privilege, asked and answered.

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1 THE WITNESS: I'd have to look.

2 BY MR. POLLACK:

3 Q You'd have to look.

4 I'm asking if it's possible whether it
5 was over a hundred thousand dollars?

6 MS. HASPER: Objection. Relevance.
7 Privileged. Asked and answered.

8 THE WITNESS: I just remember I've been
9 working on a lot of different cases at the same
10 time.

11 BY MR. POLLACK:

12 Q Sure.

13 A I don't remember.

14 Q Sure.

15 What's your hourly rate?

16 A \$650 an hour.

17 Q Okay. Have you worked over a hundred
18 hours on United Therapeutics cases?

19 MS. HASPER: Same objection.

20 THE WITNESS: I'd have to give the same
21 answer. I'd have to go back and look at my
22 invoices. I don't -- I don't recall off the top of
23 my head.

24 BY MR. POLLACK:

25 Q Okay. What about in this IPR? About how
P.19 UT Ex. 2059
SteadyMed v. United Therapeutics
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1 many hours have you worked in this IPR?

2 MS. HASPER: Same objection.

3 THE WITNESS: I don't know.

4 BY MR. POLLACK:

5 Q No idea?

6 A No.

7 Q "No." More than 40 hours?

8 MS. HASPER: Same objection.

9 THE WITNESS: Again, I don't want to give
10 an inaccurate answer, so I would need to look at my
11 invoices.

12 BY MR. POLLACK:

13 Q I understand. But I'm asking just for an
14 approximate answer. Is it more than 40 hours?

15 MS. HASPER: Same objection.

16 THE WITNESS: I don't know.

17 BY MR. POLLACK:

18 Q About how much have you invoiced for in
19 this matter?

20 MS. HASPER: Same objection.

21 THE WITNESS: Between two and three
22 invoices, so I'm not really sure.

23 BY MR. POLLACK:

24 Q Okay. About how much was this at each
25 invoice?

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1 A I do not recall.

2 MS. HASPER: Same objection.

3 BY MR. POLLACK:

4 Q Was each invoice larger than \$50,000?

5 A No.

6 MS. HASPER: Same objection.

7 BY MR. POLLACK:

8 Q Were some of the invoices larger than
9 \$50,000?

10 A No, I don't think so.

11 Q You think all of them were below \$50,000?

12 A Yes.

13 Q Okay. And there were about three
14 invoices?

15 MS. HASPER: Same objection.

16 THE WITNESS: Again, I can't exactly
17 recall.

18 BY MR. POLLACK:

19 Q Okay. Can you give --

20 A Because I'm working on other matters.
21 Completely different matters, not for United
22 Therapeutics. So --

23 Q Sure.

24 A I have a very accurate record on my
25 computer, but I don't remember.

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1 Q How many matters are you working on now?

2 MS. HASPER: Objection. Relevance.

3 THE WITNESS: Around nine right now.

4 BY MR. POLLACK:

5 Q Okay.

6 A I'm paid for about nine different
7 matters.

8 Q All right. About how much do you earn a
9 year doing matters?

10 MS. HASPER: Objection. Relevance.

11 THE WITNESS: Which -- what do you mean
12 "a year"? It varies from year to year.

13 BY MR. POLLACK:

14 Q How about this year? How much in --

15 MS. HASPER: Same objection.

16 BY MR. POLLACK:

17 Q -- 2016 so far?

18 A I haven't tabulated that yet from my
19 accountant. He's been buggin' me to give him
20 numbers to him before September 15th. So I'll be
21 doing that soon. I don't know.

22 Q Okay. Approximately how much?

23 A I don't know.

24 Q How about 2015? How much?

25 MS. HASPER: Same objection.

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1 BY MR. POLLACK:

2 Q How much have you earned in 2015 on
3 patent matters?

4 A It was somewhere around \$800,000.

5 Q And what about 2014? A similar amount?

6 MS. HASPER: Same objection.

7 THE WITNESS: I don't recall.

8 BY MR. POLLACK:

9 Q Of that \$800,000 last year, about how
10 much of that was from United Therapeutics?

11 A I have no idea.

12 MS. HASPER: Same objection.

13 BY MR. POLLACK:

14 Q Would you say half of your time --
15 (Indiscernible crosstalk)

16 THE WITNESS: I have no idea.

17 BY MR. POLLACK:

18 Q No idea at all?

19 A No.

20 Q Okay.

21 MS. HASPER: I'll just repeat what got

22 lost in the crosstalk was me saying, "Same

23 objection." Also, "privilege."

24 BY MR. POLLACK:

25 Q Have you done work in other -- you

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1 understand this is a proceeding called an "inter
2 partes review"?

3 A Yes.

4 Q Have you done work in other inter partes
5 reviews?

6 A Not yet, no.

7 Q This is your first one?

8 A Yes.

9 Q Okay. And how many cases have you
10 testified at trial in?

11 A Four times.

12 Q Four times?

13 A Four different cases.

14 Q Okay. One of those was the Sandoz case?

15 A Yes.

16 Q That case didn't involve the '393 patent;
17 is that right?

18 A No.

19 Q Okay. Are you involved also -- I think
20 there's another Sandoz case involving the '393
21 patent? Are you involved in that one?

22 MS. HASPER: Objection. Foundation.

23 THE WITNESS: Not that I'm aware of.

24 BY MR. POLLACK:

25 Q No?

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1 Okay. The Declaration?

2 MR. POLLACK: I'm going to mark as
3 Williams Deposition Exhibit 2 the Declaration of
4 Robert M. Williams, Ph.D., in support of patent
5 owner response to petition.

6 (Exhibit 2 marked)

7 BY MR. POLLACK:

8 Q If you could just verify me that that's a
9 fair and accurate copy of your Declaration?

10 A (Examining document) So this is -- yes.
11 This is a copy of my Declaration as submitted.

12 Q Okay. Were there any mistakes in your
13 Declaration that you discovered?

14 A Yes.

15 Q Okay. What are those mistakes?

16 A There is two minor mistakes. At
17 paragraph 88, there's a typographical error. One,
18 two, three, four -- fifth line down, middle,
19 Exhibit 2034 should be Exhibit 2044.

20 Q Okay.

21 A And the second error is there is a small
22 change to Exhibit B, entry --

23 Q I'm sorry, where are you?

24 A Exhibit B.

25 Q Okay.

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1 A Page 50, the entry [REDACTED] was
2 inadvertently a duplicate. So that -- that one
3 entry needs to be crossed out.

4 Q Okay. Could you tell me what page we're
5 looking at?

6 A 50.

7 Q And which entry is it?

8 A It's the -- I believe it's the [REDACTED]
9 was inadvertently a duplicate of another -- another
10 entry.

11 Q And that is the 17th one down?

12 A Yes. I think that's correct.

13 Q Okay. Other than those two corrections,
14 are there any other corrections you want to make?

15 A Not that I have found.

16 Q Okay. Are all of your opinions in this
17 matter -- are they all contained in your
18 Declaration?

19 A Yes.

20 Q Okay. Who did the first draft of your
21 expert Declaration?

22 A I actually made the draft of -- sort of
23 the template of the first draft and, Counsel, Bobby
24 Delafield, and I also worked with Katherine here.

25 We went back-and-forth by e-mail assembling

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1 different drafts as we went along, and discussed
2 issues and --

3 Q What's Katherine's last name?

4 A Hasper.

5 Q All right. Anyone else you worked with
6 at counsel?

7 MS. HASPER: You can answer to the extent
8 it doesn't reveal privileged information.

9 THE WITNESS: I primarily worked with
10 Bobby and Katherine, as I recall.

11 BY MR. POLLACK:

12 Q Who assembled the appendices "A" and "B"?

13 A Counsel did.

14 Q Did you have any questions about how
15 counsel assembled Exhibits A and B -- or appendices
16 "A" and "B"?

17 A What do you mean?

18 Q Did you ask them: How were these
19 assembled?

20 A Yes. I worked with them, and there was
21 underlying batch data that I was provided with, and
22 I was able to cross-check that the entries were all
23 accurate.

24 Q Okay. Who selected the particular
25 batches that were chosen to the analyzed?

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1 A These were -- I think these were
2 requested by counsel from United Therapeutics.

3 Q Okay. You had nothing to do with the
4 selection?

5 A Other than asking for as much batch data
6 as was available.

7 Q Okay. Did you get all batch data that
8 was available?

9 A I believe so.

10 Q Okay. Was there any batch data that you
11 saw that's not included in appendices "A" and "B"?

12 A No.

13 Q Did you ask whether there was any other
14 batch data that you could include?

15 A I did ask.

16 Q Okay. And what was the answer?

17 A That this was all they were able to find.

18 Q Okay. If we can go in your Declaration
19 to paragraph 27.

20 Here in paragraph 27, you list some
21 patent litigation matters that you were working on?

22 A Yes.

23 Q Is that right? Okay.

24 Are there -- it says here, "Process

25 chemistry patent litigation." Are there other kinds

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1 of litigation matters that you were working on that
2 aren't in this list?

3 A Yes.

4 Q Okay. About how many other matters?

5 A So this lists, I believe, seven. And
6 I've worked on somewhere around 27. So 20 other
7 matters that -- that were not dealing with process
8 chemistry issues.

9 Q Just briefly what were those other
10 matters concerning?

11 A I would need to look at my list of -- of
12 cases. I don't have a memory of all of 'em.

13 Q Sure. Do you have a recollection of some
14 of them?

15 A I did a couple of cases on behalf of
16 Apotex in Canada early on.

17 Q Apotex is a generic pharmaceutical
18 company?

19 A Yes.

20 Let me see. I did a formulation case
21 where I testified at trial on behalf of Hospira and
22 Apotex against Sanofi-Aventis. That wasn't process
23 chemistry. That was formulations. I've done a
24 bunch of formulation cases.

25 Q I see on this list there are some cases

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1 that name United Therapeutics.

2 A Hmm-hmm.

3 Q Okay. The first one lists United
4 Therapeutics is United Therapeutics Corp. versus
5 Sandoz. And there are two cases listed. Do you see
6 that?

7 A Yes.

8 Q Is the first case the case that went to
9 trial already?

10 A Yes.

11 Q Okay. And --

12 A I believe so.

13 Q And that case didn't involve the '393
14 patent?

15 A No.

16 Q Okay. And then there's a second case.
17 Do you see that? 13-316?

18 A 13 --

19 Q It's in the same -- sorry. It's in the
20 same phrase on page 11.

21 A That was -- I think that was a
22 consolidated thing where there were two different --
23 there was a formulation patent and a process patent
24 that were litigated at the trial --

25 Q Okay.

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1 A -- as I recall.

2 Q And neither of them involved the '393
3 patent? Neither of those cases?

4 A No, I don't think so. No.

5 Q At the very bottom of the page, we see
6 the words United Therapeutics starting?

7 A Yes.

8 Q And then it says, "versus Teva." That's
9 the matter you're working on now?

10 A I believe that matter is over. I believe
11 the parties settled.

12 Q Okay. Okay.

13 The matter in which you've given an
14 expert on claim construction, that's a new Teva
15 matter that's not listed here?

16 A Boy, I -- you know, just looking at the
17 case numbers, I don't remember. I'd have to look at
18 my -- at my records.

19 Q Okay. Looking here, you see this is a
20 matter filed -- this Teva matter was filed in 2014.
21 Is the matter you're working on now the one that was
22 more recent?

23 A Well, as far as I -- as far as I can
24 recall, the only two matters for UTC I'm working on
25 right now is this one.

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1 Q Right.

2 A The IPR matter.

3 Q Okay.

4 A And then the upcoming Watson case.

5 Q Okay. Okay. And you see it also lists
6 here yet another matter for Sandoz?

7 A Oh, I'm sorry, the Sandoz one is the one
8 I believe that settled. The Teva one might still be
9 ongoing. I just don't recall. Nothing's happened
10 in a while, so I don't remember.

11 Q Okay. Okay. And in addition to these,
12 there's this Watson matter?

13 A Yes.

14 Q Are you working on any matters for United
15 Therapeutics involving their -- the oral form of
16 treprostiniil?

17 MS. HASPER: Objection. Privilege.

18 THE WITNESS: Not that I can think of.

19 BY MR. POLLACK:

20 Q Okay. Nothing comes to mind?

21 A No.

22 Q Okay. When did you first get hired to
23 work on this matter?

24 A I don't recall the exact date of -- when

25 I signed my Retainer Agreement. I believe it was
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1 either late -- late last year or early this year.

2 I'm not exactly sure of the timing.

3 Q And when -- when do you actually start
4 working substantively on the matter?

5 MS. HASPER: Objection. Privilege.

6 I instruct the witness not to answer to
7 the extent doing so will reveal privileged
8 communications with counsel.

9 THE WITNESS: I just don't recall.

10 BY MR. POLLACK:

11 Q Well, was it in the Spring? You start
12 working on it in the Spring.

13 MS. HASPER: Same objection.

14 THE WITNESS: I don't remember.

15 BY MR. POLLACK:

16 Q Don't recall at all?

17 A No.

18 Q How about as late as Summer?

19 MS. HASPER: Same objection.

20 THE WITNESS: I was certainly working on
21 it by the Summer, but I don't remember how early in
22 the year or if there was anything late in 2015. I
23 just don't remember.

24 BY MR. POLLACK:

25 Q Okay. Well, you recall -- you can look

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1 at your Declaration. You filed that on or around
2 July 6th. Do you recall that?

3 A This (Indicating)?

4 Q Yes.

5 A Yes. Okay.

6 Q Okay. So using that date, about how many
7 months earlier did you start working on the IPR?

8 MS. HASPER: Objection. Privileged.

9 THE WITNESS: I just don't remember the
10 timing.

11 BY MR. POLLACK:

12 Q Three months before?

13 MS. HASPER: Objection. Privileged.

14 THE WITNESS: Counsel, I said, "I don't
15 remember."

16 BY MR. POLLACK:

17 Q Okay. But I'm trying to -- you know,
18 could it have been six months before?

19 MS. HASPER: Objection. Privileged.

20 Asked and answered.

21 THE WITNESS: I just don't recall the
22 timing. I could easily look at my invoices.

23 MR. POLLACK: I'd like to request
24 Dr. Williams's invoices in this matter.

25 MS. HASPER: I hear your request.

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1 BY MR. POLLACK:

2 Q Okay. Do you think you started working
3 on it substantively in late 2015?

4 MS. HASPER: Objection. Privileged.
5 Asked and answered.

6 THE WITNESS: I -- I don't recall.

7 BY MR. POLLACK:

8 Q Nothing at all, whether --

9 A I just don't recall.

10 Q No idea?

11 How soon after you were retained did you
12 start working on that?

13 MS. HASPER: Objection. Privileged.
14 Asked and answered.

15 I instruct the witness --

16 MR. POLLACK: None of this is privileged.

17 And your speaking objections are going so far. If
18 this continues, I'm going to ask for a second
19 deposition of him. Understood?

20 Go ahead.

21 THE WITNESS: I don't recall.

22 BY MR. POLLACK:

23 Q Okay. Other than your hourly rate, is
24 there any other compensation you expect for working
25 on this IPR?

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1 A No. Other than the opportunity to play
2 golf in Southern California tomorrow.

3 (Laughter)

4 BY MR. POLLACK:

5 Q Could you tell me about why you're
6 playing golf in Southern California tomorrow?

7 A Because there's a great golf course near
8 here that I like.

9 Q Oh, Okay.

10 A But United Therapeutics is not paying for
11 it. I am.

12 Q How many -- how many matters have you
13 worked with the law firm of Wilson Sonsini on?

14 MS. HASPER: Objection. Privileged.

15 This also refers -- it sounds like you're
16 asking about case others than this case.

17 THE WITNESS: So give me your question
18 one more time, please.

19 BY MR. POLLACK:

20 Q Sure. How many matters have you worked
21 on with the Wilson Sonsini law firm?

22 A By "matters," do you mean litigation
23 matters, because -- --

24 Q Any kind of matter.

25 A -- I was a cofounder of a biotechnology

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1 company that used Wilson Sonsini's patent counsel.

2 Q Okay.

3 A That was microcide pharmaceuticals, and
4 we use the Wilson Sonsini. So I have -- and that
5 was their Palo Alto office.

6 Q Did they take -- in exchange for that
7 legal work, did they take any kind of equity or any
8 kind of compensation of that type?

9 A That, I don't remember. It was a long
10 time ago.

11 Q Okay.

12 A It was the early '90s. I just don't
13 remember. But I know Wilson Sonsini was patent
14 counsel to Microcide.

15 Q Okay. How many other matters?

16 A Um, let me see.

17 MS. HASPER: Objection. I instruct the
18 witness not to answer to the extent doing so would
19 reveal any privileged information.

20 THE WITNESS: I have a current spinoff
21 company that I founded and am president of in Fort
22 Collins. And we have patent counsel from Wilson
23 Sonsini who volunteered to work for free.

24 BY MR. POLLACK:

25 Q Really?

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1 A Yeah.

2 Q Why did they do that?

3 A It's active-retirement-sort-of situation.
4 So retired attorney who actually still is associated
5 with Wilson Sonsini but wants to do something
6 interesting instead of just playing golf, and skiing
7 or something like that.

8 Q Okay.

9 A We were very lucky to get a very
10 qualified attorney who's interested in our company
11 and our technology.

12 Q Okay. All right. Anything else?

13 A I was retained to work on one other case
14 that never materialized. So there was no -- no
15 expert reports or anything. So I was retained, no
16 invoices that I can recall, and the matter settled
17 before anything happened.

18 Q Okay. Anything else?

19 A Not that I can think of.

20 Q Okay. I mean, other -- there's also a
21 bunch of matters with United Therapeutics. Those
22 were all the Wilson Sonsini firm?

23 A Yes.

24 Q Okay. And same set of questions for the
25 Foley & Lardner firm. How often have you worked

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1 with that firm?

2 A Who?

3 Q Do you know Mr. Maebius?

4 A Oh, I just met him for the first time
5 yesterday.

6 Q Oh, okay. Okay.

7 Have you met anyone else from
8 Mr. Maebius's firm?

9 A I don't think so.

10 Q Okay. And did you meet with Mr. Maebius
11 yesterday to prepare for today's deposition?

12 A He came to the preparation that I was
13 doing with Counselor Hasper.

14 Q Okay. Who else was at that preparation?

15 A One other attorney from UTC. Shaun -- I
16 can't remember his last name.

17 Q Okay. Anyone else?

18 A No.

19 Q And other than yesterday, were there
20 other meetings in -- that you had with counsel in
21 preparation for today's deposition?

22 A No.

23 Q About how long did you meet with counsel
24 yesterday?

25 A About nine hours.

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1 Q And prior to yesterday's meeting with
2 counsel, did you have telephone -- you know,
3 meetings by telephone or other means of
4 communication -- with counsel?

5 A A few with Counselor Delafield.

6 Q Okay. Other than Counselor Delafield,
7 anyone else?

8 A No.

9 Q What else did you do to prepare for
10 today's deposition?

11 A I reread lots of documents, patents, prior
12 art, my own Declaration.

13 Q Did you search for prior art?

14 A Did I search for prior art?

15 I don't -- I don't recall.

16 Q You don't know, one way or the other?

17 A No, I don't know, one way or the other.

18 Q Okay. Did you search for any papers,
19 articles, or documents that were relied upon in your
20 Declaration?

21 A Well, I already had a vast amount of
22 literature from the other cases. So I was already
23 fairly familiar with a massive volume of literature
24 and information relative to treprostinil. So --

25 Q Did any of the articles that were
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1 attached to your Declaration -- let me rephrase.

2 Were all of the articles attached to your
3 Declaration provided by counsel?

4 A I guess I'd need to look at my list of
5 exhibits. I don't remember. I'd have to look --

6 Q Okay. If you look at paragraph 28 of
7 your Declaration, there's a description of what you
8 considered.

9 A Well, this isn't a list.

10 Q Well, that's the only list you provided,
11 sir.

12 A Okay.

13 Q Let me ask you: It says there, "I have
14 also reviewed a number of documents in this case,
15 including all documents cited by SteadyMed and UTC,
16 as well as the materials I have cited in the
17 Declaration."

18 Other than those documents, were there
19 any other documents not described in that sentence
20 that you reviewed?

21 A No.

22 Q Okay. You say in the last sentence, "If
23 I am provided additional information or documents in
24 this proceeding, I may offer further opinions
25 regarding the additional information."

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1 Were you provided any additional
2 information or documents?

3 A No.

4 Q Okay. And, therefore, you will not be, I
5 assume, offering further opinions regarding any
6 additional information?

7 A Not at this time.

8 Q Okay. Was there anything that you asked
9 for from counsel that you wanted to review?

10 A I actually -- can I go back to a previous
11 question you asked me?

12 Q Absolutely.

13 A You asked me if I -- if I did my own --
14 any literature searching?

15 Q Yes, yes.

16 A So I actually did pull up every single
17 one of Dr. Winkler's publications.

18 Q Okay.

19 A I did that myself. And I provided all of
20 those papers to counsel and looked through all of
21 his papers.

22 Q Okay.

23 A So that was -- so I would consider that a
24 literature search. It was actually a lot of work.

25 Q Okay. He's written a lot of papers;

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1 right?

2 A That's all relative. Relative to me, no.

3 Q Okay.

4 A I've published maybe three or four times
5 the number of papers of Dr. Winkler.

6 Q Okay.

7 A So it was actually, from my point of
8 view, a modest amount. But it was still over a
9 hundred papers, I think it was.

10 Q Yeah. You know Dr. Winkler; right?

11 A Yes, I do.

12 Q In fact, you're together in a network of
13 experts; is that right?

14 A I wouldn't characterize it that way.
15 Dr. Winkler has a -- an expert witness head-hunting
16 firm called Cymedex, and he's contacted me at least
17 a half a dozen times as a potential candidate to
18 work on cases that came to his company. And none of
19 them materialized in a retained engagement, but
20 we've certainly talked on the phone. He's had my
21 CV. He obviously thinks I'm a very good expert, so
22 he's been trying to find, you know, an engagement
23 for his company that uses me.

24 Q Okay. The two of you know each other;

25 right?

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1 A Oh, yes.

2 Q Yeah.

3 A Yeah. Organic chemistry is a small
4 community.

5 Q Yeah. Would you say Dr. Winkler's a
6 distinguished organic chemist?

7 A I think he's a very solid organic
8 chemist.

9 Q How does "solid" differ from
10 "distinguished"?

11 A So I would reserve the characterization
12 "distinguished" to be with more accolades, national
13 awards, and things like that, and I don't think he's
14 quite hit that bar.

15 Q Okay. What about you? Have you hit that
16 bar?

17 A Very fortunately, yes, I would say so. I
18 got a major -- two major national ACS awards
19 recently. I'm university distinguished professor,
20 Colorado State University, which is a lifetime
21 appointment, and there's only 12 in a campus of more
22 than 1,200 faculty.

23 Q Okay.

24 A I don't mean to disparage Dr. Winkler.

25 He's a very nice man, and he's a very good chemist.

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1 Q Other than searching for Dr. Winkler's
2 articles, do you recall any other documents that
3 were provided solely by you for use in this
4 proceeding?

5 A I provided counsel with some of my own
6 papers.

7 Q And what did those papers concern? Why
8 did you provide those?

9 A So I cited those in my Declaration that
10 had to do with how I have used the word "product" in
11 my own publications. And I also -- some of the
12 papers from -- that I found from Dr. Winkler, how he
13 also very, very -- in the very same way uses the
14 word "product" in his own publications.

15 Q Okay.

16 A So we use the word the same way.

17 Q Other than those papers which were
18 attached from you regarding the meaning of the word
19 "product," was there anything else that you provided
20 for use in this proceeding?

21 A Not that I can think, off the top of my
22 head.

23 Q When counsel provided you with the data
24 for appendices "A" and "B," who did the calculations
25 based on those appendices?

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1 A Counselor Hasper did.

2 Q You didn't do the calculations?

3 A No. But I checked them.

4 Q Okay. As I understand it, one of your
5 main opinions here is that the product of the '393
6 patent has an average purity of [REDACTED] percent, while
7 the product of the Moriarty patent has an average
8 purity of 99.0 percent, approximately. Is that --
9 is that fair?

10 A There's more to it than that. Just the
11 overall purity. There's also impurity --
12 significant impurity profile differences between the
13 product of the two patented processes.

14 Q How are those different profiles
15 significant?

16 A In what context?

17 Q Well, are any of those impurities known
18 to be particularly harmful?

19 A Well, by "harmful," what do you mean
20 "harmful"? In what context?

21 Q In any context.

22 A Well, I mean, in process chemistry, the
23 goal is to try to get as pure an API as possible
24 that is free of any type of extraneous impurities.

25 And so sometimes, depending on the API material,

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1 impurities may have deleterious biological
2 consequences; sometimes they don't. Um --

3 BY MR. POLLACK:

4 Q Do any of the -- as far as you know, any
5 of these particular impurities have deleterious
6 biological consequences?

7 MS. HASPER: Objection. Beyond the scope
8 of his expert Declaration.

9 THE WITNESS: I'm not a clinician, so I
10 don't know.

11 BY MR. POLLACK:

12 Q You don't know?

13 A I don't know.

14 Q Okay. So other than the percentage of
15 the impurities, if there's no knowledge about the
16 biological deleterious effects of any of these
17 impurities, what difference does it make which ones
18 they are?

19 A So I think the stereoisomer impurities
20 would be the ones that a process chemist would be
21 particularly wary of. The dimer impurity and the
22 [REDACTED] and [REDACTED] ester impurities are hydrolyzable
23 back to treprostinil to API.

24 So those are both -- I guess,
25 operationally, you can recover, actually,

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1 treprostinil from those impurities if you needed to.
2 And, you know, in vivo, they can be hydrolyzed in
3 treprostinil. So they're not going to have a
4 deleterious effect, presumably.

5 Q But no one knows that?

6 A Not for -- not that I've seen.

7 MS. HASPER: Same objection.

8 BY MR. POLLACK:

9 Q Let me ask you this: If -- let's say the
10 difference in impurities between the '393 patent and
11 the Moriarty prior art patent was [REDACTED] for the
12 '393 -- same number you're relying on -- and 99.5
13 for the Moriarty patent, how would that change
14 your -- your opinion?

15 MS. HASPER: Objection. Foundation.

16 THE WITNESS: Well, there's a lot more to
17 it than just the -- and you're talking about
18 average --

19 BY MR. POLLACK:

20 Q Average. Yeah.

21 A -- over --

22 Q Yeah. I'll give you average.

23 A 50, 100 batches or something like this?

24 Q Sure.

25 A Again, it's not just a simple matter of

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1 that one of the significant advantages of the '393
2 process is the elimination of chromatography, which
3 from a process chemist point of view is exceedingly
4 important because chromatography is expensive, it's
5 time-consuming, it adds cost of goods, there's
6 safety issues, waste issues. And eliminating that
7 is a -- is always a very, very desirable goal.

8 So the '393 process allows for the
9 elimination of chromatography in the preparation of
10 the final drug substance. So that's very important.

11 Q I don't see that opinion expressed in
12 your Declaration, though, sir.

13 A Hmmm?

14 Q That opinion is not expressed in your
15 Declaration, is it?

16 A About the elimination of chromatography?

17 Q Yeah.

18 A I -- I think it's in there, and it's
19 certainly in the patent. The patent talks about the
20 advantages of the elimination of chromatography.

21 Q Okay. But in your opinion, you talk
22 about the difference in the impurities; correct?

23 A Yes. I certainly spend quite a bit of
24 time on the impurity profiles.

25 Q Right. Okay.

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1 A The differences.

2 Q If the difference in the quantity of
3 impurities was only [REDACTED] versus 99.5, how would that
4 affect your opinion?

5 MS. HASPER: Objection.

6 THE WITNESS: I'd have to look at actual
7 data and impurity profiles. You're asking me a
8 hypothetical --

9 BY MR. POLLACK:

10 Q Yes.

11 A -- that I'm reticent to just give an
12 opinion on without actually seeing what you're
13 talking about.

14 Q Well, you gave an opinion on the
15 difference between 99.0 and [REDACTED]. I'm trying to
16 understand how your opinion changes when it's [REDACTED]
17 versus 99.5.

18 A Again, I would need to see data and the
19 way in which the two processes operate that rendered
20 the material of those relative impurities.

21 Q So the 99.5 is the Moriarty process. Got
22 it? And the [REDACTED] is the '393 process. How would
23 your opinion change if those were the average
24 results?

25 MS. HASPER: Objection. Asked and
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1 answered.

2 THE WITNESS: So I would need to see the
3 distribution of actual impurities, and I would also
4 need to understand the process that resulted in
5 those materials.

6 BY MR. POLLACK:

7 Q What would you need to understand about
8 the process?

9 A Well, like the '393 process I just
10 mentioned eliminates chromatography. So
11 crystallization gets an incredibly pure salt.

12 Q Let me ask you this: The claims of the
13 '393 patent, you're allowed to do chromatography and
14 practice those claims; right?

15 A Yes.

16 Q Okay.

17 A But the patent enables you to eliminate
18 that step.

19 Q Okay. But the claims would include that
20 step; right?

21 A They can --

22 Q Yeah.

23 A -- but again, the process -- very
24 important part of the process is that it enables you
25 to eliminate that step.

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1 Q The --

2 A We've been going almost an hour, and my
3 63-year-old bladder is not as robust as it used to
4 be. So could we take a quick break?

5 MR. POLLACK: Absolutely. Absolutely.

6 THE VIDEOGRAPHER: We are off the record.

7 The time is 10:18 A.M.

8 (Off the record)

9 THE VIDEOGRAPHER: We are back on the
10 record. The time is 10:25 A.M.

11 BY MR. POLLACK:

12 Q Welcome back, Dr. Williams. I have --
13 we've already marked as Williams Deposition
14 Exhibit 3 a patent -- U.S. Patent No. 8,497,393, the
15 patent at issue in this proceeding.

16 (Exhibit 3 marked)

17 BY MR. POLLACK:

18 Q And I've marked as Williams Deposition
19 Exhibit 4, U.S. Patent 6,765,117, the Moriarty
20 patent, also known as Exhibit 1003 in the
21 proceeding.

22 (Exhibit 4 marked)

23 BY MR. POLLACK:

24 Q If we could start with Deposition
25 Exhibit 4.

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1 This is the Moriarty patent; correct?

2 A Yes.

3 Q Okay. And you've -- you've reviewed that
4 thoroughly for your opinion in this proceeding?

5 A Yes.

6 Q If you could turn to column -- columns 9
7 and 10. Do you see there's a compound toward the
8 bottom -- a compound 14? Do you see that?

9 A Yes.

10 Q Okay. And there's a step where it's
11 being turned into compound 15? Do you see that?

12 A Yes.

13 Q Okay. I wanted to compare that to the
14 claims in Exhibit 3, the '393 patent. And what I
15 want to know is whether or not that change from 14
16 to 15 -- is that what the '393 patent refers to as
17 "step (a)"?

18 A Okay. Which page of the '393 patent?

19 Q The claims are -- they start at column
20 17 --

21 A Oh, I'm sorry.

22 Q -- and then they go through to column 21.

23 A (Examining document) Okay. So your
24 question was, is the conversion of 14 to 15
25 step (a)? Is that your question?

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1 Q That's correct. Yes.

2 A Yes.

3 Q Okay. And my next question is: The
4 conversion from 15 to 16 in Exhibit 4, the '117
5 Moriarty patent, is that what is known as "step (b)"
6 in the claims of the '393 patent?

7 A Yes.

8 Q And looking at Exhibit 4, the '117
9 patent, this is showing a scheme for making
10 compounds of the type claimed in the '393 patent but
11 by the Moriarty method. Is that -- is that fair?

12 A Yes.

13 Q Okay. On pages 9 and 10, compound 16, is
14 that the final compound of the process? The
15 Moriarty process.

16 A Structure 16?

17 Q Yes.

18 A So that would be true where R1 is H. M
19 in brackets on both sides is 1. All three Ms are 1.
20 That would be treprostinil.

21 Q Treprostinil. But the '393 patent has a
22 lot of other compounds to the final products; right?

23 A Yes.

24 Q Okay. Would that be a structure of final
25 products -- let me start again.

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1 Would structure 16 in the Moriarty
2 patent, Exhibit -- Deposition Exhibit 4 -- would
3 structure 16 be a structure of final compounds made
4 in, for example, claim 1 of the '393 patent?

5 A No, because there's an additional step in
6 the '393 step (c).

7 Q The purification step?

8 A The contact and the product in step (b)
9 with a base to form a salt, which is then optionally
10 reactive with an acid to form the carboxylic acid
11 16.

12 Q Okay. Okay. So if you did step (1) all
13 the way through step (d) -- where step (d) is
14 optional, though, you would get a compound of 16?

15 A You said, step (1) through D? What do
16 you mean?

17 Q Sorry. I may have misspoken, then.

18 If you performed claim 1 through
19 step (d), you would get a compound of structure 16?

20 MS. HASPER: Objection. Mischaracterizes
21 the document.

22 THE WITNESS: So --

23 BY MR. POLLACK:

24 Q I was just trying to understand your last
25 answer, but --

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1 A Okay. So --

2 Q -- we can move on.

3 A Structure 16, where I specify what the
4 variables were, R1 and M, where R1 is H, and M is
5 the number 1, that structure would then be
6 treprostinil acid. And included in the Markush or
7 the more generic formula shown in claim 1, you would
8 get treprostinil after step (d).

9 Q Okay. So structure 16 would be included
10 in the products would you get in claim 1 after
11 step (d)?

12 MS. HASPER: Objection. Mischaracterizes
13 the document.

14 THE WITNESS: So included in the formula
15 1S -- I think that's what you're referring to;
16 right? In --

17 BY MR. POLLACK:

18 Q Yes. 1 --

19 A So in formula 1 -- 1S where the
20 stereochemistry of the secondary hydroxyl group,
21 there's a wavy line that has to be defined as
22 down -- would be a dashed line. And then these
23 other variables, Y1, W, M1, L1, R7 -- and I believe
24 that -- I'm certain, actually, that the definitions
25 they call out when you plug them in correctly reads

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1 on the structure of treprostinil.

2 Q Okay. Okay. I didn't want to confuse
3 you. And I may have confused you. I was actually
4 referring to structure 1, which is -- just turn to
5 the very beginning of the claim, claim 1; right?
6 The structure -- structure Ss with the base; right?

7 A Wait. So you've lost me now.

8 Q Right.

9 A We're at column 17.

10 Q Yes.

11 A On the '393.

12 Q Yeah.

13 A And you're asking me to look at structure
14 1; right?

15 Q You can look at anything you want to.
16 You referred to, just now, to structure 1S, and that
17 shows the salt -- the base salt; right?

18 A Yes.

19 Q Okay.

20 A That's the salt.

21 Q Okay.

22 A And after D, you get to formula 1, the
23 treprostinil acid.

24 Q Right.

25 A Acid.

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1 Q And 16 would be included in formula 1?

2 MS. HASPER: Objection. Mischaracterizes
3 the document.

4 BY MR. POLLACK:

5 Q The '117 patent?

6 A Well, the molecular structure of 16 reads
7 onto formula 1 where the variables are defined
8 appropriately --

9 Q Okay.

10 A -- which the claim calls out.

11 Q Okay. Looking at the -- looking at
12 columns 9 and 10, which show how to make
13 treprostinil in similar structures, do you see a
14 chromatography step?

15 A Well, I can see a chromatography step in
16 every step.

17 Q One could do it optionally?

18 A Yeah. And the way organic chemistry
19 works is that when you're going through a synthesis
20 of this complexity the first time, every
21 intermediate product is typically isolated by
22 chromatography to get an analytical sample and
23 characterize it to get it as pure as possible for
24 analytical purposes. And then as you go from small
25 scale to large scale, one hopes to eliminate

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1 chromatography steps, and you take Cree material on
2 it or crystallize intermediates if they're
3 crystalline.

4 Q Okay. But here on pages 9 and -- column
5 9 and 10, the '117 patent, it doesn't say anything
6 about chromatography?

7 A Well, a person skilled in the art looking
8 at this would understand that this is just a
9 reaction scheme structure with no details. One
10 would need to look at the actual experimental --
11 detailed experimental procedures for each step and
12 see if any of these steps require chromatography.

13 Q Okay. But as Moriarty lays out the
14 reaction here, chromatography may be optional, but
15 he doesn't -- here on pages 9 and 10 -- columns 9
16 and 10 require chromatography; is that fair?

17 A Well, that's --

18 MS. HASPER: Objection. Asked and
19 answered. Mischaracterizes the document.

20 THE WITNESS: There's not enough
21 information here. Again, I just said this is a
22 reaction scheme. One would need to look at the
23 actual published procedures, the experimental -- the
24 recipe, the detailed how to do each step.

25 ///

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1 BY MR. POLLACK:

2 Q Let me ask you this: The claims for the
3 '117 patent -- the claims, which is in the back at
4 columns 21 to 24 --

5 A Okay.

6 Q -- do the claims of the Moriarty patent
7 require a chromatography step?

8 A No, I did not see the word
9 "chromatography" in the claims. But I know that the
10 reality of doing synthesis like this, it does entail
11 chromatographic separation.

12 Q Okay. Could we go back to your
13 Declaration? That's Exhibit 2. I'd like to turn to
14 paragraph 98 of your Declaration. It's on page 33.

15 In the last two sentences, those appear
16 to be the conclusion sentence of your paragraph.
17 And it says there, "The treprostinil product of the
18 '393 patent has an average purity of [REDACTED] percent,
19 while the Moriarty product has an average purity of
20 99.05 percent. Thus, the treprostinil product of
21 the '393 patent has an average purity that
22 is [REDACTED] percent higher than that of Moriarty's."

23 Do you see -- did I read that correctly?

24 A Yes.

25 Q Why is that difference important to you?

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1 the structure memorized, but I recall that it's a
2 [REDACTED] stereoisomer. I

3 think --

4 Q Okay.

5 A -- but I'd have to check.

6 Q All right. Anything particularly
7 significant about that stereoisomer?

8 A Well, it's a carboxylic acid like
9 treprostinil. And so in terms of separating it from
10 the desired molecule, treprostinil, that's a
11 challenging impurity to remove, because it has very
12 similar PKA. They're both carboxylic acids. They
13 have the same molecular skeleton. They're just
14 different in stereochemistry.

15 Q But biologically, is there any difference
16 between [REDACTED] and treprostinil?

17 MS. HASPER: Objection. Beyond the
18 scope.

19 THE WITNESS: I don't know, but certainly
20 treprostinil is the biologically active principal.
21 And I'm not aware of any biological data on [REDACTED].
22 But there may be some, but I'm not a biologist.

23 BY MR. POLLACK:

24 Q That's not something you looked into?

25 A No.

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1 Q You didn't speak to anyone else working
2 on this case who looked into that?

3 A No.

4 Q Did you speak to any -- other than the
5 attorneys, did you speak to anyone else in working
6 on this case?

7 A No.

8 Q And are you familiar with a Dr. Ruffolo
9 who submitted a Declaration in this case?

10 A I don't know him.

11 Q Okay. You never spoke to him?

12 A No.

13 Q Did you read his Declaration?

14 A Briefly and very recently.

15 Q Was that only in preparation for your
16 deposition?

17 A No. So that was part of the big -- sort
18 of master file that I saw, and I -- I briefly
19 scanned through his -- his Declaration.

20 Q Let me ask you: Did you read his
21 Declaration before you signed and completed your
22 Declaration on July 6th?

23 A No.

24 Q Okay. So it was only after --

25 A Only after.

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1 THE REPORTER: Try to pause a little bit,
2 please.

3 THE WITNESS: I'm sorry.

4 BY MR. POLLACK:

5 Q We both have that habit.

6 THE REPORTER: Yes, do you.

7 THE WITNESS: I will try and speak much
8 slower. Is that what you want?

9 THE REPORTER: Like that will happen.

10 BY MR. POLLACK:

11 Q Are you originally from New York?

12 A How did you guess?

13 Q I'm a New Yorker, also. So we're both
14 fast-talkers.

15 A Huntington.

16 Q I'm Brooklyn, lucky you.

17 A But I hate the Yankees. Red Sox fan.

18 Q Oh, Mayor Bloomberg was; right?

19 Let me ask you -- you make this point
20 about the [REDACTED] versus the 99.05. I'm really trying
21 to understand, how far can the 99.05 number increase
22 before that point is no longer that significant to
23 your opinion?

24 A You know, I didn't -- I didn't do that
25 analysis or consider -- consider that.

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1 Q Understand. I'm asking you to just
2 consider that now.

3 A I'd need to look at data -- impurity
4 profiles and data.

5 Q Let's say the impurity profiles were all
6 the same as we're seeing now, just the number has
7 changed. So if the number is changed, and they
8 change in such a way that we go from 99.05 to 99.5,
9 how would that change your opinion?

10 MS. HASPER: Objection. Incomplete
11 hypothetical. Beyond the scope.

12 THE WITNESS: Okay. So you're asking me,
13 again, sort of a make-believe Moriarty series of
14 batches that I've never seen. I haven't seen any
15 such material. And Dr. Winkler didn't produce any
16 Moriarty material batches, or he didn't do his own
17 experiments to show that he would get that. But,
18 again, I -- you know, I -- I'd -- I'd have to look
19 at the data.

20 BY MR. POLLACK:

21 Q Let me ask you: What if -- what if the
22 Moriarty batches -- the average value for the
23 Moriarty batches was [REDACTED] -- the very same as your
24 number there --

25 MS. HASPER: Same objection.
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1 BY MR. POLLACK:

2 Q -- how would that change your opinion?

3 MS. HASPER: Same objection.

4 BY MR. POLLACK:

5 Q So no difference in the purity level.

6 MS. HASPER: Same objection.

7 THE WITNESS: Okay. So, again, I think
8 your question's about overall impurity -- overall
9 purity, [REDACTED] percent, which is total related
10 substances, which is known, plus unknown
11 impurities -- so it's just not a simple matter of
12 overall purity. You also have to look at the
13 impurity profiles, because that is the significant
14 difference in the product between the '393 and the
15 Moriarty process.

16 BY MR. POLLACK:

17 Q So you're saying even if the overall
18 purity is the same, the distribution of those
19 impurities -- which we don't know anything about in
20 regard to their biological property -- but that
21 really matters? That's your opinion?

22 A That's my understanding, that in
23 product-by-process patents, the -- the new product
24 by the new process has to have structural,
25 functional differences. And impurity profiles are

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1 structural differences.

2 Q Are there any functional differences,
3 though, between a material -- a new material which
4 has a impurity level -- or purity level of [REDACTED] and
5 another material which has a purity level of, say,
6 [REDACTED]?

7 MS. HASPER: Objection. Beyond the
8 scope. Incomplete hypothetical.

9 THE WITNESS: I don't know. And, again,
10 the -- you know, the -- really, the significant
11 thing about the '393 process is the elimination of
12 the chromatography. The way I view it, that's a
13 functional difference. It reduces cost of goods,
14 and solvent safety. So it's -- it's not a
15 insignificant matter.

16 BY MR. POLLACK:

17 Q Let me ask you something: In the -- if
18 you go to the '393 patent -- pick up Exhibit 3,
19 again -- there's a claim 16. Do you see that claim?

20 A Yes.

21 Q It's in column 20.

22 A Yes.

23 Q Now, do you have any patents?

24 A Yes.

25 Q Okay. You understand how patent claims

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1 work; correct?

2 A Generally.

3 Q Okay.

4 A I'm not a patent expert, but --

5 Q You know -- do you know what an

6 independent and a dependent claim is?

7 A Yes.

8 Q Okay. What's your understanding of what

9 a dependent claim is?

10 MS. HASPER: Objection to this, that it
11 seeks a legal conclusion.

12 THE WITNESS: Well, generally, a
13 dependent claim is -- follows an independent claim
14 and typically narrows down the scope of the
15 independent claim to a more -- some type of
16 parameter.

17 BY MR. POLLACK:

18 Q It adds something the independent claim
19 doesn't require; is that fair?

20 A Again, I'm not a lawyer. I don't know if
21 that's ubiquitously true, but that sounds
22 reasonable.

23 Q Is claim 16 -- is that a dependent claim?

24 A Yes. It's dependent from claim 9.

25 Q Okay. What is claim 16 adding?

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1 MS. HASPER: Same objection.

2 THE WITNESS: So claim 16 says, "The
3 product is claim" --

4 THE REPORTER: Speak up, please.

5 BY MR. POLLACK:

6 Q If you could read more slowly. He's got
7 to type it all.

8 A "The product of claim 9 wherein the
9 process does not include purifying the compound of
10 formula VI produced in step (a), which is the
11 nitrile."

12 Q What does that mean?

13 A So this is -- this claim is saying that
14 you do -- you perform step (a) and then carry the
15 nitrile through to the next step without doing a
16 purification step, like a chromatography.

17 Q Okay. In your understanding, though,
18 does that mean that claim 9 could be carried through
19 with the chromatography?

20 A It could, but importantly, this patent
21 and the process that's being used eliminates that.

22 Q Right. But claim 9 doesn't; right?
23 Claim 9, you can do the chromatography.

24 A You could if you wanted to. It seems
25 like a nonsensical thing to do when we know it works

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1 really great without.

2 Q But claim 9 does include with the
3 chromatography?

4 A It's agnostic as to chromatography;
5 right? Doesn't say, one way or the other.

6 Q Sure. But claim 16 is very specific.
7 That's done without the chromatography; right?

8 A Yes.

9 Q So that means claim 9 includes both with
10 or without the chromatography; is that fair?

11 A Again, I'm not -- I'm not a patent
12 lawyer, so I'm not sure that that is necessarily the
13 way that's read.

14 Q What's your understanding?

15 A Yeah. It's -- I mean, it's silent on
16 that issue. So --

17 Q And based on that, what do you conclude
18 about whether chromatography is included in claim 9?

19 MS. HASPER: Objection to the extent it
20 seeks legal conclusion.

21 THE WITNESS: So, you know, I think a
22 person skilled in the art looking at this, again,
23 would be informed by the specification and column
24 15, a real-world 5-kilogram example, says no column
25 for that step. Whereas in the prior art process,

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1 there's a purification column chromatography step.

2 So --

3 BY MR. POLLACK:

4 Q Let's take a look at claim 1.

5 Now, you'll agree with me that claim 1
6 also would include the chromatography; is that fair?

7 A I don't know if I would read in the
8 requirement for chromatography. It doesn't say
9 anything about it. It's also silent on that issue.

10 Q But it couldn't -- since it's silent and
11 there's a claim that says, "Don't use
12 chromatography," we could probably conclude that it
13 does include chromatography, just on basic logic?

14 A Yeah. I suppose it could, but we --
15 again, the patent talks in several places about the
16 advantage of elimination of the chromatography step.

17 Q Let me ask you: About how many compounds
18 do you think there are in claim 1?

19 A Oh, lots. I don't know the -- I don't
20 know the exact number.

21 Q Hundreds of thousands? At least?

22 A Very likely. But I'm not sure.

23 Q Okay. So for all of those hundreds of
24 thousands of compounds, is there any information in
25 the '393 patent about whether those hundreds of

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1 thousands of compounds will be pure without
2 chromatography?

3 A Well, the specification only deals with
4 treprostinil itself so that's the -- I guess the
5 important enabling example that's in the
6 specification of the patent. But the patent teaches
7 that if you applied this salt formation,
8 crystallization, that -- in this structural family,
9 one would have a reasonable expectation that you'd
10 also be able to crystallize and purify just as was
11 done for treprostinil.

12 Q Okay. You don't see any data in this
13 patent, though, about the purity of any of these
14 other thousands of compounds, do you?

15 A No. There's no data for the other
16 compounds, but there is really great data for
17 treprostinil.

18 Q Now, do you understand that claim 9 also
19 includes treprostinil diethanolamine salt as a
20 product?

21 A Yes.

22 Q Okay. And, in fact, if I don't carry out
23 step (d), the optional step, and I use
24 diethanolamine as my salt, I'm going to get
25 treprostinil diethanolamine salts; correct?

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1 A Yes.

2 Q If I don't carry out step (d), does the
3 claim include chromatography?

4 A So your question is, if I do not carry
5 out --

6 Q Let me rephrase my question.

7 If I don't carry out step (d), would it
8 be necessary to use chromatography?

9 A If I -- so your question is, if you do
10 not carry out step (d) --

11 Q Right.

12 A -- would it be necessary to use
13 chromatography?

14 Q Correct.

15 A So I would say that you're forming a
16 salt. And it's -- salts are perhaps the most
17 obnoxious compounds to purify by chromatography.
18 And it's very, very rare to, in fact, purify salts
19 by chromatography. So the whole reason a person
20 skilled in the art would form a salt in the first
21 place is by trying to avoid chromatography, 'cause
22 you can crystallize salt. Salts -- and particularly
23 salts like this that are water soluble, that's the
24 whole purpose of forming the salt.

25 Q Okay. However, if I carry out steps (a)

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1 through (c), the claim 9 allows me to do
2 chromatography if I so wish; correct?

3 A Chromatography at which step? A? I
4 don't know where you're talking about.

5 Q At any of the steps.

6 A Well, could you, but the whole purpose of
7 this invention is to eliminate the chromatography
8 step.

9 Q Okay. By the way, you don't see in the
10 claims where it says the invention is carried out
11 without the chromatography step, other than the one
12 claim, claim 16?

13 A No. But the spec also prominently talks
14 about the elimination of chromatography.

15 Q Okay.

16 A And a process chemist really would zero
17 in on that important advantage.

18 Q What can you tell me about the impurity
19 profile of the thousands of compounds in claim 1?

20 MS. HASPER: Objection. Beyond the
21 scope.

22 THE WITNESS: I could tell you about the
23 impurity profile of one of the thousands of
24 compounds in claim 1, treprostinil, because I have
25 data on that.

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1 BY MR. POLLACK:

2 Q Does any person of ordinary skill in the
3 art or any person of any skill in the art know
4 anything about the purity [sic] profile of the
5 thousands of compounds in claim 1, other than
6 treprostiniil?

7 MS. HASPER: Objection. Beyond the
8 scope.

9 THE WITNESS: Well, because all the
10 structures that are called out under claim 1 have
11 the same molecular framework as treprostiniil, one
12 would expect that the impurity profiles would very
13 likely be similar in that you'd have to
14 stereoisomeric impurities, and dimers, and esters,
15 and the triol and so on.

16 It's very similar types of species would
17 very likely be present, if you change the variables,
18 like added a carbon atom to the side chain, or what
19 have you.

20 BY MR. POLLACK:

21 Q But some of the species would be
22 different; correct?

23 A What do you mean by "different"?

24 Q Some of the impurities would be ones not
25 seen in treprostiniil; correct?

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1 MS. HASPER: Objection. Foundation.

2 THE WITNESS: Well, they would
3 necessarily be different because you've already
4 changed the structure. So -- so if you change even
5 by one carbon atom, now longer -- you can't get the
6 same exact impurities from treprostinil because
7 you've already changed the molecular structure to a
8 different molecule.

9 BY MR. POLLACK:

10 Q So all of those molecules would have
11 different impurity profiles from treprostinil; is
12 that fair?

13 MS. HASPER: Objection.

14 THE WITNESS: So -- I think -- I'm trying
15 to give a good answer here, that you would have
16 similar -- I guess you call them "homologous series
17 of impurities," stereoisomeric impurities, that
18 would almost certainly be similar. So they'd be the
19 -- like [REDACTED] could be [REDACTED] prime for another
20 compound, but it would be a similar stereoisomeric
21 impurity, because they're made by the same kind of
22 chemical steps.

23 BY MR. POLLACK:

24 Q You referred to [REDACTED]. Is that a name
25 used in the literature?

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1 A No. I think that's a UTC code number
2 for -- for that.

3 Q It's a secret code number; right?

4 A I don't know if it's secret or not. I
5 know that in Moriarty's GOC paper, he used UT-15 or
6 something, which is the United Therapeutics code
7 number. So that one wasn't secret. So I don't know
8 if they're secret or not.

9 Q Right. UT-15 is the published name for
10 treprostinil; correct?

11 A Yes.

12 Q Okay. But [REDACTED], you've never seen that
13 in the literature; correct?

14 A Not that I can recall.

15 Q Okay. None of the -- have you seen in
16 the literature where any of these impurities are
17 characterized?

18 A I don't recall.

19 Q What about in the '393 patent? Do you
20 see any mention in Exhibit 3 of what impurities are
21 present in any of the compounds in the '393 patent?

22 A No. I don't believe they're specifically
23 called out.

24 MR. POLLACK: To make things a little
25 easier for us, I'm going to mark as separate

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1 exhibits your appendices to your Declaration. I'm
2 going to mark Appendix A as Williams Deposition
3 Exhibit 5.

4 (Exhibit 5 marked)

5 MR. POLLACK: And I'll mark Appendix B as
6 Williams Deposition Exhibit 6.

7 (Exhibit 6 marked)

8 BY MR. POLLACK:

9 Q If you could just verify for me that
10 Deposition Exhibits 5 and 6 are true and accurate
11 copies of your appendices A and B, respectively?

12 A (Examining documents).

13 (Brief pause)

14 Okay. Appendix A is identical. And
15 Appendix B is identical to the one submitted but
16 does not have the one correction that we made at the
17 beginning of the deposition.

18 Q Could you do me a favor? Could you take
19 Exhibit 6 and make the correction on there by pen?

20 A Okay. I don't have a pen. Can I borrow
21 yours?

22 And I think it was -- oh. I think it's
23 this one. 11 -- wait. I think it's this one.

24 Okay. So I've just crossed out that [REDACTED].

25 Q Okay. I'd like to turn to Exhibit 5.

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1 That's Appendix A.

2 A Okay.

3 Q Okay. And I want to look at your Data
4 Source column. Do you see you have a column that
5 says, "Data Source"?

6 A Yes.

7 Q Okay. This is a column that counsel
8 created for you -- right? -- and then you checked
9 this?

10 A Yes.

11 Q Okay. So the first -- well, let's
12 count 'em -- one, two, three, four, five, six,
13 seven, eight, nine, ten -- the first ten entries are
14 all solely from an exhibit called "Exhibit 2052."
15 Do you see that?

16 A Yes.

17 Q Okay. And then after that, all of the
18 entries are included in an exhibit called "2036"
19 that you attached to your Declaration. Do you
20 recall that?

21 A Well, no. I think it's 2053, page 19.
22 And then Exhibit 2036. So there's two --

23 Q But those were identical; right?

24 A Okay.

25 Q The 2053 and 2036, did you check that,

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1 that they were identical?

2 A I don't recall right now.

3 Q Okay. Let me say, I also misspoke as
4 well.

5 If you look on page 44, there are two
6 samples, UT-15-011001 and UT-15-020101, about four
7 and five rows up from the bottom? Do you see where
8 I'm reading?

9 A Hmm-hmm.

10 Q Okay. Those two were listed as -- wait.
11 Did I -- I think I did -- as just being from 2053;
12 is that correct?

13 A That's what it says, yeah.

14 Q Okay. But all of the other ones are in
15 both 2053 and 2036; is that fair?

16 A Yes.

17 MR. POLLACK: Okay. If we can mark as
18 Deposition Exhibit 7 what was formerly called
19 "Exhibit 2036."

20 (Exhibit 7 marked)

21 BY MR. POLLACK:

22 Q Did you review in detail all of the
23 Certificates of Analysis in Exhibit 2036?

24 A I laid my eyes on every page, and I

25 cross-checked some of them in detail. I didn't look
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1 at every number on every batch record.

2 Q Okay. You didn't compare each one to
3 make sure it was correct on your table?

4 A I said I spot-checked them, and they all
5 seemed fine.

6 Q Okay. By spot-checking, though, you
7 didn't do every single one, you --

8 A I didn't do every single one. I just
9 randomly picked and found no errors.

10 Q Okay. Did you calculate what the average
11 purity was of the samples in Exhibit 2036?

12 A Well, counsel did the calculation. And
13 that's the summary at the bottom.

14 Q That's all of the samples; right? That's
15 2036 and 2052 and 2053; correct?

16 A Yes.

17 Q Okay. Did you calculate just what it
18 would sum up to in 2036?

19 A So, in other words, eliminating the 2052,
20 the development batches is what you're asking?

21 Q Yes.

22 A No.

23 Q Why -- do you have an understanding why
24 2052 was added -- why the samples from 2052 were
25 added to the samples from 2036?

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1 A Yes, because we also added development
2 batches for the '393 process. And we -- and I
3 thought that the fairest comparison was to look at
4 the development batches that were used in UTC's
5 development of the Moriarty process and the
6 development batches from the '393 as well. I
7 thought that was the fairest comparison.

8 Q That was your idea or counsel's idea?

9 A We discussed it. I -- I don't remember
10 if who -- who came up with the first idea, but we
11 agreed this was a reasonable thing to do.

12 Q Okay. Guess what? Ms. Choksi did the
13 calculation for us, so I'm going to provide that to
14 you.

15 So I'm going to mark as Williams
16 Deposition Exhibit 8 a chart of all of the purities
17 and total related impurities from the Appendix A,
18 Deposition Exhibit 5.

19 (Exhibit 8 marked)

20 BY MR. POLLACK:

21 Q And I'm also going to mark -- just so you
22 can see how we created this -- I'm going to mark as
23 Deposition Exhibit 9 a chart containing all samples,
24 including the ones from 2052.

25 (Exhibit 9 marked)

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1 BY MR. POLLACK:

2 Q What we've done here is, we've just
3 marked in highlighting which ones are from 2052.

4 And so what we've done here is, we've used all of
5 the samples that you did, and we also used the HPLC
6 analysis. Do you know what I mean by that?

7 A Why don't you explain.

8 Q Yeah. If you look at, for example, 2036,
9 Deposition Exhibit 7 -- let's go to the third page
10 of the document, the one that says, "Page 3 of 3."
11 And on the bottom, it says -- well, it says,
12 "Page 3" at the bottom center. Do you see where I'm
13 looking?

14 A Hmm-hmm.

15 Q Okay. Now, do you see there's a -- it
16 says, "Test," and there's a number, "Assay HPLC."
17 Do you see that?

18 A Yes.

19 Q And do you see it says, "98.4"?

20 A Yes.

21 Q Okay. So what we've done on this chart
22 is, we've put in all of those values as well. Do
23 you see where it says, "Assay Purity"?

24 A Okay. Which --

25 Q You can pick either 8 or 9. The only

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1 difference is, we highlighted the ones from 2052 on
2 9.

3 A Okay.

4 Q Okay. So do you understand what I mean
5 by the HPLC assay?

6 A So this one corresponds to --

7 Q Let's see. This one here that we're
8 looking at is lot UT15-99H001. Do you see that on
9 Exhibit 2036?

10 A Yes. So that's entry 11; right?

11 Q That's correct.

12 A Okay.

13 Q Okay. Is that number recorded fairly?

14 A It appears to be.

15 Q Okay. And what we've done at the end is,
16 we've taken -- we'll let you go through,
17 electronically, these spreadsheets -- we've taken
18 all the data you used, and we did an average, as did
19 you, and we got 99.0 by both methods, whether you
20 use the HPLC assay, or what I'm calling "implied
21 purity" where you subtract the total related
22 substances.

23 A Wait. What --

24 Q On the very last page of either document.

25 A Oh.

1 Q Do you see that?

2 A Yes.

3 Q Okay. That's the same number you got;
4 correct? Appendix A.

5 A Yes. Basically the same.

6 Q Okay. Now what I'm going to mark as
7 Deposition Exhibit 10 is the same document, except
8 with the first ten samples, the ones that came from
9 Exhibit 2052 removed.

10 (Exhibit 10 marked)

11 BY MR. POLLACK:

12 Q If you would verify for me that
13 Exhibit 10 is the same as 8 or 9 except with the
14 highlighted exhibit -- lots removed.

15 A Okay. That appears to be the case.

16 Q Okay. And then what we did is, we -- we
17 did the same thing you did. We took the average,
18 but we did it two ways. We did it with the HPLC
19 assay --

20 A Hmm-hmm.

21 Q -- so taking each of those numbers from
22 2036. You understand what I'm referring to?

23 A Yes.

24 Q And we also did it the way you did it,
25 subtracting the total related substances from 100.

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1 A Yes.

2 Q Okay. If you look on page 5, there's the
3 result of our average. Do you see that?

4 A Yes.

5 Q And do you see that the HPLC assay -- the
6 average was [REDACTED]?

7 A I see that.

8 Q Okay. Instead of 99.0. Do you see that?

9 A Hmm-hmm.

10 Q And doing it your way, the way you
11 prefer, the result was 99.5. Do you see that?

12 A What do you mean --

13 Q Subtracting the total related substances
14 from 100, the average was 99.5.

15 A Okay.

16 Q Do you see that?

17 A I'm not sure what this implied impurity
18 is. I don't -- I don't -- what's implied impurity?

19 Q So that's the language I'm using. If you
20 want to call it "purity," that's fine. It is the
21 100 minus the total related substances.

22 A Okay.

23 Q How did you calculate the purity of each
24 sample?

25 A Okay. So the total related substances is
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1 the -- the sum of the known impurities plus the
2 unknown impurities.

3 Q Is it?

4 A That's my understanding.

5 Q Well, let's take -- let's take, for
6 example -- let's go to the top of page 44; all
7 right? So there's all of the impurities, and that
8 sum is .4. Do you see that in the right?

9 A Yes.

10 Q Okay. Now, do you get .4 when you add
11 all those numbers up?

12 A I have to do the calculation. Can I use
13 my phone --

14 Q Absolutely.

15 A -- here? (Using phone).

16 MS. HASPER: Counsel, while Dr. Williams
17 does the math, may I ask a question to clarify
18 something, perhaps to avoid an extraneous objection?

19 You introduced Exhibit 10 and said that
20 the highlighted rows had been removed. I noticed
21 highlighting on two rows. Is that merely a printing
22 error, or is that --

23 MR. POLLACK: Those are just simply --
24 I'll point that out to him. Those are simply the
25 highlighted two rows from Exhibit 2053. Different

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1 exhibit.

2 MS. HASPER: They're not also in 2036?

3 MR. POLLACK: -36. Correct.

4 MS. HASPER: All right. Thank you.

5 THE WITNESS: So that line -- we're

6 talking about the top line on the top of page 44?

7 BY MR. POLLACK:

8 Q Correct.

9 A Let me check this again. First time I
10 got .55.

11 Q That's what I get. But please feel free
12 to do it again.

13 A Okay. So it's -- I get .55, the addition
14 of those.

15 Q Yes.

16 A Known -- and those are all known
17 impurities, I believe.

18 Q Right. And then the total related
19 substances is .4?

20 A So I believe the reason that the -- that
21 the numbers don't add up is that the -- the -- where
22 the amount of impurity was less than .05, a number
23 of .05 was put. So it's -- it's estimated
24 conservatively high. But the actual total, which
25 comes from, I believe, these batch documents, is

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1 what's in this column.4.

2 Q Right. But, in fact, what's in that
3 column is not the sum of the known impurities listed
4 in your prior columns; correct?

5 A Again, I just explained what -- is there
6 any confusion to what I just said?

7 Q Yes.

8 A Hmmm?

9 Q Yes, there is. The -- you said earlier
10 that the sum of total related substances was the sum
11 of each of the known impurities; correct?

12 A And unknown impurities.

13 Q And unknown impurities.

14 A Yes.

15 Q Okay.

16 (Mr. Snader entered the deposition at
17 11:24 A.M.)

18 BY MR. POLLACK:

19 Q And here we see that summing those up,
20 they don't equal the same number; correct?

21 A So maybe the place to go is the source
22 document here. This is 20 -- so the source document
23 at page 36 shows total related substances as
24 .4 percent.

25 Q I see that.

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1 A So that's -- that's -- where these
2 numbers came from. They weren't from the linear
3 addition here (Indicating).

4 Q Right.

5 A Yeah.

6 Q Okay. We're both agreed on that; right?

7 A Yeah.

8 Q Okay. And, actually, your way of putting
9 in what the total related substances are for
10 compounds that are not detected or ones which are
11 less than .05, that's sort of arbitrary, isn't it?

12 A No. Arbitrary?

13 Q Well, you could have done instead of .05,
14 you could have made it zero for example; right?

15 A Yeah. So I was conservative and
16 estimated on the high side. So less than .05 could
17 be .000001; okay?

18 Q And, actually, putting it on the high
19 side, that makes the purity lower, doesn't it? It
20 makes it seem like it's less pure than it actually
21 is, doesn't it?

22 A Yes. And I did the same thing for the
23 '393 process batches. So they -- so the same -- to
24 be fair, that same conservative method was used to
25 compare both.

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1 Q Okay. Here's what I want to know: So
2 when -- the batches 2036 all done by Magellan, even
3 the ones from 2053, are included to make an average,
4 the average value is either █████ percent pure for
5 HPLC analysis or a total of .5 percent impurities by
6 total related substances. What I want to know is,
7 who, then, decided to go out and find ten other
8 pieces of data to try to drag that number lower to
9 99?

10 A I sort of don't like the way you just
11 characterized that, 'cause it sounds like this was
12 done deliberately to make the Moriarty process look
13 worse than it is. That's not really fair.

14 Q Really?

15 A So what we did was, we looked at
16 development batches from the '393, and we also
17 looked at development batches from Moriarty. And,
18 you know, either way -- I mean, if you put them in
19 or drop them out, the impurity profiles between the
20 two processes are different; okay? So you can't
21 just look at the overall total related substances
22 purity; you have to look at the actual distribution
23 of the impurities. Because the '393 process
24 unexpectedly -- okay? -- because of the
25 crystallization of the salt, removes stereoisomeric

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1 impurities -- two of them completely -- and leaving
2 only the very small amount of the enantiomer, which
3 is [REDACTED].

4 Q Okay.

5 A So just doing these -- these overall
6 impurity comparisons and percentages, I don't think
7 is -- is valid.

8 Q But you actually submitted this to the
9 Patent and Trademark Office and told them that that
10 was one of the significant differences between
11 Moriarty and the '393 process, that the purity was
12 99.0 versus [REDACTED], isn't that true?

13 A I didn't submit anything to the Patent
14 and Trademark Office.

15 Q You understand this is your Declaration
16 that you signed.

17 A Yes.

18 Q That was submitted to the Patent and
19 Trademark Office. You understand that?

20 A I thought you were talking about the --
21 the batch records.

22 Q Well, those are submitted as well.

23 A Yeah.

24 Q You understand that --

25 ///

1 (Indiscernible crosstalk)

2 THE WITNESS: I'm sorry. I don't
3 understand where you're --

4 BY MR. POLLACK:

5 Q You understand your Declaration?

6 A Yeah.

7 Q That it was used as evidence at the
8 Patent and Trademark Office in this proceeding. You
9 understand that; right?

10 A Yes.

11 Q Okay. And in that Declaration, you
12 represented to the Patent and Trademark Office that
13 the difference between Moriarty -- one of the
14 differences between Moriarty and the '393 patent was
15 that Moriarty produced an average of only 99.0,
16 while the '393 patent produced an average of [REDACTED].
17 You recall saying that; right?

18 A Yes.

19 Q Okay. And now what we're seeing is, if
20 we take only the data, the two data sets, created by
21 Magellan, one for the '393 and one for the Moriarty
22 process, in fact, the numbers are [REDACTED] and [REDACTED].

23 A But, again, you're talking about the
24 overall purity. You're not talking about impurity
25 profile.

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1 Q Sure. I understand. I'm not disagreeing
2 with you on that. I'm just saying, you told the
3 Patent Office that these two differed. And one of
4 the ways they differed was one was 99.0 and the
5 other was [REDACTED]. Now we see that both are [REDACTED]. How
6 does that jive with acceptable scientific conduct?

7 A Well, the -- again, the '393 batches were
8 produced without chromatography. So you could
9 repurify and purify anything you want --

10 Q Of course.

11 A -- by chromatography to [REDACTED] percent
12 if you wanted to --

13 Q Right.

14 A -- okay? -- but, you know, in large-scale
15 manufacturing, that's not practical. It's not
16 economical. It's not safe. It's not
17 environmentally appropriate; okay? So -- but,
18 again, I think the -- what I was focused on was
19 looking at -- the -- the -- the structural
20 differences between the impurities between the two
21 processes is different. And that is not reflected
22 in the overall purity, no matter however you want to
23 eliminate batches, and cherry-pick batches or
24 however you want to do that.

25 Q You'd agree with me somebody here

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1 cherry-picked some batches, didn't they?

2 A No, I don't think so.

3 Q You don't think somebody added 10 batches
4 to take the number down from [REDACTED] to 99.0?

5 A No. We -- my understanding is, we asked
6 for -- these were all the batches we could find
7 records for. And these were the same -- I think
8 these are the same 56 batches that were used by
9 Dr. Aristoff in the -- the Sandoz litigation.

10 THE VIDEOGRAPHER: Sorry to interrupt, we
11 have five minutes of video left.

12 MR. POLLACK: Why don't we take a short
13 break.

14 THE WITNESS: Sure.

15 MR. POLLACK: Whatever you want.

16 THE WITNESS: Yeah. 15 minutes? I need
17 a bathroom break, anyway.

18 THE VIDEOGRAPHER: This ends Media No. 1
19 in the deposition of Robert M. Williams, Ph.D. The
20 time is 11:32 A.M.

21 (Off the record)

22 THE VIDEOGRAPHER: This begins Media
23 No. 2 in the deposition of Robert M. Williams, Ph.D.
24 We are back on the record. The time is 11:53 A.M.

25 MR. SNADER: And this is Shaun Snader, UT Ex. 2059
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1 United Therapeutics Corporation, Washington, D.C.,
2 counsel for patent owner.

3 BY MR. POLLACK:

4 Q Welcome back, Dr. Williams.

5 A Hmm-hmm.

6 Q During the break, did you speak to
7 counsel about this case, the deposition, or any --
8 any matter having to do with treprostinil?

9 A No. We talked about golf, hotels, and
10 restaurants.

11 Q Okay. If you can go back to your
12 Exhibit 2 -- that's your Declaration.

13 A Okay.

14 Q If you turn to paragraph 98, you see
15 there, it says, "The treprostinil product of the
16 '393 patent has an average purity of [REDACTED] percent,
17 while the Moriarty product has an average purity of
18 99.05." Do you see that statement?

19 A I see that statement.

20 Q And then you say, "Thus, the treprostinil
21 product of the '393 patent has an average purity
22 that is [REDACTED] percent higher than that of Moriarty's."
23 Do you see that statement?

24 A Yes, I do.

25 Q And you understand that those statements

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1 were given to the Patent and Trademark Office --
2 right? -- in this proceeding?

3 A Yes.

4 Q Are those statements not important to
5 your opinion?

6 A They're important. But if we also read
7 above, I say, "It is clear the treprostiniil product
8 produced by the '393 patent process has a markedly
9 different impurity profile than the treprostiniil
10 product of the Moriarty prior-art process and as
11 such is physically distinct from the prior-art
12 product."

13 So my opinion in total is important in
14 paragraph 98, not just that one little aspect.

15 Q Okay. Although, I know that one little
16 aspect is the -- what's called a "conclusory
17 sentence"?

18 A I don't know if I would label that as the
19 final conclusion.

20 Q Even though it follows the word, "Thus"?
21 Begins with the word, "Thus"?

22 A Well, I sort of begin the paragraph, ". .
23 . from these data." That's also -- I'm making a
24 conclusion about the impurity profile. So I'm
25 actually making two different important conclusions

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1 in this paragraph. So the overall purity, and I
2 think very significantly, the impurity profile,
3 which is different. That's the structural
4 difference.

5 Q But it seems like you made the impurity
6 profile point in paragraph 97, isn't that right?

7 A Let me just read that.

8 Well, I talked about the differences in
9 impurity -- I talked about salient features of the
10 impurity profile for the '393 patent process in
11 paragraph 97.

12 Q Now, you said that the statement about
13 the [REDACTED] versus the 99.5 was also important. Why
14 was it important to your opinion?

15 A Well, it shows that in addition -- in
16 addition to the differences in impurity profile, the
17 structural differences is also an overall purity
18 difference.

19 Q And why didn't you think that was
20 important?

21 A Well, because you're looking at various
22 aspects of the product. The overall purity, as well
23 as the detailed components of the impurities.

24 Q Yeah. So why was the overall purity
25 important for distinguishing -- if it was -- for

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1 distinguishing the '393 product from the Moriarty
2 product?

3 A Well, the Moriarty product, again,
4 involves a very time-consuming, expensive
5 chromatography. And if that step weren't conducted,
6 you'd get an even worse product. So you have to
7 perform that step, which is very, very deleterious
8 in so many ways, as we discussed earlier. And so
9 you still want to have a high overall purity. But
10 it's also important to recognize that there is a
11 difference in the individual impurities between the
12 two processes. And the data shows that so
13 incredibly clearly.

14 Q Let me ask you -- you have a
15 paragraph 103, if you go a couple pages later. And
16 you see there, again, you talk about the difference
17 in purity between Moriarty or Phares and the '393
18 patent. Do you see that?

19 A So this is with regard to the
20 treprostinil diethanolamine salt?

21 Q Yes. The first sentence is, but further
22 down, you say, "Regardless of the purity identified
23 in Moriarty, a further analysis of all batches made
24 by the Moriarty process up to the time of the
25 reference itself, reveals an average purity of

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1 99.05 percent, while the average purity of the '393
2 patent batches is [REDACTED]." Do you see that sentence?

3 A I see that.

4 Q Okay. And that's referring to the
5 treprostiniil free acid; correct?

6 A Um, so the -- the [REDACTED] percent, this is
7 the 121 batches in the table that I have. And that
8 includes some batches of just salt, but most of them
9 are acid.

10 Q So you actually looked at both salt and
11 acid in your analysis?

12 A Yes. And the salt is amazing. The salt
13 is just stunningly pure.

14 Q Salt, in fact, is somehow purer than the
15 free acid, isn't it?

16 A That's correct.

17 Q Even though the last acidification step
18 hasn't been performed?

19 A On the salt.

20 MS. HASPER: Objection.

21 BY MR. POLLACK:

22 Q On the salt.

23 A Sorry.

24 Q Yes.

25 MS. HASPER: Objection. Mischaracterizes
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1 the document.

2 THE WITNESS: Yeah. So at the salt
3 stage, the step (d) has not been performed.

4 BY MR. POLLACK:

5 Q Right.

6 Why did you think it was important in
7 this one paragraph -- 103 that's about the salt to
8 point out the differences in the purity of 99.05
9 versus [REDACTED] in the prior art versus the patent?

10 A So you've already asked me this question
11 and I've already given you have the answer. So
12 you're asking me the same question over and over.

13 Q So what's the answer?

14 MS. HASPER: Objection. Asked and
15 answered.

16 THE WITNESS: I told you that the overall
17 purity is important, but I also looked at the
18 individual components of the impurities. And
19 they're different.

20 BY MR. POLLACK:

21 Q Okay. Since it is an important point
22 that the overall purity is important, isn't it a
23 problem for your opinion if data points were
24 cherry-picked to try to bring the actual purity down
25 from [REDACTED] to 99.0?

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1 MS. HASPER: Objection. Mischaracterizes
2 his testimony and the document.

3 THE WITNESS: No. So I -- I -- I don't
4 like your question, because it's -- it's accusatory
5 and mischaracterizes the analysis that I did that I
6 thought was very fair. I included development
7 batches for both the Moriarty process, and I also
8 included development batches for the '393 process.
9 So the development batches for the '393 are also
10 poorer than the later commercial batches. And so by
11 the same token, those numbers bring down the average
12 purity of the '393 process. So I thought I was
13 being very fair.

14 BY MR. POLLACK:

15 Q Oh, really? To bring it down when it's
16 [REDACTED], even with those batches?

17 What did it bring it down from?

18 A Well, I didn't -- I didn't do the
19 calculation to eliminate those. I included both.
20 But if you did eliminate the development batches, it
21 would certainly improve the overall purity of the
22 '393 batches.

23 MR. POLLACK: I'm going to mark as
24 Williams Deposition Exhibit 11 a document known as
25 "Exhibit 2052" in the case, the UT-15 injection

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1 drug-substance chemistry manufacturing and controls
2 submission for an NDA No. 21-272.

3 (Exhibit 11 marked)

4 MS. HASPER: And just to let you know, my
5 realtime has not been working since we came back
6 from the break.

7 THE REPORTER: Off the record.

8 THE VIDEOGRAPHER: Off the record. The
9 time is 12:03 P.M.

10 (Off the record)

11 THE VIDEOGRAPHER: We are back on the
12 record. The time is 12:05 P.M.

13 BY MR. POLLACK:

14 Q All right, Dr. Williams, I've put in
15 front of you the Exhibit 2052, which is the source
16 of the ten additional data points you added to your
17 analysis. Is this 2052 the document that you relied
18 upon?

19 A (Examining document) Yes.

20 Q Okay. Now, if you would turn to what's
21 called at the bottom of the document in the center,
22 "Page 25"?

23 A Okay.

24 Q Are these the lots that you added to the
25 analysis of the average purity of the Moriarty

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1 process?

2 MS. HASPER: Objection. Mischaracterizes
3 his testimony and the documents.

4 THE WITNESS: So I don't think I would
5 agree with the way you phrased your question -- that
6 I added these. I was given all of the data
7 together.

8 BY MR. POLLACK:

9 Q By counsel?

10 A Yes.

11 Q Hmm-hmm.

12 A So there was no importing separately
13 these batches to try and obfuscate the data.

14 Q Right. 'Cause counsel had already
15 calculated the average value so that you just
16 checked that calculation; correct?

17 A Yes. I checked the calculation, and we
18 did the same thing for the '393 batches. We
19 added -- the development batches were there to do a
20 fair comparison.

21 Q When you did the check of the
22 calculation, you didn't say: Hey, why are we adding
23 that other exhibit? Let me see how these numbers
24 come out if I just use the set that was presented as
25 existent 2036.

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1 MS. HASPER: Objection.

2 BY MR. POLLACK:

3 Q You didn't do that; right?

4 MS. HASPER: Objection. Mischaracterizes
5 the document and the testimony.

6 THE WITNESS: So I didn't do a separate
7 calculation. I certainly looked at the charts, the
8 exhibits. And either way you slice it, if you want
9 to include the development batches, or you want to
10 exclude them, my opinion does not change; okay?
11 Because with the -- with the -- the Moriarty
12 process, you're starting with an inferior process.

13 So the development batches were not as
14 nice as the development batches that you started
15 with the '393, 'cause it's a better, distinct,
16 process; okay? But even if you wanted to eliminate
17 both of them either way, the impurity profiles are
18 different. And the '393, no matter how you slice
19 it, gives you a superior product, a different
20 product.

21 BY MR. POLLACK:

22 Q Okay. But one part of your opinion --
23 and you definitely stated this a number of places in
24 your Declaration -- was that the Moriarty process
25 gave you 99.0 while the '393 process gave you [REDACTED];

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1 right? That was one opinion that you stated?

2 A That's one aspect of my opinion.

3 Q It's one opinion that you stated?

4 A One aspect of my opinion.

5 Q Looking now and seeing that certain of
6 the data points were added from these older
7 development batches and that brought down the purity
8 from ██████ to 99.0, do you want to now remove just
9 that one aspect of your opinion?

10 MS. HASPER: Objection. Mischaracterizes
11 his testimony and the documents.

12 THE WITNESS: No, because, you know, the
13 development batches are compared fairly to
14 development batches between two processes; okay?
15 So, again, we're looking at an average of many, many
16 batches over time. And so what I did not do is, I
17 did not cherry-pick a single batch from the '393 and
18 compared it to a single batch of the Moriarty
19 process. So I thought it was much more significant
20 to look at the overall picture. And I think my
21 report very fairly and accurately provides the
22 overall picture with the exception of that one
23 duplicate entry, which doesn't change the number
24 very much.

25 ///

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1 BY MR. POLLACK:

2 Q Let's think about it this way: So 46
3 batches show an average value for the purity of
4 [REDACTED]. And 10 batches bring that number down to
5 99.0.

6 Is it not true that, fairly, one should
7 take the 46 rather than throwing in 10 outliers?
8 Isn't that how science is done?

9 MS. HASPER: Objection. Mischaracterizes
10 the documents.

11 THE WITNESS: No. I don't -- I don't
12 agree.

13 BY MR. POLLACK:

14 Q Let's take a look at this page 25 that I
15 asked you to look at in Exhibit 11. The dates of
16 manufacture of these lots -- do you see them?
17 There's a line that says, "Date of Manufacture."

18 A Okay.

19 Q The first two lots are dated in 19 --
20 they're both in 1986. My eyes are a little weak,
21 but I think one's July 1986, and the other one is
22 August 1986? Do you see that?

23 A Okay.

24 Q And then the next batches are all dated
25 in -- their date of manufacture is either 1997 or

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1 1998; correct?

2 A Yes.

3 MR. POLLACK: I'm going to mark as
4 Williams Deposition Exhibit 12 a document known in
5 this case as "Exhibit 1004," which is the Moriarty
6 Journal of Organic Chemistry Article.

7 (Exhibit 12 marked)

8 BY MR. POLLACK:

9 Q And can you verify for me that Exhibit 12
10 is the Moriarty article that's prior art that we've
11 been referring to in this deposition?

12 A Yes.

13 Q What's the date on the Moriarty article?

14 A 2004.

15 Q Okay. What date was it received by the
16 journal?

17 A June 5th, 2003.

18 Q Okay. How many years after was this
19 article published compared to when these lots were
20 manufactured in -- sorry. Let me ask my question
21 again.

22 How many years are there between the lots
23 described in Exhibit 2052 and the Moriarty article?

24 MS. HASPER: Objection. Vague.

25 Relevance.

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1 THE WITNESS: So the earliest -- the
2 earliest date is July of '86 to 2003. Is that -- is
3 that the year-spread that you're asking me about?

4 BY MR. POLLACK:

5 Q Year-spread. Right. Okay.

6 Many of the lots are from 1998 and 1999?

7 A So there's the date of manufacture and
8 date of testing.

9 Q I'm asking the date of manufacture.

10 A Yes.

11 Q Isn't that what's relevant here, date of
12 manufacture?

13 A Relevant -- relevant to what?

14 Q Relevant to -- I'll withdraw that
15 question.

16 Okay. So, for example, one of the lots
17 you included -- and you're free to look at your
18 chart -- is lot No. LRX97J01, made in October 1997.
19 Do you see that?

20 A I see that.

21 Q Okay. That is seven years before the
22 Moriarty article was published?

23 A Yes.

24 Q Okay. Let me ask you: There's two lots
25 you didn't include in your analysis. They're the

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1 two that are made by -- you see there's also a line
2 that says "Manufacturer"; correct? On the top?

3 A Yes.

4 Q Okay. And -- by the way, none of these
5 lots that are on page 25 were manufactured by United
6 Therapeutics; correct?

7 A So I believe that Steroids and SynQuest
8 are contract manufacturers that were making the drug
9 for United Therapeutics.

10 Q Right. It wasn't made by United
11 Therapeutics itself?

12 A I'm not really privy to the detailed
13 relationship between United Therapeutics and its
14 suppliers. But if a supplier is making the drug for
15 UTC, I believe that UTC would be the -- you know,
16 ultimately be the manufacturer.

17 Q Okay. Do you know who makes treprostinil
18 now for United Therapeutics?

19 A I know that there's suppliers that --
20 different suppliers that make different -- do
21 different parts of the synthesis, but I'm actually
22 not sure of the whole picture of how -- who's
23 contributing what pieces, what companies.

24 Q Okay. Now, you understand the first two
25 lots were made by Upjohn back in the '80s; correct?

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1 A Yes.

2 Q Okay. And you'll agree with me that it
3 can't be the case that way back in the '80s, Upjohn
4 was using the Moriarty process; correct?

5 A No. It's not possible.

6 Q Okay. Now, do you notice that there's a
7 footnote -- it's a little hard to read the typeface
8 is small -- it's footnote 4. Do you see that
9 footnote 4?

10 A Yes.

11 Q Can you read footnote 4 for us into the
12 record?

13 A "These lots were manufactured by
14 Pharmacia and Upjohn using a slightly different
15 route of synthesis."

16 Q In reading that, is it your understanding
17 that what they mean by that is all the other lots
18 here were made in a way that's only slightly
19 different from the way Upjohn made treprostinil?

20 MS. HASPER: Objection. Calls for
21 speculation.

22 THE WITNESS: Yeah. I don't know.

23 BY MR. POLLACK:

24 Q What's your understanding of what that
25 says?

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1 A What? Footnote 4?

2 Q Yeah. Footnote 4.

3 A So --

4 MS. HASPER: Objection. Relevance.

5 THE WITNESS: That these -- these two
6 1986 lots were made by Pharmacia and Upjohn using a
7 different -- a slightly different route of
8 synthesis.

9 BY MR. POLLACK:

10 Q Okay.

11 A That's what it says.

12 Q Sure. Okay. And is it your
13 understanding that the other lots, then, were not
14 made exactly the way Upjohn made them but a fairly
15 similar process was used?

16 MS. HASPER: Objection.

17 THE WITNESS: You know, I don't know the
18 details.

19 BY MR. POLLACK:

20 Q You don't know the details of how all
21 these lots were made?

22 A No. I haven't seen the detailed batch
23 records of what went into those lots.

24 Q Okay. So you don't know whether or not
25 these lots were made by the '393 process, the

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1 Moriarty process, the older Aristoff process; is
2 that right?

3 MS. HASPER: Objection. Mischaracterizes
4 testimony and the documents.

5 THE WITNESS: Um, you know, I -- I'd have
6 to investigate further. I don't know.

7 BY MR. POLLACK:

8 Q Right. You -- you don't know if any of
9 these are from the Moriarty process?

10 A Um --

11 Q At least not the ones on page 25?

12 A So the Moriarty paper came out in 2003.

13 Q 2004 it came out.

14 A Well, yes. Yeah. The paper was
15 published in 2004, but the technology had been put
16 together as easily as early as 2003.

17 Q Okay.

18 A So I don't think it's possible that any
19 of these could have been made by Moriarty process
20 just based on the dates.

21 Q And yet these are the ten additional
22 samples that you added to your analysis that brought
23 the value down from [REDACTED] to 99.0; correct?

24 MS. HASPER: Objection. The testimony --
25 mischaracterizes testimony and the documents.

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1 THE WITNESS: So I -- I guess I don't
2 know.

3 BY MR. POLLACK:

4 Q Well, do you want to compare the lot
5 numbers here to the lot numbers on -- if you take
6 the exhibit that has the yellow highlighting --
7 that's our Exhibit 9 -- this one here (Indicating).
8 Or you can compare it to your appendix. Either one.

9 A (Examining documents) So it begins with
10 9 -- 97J01.

11 Q Right. That's the third -- third column?

12 A Yes.

13 Q And that's on your -- that is on one of
14 the ones you analyzed on your -- on your chart?

15 A Yes.

16 Q Okay. And LRX99801, you analyzed that
17 one, too?

18 A Yes. That's the second entry. And then
19 BO-1. And then they go to -- the next one is UT,
20 but it's -- oh, that's -- yeah. So they're just in
21 sequential order.

22 Q Okay. And each of these lots were
23 just -- we were just reviewing, you're not sure what
24 method was used to make any of these. You haven't
25 seen the batch sheets?

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1 A I haven't seen the batch sheets.

2 Q Does that -- looking at this data now,
3 are you prepared to change your opinion about
4 whether or not the Moriarty method, in fact, gives a
5 [REDACTED] percent purity just like the '393 patent?

6 A No.

7 And you keep asking me the same question
8 30 different ways, and I already told you: If you
9 wanted to throw out all the development batches from
10 both processes and both analyses, fine --

11 Q Okay.

12 A -- that doesn't change the differences in
13 impurity profile. And it also is not going to
14 change the overall fact that the '393 process gives
15 an overall higher purity than Moriarty.

16 So, you know, fine. Scratch out those 10
17 entries if you want to. It doesn't change my
18 opinion.

19 Q Okay. You understand if we scratch out
20 those 10 entries, we're going to get [REDACTED] for
21 impurity --

22 A We're still never going to change the
23 impurity profile.

24 Q I understand. I'm just talking about the
25 one -- you said twice, at least -- I think much more

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1 than twice -- in your opinion that the purity
2 profile between Moriarty and the '39 -- I'm sorry --
3 that the purity level between the '393 patent and
4 Moriarty were different -- let me start my question
5 again.

6 You've said -- now seeing, at least twice
7 -- and I think there were some more times -- in your
8 Declaration that the -- an important point is that
9 the purity level between Moriarty and the '393
10 patent is different, and it's different by 99.0
11 versus [REDACTED]. I just want to focus on that one
12 opinion, nothing else.

13 A Okay.

14 Q Do you want to retract that opinion now,
15 having seen this information at this deposition?

16 MS. HASPER: Objection. Asked and
17 answered.

18 THE WITNESS: No.

19 BY MR. POLLACK:

20 Q No? Why not?

21 A Because, you know, even if the -- you
22 eliminate these development batches, the overall
23 purity for both processes goes up, but Moriarty's
24 never going to catch the '393 purity.

25 Q Okay.

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1 A So no matter how you want to add or
2 eliminate data, the -- the important -- the really
3 important thing that these spreadsheets show of
4 these -- from these batch records is that the
5 Moriarty process does not provide, on average, a
6 purer material than the '393, and the impurity
7 profiles are distinctly different. And it was
8 unexpected that you would be able to eliminate, for
9 example, two to three stereoisomeric impurities
10 entirely.

11 Q Okay. You said it doesn't provide -- the
12 Moriarty process doesn't provide on average a higher
13 purity than the '393. But let me ask you another
14 direction. Does the '393 process significantly
15 provide a higher purity than the Moriarty process?

16 MS. HASPER: Objection. Asked and
17 answered.

18 THE WITNESS: Yes, on average, that is
19 definitely the case. That's what the data shows.

20 BY MR. POLLACK:

21 Q Did you include standard deviation -- you
22 know what standard deviation is; right?

23 A Yes.

24 Q And I notice you didn't calculate any
25 standard deviations for your average, isn't that

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1 true?

2 A That is true. I did not. That's not the
3 sort of thing anyone would do.

4 Q Isn't that the standard scientific
5 method?

6 A It may be for some sciences, but organic
7 chemistry and even process chemistry, you know, it's
8 very rarely, in my experience, done.

9 And, you know, if you wanted to put
10 instead deviations, I didn't calculate that. You
11 know, I don't think it's going to change the
12 picture. The impurity profiles are different, and
13 the '393 process produces a superior product.

14 Q I'm going to -- and we'll provide this
15 spreadsheet electronically to counsel -- but for you
16 for now --

17 MS. HASPER: Is there a way I can see the
18 spreadsheet?

19 MR. POLLACK: You can go look over his
20 shoulder. That's perfectly fine.

21 BY MR. POLLACK:

22 Q We have calculated the averages and the
23 standard deviations for all of the samples,
24 excluding 2052. And I've given you the spreadsheet
25 there.

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1 You know how to use Excel; right?

2 A Yes.

3 Q Okay. So I've given you the Excel
4 spreadsheet there. You're free to play with it and
5 verify we did everything correctly. You'll see the
6 standard deviations are recorded there; right?

7 A I see them.

8 Q Okay. And those were calculated using
9 the standard Excel method. And you see that for the
10 HPLC assay, I believe it's .6 is the standard
11 deviation? Do you see that?

12 A I see that.

13 Q And .24, the total impurities.

14 A I see that.

15 Q Okay. Let's start with the .6.

16 If the standard deviation -- if it's
17 ██████, plus or minus .6, is there any value that the
18 '393 patent purity could have that would be
19 statistically different from ██████, plus or minus .6?

20 MS. HASPER: Objection. Beyond the
21 scope.

22 THE WITNESS: So, Counsel, I know that
23 your focus is on this overall average purity, but my
24 opinion is not on this average overall purity in
25 isolation; it's the overall purity in combination

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1 with the impurity profile. And I can't separate
2 those two, because they're inseparable from the
3 reality of how this drug is made and what the
4 characteristics of the product are.

5 BY MR. POLLACK:

6 Q Okay. Yeah. I'm not trying to attack
7 the whole of your opinion. You can keep the
8 impurity profile part. I'm trying to understand the
9 other prong -- the total impurities level. Is
10 that -- you've said it's important to your opinion.
11 So I'm now exploring why it's important to your
12 opinion. And now seeing that that value really
13 doesn't change much, how does removing that one leg
14 change your opinion?

15 A It doesn't.

16 Q Okay. And should we -- since your
17 opinion is fine without that one leg -- without the
18 purity comparison, should we just eliminate the
19 purity comparison from your opinion and just rely on
20 the difference in impurity profile?

21 MS. HASPER: Objection. Mischaracterizes
22 his testimony.

23 THE WITNESS: No.

24 BY MR. POLLACK:

25 Q Why not?

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1 A Because, even if you eliminate these
2 development batches, the -- the overall purity of
3 the '393 product that is being manufactured on a
4 commercial scale is still better than what UTC was
5 getting with the Moriarty process. And
6 significantly, we've eliminated chromatography, and
7 the impurity profiles themselves are distinct.

8 Q You understand that the two purity-level
9 values hardly change. You understand that --
10 right? -- between the Moriarty process and the '393
11 process?

12 A I don't agree.

13 Q Why not?

14 A Well, again, if -- even if we're going to
15 chop off the tops of both of those Exhibit A and B
16 charts, the overall -- the overall purities are
17 still different.

18 Q Let me ask you something: Did you notice
19 that the HPLC assay analysis of the -- all of the
20 samples, excluding those ten that were made by
21 method -- you're not even sure what method was
22 used -- just including those, did you notice that
23 the value was [REDACTED] and that that's the same value
24 reported in the Moriarty prior art? Did you notice
25 that?

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1 A For the single batch made in the Moriarty
2 paper?

3 Q Yes. Yes.

4 A Yeah. So that's not in my opinion
5 representative.

6 Q Well, having now seen 56 batches that
7 average [REDACTED], doesn't that show that, in fact, the
8 [REDACTED] number is quite representative is? Isn't that
9 so?

10 MS. HASPER: Objection. Objection.
11 Mischaracterizes the documents.

12 THE WITNESS: Ask me your question one
13 more time, please?

14 BY MR. POLLACK:

15 Q Sure. Having seen 56 samples now which
16 came to an average of [REDACTED] for the purity level --
17 and comparing that to the [REDACTED] number that Moriarty
18 reported, doesn't that show that Moriarty's value,
19 in fact, was representative?

20 MS. HASPER: Objection. Same objection.

21 THE WITNESS: No. So 56 batches give
22 99.1 percent.

23 BY MR. POLLACK:

24 Q I'm sorry. 46 batches -- I apologize.

25 Having seen now that 46 batches give a

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1 value of [REDACTED], isn't that consistent with the [REDACTED]
2 value reported by Moriarty in the prior art?

3 A So those -- they're the same number.

4 MS. HASPER: Objection.

5 THE WITNESS: Sorry.

6 MS. HASPER: Objection. Mischaracterizes
7 the document.

8 THE WITNESS: So, you know, I'm not
9 really sure -- so you're referring to in here --

10 BY MR. POLLACK:

11 Q Yes.

12 A -- [REDACTED] percent of, apparently,
13 recrystallized treprostinil in the JOC paper; right?

14 Q Yes.

15 A That's the number you're referring to;
16 right?

17 Q Yes. That's the number that Moriarty
18 reports; correct?

19 A Right.

20 Q That is on, for the record, if we look
21 at -- let's call it page 13 of the exhibit --
22 page 1902 of the original article. The right-hand
23 column, and it's just above where it says,
24 "Acknowledgement"; right?

25 A Yes.

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1 Q Is that where we're looking?

2 And there, it refers to a purity of
3 [REDACTED] percent, and that is for the compound
4 treprostinil, which was also known as UT-15;
5 correct?

6 A Yes.

7 Q Okay. And that number, [REDACTED], is
8 consistent with the [REDACTED] we see for the average of
9 46 samples; correct?

10 MS. HASPER: Objection. Mischaracterizes
11 the document.

12 THE WITNESS: So -- okay. So, you know,
13 even if those numbers are the same, if you eliminate
14 development batches from the '393, that number goes
15 up. And I -- again, the data in the '393 chart is
16 very conservative because less than [REDACTED] was put in
17 as [REDACTED] -- as [REDACTED]. So it's actually much purer.

18 BY MR. POLLACK:

19 Q What's much purer?

20 A The '393 product.

21 Q Well, the same is true for the Moriarty
22 product.

23 A No. So you've -- you might max out if
24 you do your own type of cherry-picking of
25 eliminating these early development batches, but the

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1 '393 data, again -- all of those -- all of those
2 percentages are going to be improved if you
3 eliminate those -- whatever it was -- number of
4 development batches that were also -- that I also
5 included for the '393.

6 Q Oh, what if I represent to you that
7 actually that's not the case that they won't be
8 improved?

9 A Okay. But, again, you can look at the
10 impurity profiles, and there is -- [REDACTED] appears in
11 only one batch and [REDACTED] only appears in one batch
12 and the rest of them have zero. You cannot say the
13 same for any -- any -- for the Moriarty on average.
14 So the -- there's only two batches: [REDACTED]
15 and [REDACTED]. Those are the only two batches where
16 the stereoisomeric impurities appear. And then if
17 you scan down the column 0000000 -- all the way
18 down.

19 So that crystallization step completely
20 obliterates those two stereoisomeric impurities.
21 And a person skilled in the art couldn't have
22 predicted that. And the triol, t-r-i-o-l, also was
23 completely obliterated.

24 Q And did you look at -- if you look at
25 Appendix A -- and Appendix A, that's the Moriarty

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1 method; right?

2 A I'll give you your computer back.

3 MS. HASPER: Could I just ask counsel --
4 since you've been showing him an electronic
5 document, can we get that in electronic form
6 immediately?

7 MR. POLLACK: We will provide it after
8 the --

9 MS. HASPER: Perhaps before lunch?

10 No, I'd like it before the deposition is
11 over, please.

12 MR. POLLACK: I don't know if we'll be
13 able to do that.

14 MS. HASPER: Well, I'm going to insist on
15 it.

16 MR. POLLACK: I heard what you said.

17 BY MR. POLLACK:

18 Q Sir, take a look at Appendix A.

19 A Okay.

20 Q And if you look at [REDACTED] starting below
21 the ten lots -- the first ten lots on your chart,
22 you notice they're all zeros.

23 A Okay. Which entry?

24 Q Let's start on page 43.

25 A Okay.

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1 Q Okay. And let's start below where --
2 below the 2052s that you used; okay? So look at
3 Data Source and get to the line that's below the
4 2052s.

5 A Okay.

6 Q Okay? Do you see a bunch of zeros for
7 [REDACTED]?

8 A Yes. And I see [REDACTED] for [REDACTED].

9 Q Right. But those are [REDACTED] you put in
10 because it said less than [REDACTED]; right? That's why
11 they're all [REDACTED]?

12 A Some of them may be actually [REDACTED]. [REDACTED] or
13 --

14 Q Or less?

15 A Or less.

16 Q Okay.

17 A But they're detectable.

18 Q Okay. But, similarly, though, even under
19 Moriarty [REDACTED], barely detectable, in most cases?

20 A Okay. But the profiles are still
21 different, on average.

22 Q I'm going to mark --

23 A So I'm -- I need a nature break, and
24 maybe this is a good time for lunch, perhaps?

25 MR. POLLACK: It's up to you.

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1 THE WITNESS: Yeah. And it's gotten
2 warmer in here.

3 MS. HASPER: Yes, it has.

4 THE WITNESS: Maybe we can adjust the
5 thermostat again?

6 MS. HASPER: Why don't we go ahead and go
7 off the record, and maybe we can adjust the
8 environmental.

9 THE VIDEOGRAPHER: We are off the record.
10 The time is 12:38 P.M.

11 (Luncheon recess taken at 12:38 P.M.)

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1 A F T E R N O O N S E S S I O N

2 Commenced at 1:34 P.M.

3

4 THE VIDEOGRAPHER: We are back on the
5 record. The time is 1:34 P.M.

6

7 EXAMINATION (Resumed)

8 BY MR. POLLACK:

9 Q Welcome back from lunch, Dr. Williams.

10 A Thank you.

11 Q Over lunch, did you have a chance to
12 review the spreadsheet of the 46 data points in
13 Excel form?

14 A No.

15 Q Okay. You didn't look at that at all?

16 A No. I ate lunch.

17 Q Okay. That was it. Okay.

18 I'm going to mark as -- let me just do
19 one more, sort of, housekeeping thing. I think what
20 we'll do is, we'll mark the spreadsheet in
21 electronic form which we've now sent to United
22 Therapeutics' counsel, and we've now e-mailed it to
23 the court reporter as well.

24 MR. POLLACK: We'll mark that as Williams

25 Deposition Exhibit 13 so it exists on the record.

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1 (Exhibit 13 marked)

2 MR. POLLACK: Now, I'm going to mark as
3 Williams Deposition Exhibit 14 a document currently
4 called on the record "Exhibit 2006."

5 (Exhibit 14 marked)

6 BY MR. POLLACK:

7 Q Exhibit 2006, also known as "Williams
8 Deposition Exhibit 14," appears to be a letter from
9 United Therapeutics to the FDA, dated January 2nd,
10 2009.

11 Dr. Williams; is that correct? Is that
12 what this is?

13 MS. HASPER: Objection. Beyond the
14 scope.

15 THE WITNESS: Wait. What are you asking
16 me?

17 BY MR. POLLACK:

18 Q I'm asking you if Williams Deposition
19 Exhibit 14 is a letter from United Therapeutics to
20 the FDA, dated January 2nd, 2009.

21 A That's the date, and it's on United
22 Therapeutics letterhead, and it's addressed to the
23 Division of Cardiovascular and Renal Products --
24 FDA, yes.

25 Q Is my answer -- is the answer "yes"?

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1 A Yes.

2 Q Okay. And this is one of the documents
3 you relied upon in forming your opinion?

4 A I looked at a lot of documents. I
5 believe I've seen this before.

6 Q If you turn to page 3 of the document --
7 no, let me step back.

8 Let me ask you: Do you know what this
9 letter is about?

10 A I have to refresh my memory. I don't
11 remember --

12 Q Okay.

13 A -- just by looking at the face page.

14 Q Let me ask you -- if you don't remember,
15 you can just tell me.

16 If we go to page 3, you see there's a
17 paragraph that begins, "In conclusion . . ."

18 A I'd like to read the letter --

19 Q Absolutely.

20 A -- to just familiarize myself with the
21 content if you don't mind.

22 Q I don't mind.

23 A (Examining document) Okay. I've had a
24 chance to review the document.

25 Q Okay. Was this a documented you used in

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1 forming your opinion?

2 A Yes. I -- I remember looking to this.

3 This is the change in the spec for the API.

4 Q Okay. So if we turn to page 3,

5 Exhibit 14, you see there's a paragraph that says,

6 "In conclusion . . .," just above the bolding? Do

7 you see that?

8 A Yes.

9 Q And the conclusion says, "In conclusion,

10 the lots of treprostinil API" -- that means "active

11 pharmaceutical ingredient"; is that right?

12 A Yes.

13 Q "In conclusion, the lots of treprostinil

14 active pharmaceutical ingredient produced by the new

15 process in Silver Spring are of the same

16 high-quality impurity as the commercial lots of API

17 produced by the existing process at the Chicago

18 facility."

19 Did I read that correctly?

20 A That's what it says.

21 Q Okay. Do you have any reason to disagree

22 with that statement?

23 A No.

24 Q Okay. And when it says here, "the new

25 process in Silver Spring," that's a process that now

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1 includes the '393 process, is that your
2 understanding?

3 A That's correct. Yes.

4 Q And the -- in that process, the quality
5 and purity are being compared to the existing
6 process at the Chicago facility. Do you see that?

7 A Yes.

8 Q Okay. And the existing processes at the
9 Chicago facility, that was done using the Moriarty
10 process; is that correct?

11 A I believe that's correct. That's what
12 I've been told.

13 Q Okay. Go down just a couple paragraphs.
14 There's a paragraph that begins with the word,
15 "During." Do you see that?

16 A Yes.

17 Q And it says, "During the initial
18 analytical method validation for the treprostini
19 assay, the results indicated that there is about
20 2 percent variability in the assay." Did I read
21 that correctly?

22 A That's what it says.

23 Q Okay. Do you have any reason to disagree
24 with that statement?

25 A No.

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1 Q Okay. When referring to the treprostinil
2 assay, that's the HPLC assay of how pure the
3 treprostinil is?

4 A I don't know for certain. It doesn't
5 say, "HPLC assay."

6 Q What's your understanding?

7 A That sounds reasonable, but I can't be
8 certain.

9 Q Well, did you review this document in
10 forming your opinion; correct?

11 A Yeah.

12 Q Okay. And when you read that, did you
13 wonder what it was referring to?

14 A Not in that context, no.

15 Q Maybe I can help you. Let's go to
16 page 6. And do you see there, it says, "Assay
17 HPLC"? Do you see that row?

18 A Yes.

19 Q Okay. And do you see it refers to
20 certain numbers --

21 A Yes.

22 Q -- in the next two rows -- columns? Yes?

23 A Yes.

24 Q Okay. Looking at page 6 and then looking
25 back at page 3, reading those sections, can you now

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1 conclude for me that the 2 percent variability in
2 the assay refers to the HPLC assay?

3 A Yeah. I believe that's what they're
4 talking about.

5 Q And so what this sentence on page 3 says
6 is that the HPLC assay analysis for treprostinil has
7 a plus or minus 2 percent variability; is that fair?

8 A So variability -- but -- I don't think
9 that's accuracy -- variability.

10 Q Am I correct that what that means is that
11 the HPLC assay analysis can only be controlled such
12 that the outcome falls somewhere between plus
13 or minus 2 percent of the desired amount?

14 A Yeah, I'm not sure about that. I mean,
15 HPLC is an extremely sensitive technique, and you
16 can detect levels of impurities at much, much lower
17 than 2 percent.

18 Q Let me ask you: Are you an expert at
19 analytical chemistry?

20 A I have a lot of expertise in analytical
21 chemistry, yes.

22 Q What's your expertise in analytical
23 chemistry?

24 A I have extensive experience with NMR --
25 nuclear magnetic resonance spectroscopy -- infrared

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1 spectroscopy, HPLC, thin-layer chromatography, mass
2 spectrometry, ultraviolet spectroscopy, X ray
3 crystallography.

4 Q Okay. And you've used all those
5 techniques?

6 A Yes.

7 Q Okay. But your research area is not
8 analytical chemistry; is that fair?

9 A I wouldn't say it that way. My research
10 area relies, on a daily basis, on analytical
11 technologies and instrumentation.

12 Q Sure.

13 A So I can't -- my laboratory can't
14 function without daily routine access to all the
15 techniques I just enumerated.

16 Q Sure. But your specialty is not the
17 design, development, construction of analytical
18 instruments; is that fair?

19 A I have not designed analytical
20 instruments. But for my entire career as a chemist,
21 I have been using extensively all these analytical
22 instruments, including with my own hands.

23 Q Let me ask you: Did you take analytical
24 chemistry in graduate school?

25 A I actually didn't take any courses in

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1 graduate school.

2 Q Okay. Even for the master's?

3 A Hmmm?

4 Q Even for the master's portion of your
5 graduate school?

6 A So my master's degree, the way it works
7 at MIT when you get a Ph.D. degree, you
8 automatically get a master's degree. It wasn't like
9 a separate thesis. I sat in on a lot of courses,
10 but I didn't actually take any courses in graduate
11 school.

12 Q Did you sit in on analytical chemistry?

13 A No.

14 Q Did you take analytical chemistry in
15 college?

16 A Yes.

17 And I also taught graduate level
18 spectroscopy courses when I started my independent
19 career at Colorado State University. So I have also
20 taught mass spec and NMR and HPLC to graduate
21 students.

22 Q Okay. That course didn't include HPLC?

23 A The course I taught was mostly centered
24 on spectroscopy. We did talk a little bit about
25 HPLC, but I also teach my own graduate students

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1 about HPLC.

2 Q Okay. And as part of your teaching of
3 HPLC, do you discuss error analysis of the HPLC
4 instrument?

5 A Yes, because sometimes we have to report
6 very accurate data based on HPLC. So, yes, HPLC is
7 much, much more sensitive than NMR.

8 Q I think one of the things you say in your
9 Declaration, though is that -- let me ask you this:
10 Is there in your view any preference for using HPLC
11 assay analysis where you measure the peak of the
12 substance of interest versus measuring the total
13 related impurities?

14 A I didn't quite follow your question.

15 Q Yeah. In determining the purity of a
16 substance, which technique is better? Using the
17 HPLC peak of the substance of interest or using a
18 sum of the peaks of the impurities?

19 A I really am sorry. I'm not following
20 your question. It doesn't make sense to me.

21 Q Let me break it down, then.

22 The HPLC assay analysis described here --
23 that's an analysis in which the area under the curve
24 for -- in this case, treprostinil, but for any other
25 substance as well -- is compared to a reference

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1 standard; is that fair?

2 A Yes.

3 Q Okay. And that's one technique of
4 determining the purity of a substance; right?

5 A Yes.

6 Q Now, something else that you did in your
7 Declaration, I believe, is you looked at a table of
8 total related substances; correct?

9 A Yes.

10 Q And you subtracted those from 100 to get
11 the purity analysis; right?

12 A Yes.

13 Q Okay. Which of those two techniques is
14 preferable?

15 A Well, I think you need to do both. In
16 fact, in my own research, I don't rely exclusively
17 on HPLC. I always ask my students to corroborate
18 through NMR as well, because some compounds are
19 invisible by HPLC if they don't have a chromophore,
20 if you're using a UV detector.

21 Q Right.

22 A So it's -- but for industrial process
23 validation, you know, the assumption is that the
24 analytical group who has established the protocols
25 and methods is already thoroughly vetted and

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1 confirmed and verified that the analytical technique
2 that's going to be use San Diego reliable and
3 sensitive within a given set of parameters for a
4 given type of compound and impurities.

5 Q Right. But there could be some
6 compounds -- some impurities in there that don't
7 have a chromophore and wouldn't be seen in a
8 particular HPLC analysis?

9 A That's possible, yes.

10 Q Okay. And you said you would do both.
11 Is there any preference for one or the other, or
12 they're both equal?

13 A Well, HPLC is typically faster,
14 particularly if you have it set up in a -- you know,
15 a robotic auto-sampler type of thing.

16 So NMR takes more time. You gotta
17 prepare the samples, you have to get the
18 spectrometer, and you have to look at everything in
19 the spectrum. But in my own research, I insist that
20 my students use every technique available to figure
21 out what's in that product mixed or purified
22 product.

23 Q Now, let me also ask you, though -- so I
24 can do HPLC and just look at the peak for the
25 substance of interest, say, treprostinil or

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1 something else.

2 A Hmm-hmm.

3 Q Or I could look at the total related
4 substances. And I think you said it's probably best
5 to do both. Is there a preference, though, for
6 total related substances or for the looking at the
7 larger peak?

8 MS. HASPER: Objection. Asked and
9 answered.

10 THE WITNESS: Okay. I'm not sure about
11 this preference issue. I mean, it's important to
12 understand -- like for batches -- you know,
13 commercial batches of treprostinil with what the
14 individual impurities are and how pure the main
15 component is, and so there's impurities that are
16 known, we know exactly what -- like the enantiomer
17 where that --

18 BY MR. POLLACK:

19 Q Right.

20 A -- peak is and that type of thing, as
21 well as unidentified impurities -- these other
22 things that are there that you're not sure exactly
23 what that is.

24 Q Okay.

25 A May be a mixture of things.

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1 Q Okay. Now, in your Declaration -- and
2 you may have misunderstood -- I thought there was
3 some criticism of the use of reference standards.
4 Did I misinterpret?

5 A You want to point me to where you think
6 I've got a criticism?

7 Q Let me just ask you first: Do you have
8 any criticism of reference standards?

9 A In general or specifically with respect
10 to this matter?

11 Q Both.

12 A Well, it's important -- I mean, the
13 reference standard itself has to be a highly
14 purified material, and there's no such thing
15 anywhere on this planet of something that's
16 100.0 percent pure.

17 So no matter how many times you
18 recrystallize or do chromatography over and over
19 again, you can approach 100 percent, but you can
20 never get there.

21 So the goal is to try and have as pure a
22 reference standard as possible, and then you measure
23 against that, if you can ascertain what the purity
24 of the reference standard is.

25 Q And that's an initial that's inherent in

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1 all HPLC measurements; is that right?

2 A Yes.

3 Q And that's true, even if you're measuring
4 the total related substances, you need to use a
5 reference standard, isn't that correct?

6 A Well, I think -- the reference standard
7 is the same reference standard, and they're just
8 measuring area under the curves of other peaks. And
9 that's added to the known ones.

10 Q Okay. They're not using reference
11 standards for each impurity?

12 A I don't believe so, no. I mean, they
13 know what each -- they use reference standards
14 because they've identified for example where
15 [REDACTED] -- what the retention time is that so they
16 know where that comes.

17 Q Right.

18 A For the known ones.

19 Q They would use a reference standard for
20 the known ones?

21 A Well, they know where that is. I don't
22 know -- I do not believe that they separately
23 calibrate the small peak for, like, [REDACTED] against
24 the reference standard for [REDACTED]. It's a single
25 reference standard for treprostinil.

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1 Q Okay.

2 A Otherwise, it would just take too long.

3 Counselor, I apologize. The coffee here
4 after lunch just came --

5 MR. POLLACK: No problem.

6 THE VIDEOGRAPHER: Going off the record,
7 the time is 2:00 P.M.

8 (Off the record)

9 THE VIDEOGRAPHER: We are back on the
10 record. The time is 2:03 P.M.

11 MS. HASPER: Mr. Pollack, just before you
12 begin, I'd like to interject a posthumous objection
13 to the introduction of the electronic document that
14 was introduced as Exhibit 13. It's just irregular
15 to introduce an electronic copy of something, rather
16 than a printed copy.

17 MR. POLLACK: I believe we did provide a
18 printed copy as well, which was --

19 MS. HASPER: Are you saying that what you
20 introduced as Exhibit 13 was identical to what you
21 printed out and provided as a printed copy?

22 MR. POLLACK: Yes. The information is
23 identical.

24 MS. HASPER: Could you show me which of
25 the other exhibits is the same as --

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1 MR. POLLACK: We can do that off the
2 record at some other time.

3 MS. HASPER: Okay. Until I have that,
4 then I will let the objection stand. I may retract
5 it later.

6 BY MR. POLLACK:

7 Q If you could go to -- back to an exhibit
8 we had looked at before -- it's Exhibit 11. It's
9 this giant book here that is also known as
10 "Exhibit 2052."

11 If you could turn to -- there's a lot of
12 numbers, I know, on these pages, but there's a P.43
13 at the bottom of the page.

14 A Okay.

15 Q Okay. Do you see on that page it has an
16 explanation of total related substance equals some
17 of all reported peaks except UT-15? Do you see
18 that?

19 A Yes.

20 Q Okay. And what I was trying to
21 understand here is, when it says, "reported peaks,"
22 those are peaks of the known and identified
23 substances; is that right?

24 A My understanding was that total related
25 substances includes known plus unknown.

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1 Q Where did you get your understanding?

2 A I don't remember what document. I know
3 that we -- I discussed this several times with --
4 with counsel, and we referred to documents. I can't
5 remember off the top of my head which one confirmed
6 that, but that was my understanding, anyway.

7 Q And that was your understanding from
8 counsel?

9 A Yes.

10 Q Okay. Looking here, can you tell whether
11 -- from this definition whether unidentified
12 substances are included?

13 A So reported peaks is not, to me,
14 synonymous with known species. So there could be a
15 peak that's reported, but -- it has a certain height
16 and area under the curve. And --

17 Q Okay.

18 A So I'm not really sure what you're asking
19 me.

20 Q Yeah. I was asking you whether this
21 indicated that it was only those peaks which were
22 identified with a code number or other kind of name.

23 A No. So I believe at the -- the batch
24 records themselves show separately the known
25 impurities, and then unknown impurities, and then

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1 total related substances. They're broken out
2 separately.

3 Q Right. Right. Right. Earlier, though,
4 remember we went through those numbers, and we
5 weren't able to sum them to the number which was the
6 total related substances? Do you recall that?

7 A Yes.

8 Q Okay.

9 A But I -- I explained that that's because
10 they come from two different types of -- and that
11 the .05 was less than .05 and the actual total
12 related substances gives the net amount of other
13 things besides UT-15.

14 Q Okay. Do you know how the less than .05s
15 were handled?

16 A Well, the less than .05s were given a
17 value in my chart of .05. So rounded up,
18 essentially.

19 Q Right. I'm asking you how -- United
20 Therapeutics, or whoever else, was compiling that
21 data, how did they handle it?

22 A Well, they're reported just like that.
23 It's less than .05. So it was detectable, but then
24 the sum of those end up -- my understanding is, the
25 sum of those all end up in the total related

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1 substances value. So known plus unknown.

2 Q But if one's not detected or .05, how is
3 that handled by UT or whoever was reporting the
4 values?

5 MS. HASPER: Objection. Asked and
6 answered.

7 THE WITNESS: You're -- I think I just
8 explained exactly the answer to your question.

9 BY MR. POLLACK:

10 Q What was the answer? Maybe I didn't
11 follow it.

12 MS. HASPER: Same objection.

13 THE WITNESS: I said, so if you look in
14 the batch records themselves, they split out the
15 individual known impurities and the unknown
16 impurities; okay? And so the ones that are --
17 record a value of less than .05 percent in the
18 summary that I gave were given a value of .05.

19 So that's erring on the high side --
20 okay? -- 'cause it could be .00001 percent, but the
21 total related substances value, then, would have
22 built in, you know, say one peak was .0003 -- okay?
23 -- so it wouldn't be added in as .05. It comes just
24 through the standard protocols that they have for --
25 for measuring this.

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1 BY MR. POLLACK:

2 Q So you're saying even though they don't
3 report a value, they have some value for these very,
4 very small peaks in your view?

5 A Yeah. Of course, there's a value.
6 They're visible in the chromatogram. And the
7 computer, you know, measures the area under the
8 curve, and you get a -- you know, this total related
9 substances number.

10 Q Okay. And that -- even for peaks that
11 are so small that there's a signal to noise problem?
12 Those are included?

13 A I can't speak to signal to noise. I
14 don't -- you know -- you know, I'm sure this has all
15 been vetted in their validation procedures for that.

16 Q Okay. I mean, did you speak to anyone
17 or --

18 A No.

19 Q -- look into --

20 A No.

21 Q Let me ask my question again: Did you
22 speak to anyone or look into how United Therapeutics
23 determined those values?

24 A No.

25 Q Okay.

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1 A No. I took these -- this data -- I mean,
2 these are all things that are produced to the FDA,
3 and they have to be validated, and confirmed and --
4 so I didn't question the veracity or authenticity,
5 accuracy, because these are, you know, important
6 documents.

7 Q Let me ask you -- if you go back to
8 Exhibit 2006, also known now as "Williams Deposition
9 Exhibit 14" --

10 A Okay.

11 Q -- if you could turn to page 6. You see
12 it says, "Assay HPLC"; right?

13 A Yes.

14 Q Okay. And in the right-hand column,
15 they've set a standard for that; right? It says,
16 "not less than [REDACTED] percent and not more than
17 [REDACTED] percent"?

18 A Yes.

19 Q Okay. So if I have a batch and I run an
20 HPLC assay on the batch, and the purity comes out as
21 [REDACTED] percent -- by the way, that's done by -- let me
22 make sure I understand.

23 These assay HPLCs, those are done by
24 taking the area under the curve for the treprostinil
25 and comparing that to the standard?

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1 A I believe so, yes.

2 Q Okay. So if I have -- if I make a batch
3 of treprostinil, and I measure its HPLC assay, and I
4 get [REDACTED] percent, that batch passes the FDA
5 specification; right?

6 A Yes.

7 Q I can sell that batch to the public?

8 A That's my understanding, yes.

9 Q Okay. In fact, as far as the FDA is
10 concerned, any batch that has a purity better than
11 [REDACTED] percent -- so long as it meets these other
12 specifications -- that batch can be sold to the
13 public; right?

14 MS. HASPER: Objection. Beyond the
15 scope.

16 THE WITNESS: Well, I'm not an FDA
17 expert, but my understanding is, it has to be
18 between [REDACTED] percent and [REDACTED] percent.

19 BY MR. POLLACK:

20 Q Fair enough.

21 But if it's between those numbers, then
22 it can be sold to the public?

23 MS. HASPER: Same objection.

24 THE WITNESS: As far as I know, but I'm
25 not an FDA expert.

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1 BY MR. POLLACK:

2 Q You've done a lot of ANDA litigation? Do
3 you know what I mean by, "ANDA litigation"?

4 A Yes. "Abbreviated New Drug Application."
5 The Hatch-Waxman Act.

6 Q And that's where a generic company tries
7 to sell a copy of something very similar?

8 A Yes.

9 Q And the ANDA litigation you've been
10 involved in, including some for treprostinil; right?

11 A Yes.

12 Q The ANDA filer, they report a purity as
13 well -- right? -- for their API?

14 A I believe so.

15 MS. HASPER: Objection. Beyond the
16 scope.

17 THE WITNESS: I believe so. That's what
18 I've seen previously.

19 BY MR. POLLACK:

20 Q Okay. Have you seen that in your other
21 litigations?

22 A I have.

23 Q Yeah. Okay.

24 And they need to meet the same purity
25 specifications for their active pharmaceutical

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1 ingredient that the brand name does; right?

2 MS. HASPER: Same objection.

3 BY MR. POLLACK:

4 Q Is that your understanding?

5 A So, again, I'm not an FDA expert, but I
6 know that the generic also has to meet some target
7 specification. I don't know if it's the same as the
8 branded drug or not in every case.

9 Q Okay. In your experience, when you've
10 done your ANDA cases, have you seen that the generic
11 company meets the same purity specification as the
12 brand name?

13 MS. HASPER: Same objection.

14 THE WITNESS: You know, I just don't -- I
15 just don't recall, because in the ANDA cases that I
16 have worked on, this is all prelaunch, end of
17 product, so they have a proposed product and a
18 proposed spec. So I don't know what happens at --
19 you know, after, when they're actually selling, if
20 they, you know, start to sell their product.

21 BY MR. POLLACK:

22 Q Although, they've created a -- a batch
23 which they provide to the FDA. You've seen that;
24 right?

25 A Yes.

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1 Q Okay. And they've made purity
2 measurements of their batches in order to try to
3 gain approval of their ANDA?

4 MS. HASPER: Same objection.

5 THE WITNESS: I think that's generally
6 how it works, yeah.

7 BY MR. POLLACK:

8 Q Okay. And they've done an HPLC assay
9 purity analysis of their active pharmaceutical
10 ingredient. You've seen that; right?

11 MS. HASPER: Objection. Scope.
12 Relevance.

13 THE WITNESS: Perhaps, if that's the
14 assay that's used for that particular drug. I would
15 assume they would be doing the same thing. But I
16 suppose there could be other types of assays.

17 BY MR. POLLACK:

18 Q Okay. What about for treprostinil? Did
19 companies like Sandoz, or Watson or Teva, did they
20 submit an HPLC assay analysis for their active
21 pharmaceutical ingredient?

22 MS. HASPER: Objection. Scope.
23 Relevance.

24 I advise the witness not to answer if it
25 would reveal privileged or confidential information.

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1 THE WITNESS: I actually don't recall.

2 BY MR. POLLACK:

3 Q Okay. Let me ask you this: When a
4 generic company is measuring the purity of their
5 active pharmaceutical ingredient by HPLC assay
6 analysis, they, too, need to use a reference
7 standard; right?

8 MS. HASPER: Same objection.

9 THE WITNESS: I presume they also have to
10 do that as well to validate their Assay Purity to
11 the FDA.

12 BY MR. POLLACK:

13 Q And when they're doing that with their
14 reference standard, they don't have access to the
15 brand-name company's reference standard; right?
16 They have to create their own?

17 MS. HASPER: Same objection.

18 THE WITNESS: I actually don't know.

19 BY MR. POLLACK:

20 Q Okay. No idea?

21 A I have no idea.

22 Q Okay.

23 MR. POLLACK: I'm going to mark as
24 Williams Deposition Exhibit 15, an article by
25 Terence L. Threlfall titled, "Analysis of Organic

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1 Polymorphs," a review that appeared in "The
2 Analyst," October 1995.

3 (Exhibit 15 marked)

4 BY MR. POLLACK:

5 Q Let me ask you: Are you familiar with
6 Terry Threlfall?

7 A I don't recall. I think I've seen this
8 before.

9 Q Okay.

10 A Are you going to tell me that I cited it
11 in my Declaration?

12 Q No, I'm not. I'll tell you that you have
13 not.

14 A I actually don't recognize this.

15 Q Okay. Do you know Dr. Threlfall?

16 A No.

17 Q Okay. I want to turn to -- if you look
18 on the first page, 2435 and going over to 2436,
19 there's a discussion there about how to name
20 polymorphs.

21 What are polymorphs, if you could --

22 A Actually, polymorphs are different
23 crystalline forms of solid compounds. They adopt
24 different crystal-lattice configurations.

25 Q Do you consider yourself an expert on

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1 crystal forms of organic molecules?

2 A No.

3 Q But you're -- you've heard of this
4 phenomenon before?

5 A Yes, yes.

6 Q So, Dr. Threlfall discusses here, there's
7 no clear choice on how to designate polymorphs. And
8 one of the suggestions he has is numbering, based on
9 order of discovery. Were you familiar with that
10 system for naming polymorphs?

11 MS. HASPER: Objection. Beyond the
12 scope.

13 THE WITNESS: No.

14 BY MR. POLLACK:

15 Q No? Okay.

16 You've never seen polymorphs named "Form
17 1," "Form 2," "Form 3"?

18 A I have.

19 Q Are you aware that's usually based on the
20 order of discovery?

21 A I have no idea.

22 MS. HASPER: Same objection.

23 BY MR. POLLACK:

24 Q Okay. Now, further down, he has some
25 other suggestions. If we go on to 2436, top of the

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1 page, he says -- the second sentence, "The addition
2 of a melting or upper transition point to a Roman
3 numeral is possibly the best compromise, although
4 care must be taken to distinguish the melting point
5 of the polymorph and that of the transformed
6 product."

7 Do you see where I'm reading?

8 A Yes.

9 Q Okay. Did I read that correctly?

10 A That's what it says.

11 Q Am I correct that one of the ways of
12 naming polymorphs that's been proposed is to name
13 them by assigning their -- the melting point in
14 addition to a Roman numeral?

15 MS. HASPER: Objection. Scope.
16 Relevance.

17 THE WITNESS: Yeah. So I'm not a
18 polymorph expert. So --

19 BY MR. POLLACK:

20 Q Well, why do you think they do that?

21 Why do you think they append a melting
22 point to each polymorph?

23 MS. HASPER: Same objection.

24 THE WITNESS: Well, certainly, that's a
25 physical characteristic of an individual solid form.

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1 BY MR. POLLACK:

2 Q The melting point is something that's
3 unique to that particular solid form?

4 MS. HASPER: Same objection. Also
5 speculation.

6 THE WITNESS: Yes. But I know enough
7 about crystallization that melting points are highly
8 dependent upon the solvent that was used, the
9 conditions that the crystals were grown under, time,
10 scale. There's lots of variability in that. And
11 I've run into this many, many times over the years
12 in my own research.

13 BY MR. POLLACK:

14 Q Okay. But those conditions create
15 different polymorphs, isn't that the issue?

16 A No. It could be the same --

17 MS. HASPER: Same objection.

18 THE WITNESS: It could be the same
19 polymorph, but depending on how the crystal was
20 grown, there's lots of -- you know, I've consulted
21 on this issue. Inclusion of solvent can sometimes
22 affect melting ranges and things like this.

23 BY MR. POLLACK:

24 Q Well, if there's solvent in it, then it's
25 known as a "solvate"; right?

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1 A Not necessarily.

2 Q Why not?

3 A Solvates are different. Solvates are
4 actually -- for example, hydrates are solvates where
5 there's a certain number of water molecules that
6 will be noncovalently associated with a molecule in
7 the crystal lattice. And sometimes these can be
8 highly well-defined numbers like a trihydrate. So
9 every molecule -- say a treprostinil trihydrate,
10 each one would have three molecules of water
11 associated with it. And sometimes there is a range
12 that, you know, it's not exactly 3; it's 3.6. Okay.

13 Q You know, we're talking about -- in this
14 proceeding, we're talking about treprostinil
15 diethanolamine salt Form B. You'll agree with me
16 that they've verified that that salt is neither a
17 hydrate nor a solvate in the Phares reference;
18 right?

19 MS. HASPER: Objection.

20 THE WITNESS: I don't recall. I'd have
21 to look at --

22 BY MR. POLLACK:

23 Q Do you want to look at it?

24 A Sure.

25 Q You could have "Exhibit 1005" as it was
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1 called.

2 MR. POLLACK: I'm going to mark as
3 Williams Deposition Exhibit 16 a document currently
4 known in the case as "Exhibit 1005," also known as
5 the "Phares," P-h-a-r-e-s, "reference."

6 (Exhibit 16 marked)

7 BY MR. POLLACK:

8 Q In order to make this a little bit easier
9 for you, the discussion of the characterization of
10 treprostinil diethanolamine salts starts on what's
11 called "Page 90" in the bottom right-hand corner of
12 the document. It's page 87 in the original
13 pagination.

14 A (Examining document) Okay. I've looked
15 at the paragraph on that page 90, or 87.

16 Q Okay. If you could move on to the
17 section on Form B, which starts at the bottom of --

18 A I'm sorry.

19 Q -- 87 and goes onto 88. I particularly
20 wanted to focus on moisture sorption/desorption data
21 and thermal data, but feel free to read all of it.

22 A (Examining document) Okay. I've read
23 that.

24 Q Okay. Based on what you've read here,
25 can you tell whether or not the Form B described

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1 here is a hydrate solvate or is otherwise wet with
2 solvent?

3 A Well, in contrast to Form A, where it
4 specifically says -- indicated the material is not
5 solvated, they don't make such an affirmative
6 statement with Form B. But I'm not a polymorph
7 expert, so -- you know, I'm -- I wouldn't be
8 certain.

9 Q Okay. So you don't understand what it
10 says there about the minimum weight loss. That's
11 not an indication to you that there's -- no water
12 was contained in the crystal?

13 A Well, it's certainly hydroscopic.
14 Absorbs water.

15 Q Hmm-hmm. Okay. But this information
16 here, can you tell from that -- the fact that water
17 is not desorbing? Does that indicate to you -- and
18 I recognize you're not a crystal-form expert, but
19 does it indicate to you that it's not a solvate, or
20 is this outside of your area?

21 A It's really outside of my area.

22 Q Okay. And what about -- you see there it
23 says -- do you know what a "TG" is? It says, "A TG
24 shows minimum weight loss up to 100 degrees C."

25 A I've seen that acronym before. I don't

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1 remember off the top of my head exactly what it
2 means.

3 Q Have you ever seen the acronym "TGA" as
4 it's sometimes referred to?

5 A Is that "thermographic metric analysis"?
6 Yeah.

7 Q Yes. Are you familiar with how that
8 technique is used with polymorphs?

9 A Not intimately, no.

10 Q Okay. You're not aware that technique is
11 sometimes used to show that there's a solvent or
12 solvate in a -- in a polymorph?

13 MS. HASPER: Objection. Asked and
14 answered. Scope.

15 THE WITNESS: Yeah. I mean, I'm not very
16 familiar with the technique, so --

17 BY MR. POLLACK:

18 Q Okay. Fair enough.

19 If we could go back just quickly in the
20 Threlfall article.

21 You know, never mind.

22 A Okay.

23 MR. POLLACK: I'm going to mark as
24 Exhibit Williams Deposition Exhibit 17 an excerpt
25 from the book "Solid-State Chemistry of Drugs," by

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1 Steven R. Byrn, Ralph R. Pfeiffer and Joseph G.
2 Stowell.

3 (Exhibit 17 marked)

4 BY MR. POLLACK:

5 Q And, no, this wasn't attached to your
6 report.

7 Have you either seen or read this book,
8 ever, before?

9 A No.

10 Q Okay. Do you know any of the authors?

11 A No.

12 Q Okay. Are there any textbooks on the
13 solid-state form of drugs that you have read?

14 A Not that I can think off the top of my
15 head, no.

16 Q Okay. Turn to the first page of this
17 document. This is Chapter 10 on polymorphs. Let me
18 just ask you about the second sentence which says
19 that, "Compounds that crystallize as polymorphs can
20 show a wide range of different physical and chemical
21 properties, including different melting points and
22 spectral properties."

23 I just want to know if you agree with
24 that sentence or have any reason to disagree with
25 it?

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1 MS. HASPER: Objection. Scope.

2 THE WITNESS: I don't have any reason to
3 disagree.

4 BY MR. POLLACK:

5 Q Okay. Do you agree with it?

6 A I have no reason to disagree.

7 Q Okay. One of the things that
8 characterizes a polymorph is its melting point.
9 It's one of the things that uniquely identifies a
10 polymorph; is that right?

11 MS. HASPER: Objection. Scope. Asked
12 and answered.

13 THE WITNESS: Again, based on my limited
14 understanding that this can be quite dependent on
15 conditions, the solvent that was used, the scale.

16 BY MR. POLLACK:

17 Q If you look a little further down on
18 page 143, there's a second paragraph. This, again,
19 talks about how polymorphs are made. Do you see --
20 or named. Do you see that?

21 A Yes.

22 Q Okay. And they point out there's no
23 standard numbering systems for polymorphs; right?

24 A That's what it says.

25 Q Okay. And if you go down about three,

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1 four, five sentences, there's a sentence beginning
2 with the word, "It." Do you see that sentence?

3 It says, "It has been suggested?"

4 A Yes.

5 Q Okay. And I'll read it into the record.

6 "It has been suggested that polymorphs be
7 numbered consecutively in the order of their
8 stability at room temperature or by their melting
9 point."

10 Did I read that correctly?

11 A That's what it says.

12 Q Okay. And so what he's proposing here is
13 that a polymorph would be identified by its melting
14 point. Do you see any place where he says: And it
15 needs to be further identified by what solvent was
16 used?

17 MS. HASPER: Objection. Relevance.

18 THE WITNESS: No, but I guess I'd have to
19 read a lot more on -- on this -- in this article.
20 It may be discussed later.

21 BY MR. POLLACK:

22 Q Okay. Well, this is a -- I'll represent
23 to you, it's not discussed later. But this is the
24 second time we've seen a proposal that polymorphs be
25 named by their melting point; right? You saw that

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1 in the Threlfall article as well?

2 A Okay. Yes. That's what it says.

3 Q And Threlfall also, he doesn't suggest:

4 Oh, it needs to be named also by what solvent was
5 used -- right?

6 A I didn't see that mentioned, no.

7 Q While we're getting that out, could you
8 go back to the patent for me.

9 A The patent? Which patent?

10 Q The patent. The '393 patent,
11 Exhibit 1001, now known as "Williams Deposition
12 Exhibit 3."

13 A Okay.

14 Q And I'd like to turn to what's called
15 "Page 8" in this exhibit. It's column 12 of the
16 patent. And if you look in that column in the
17 paragraph starting -- two paragraphs starting around
18 line 35, you see it refers to, "Polymorph B of the
19 treprostinil diethanolamine salt"; right?

20 A What line?

21 Q I'm sorry. Line 40 -- it starts around
22 line 42 and continues down the page.

23 A Okay.

24 Q Okay. Now, that polymorph B, that's the
25 same polymorph B that's referred to in Exhibit 1005,

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1 the Williams Deposition Exhibit 16, the Phares
2 reference?

3 A I can't be certain they're the
4 same, 'cause Phares doesn't tell us where the
5 treprostiniil comes from.

6 Q It's the same polymorph, though; is that
7 fair?

8 A Well, that's what it's called, "polymorph
9 B."

10 Q Okay. They're both polymorph Bs; right?

11 A That's what they're called.

12 Q Do you have any reason to believe that
13 they're different?

14 A Well, I certainly know where polymorph B
15 in the patent comes from. In Phares, they do not
16 identify the source of the treprostiniil.

17 Q Yeah. I'm not asking about how it was
18 made or other differences. I'm just asking in
19 regards to what crystal form it is.

20 Are both of these the same crystal form,
21 the crystal form of treprostiniil diethanolamine salt
22 in the '393 patent and the crystal form in the
23 Phares prior art reference, which are both called
24 Form B? Are they the same crystal form?

25 A I can't be 100 percent certain. This UT Ex. 2059
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