IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

UNITED THERAPEUTICS CORPORATION,
Plaintiff,
v.
LIQUIDIA TECHNOLOGIES, INC.,
Defendant.

C.A. No. 20-755-RGA-JLH

Volume II

J. Caleb Boggs Courthouse
844 North King Street
Wilmington, Delaware

Tuesday, March 29, 2022
8:30 a.m.
Bench Trial

BEFORE: THE HONORABLE RICHARD G. ANDREWS, U.S.D.C.J.

APPEARANCES:

MORRIS NICHOLS ARSHT & TUNNELL LLP
BY: JACK B. BLUMENFELD, ESQUIRE
BY: MICHAEL J. FLYNN, ESQUIRE
BY: SARAH E. SIMONETTI, ESQUIRE

-and-

GOODWIN PROCTER LLP
BY: WILLIAM C. JACKSON, ESQUIRE
BY: HUIYA WU, ESQUIRE
BY: IAN B. BROOKS, ESQUIRE
BY: JOEL BROUSSARD, ESQUIRE
BY: HARRISON GUNN, ESQUIRE
BY: ERIC LEVI, ESQUIRE

- and -

APPEARANCES CONTINUED:

McDERMOTT WILL & EMERY LLP
BY: DOUGLAS H. CARSTEN, ESQUIRE
BY: ADAM W. BURROWBRIDGE, ESQUIRE
BY: KATHERINE PAPPAS, ESQUIRE
BY: TIMOTHY M. DUNKER, ESQUIRE
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BY: BRITTANY CAZAKOFF, ESQUIRE
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BY: JONATHAN R. DAVIES, ESQUIRE
BY: IVOR ELRIFI, ESQUIRE
BY: DEEPA KANNAPPAN, ESQUIRE
BY: LAUREN KRICKL, ESQUIRE
BY: ERIK B. MILCH, ESQUIRE
BY: KYUNG TAECK MINN, ESQUIRE

For the Defendants

*** PROCEEDINGS ***

08:30:06 DEPUTY CLERK: All rise. Court is now in session. The Honorable Richard G. Andrews presiding.

08:30:14 THE COURT: Good morning, everyone.

08:30:15 (Everyone said good morning.)

08:30:17 THE COURT: All right. Let's be seated. And I
08:30:19 take it, Defendant, you're ready to go.
08:30:23 MR. CARSTEN: Your Honor, I have an evidentiary
08:30:24 issue with respect to one of the witnesses today that I'd
08:30:27 like to raise with the Court, if I might.
08:30:28 THE COURT: All right.
08:30:29 MR. CARSTEN: Thank you. This is -- pertains to
08:30:31 Dr. Winkler.
08:30:31 THE COURT: Okay.
08:30:32 MR. CARSTEN: He'll be testifying later today.
08:30:35 We received his demonstratives, and he's got three
08:30:38 demonstratives that pertain to Dr. Toste's opinions, and the
08:30:47 man never issued any opinions pertaining to Dr. -- rebutting
08:30:52 Dr. Toste's opinions. So we've got these three
08:30:54 demonstratives, DDX 2.6, 2.7, and 2.8. The sum total of the
08:31:06 disclosures are contained in two paragraphs of Dr. Winkler's
08:31:13 rebuttal expert report, paragraphs 53 and 54. In pertinent
08:31:17 part, they say, "Thus, Dr. Toste's discussion of HPLC
08:31:22 sensitivities as it relates to this 15-epi compound is not
08:31:26 relevant to the claim limitation." That's essentially all
08:31:29 the man said in his expert reports. I have a copy of the
08:31:33 expert reports here to show you as well, Your Honor. And
08:31:35 this would be --
08:31:39 Oh, I apologize, Your Honor. Apparently, I am
08:31:42 so persuasive that they decided to withdraw those three.

And the second minor issue, which I'm not sure and hopeful --

THE COURT: So want to check whether this is withdrawn too?

MR. CARSTEN: Exactly. Let's try it. Maybe I shouldn't say anything, Your Honor.

Your Honor had motion in limine number one, which was granted pertaining to the products of the '393 patent. And Your Honor said in his order "Whether the same product, Treprostinil, is the product of the claims of the '393 patent is also irrelevant to obviousness."

We had a demonstrative yesterday -- two days ago, I apologize, with respect to -- they intend to use with Dr. Winkler, Demonstrative 14. And it says right there the Treprostinil product of the '393 patent has an average purity of 99.71 percent. It seems to me this is in direct violation of the Court's motion in limine number one. It may be they're trying to use it in a different way. I don't quite understand that yet, Your Honor, and so perhaps it's better served to hold off until they seek to -- seek to use it in some sense. But, to talk about the product of the '393 patent in view of that motion in limine order, I just don't understand, Your Honor.

THE COURT: Well, just because you don't understand doesn't mean they don't have a theory. Is this

something -- when is Dr. Winkler testifying?

MS. KANNAPPAN: He should be testifying today, Your Honor.

THE COURT: Well, I mean, like, after lunch or --

MS. KANNAPPAN: Hopefully before lunch. In probably, like, an hour and a half or so.

THE COURT: All right. Do you -- do you have a response to what Mr. Carsten has said?

THE WITNESS:

MS. KANNAPPAN: Yes, Your Honor. The reason that that is on that slide is because the underlying data that was used in that IPR is relevant to the '066 patent. We actually offered to change the word '339 to '066 with brackets. That didn't seem to be acceptable to them. We're not actually going to be talking about the '393 patent or the claims.

MR. CARSTEN: All right, Your Honor. Fair enough. Fair enough. We'll police it as it come up. Thank you. I apologize for the delay.

THE COURT: That's all right. Time is charged to you, so if you want, we can spend all day arguing this stuff.

All right. Well, then, let's go.

MR. DAVIES: Good morning, Your Honor. Jonathan

Davies for Liquidia, and Liquidia now calls Jeffrey Kindig.

DEPUTY CLERK: You can stand up there. Sure.

You can stand.

Please state and spell your name for the record.

THE WITNESS: Sure. It's Jeffrey Kindig, J-E-F-F-R-E-Y K-I-N-D-I-G.

DEPUTY CLERK: Do you affirm that the testimony you are about to give to the Court in the case now pending will be the truth, the whole truth, and nothing but the truth, you do so affirm?

THE WITNESS: Yes, I do.

JEFFREY KINDIG, the witness herein, after having been duly sworn under oath, was examined and testified as follows:

DEPUTY CLERK: Make sure you speak into the microphone.

MR. DAVIES: Your Honor, may I have privilege approach to -- just to give to the witness?

THE COURT: Sure. Yeah.

DIRECT EXAMINATION

Q. Good morning, Mr. Kindig.

A. Good morning.

Q. Can you please state your full name for the record.

A. Jeffrey Kindig.

Q. And where are you currently employed?

08:35:14 A. Liquidia Technologies.
08:35:16 Q. And what's your position at Liquidia?
08:35:17 A. I'm the executive director of analytical operation.
08:35:21 Q. And how long have you held that position?
08:35:23 A. It's been about five years.
08:35:25 Q. And when did you join Liquidia?
08:35:27 A. I joined Liquidia October 2007.
08:35:31 Q. What are your job responsibilities in your current position?
08:35:33 A. I supervise the group that performs quality control testing on raw materials, intermediates, and finished products. I also have responsibility over the external contract labs that we use to do some of that testing.
08:35:49 Q. Does the testing that your group performs include testing than on Treprostinil sodium?
08:35:54 A. Yes, it does.
08:35:55 Q. And does that include the Treprostinil sodium that's use inside Liquidia's '861 product?
08:35:59 A. Yes, that's correct.
08:36:03 Q. What do you mean by "quality control testing"?
08:36:05 A. Materials and products have specifications that include a series of tests and acceptance criteria that need to be met for them to be considered acceptable for use. So, I supervise a laboratory group that performs those types of tests.

08:36:21 Q. Where does Liquidia store the Treprostinil sodium
08:36:24 that it receives for use in Liquidia's '861 product?
08:36:28 A. We store it in a GMP materials storage room that has,
08:36:34 among other things, two refrigerated chambers in there.
08:36:37 They are 2 to 8 degrees C. That's where Treprostinil sodium
08:36:40 is stored.
08:36:40 Q. Are those chambers monitored in any way?
08:36:42 A. Yeah, we have something called the SmartView
08:36:46 Monitoring System. It's a logger on the outside with a
08:36:50 temperature probe inside. It monitors the temperature and
08:36:53 feeds the data to a software system.
08:36:55 Q. How do you know that Liquidia stores the Treprostinil
08:36:58 sodium in these two GMP remember refrigerators?
08:37:01 A. I've seen it. I have access to the space.
08:37:04 Q. Why do you have access to the space?
08:37:05 A. Because my team performs sampling and testing of the
08:37:10 material. We have to be able to access it. There's other
08:37:13 materials stored in there as well that we would have access
08:37:15 to.
08:37:16 Q. Are there any Liquidia documents that the define the
08:37:20 storage conditions for Treprostinil sodium?
08:37:21 A. Yes. There's a raw materials specification for the
08:37:25 for Treprostinil sodium that indicates the storage
08:37:28 condition.
08:37:28 Q. Can you turn to DTX 150. Can you bring that up on

the screen.

And what is DTX 150?

A. This is the raw materials specification that I just spoke about for Treprostinil sodium.

MR. DAVIES: Your Honor, I'd like to enter DTX 150 into evidence.

MR. JACKSON: No objection, Your Honor.

THE COURT: Admitted without objection.

(DTX Exhibit No. 150 was admitted into evidence.)

BY MR. DAVIES:

Q. Were you involved in preparing this specification, Mr. Kindig?

A. Yes, I was.

Q. And what portion of the specification indicates the storage requirements for Treprostinil sodium?

A. About halfway down the page, there's a box marked Storage Conditions that states "2 to 8 degrees C protected from light and moisture."

Q. And do you know why Liquidia requires storage of 2 to 8 degrees C for Treprostinil?

A. Yes, we wrote this specification based on Yonsung's labeling for the material.

Q. And is storage at 2 to 8 degrees C optional at Liquidia?

08:38:23 A. No, it's required by the specification.
08:38:39 Q. Mr. Kindig, can you please turn to DTX 208. And can
08:38:45 we bring that up as well.
08:38:53 Mr. Kindig, do you see 208?
08:38:57 A. Yes, I do.
08:38:58 Q. Okay. What is DTX 208?
08:39:00 A. This is Liquidia's standard operating procedure for
08:39:04 receipt, handling, and control of materials.
08:39:07 Q. And would this be a document that governs the
08:39:09 receipt, handling, and control of Treprostinil sodium at
08:39:12 Liquidia?
08:39:12 A. Yes, it would.
08:39:14 MR. DAVIES: Your Honor, I'd like to enter DTX
08:39:16 208 into evidence.
08:39:17 MR. JACKSON: No objection, Your Honor.
08:39:18 THE COURT: Admitted without objection.
08:39:18 (DTX Exhibit No. 208 was admitted into
08:39:18 evidence.)
08:39:21 BY MR. DAVIES:
08:39:21 Q. Mr. Kindig, what's a standard operating procedure at
08:39:24 Liquidia?
08:39:25 A. Standard operating procedures are a set of
08:39:28 instructions for a particular operation. This particular
08:39:32 standard operating procedure is SOP 16, or receipt,
08:39:35 handling, control of materials, as we just mentioned.

08:39:37 Q. If you turn to Section 2.1. And what does that
08:39:44 section indicate?
08:39:45 A. This is the scope of the document. 2.1 states that
08:39:50 it applies to GMP materials used in manufacture, testing,
08:39:54 holding, and distribution of API and regulated drug product.
08:39:59 Specifically for materials for clinical trials and
08:40:03 commercial production.
08:40:04 Q. You mentioned GMP a couple times. What does that
08:40:07 stand for?
08:40:07 A. It's stand for good manufacturing practices.
08:40:10 Q. And what is GMP material at Liquidia?
08:40:13 A. So, we use the term "GMP materials" to refer to,
08:40:17 again, those material that is would be used in regulated
08:40:21 studies, such as clinical trials or for commercial
08:40:24 production.
08:40:25 Q. Does Liquidia ever receive material that is not GMP?
08:40:30 A. Yes. We have designation for R & D material as well
08:40:34 that we can receive for other purposes that aren't for human
08:40:37 use.
08:40:38 Q. Does Liquidia refer to the R & D material also as
08:40:42 developed -- or material for developmental purposes?
08:40:44 A. Yes. I think somewhere in this document, it refers
08:40:48 to development material, material for development purposes,
08:40:51 or something like that, but R & D use only is also a
08:40:53 designation that we use.

08:40:55 Q. Can you turn to Section 5.2 through 5.2.2. It should
08:41:01 be on Page 4 of this document.
08:41:07 A. Yes, I see it.
08:41:08 Q. And do you see a reference to quarantined materials?
08:41:12 A. Yes.
08:41:12 Q. What are quarantined materials?
08:41:14 A. So, when materials first come in the door, they go
08:41:18 into a quarantine state. So a quarantine material is when
08:41:22 it first arrives, it will be put in a quarantine to await
08:41:27 the required testing by the specification. It will be in
08:41:31 quarantine status.
08:41:32 Q. And would that also apply to receipt of Treprostinil
08:41:34 sodium?
08:41:34 A. Yes, when it first comes in, it's in quarantine.
08:41:39 That's right.
08:41:39 Q. And how does SOP require the storage of quarantined
08:41:43 materials?
08:41:43 A. Quarantined materials would be stored depending on
08:41:47 their labeled storage per the raw material specification.
08:41:52 So if a material has a storage condition of 2 to 8 degrees
08:41:56 C, it's also in 2 to 8 degrees C while it's quarantined.
08:41:59 Q. And how would quarantined shipments of Treprostinil
08:42:02 sodium be stored at Liquidia?
08:42:03 A. Treprostinil sodium would be quarantined at 2 to
08:42:07 8 degrees C because that aligns with the specification.

Q. Would they be stored in the GMP refrigerators that you mentioned earlier?
A. Yes, they would go into the GMP materials control room's storage room into one of the two refrigerators that are in that room.
Q. If you look at Section 5.2.5 to 5.2.7, does this SOP permit the use of quarantined materials for GMP purposes?
A. No, you can't use them for GMP manufacturing before they've been released, so while they're in quarantine, they're not allowed for that.
Q. Can you turn to Section 5.4 to 5.4.6. It should be on Page 6 of this document.

What happens after Treprostinil sodium is received and quarantined?
A. So, the required testing for the raw material specification would have to be performed and then after performance of those tests, if it is all acceptable and everything else about the documentation is considered acceptable by the quality unit, it can get released for use.
Q. Who performs the testing that you just mentioned prior to release?
A. So the testing is performed by a combination of my team and there's an external contract lab that does some portion of the testing as well.
Q. Do you see a reference here to release label?

08:43:33 A. Yes, I see it.
08:43:35 Q. And what is a release label?
08:43:37 A. So, if a material is deemed suitable for release, a
08:43:43 new label would be applied that indicates that it's
08:43:46 released, and it includes information that you see listed
08:43:49 here with respect to the lot number, the date received,
08:43:53 expiration date, et cetera.
08:43:54 Q. So until Treprostinil sodium in these refrigerators
08:43:57 would have a release label applied to it, it could not be
08:44:01 used for any GMP purposes?
08:44:03 A. That's right. It would be in quarantine status
08:44:05 before it received that release label, and it could not be
08:44:08 used until it's released.
08:44:09 Q. Which group at Liquidia is responsible for release of
08:44:12 GMP Treprostinil sodium?
08:44:13 A. The quality unit.
08:44:16 Q. Can we turn to PTX 103 in your binder 103. Sorry.
08:44:33 No, that's -- we need the PTX. P as in Peter.
08:44:39 No problem.
08:44:40 Yeah. Do you have that document, Mr. Kindig?
08:44:47 A. PTX 103, yes, I have it here.
08:44:50 Q. And what is PTX 103?
08:44:51 A. This is the raw material file. We call it the GMP
08:44:56 raw material file for a particular batch of Treprostinil
08:44:59 sodium.

08:45:04 Q. What lot of Treprostinil sodium is this material file
08:45:07 for?
08:45:08 A. The manufacturing manufacturers lot number is
08:45:12 indicated at the top TN120I010, and it was assigned internal
08:45:19 Liquidia lot number LIQ 00572.
08:45:24 Q. Do you see some signatures at the bottom of this
08:45:26 document?
08:45:26 A. Yes, I do.
08:45:30 Q. Do these signatures on the first page indicate that
08:45:32 this material was released for GMP use?
08:45:35 A. No, they do not.
08:45:37 Q. Who is Dana Paris?
08:45:39 A. Dana Paris is a former employee of Liquidia who
08:45:42 worked in the supply chain group and has signed here as
08:45:45 material control personnel.
08:45:46 Q. Did Dana Paris ever worked in the quality unit at
08:45:49 Liquidia?
08:45:49 A. No, she did not.
08:45:51 Q. And who is Jim Gattis?
08:45:52 A. Jim Gattis is an analytical scientist.
08:45:56 Q. Has Jim Gattis ever worked in the quality unit?
08:45:59 A. No.
08:46:02 Q. During shipment of to Liquidia, do you know whether
08:46:04 this lot experienced temperatures above 8 degrees Celsius?
08:46:09 A. Yeah, I recall from having been shown this during my

08:46:14 deposition that that occurred.
08:46:17 Q. And how, in this document, would you know that?
08:46:19 A. On page -- the page that ends in 8158, there's a -- a
08:46:28 temperature graph that shows the temperature data from the
08:46:32 batch during shipment.
08:46:34 Q. And where -- what is that temperature data generated
08:46:37 by?
08:46:37 A. There's a data logger that's put in the shipment that
08:46:43 records temperature during the shipment and outputs the
08:46:49 data.
08:46:50 Q. Was this lot of Treprostinil sodium released by the
08:46:53 quality unit for GMP use?
08:46:55 A. No, it was not.
08:46:56 Q. What happened to it?
08:46:57 A. It got rejected by the quality unit due to the -- the
08:47:04 temperature excursion above 8 degrees C. It was relocated
08:47:08 to an R & D refrigerator at Liquidia and labeled for NDA use
08:47:14 only.
08:47:14 Q. How do you know that?
08:47:15 A. I've seen the material in that refrigerator.
08:47:17 Q. Were there any stickers on the material?
08:47:19 A. Yes. So, the original quarantine label was present,
08:47:23 but crossed through because it was no longer in quarantine
08:47:27 status, and R & D use only label was applied in -- it was
08:47:31 added to the in the container to indicate R & D use only.

08:47:35 Q. Do you know why this Treprostinil sodium lot was not
08:47:38 released for GMP use?
08:47:39 A. Yes, it was -- it was rejected by the quality unit
08:47:42 due to the shipping excursion above 8 degrees C.
08:47:45 Q. Can material that Liquidia designates for R & D use
08:47:50 ever be used by Liquidia in a human?
08:47:51 A. No.
08:47:54 Q. Can material that's designated for R & D use ever be
08:47:58 requalified by Liquidia for use in a human?
08:48:01 A. No, it cannot.
08:48:02 Q. Mr. Kindig, can you please turn to PTX 104 in your
08:48:06 binder.
08:48:09 A. Yes, I have it.
08:48:10 Q. And what is PTX 104?
08:48:12 A. This is another GMP material file for a different lot
08:48:17 of Treprostinil sodium API.
08:48:18 Q. And what lot is this?
08:48:20 A. This is -- at the top, it has the manufacturer lot
08:48:26 number, TN120G010, and at the bottom is indicated the
08:48:31 Liquidia lot number, which is LIQ 00571.
08:48:35 Q. And again, you see the same signatures at the bottom
08:48:38 that we looked at the other previous document?
08:48:41 A. Yes, I did do.
08:48:42 Q. And again, those are not quality individuals?
08:48:44 A. Correct, neither of those individuals are in the

quality unit.

Q. And they would not indicate releasing the material for GMP purposes; correct?

A. Correct. This is not -- those signatures do not release the material for use.

Q. During shipment to Liquidia, do you know whether this lot experienced temperatures above 8 degrees Celsius?

A. Yes, this lot was part of the same shipment as the one we just looked at, so it experienced the same temperature above 8 degrees C.

Q. And was this lot released for GMP use by Liquidia?

A. No, similar to the last lot, it was rejected and not released.

Q. Why was it rejected?

A. It was rejected due to the temperature above 8 degrees C during shipment.

Q. How do you know that this material was not released?

A. It is similar to the one we just spoke about. It is also labeled now for R & D use only. It has been relocated to an R & D use refrigerator at Liquidia.

Q. Can we turn to the last page of PTX 104.

And what is -- if we could blow up the chart. That's great.

And what is this document? What is this chart indicating, Mr. Kindig?

08:49:53 A. This is the packing slip for the shipment, so the two
08:49:57 batches we just spoke about are the rows 2 and 3 of this.
08:50:02 There was also a third batch in the same shipment, TN120C010
08:50:08 in the top line.
08:50:08 Q. And do you know what the disposition is for that
08:50:11 third batch at Liquidia?
08:50:12 A. Yes. That batch, when it came in, was issued
08:50:16 straight to R & D. It was never logged into the GMP system
08:50:21 because it was ordered for the purpose of R & D use.
08:50:24 Q. How do you know that that was designated for R & D
08:50:27 use, the third batch?
08:50:28 A. I've seen it in the same R & D refrigerator. It has
08:50:32 an R & D use only label on it.
08:50:34 Q. For these three batches that we just talked about,
08:50:37 will Liquidia ever use any of these batches for GMP
08:50:40 purposes?
08:50:40 A. No, we will not.
08:50:44 Q. At Liquidia, have you ever received GMP materials
08:50:47 that were shipped with data loggers?
08:50:48 A. Yes, I have.
08:50:51 Q. And when you've received those materials with these
08:50:53 temperature data loggers, what do you do with the material?
08:50:56 A. When the package comes in, you have to open the box,
08:51:02 you know, get the -- get any shipping paperwork off of the
08:51:06 outside of the box. For things that are shipped cold,

there's ice packs and things to get out of the way.

You get inside the box. You would remove the data logger. You would remove any paperwork that's in there with the -- with the shipment, and you would get to the material. If it's cold, you know, cold chain shipment, you would verify that the quantity of the material matches the packing list and then transfer it to the GMP material storage room and get it into a refrigerator there in quarantine.

Q. How quick -- how close are the GMP refrigerators to where you're unpacking this material?

A. It's the same hallway, so maybe 50 feet down the hall between the receiving area and the GMP materials storage room.

Q. When you take the material to the cold room area with the Treprostinil sodium, do you keep the temperature data logger with you?

A. No, the data logger and any paperwork would be, you know, set aside. It would eventually go to somebody's desk to fill out the Receiving Inspection Reports that we were just looking at and to download data from the temperature logger.

Q. When you've opened boxes with temperature data loggers them, do they automatically stop recording temperature?

08:52:21 A. No, they don't. There's a stop button that has to be
08:52:25 pressed to stop the data logging.
08:52:29 Q. Would leaving Treprostinil sodium at room temperature
08:52:32 after receipt by Liquidia comply with Liquidia's SOPs and
08:52:35 spec that we looked at earlier?
08:52:37 A. No, it would not. It needs to go into the required
08:52:40 storage condition of 2 to 8 degrees C when you receive it.
08:52:46 Q. Can we go back to PTX 104. And can we go to page 29
08:52:58 of this document.
08:52:59 What is this document that we see?
08:53:05 A. What page number is it? Sorry.
08:53:07 Q. I'm sorry. This would be --
08:53:09 Derrick, what's the --
08:53:11 Ending in 191?
08:53:14 A. Okay. I have it.
08:53:15 Q. And what is this document?
08:53:16 A. This document is a declaration letter from Yonsung
08:53:21 regarding material being exposed to conditions below 2
08:53:29 degrees C during shipment and that they guarantee the
08:53:33 quality if it goes to a freezing temperature.
08:53:36 Q. If Treprostinil sodium experiences temperatures below
08:53:39 2 degrees Celsius during shipment, can Liquidia use the
08:53:42 material for GMP use?
08:53:44 A. Below 2 degrees? Yes, we could.
08:53:47 Q. Would the quality unit still make a determination on

whether it's suitable?

A. Oh, yes, of course. You'd have to still go through the testing and the release disposition decision by the quality unit.

Q. Has Liquidia, to your knowledge, ever received a similar declaration of quality from Yonsung for Treprostinil sodium that experiences temperatures above 8 degrees Celsius?

A. No, I have not seen a similar declaration for that circumstance.

Q. Can you please turn to PTX 117 in your binder.

Do you have that?

A. Yes, I have it. Yes.

Q. And what is -- what is this document?

A. This is another GMP material file for another batch of Treprostinil sodium API.

Q. And what's the lot number? It's a little bit difficult to read, but what's the lot number for this Treprostinil sodium?

A. So the manufacturer lot number, it's a little -- but it's TN117I010, and the Liquidia lot number is LIQ 00432, as indicated at the bottom.

MR. DAVIES: Your Honor, I'd like to enter PTX 117 into evidence, to the extent it's not already in evidence.

08:55:02 MR. JACKSON: I don't believe it's in evidence, and no objection.

08:55:03 THE COURT: Admitted without objection.

08:55:04 (PTX Exhibit No. 117 was admitted into evidence.)

08:55:09 Q. What date did Liquidia receive this batch of Treprostinil sodium?

08:55:12 A. The date received is indicated at the top, 11th of December, 2017.

08:55:15 Q. And can you turn to -- there's some Bates numbers at the bottom. Can you turn to the Bates -- turn to the Bates number ending 7862.

08:55:17 A. Yes, I have that.

08:55:26 Q. Where was this lot shipped from?

08:55:32 A. It was shipped from Korea. At Yonsung in Korea.

08:55:33 Q. When was it shipped to Liquidia?

08:55:38 A. The ship date is indicated as December 7th, 2017.

08:55:40 Q. Was it shipped directly to Liquidia?

08:55:44 A. Yes, it was.

08:55:47 Q. Were there any other Treprostinil sodium batches in this same shipment?

08:55:49 A. This packing list indicates three batches were part of it, in addition to -- the one we've just spoken about is in the middle row. There's, additionally, TN116J010 and TN117K010 in the same shipment.

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08:56:10 Q. Can we turn to -- again, let me give you the Bates
08:56:15 number. Can we turn to the document ending 7863.
08:56:20 A. Yes, I have it.
08:56:22 Q. And what is shown here?
08:56:23 A. This is a temperature graph of the shipment from
08:56:30 Korea to the U.S.
08:56:32 Q. What was the start time of the temperature data
08:56:36 logger?
08:56:36 A. It's indicated at the top December 7th, 2017. It
08:56:40 looks like 8:15 is the time.
08:56:44 Q. Do you know whether those dates and times for the
08:56:46 logger are Korean time?
08:56:48 A. I presume it to be because the shipment originated in
08:56:53 Korea.
08:56:53 Q. And what's the stop time for the data logger?
08:56:57 A. It's indicated here as December 13th, 2017, at 00:30,
08:57:03 after midnight.
08:57:05 Q. And when, again, was this batch received by Liquidia?
08:57:08 A. It was received on December 11th, 2017.
08:57:13 Q. Going to the start of this trace, do you see where
08:57:16 the temperature drops?
08:57:18 A. Yeah. So it looks to me like that would be when the
08:57:23 data logger was started and then put in the package, allowed
08:57:26 to cool down.
08:57:28 Q. What would cause it to cool down in the package?

A. Yonsung ships their Treprostinil sodium in a package with dry ice. It's got a Styrofoam cooler and dry ice in there to keep it cold during shipment, and so the data logger would go in and cool down to that temperature once it's put inside.

Q. If you look down at the bottom, do you see that there's a rise in temperature between December 11th at 18:25 and December 12th, 02:00?

A. Yes, I see that.

Q. And from the labels, how many hours would have passed between those two time points?

A. It looks like the hash marks on the bottom are about seven and a half hours apart.

Q. Based on that, do have you a sense for how quickly that temperature went up for the data logger?

A. Based on that, it looks to me like a matter of minutes. Very quickly.

Q. Do you have any explanation, based on your experience receiving shipments like this, for the temperature increase?

A. Yeah, I mean, this looks to me like when the package arrived at Liquidia and somebody opened the box and then removed the data logger, that it would have relatively quickly about gone up from the cold temperature that it had been at to the room temperature.

Q. And do you believe that the Treprostinil sodium would

have been left at room temperature with the data logger for the proceeding time?

A. No, it would have been the practice to remove the data logger, set it aside, set aside the paperwork, get the -- you know, we know the Treprostinil needs to be cold. So get it out of the box and take it down to the GMP refrigerator like we just spoke about, and the data logger and paperwork would be dealt with later.

Q. Thank you, Mr. Kindig. No further questions at this time.

MR. JACKSON: May I approach, Your Honor?

THE COURT: Yes.

CROSS-EXAMINATION

BY MR. JACKSON:

Q. Good morning --

MR. JACKSON: May I proceed?

THE COURT: Yes.

BY MR. JACKSON:

Q. Good morning, Mr. Kindig.

A. Good morning.

Q. You have no personal knowledge of what goes on at Yonsung's facilities other than the description in the open portion of Yonsung's DMF; correct?

A. Yeah, my knowledge is limited to the open portion of DMF.

09:00:13 Q. And so, you don't know the temperature at which
09:00:16 Yonsung makes its Treprostinil sodium; correct?
09:00:18 A. I do not.
09:00:21 Q. And you don't know how Yonsung stores its isolated
09:00:25 Treprostinil sodium before it's labeled for shipping;
09:00:27 correct?
09:00:28 A. No, I do not.
09:00:31 Q. And you don't know where Yonsung stores its isolated
09:00:35 Treprostinil sodium before it's labeled for shipping;
09:00:38 correct?
09:00:39 A. That's correct.
09:00:42 Q. Now, I'd like to show what's been marked as Exhibit 9
09:00:46 -- PTX 9. This is the quality agreement between Liquidia
09:00:55 and LGM and Yonsung; correct?
09:00:58 A. Yes, that's what it's indicated as.
09:01:01 Q. Okay. And this is for the Treprostinil sodium that
09:01:04 Liquidia is buying from Yonsung; correct?
09:01:06 A. I have to look to see if that's indicated.
09:01:13 Q. If you look at Appendix 1, products listed in
09:01:16 Appendix 1.
09:01:16 A. Appendix 1.
09:01:36 Yes, I see that indicated. Treprostinil sodium.
09:01:38 Q. All right. Now, at Page 3, the quality agreement
09:01:41 requires Yonsung to provide a Certificate of Analysis to
09:01:44 Liquidia for each batch of that Treprostinil sodium shipped

09:01:48 from Yonsung eventually to Liquidia; correct?

09:01:58 Do you see the certificate of compliance

09:01:59 analysis. Do you see --

09:02:00 A. Certificate of Analysis is required for each

09:02:02 product -- batch of products shipped to client. I see that

09:02:02 sentence, yes.

09:02:06 MR. JACKSON: Move to admit PTX 9.

09:02:08 MR. DAVIES: No objection Your Honor.

09:02:09 THE COURT: Admitted without objection.

09:02:10 (PTX Exhibit No. 9 was admitted into evidence.)

09:02:10 BY MR. JACKSON:

09:02:11 Q. Now, Liquidia did an audit of Yonsung's facilities;

09:02:14 right?

09:02:15 A. Yes, Liquidia did do an audit of Yonsung. That's

09:02:18 correct.

09:02:19 Q. And as part of that audit, Liquidia audited Yonsung's

09:02:23 warehouse controls; right?

09:02:24 A. I'd have to see the audit report to know for sure. I

09:02:30 think I recall that from my deposition last fall.

09:02:32 Q. Sure. Let's pull up PTX 113, please, and go to

09:02:35 Page 9.

09:02:41 A. Sorry. PTX 113, did you say?

09:02:43 Q. I did. It's on the screen if that's going to be

09:02:46 easier.

09:02:47 A. Oh, yeah. Okay.

09:02:49 Q. Do you see warehouse controls there in the 9:30 to
09:02:54 12:00?
09:02:55 A. Yeah, I see warehouse control side.
09:02:58 Q. Now, other than Yonsung's warehouse, you don't know
09:03:00 where Yonsung might store the Treprostinil sodium it's
09:03:02 making for Liquidia; correct?
09:03:04 A. I do not.
09:03:06 Q. And you don't know how long Yonsung stores its
09:03:10 Treprostinil sodium in the -- its warehouse; correct?
09:03:12 A. Correct.
09:03:13 Q. And you don't know the temperature of Yonsung
09:03:15 warehouse; correct?
09:03:16 A. That's correct.
09:03:18 Q. Now, you testified about some shipments from Yonsung.
09:03:21 But isn't it true that you don't know whether some shipments
09:03:24 go through LGM, that company that's in between Yonsung and
09:03:30 Liquidia; right?
09:03:31 A. Yeah, my understanding is our current process
09:03:34 involves shipment from Yonsung to LGM first and then from
09:03:38 LGM to Liquidia, and I don't believe that was always the
09:03:40 case, as we just looked at.
09:03:41 Q. Okay. So let's look at PTX 117 that you were looking
09:03:45 at a minute ago.
09:03:50 Now, it's your testimony that the standard
09:03:53 operating procedure for the Treprostinil sodium is storage

09:03:56 at 2 to 8; right?
09:03:57 A. Liquidia's raw material specification and Yonsung'
09:04:01 label link require 2 to 8 degrees C storage.
09:04:03 Q. Okay. But you'll agree with me that often it's not
09:04:06 stored at 2 to 8; right?
09:04:08 A. I don't agree with that.
09:04:10 Q. Okay. So while -- the graph that Mr. Davies showed
09:04:13 you a few minutes ago, let's go to that page. It's Page 14.
09:04:17 So, would you agree with me that the -- this
09:04:23 shows that it's -- it starts out at about 19 degrees here,
09:04:28 halfway between 9 and a half and 28 and a half; right?
09:04:31 A. That is where the graph starts, yes.
09:04:34 Q. Okay. And so that's where the numbering starts, so
09:04:36 the temperature at that point is about 19 degrees or so C;
09:04:40 correct?
09:04:41 A. The temperature of the data logger is, yes.
09:04:44 Q. Okay. And then you say it's placed in this box, and
09:04:47 the temperature briefly passes through that 2 to 8 degree C
09:04:51 right here, just very briefly. And using your phraseology a
09:04:56 few minutes ago, in minutes; right?
09:04:57 A. Yeah, it looks like it's probably a matter of minutes
09:05:01 to maybe an hour. It's hard to say for sure. Something
09:05:04 like that.
09:05:04 Q. Okay. And it drops down all the way down to negative
09:05:07 50 degrees; right?

09:05:08 A. That's right.
09:05:09 Q. And then it stays at negative 50 degrees all here,
09:05:12 all on the 7th, all on the 8th, all on the 9th. It stays
09:05:17 well below 0 degrees all on the 10th, and all the way up
09:05:21 until right here on the 11th of December; right?
09:05:24 A. Yes, all those temperatures are below -- below
09:05:29 0 degrees, it looks like.
09:05:30 Q. Okay. So from the moment it hits this drop -- this
09:05:35 dry ice box, for multiple days, it's below 0; right?
09:05:39 A. Yes, for multiple days, it's below 0 while it's being
09:05:44 shipped. Yes.
09:05:44 Q. And you'll agree with me that, therefore, these
09:05:46 multiple days are not within the 2-to-8-degree-C zone;
09:05:50 correct?
09:05:50 A. They're below 2 degrees. The -- the declaration
09:05:54 letter that we talked about earlier talks about that the
09:05:56 quality is guaranteed during that shipping period.
09:05:59 Q. Okay. But the -- that declaration letter, we'll come
09:06:02 back to that, but that was later, wasn't it?
09:06:03 A. Can you -- I'm not sure I understand the question.
09:06:08 Q. Okay. So let's look at -- we're looking at TN -- at
09:06:11 PTX 117; right?
09:06:13 A. Yes, that's right.
09:06:14 Q. There's no declaration letter in this document, is
09:06:16 there?

09:06:16 A. I do not see that declaration letter in this
09:06:44 document.
09:06:45 Q. And this document is dated from 2017; right?
09:06:49 Can -- if we --
09:06:49 A. The day it was received was December 11th, 2017.
09:06:52 That's right.
09:06:53 Q. And the -- let's turn quickly to -- to PTX 103. And
09:07:13 let's go to page Bates ending in 161. It's the declaration
09:07:17 letter we were -- Mr. Davies showed you.
09:07:22 A. PTX 103?
09:07:26 Q. Right there. Let's zoom in on that.
09:07:31 A. Do I have PTX 103?
09:07:32 Q. It's in the binder that -- the black binder that you
09:07:35 had in front of a moment ago.
09:07:36 A. Okay.
09:07:37 Q. But it's also on the screen if that will help.
09:07:39 A. Okay.
09:07:39 Q. So this is the declaration Mr. Davies showed you a
09:07:42 minute ago; right?
09:07:43 A. Yes, that's right. This is what we looked at a few
09:07:46 minutes ago.
09:07:46 Q. And that date, upper right corner, it's November of
09:07:48 2019; right?
09:07:49 A. Yes, that's the date on there.
09:07:51 Q. Okay. So that's two years later than the lot we were

09:07:54 just looking at in 117; right?
09:07:57 A. That's correct.
09:07:58 Q. Okay. So let's now go back to 117 for a second.
09:08:04 So again, we're here, and we were just looking
09:08:07 at the graph, I think some pages in, with the temperature
09:08:10 logger. And you agreed with me that for a lengthy period of
09:08:14 time, it was stored outside of the 2-to-8-degrees zone here;
09:08:19 correct?
09:08:20 A. It was shipped outside 2 to 8 degrees, yes.
09:08:23 Q. Okay. And was it stored during that shipment?
09:08:25 A. I wouldn't call -- classify shipping as storage.
09:08:29 Q. Okay. But nothing was happening to it. There
09:08:32 weren't any chemical reactions going on during that period;
09:08:35 right?
09:08:35 A. I would not expect any chemical reactions during
09:08:37 shipment.
09:08:37 Q. Or at least there weren't intending to be any
09:08:40 chemical reactions; correct?
09:08:41 A. Correct.
09:08:44 Q. Now, let's go back to the first page of this
09:08:48 document. And let's zoom in on that top section where --
09:08:53 so, about -- right below the heat treated plastic and N/A.
09:08:57 Do you see that? It says verify transport
09:09:00 conditions?
09:09:00 A. Yes, I see that.

09:09:01 Q. And that's a box that's been checked by Liquidia; right?
09:09:04 A. Yes, I see a checkmark in the box.
09:09:06 Q. So Liquidia verified the transport conditions were met here; right?
09:09:11 A. That's what the box indicates.
09:09:12 Q. Including temperature if applicable: Right?
09:09:15 A. I see that here.
09:09:17 Q. Okay. But this is -- you'll agree with me that this was not stored at 2 to 8 degrees; right?
09:09:18 A. I don't agree with that. I don't consider shipping to be storage.
09:09:20 Q. Okay. But during transport conditions, the material that was being transported was not within the specification of 2 to 8 degrees; right?
09:09:23 A. The transport conditions show that there were temperatures below 2 degrees.
09:09:25 Q. In fact, the entire time between when it was put in the box and it was taken out of the box, it was below 0 degrees; right?
09:09:26 A. Most of the time, yes, it looked like it was.
09:09:31 Q. Okay. And then two lines lower, it says verify temperature conditions against COA or packaging documentation. Do you see that?
09:09:35 A. Yes, I see that.
09:09:36
09:09:40
09:09:41
09:09:45
09:09:48
09:09:49
09:09:51
09:09:56
09:09:58
09:10:00

09:10:01 Q. What's a COA?
09:10:03 A. Certificate of Analysis. And that's the Certificate
09:10:07 of Analysis that Yonsung provides that includes the
09:10:09 reference about 2 to 8 degrees; right? I believe it's on
09:10:13 the Certificate of Analysis. Let's look.
09:10:23 Q. Let's just -- I am a tight on time, so let me just
09:10:25 keep moving.
09:10:26 You'll agree with me that Yonsung or Liquidia
09:10:29 verified the temperature conditions were met here; right?
09:10:31 A. Liquidia -- Liquidia has checked the box next to
09:10:37 verify temperature conditions. Yes.
09:10:39 Q. Okay. And despite the fact that the material that
09:10:42 was being shipped was below 0 degrees for multiple days
09:10:46 during shipment; right?
09:10:47 A. Yes, the temperature graph showed that there was
09:10:52 temperatures below 0 degrees during the shipment on dry ice.
09:10:56 Yes.
09:10:56 Q. Okay. Now, you'll agree with me that this batch of
09:11:00 -- - that this batch is TN110 -- 117I010; correct?
09:11:05 A. Yes, that's the batch number.
09:11:07 Q. Okay. Now, this batch was used in the human clinical
09:11:10 trials for Liquidia; correct?
09:11:13 A. I don't recall. I'd have to look at the --
09:11:16 Q. Sure.
09:11:17 A. -- the list of the batches that we used.

09:11:18 Q. Sure. Let's go to PTX 25 at Page 8, which is Bates ending in 712.
09:11:23
09:11:31 A. Sorry, which page did you say? I am sorry.
09:11:35 Q. Bottom number ending in 712. It's also on the screen if that helps.
09:11:43
09:11:44 A. I have it.
09:11:44 Q. And do you see about two-thirds of the way down 117I010 was used in the clinical phase trials and also in the primary stability?
09:11:48
09:11:53
09:11:55 A. Yes, I see that.
09:11:56 Q. Okay. So these -- this material that was used that was outside -- for multiple days outside of the 2 to 8 was used for human clinical trials; correct?
09:11:59
09:12:04
09:12:06 A. Yes, the material that was shipped below 2 degrees on dry ice, yes, it was used in the clinical trial.
09:12:10
09:12:13 Q. Okay. Now, would you agree that this was a -- this TN117I010 was a representative batch of sodium -- of Treprostinil sodium?
09:12:25
09:12:28
09:12:30 A. The header and the title says summary of representative batches, so, yes.
09:12:32
09:12:34 Q. Okay. Now, let's look at the next one below it. Do you see where it says 116J010?
09:12:38
09:12:41 A. Yes, I see that.
09:12:42 Q. And that was also used in both Phase III clinical trials and stability; correct?
09:12:46

09:12:48 A. That's what's indicated here, yes.
09:12:50 Q. Okay. And that also had a similar drop in
09:12:53 temperature during the transit where it went well below 0
09:12:58 for an extended period of time; correct?
09:13:01 A. I think we saw earlier that this batch was shipped
09:13:05 with the other batch, yeah. So, they would have experienced
09:13:08 the same temperature conditions on shipping, yes.
09:13:11 Q. Okay. So just to make sure we know which batches it
09:13:14 was, let's turn to PTX 116 in your binder. And let's go to
09:13:19 that same chart, which I think ends in Bates Number 963 at
09:13:23 the bottom.
09:13:24 Are you with me?
09:13:30 A. Yeah, I am.
09:13:31 Q. Again, this shows material that Liquidia used for
09:13:35 human clinical trials where the Treprostinil sodium dropped
09:13:38 well below 0 degrees C and was there for multiple days until
09:13:44 the box, you say, was opened here and the temperature shot
09:13:48 up; right?
09:13:49 A. Yes, this temperature is below 2 degrees during the
09:13:54 shipment.
09:13:54 Q. Right. And so the temperature here was not within
09:13:57 that 2-degree to 8-degree specification that you talked
09:13:59 about; right?
09:14:01 A. It is not being -- is it is not between 2 to 8
09:14:05 degrees C during shipment.

09:14:06 Q. And nonetheless, let's turn back to the first page of this, once again, Liquidia confirmed that the transport conditions, including temperature, was -- requirements were met. Do you see that?

09:14:17 A. Yes, I see the checked box there.

09:14:21 Q. And again, two lines below, verify temperature conditions, again, checked; correct?

09:14:26 A. Yes, I see that.

09:14:32 Q. Now, let's go back to PTX 125 for a minute. Sorry, let's go back sorry to PTX 20. And let's go to page ending in 674. It's a couple pages after the page I was looking at having you look at a minute ago.

09:15:08 A. Yes, I see it.

09:15:09 Q. Okay. And do you -- can you pull up that page? So, a couple pages later. I'm looking at ends in Bates 674.

09:15:32 So, PTX 20, Page 93, which the Bates number ends in 674.

09:15:50 Okay. Now, let's look at that -- I want to look at that -- that top row. And that's -- so, yeah, sorry the top row is 118H010. Do you see that?

09:16:31 A. So you're talking about the row that starts with batch Number 190172 at the far left?

09:16:39 Q. Yeah, Treprostinil batch number --

09:16:41 A. Yes.

09:16:41 Q. -- do you see 118H010?

09:16:44 A. Yes, I see that.
09:16:48 Q. You would agree that 118H010 is used in human
09:16:54 clinical trial; correct?
09:16:55 A. Yes, it was. It's where -- it's indicated that way
09:17:01 here.
09:17:01 Q. And let's go to PTX 127. It should be in your
09:17:07 binder, but we'll pull it up on the screen as well.
09:17:10 And do you see this is the Receiving Inspection
09:17:14 Report for 118H010?
09:17:18 A. Yes, I see that.
09:17:19 Q. Okay. And it verifies that the transport conditions
09:17:23 temperature if applicable was met. Do you see that?
09:17:27 A. I see that.
09:17:28 Q. And again, it says verify temperature conditions
09:17:31 against COA or packaging documentation. Do you see that?
09:17:34 A. Yes, I see that box checked.
09:17:35 Q. And again, that's been checked; right?
09:17:37 A. Yes, it is.
09:17:39 Q. And you'll agree with me -- I think you agreed with
09:17:42 me a minute ago that this batch was used for human clinical
09:17:45 trials; right?
09:17:46 A. That's how it was indicated on the page we just
09:17:49 looked at a minute ago.
09:17:50 Q. Okay. Would you agree with me that there's no data
09:17:52 logger showing the temperature of this lot during shipment

09:17:58 in this documentation?
09:17:59 A. I agree. I do not see a temperature data logger
09:18:26 chart in this exhibit.
09:18:28 Q. Okay. Now, let's look at -- I'm looking at another
09:18:33 one where I think there's no temperature log. So let's look
09:18:35 at 118. Let's look at PTX 823, which should be in your
09:18:39 binder.
09:18:44 A. Yes, I'm -- I have it.
09:18:46 Q. And that's for TN118F010; correct?
09:18:50 A. Yes, it is.
09:18:52 Q. And would you agree with me that there's no
09:18:54 temperature log in this documentation?
09:18:56 A. I do not see any temperature log data.
09:19:21 Q. Okay. But nonetheless, once again, Liquidia verified
09:19:24 that the transport conditions temperature if applicable was
09:19:27 checked; correct?
09:19:28 A. Yes, I see that.
09:19:29 Q. And verified temperature conditions against the COA
09:19:33 or packaging documentation, again, checked; right?
09:19:37 A. Yes, I see that.
09:19:37 Q. Okay. And you'll agree with me that this -- even
09:19:40 without the temperature log, you'll agree with me that
09:19:44 Liquidia used this material in Liquidia -- in human clinical
09:19:49 trials; correct?
09:19:50 A. This particular batch? I don't know if we looked at

this one yet, have we?

Q. Sure. Let's look back at PTX 20 and let's go to Page 91. It's a couple pages up. Actually, I think you've got it.

118F010. It's the next row. Do you see that?

A. Yes, I see it.

Q. Okay. So 118F010 was used in human clinical trials without temperature logs; correct?

A. I see it indicated as it was used in clinical over there on the right. Yes.

Q. And we determined just a minute ago that there was no temperature log in the receiving documentation; right?

A. I do not see a temperature log.

Q. Okay. Now, the Court has heard a bunch about the various shipments that went above 16 degrees C; correct?

You provided some testimony on that this morning; right?

A. We just talked a little bit ago about two batches that were above, yeah, above -- above 8. I think they were both 16.

Q. Okay. So let's go ahead and look at PTX 19, which I believe is already in evidence?

A. PTX 19. Yes, this is one of the ones. Okay.

Q. Right. And this is for TN 11 -- 120I010; right?

A. That's correct.

09:21:18 Q. And it -- Liquidia verified that the transport
09:21:22 conditions temperature if applicable, the requirements were
09:21:29 met?
09:21:29 Do you see that?
09:21:30 A. Yes, I see the box checked.
09:21:31 Q. So in this box and in this document, Liquidia
09:21:34 verified that the transport conditions were met; correct?
09:21:38 A. That is what the box indicates.
09:21:41 Q. And two lines later, again, says verify temperature
09:21:43 conditions against COA or packaging documentation; correct?
09:21:46 A. Yes, I see the box checked.
09:21:48 Q. And again that's been checked; right?
09:21:50 A. I see that.
09:21:52 Q. Now, you will agree with me that this particular
09:21:55 shipment went above 16 degrees for extended period of time;
09:21:59 correct?
09:21:59 A. The date -- yeah, the data that we looked at earlier
09:22:03 had shipping temperatures above -- it looks like the high
09:22:08 was 16.7 degrees.
09:22:09 Q. Yeah, so let's look at Page 26 of this document,
09:22:12 please. And right at the bottom, it says high/low
09:22:22 measurement. Do you see that? It says high is 16.7.
09:22:26 That's what yours is referring to; right?
09:22:28 A. Yeah, that's what I see.
09:22:29 Q. And so it only briefly passes through the 2 to 8

09:22:33 right here; right?
09:22:37 Right there?
09:22:38 A. Let's see. There's a period over -- it's hard to
09:22:42 say, maybe a day or so that it passes through 2 to 8.
09:22:45 Q. And then for eight or nine days, it's way -- it's
09:22:49 above the 2-to-8 zone. Sorry. I'm sorry. It passed
09:22:53 through 2 to 8 here. I apologize and then for nine days
09:22:56 here, it's above that 2-to-8 zone; right?
09:22:58 A. Yeah, it looks like maybe eight or nine days,
09:23:01 something like that.
09:23:02 Q. Now, even with those temperature logs and that data,
09:23:07 LGM stated that we can move forward with this product based
09:23:10 on stability data; correct?
09:23:11 A. Yeah, I believe that is -- if I can find it.
09:23:17 Q. So let's go to page 20 of this document. And I'm
09:23:25 looking at the email at the top. Now, again, this is all
09:23:29 part of this shipping documentation for this lot; right?
09:23:32 A. Yes, this is the -- this is all of the documentation
09:23:36 for this lot.
09:23:36 Q. So this is contained all within Liquidia's files for
09:23:39 this lot; right?
09:23:40 A. That's correct.
09:23:41 Q. Okay. And this is an email that says we can move
09:23:45 forward with this product based on stability data results;
09:23:50 right?

09:23:50 A. That is -- that is what LGM said yeah.
09:23:52 Q. And that's similar to the certification that you were
09:23:55 focusing on a few minutes ago with Mr. Davies about Yonsung
09:23:59 verifying that it's okay if it goes below -- if it goes
09:24:03 below freezing; right?
09:24:04 A. I wouldn't call those similar at all, no.
09:24:06 Q. Okay. But it's a statement by LGM. LGM is the
09:24:10 intermediary between Liquidia and Yonsung; right?
09:24:14 A. It -- it is a statement by LGM, and LGM is the U.S.
09:24:19 supplier between Yonsung and Liquidia.
09:24:22 Q. So, the supplier is telling and it's providing
09:24:27 information to Liquidia that we can move forward with this
09:24:30 forward based on stability results; right?
09:24:33 A. That was the decision their quality group made.
09:24:36 Q. And then the next -- if you go back one page, further
09:24:38 up -- so this is further up in the same chain.
09:24:40 Now, you said Dana Paris. That's the person at
09:24:45 the top; right? Do you do you see that?
09:24:47 A. Yes, Dana is on at the top. Yes, I see that.
09:24:49 Q. And she works for Liquidia; right?
09:24:51 A. Yes, she works for Liquidia.
09:24:52 Q. So this is LGM Pharma Robert Hoppes -- I'm not sure
09:24:56 if I'm mispronouncing his name -- is telling Dana Paris
09:25:00 about these -- this detail; correct?
09:25:03 A. Yes, this is an email from Robert Hoppes to Dana

09:25:03 Paris.
09:25:07 Q. Okay. And it says "A quick note, the Treprostinil
09:25:09 shipment from Korea to LGM had a temperature deviation up to
09:25:14 16 degrees C for nine days. However, our QC released the
09:25:18 shipment because Yonsung has long-term stability showing
09:25:21 that Treprostinil is stable at room temperature for six
09:25:24 months."
09:25:25 Do you see that?
09:25:26 A. I see that.
09:25:27 Q. And again, LGM provided all that information to
09:25:32 Liquidia at the time; right?
09:25:34 A. Yes, it looks like they did.
09:25:38 Q. And in fact, we already noted that Liquidia verified
09:25:42 the temperature conditions. On the first page, it verified
09:25:46 the temperature conditions requirements were met; right?
09:25:49 A. The box is checked on the first page indicating
09:25:54 verified temperature conditions were met, yes.
09:25:57 Q. Now, you mentioned that materials are -- all
09:26:02 materials, when they get to Liquidia, are quarantined;
09:26:05 right?
09:26:05 A. For -- if they're for GMP purposes, yes, they go into
09:26:11 quarantine.
09:26:11 Q. Not just for GMP purposes. All material is
09:26:15 quarantined; right?
09:26:16 A. The SOP that defines quarantine is for materials that

are controlled by our SOPs, which are GMP materials. R & D material -- and reference standards, things like that. R & D materials don't necessarily go to quarantine. They would go straight to R & D.

Q. Okay. Now, after the required testing, the quarantine materials -- strike that.

The quarantine materials have to be tested before they are allowed to be used; correct?

A. If the raw materials specification requires testing, the testing would have to occur before they could be used. Yes.

Q. Now, you're the supervisor of the team that does that analytical testing; correct?

A. Yes.

Q. Okay. Now, the lots that we just received in PTX 19, those were received in January 2021; right?

A. Yes, that's right.

Q. Now, that was more than a year ago; right?

A. Yes, that's correct.

Q. Now, you testified this morning that those -- those had been released to the R & D group; is that right?

A. They were rejected for GMP use and dispositioned by transferring to the R & D group. That's correct.

Q. Okay. But as of your deposition, that wasn't the case, was it?

09:27:30 A. They had not been rejected, yeah, as of my
09:27:34 deposition. That's correct.
09:27:34 Q. And you were deposed at the end of October; correct?
09:27:37 A. I was deposed twice. I think it was September and
09:27:40 October.
09:27:40 Q. Okay. But as of the end of October, they had not yet
09:27:43 been rejected; right?
09:27:44 A. That's correct. They were still in quarantine at the
09:27:47 end of October.
09:27:47 Q. So let's see. It came in in January, and they were
09:27:50 kept in quarantine all the way through October; right?
09:27:53 A. That's correct.
09:27:54 Q. And as of your deposition, when we asked you about
09:27:56 what was going to happen to them, you said you didn't know;
09:27:59 right?
09:27:59 A. I said that they were not intended to be used for GMP
09:28:04 use.
09:28:05 Q. So let's actually go to your deposition, and let's
09:28:08 look at your first deposition, 261 lines 6 through 9,
09:28:15 please.
09:28:20 (Video playing.)
09:28:28 BY MR. JACKSON:
09:28:28 Q. Do we have sound?
09:28:31 Okay. Well, you were asked what is Liquidia
09:28:34 going to use it for, and you said I don't know; right?

09:28:37 A. I see that on the screen. I have no idea what it is
09:28:41 in the context of that question.
09:28:43 Q. Okay. So during your deposition, we asked you about
09:28:47 these lots; right?
09:28:48 A. Yes, I was asked about these lots.
09:28:51 Q. And it was at your -- you were a 30(b)(6) for the
09:28:53 company in that deposition; correct?
09:28:55 A. I was -- yes.
09:28:56 Q. You know he what a 30(b)(6) witness is. It's a
09:29:00 representative of the company; right?
09:29:00 A. I was representing both my personal knowledge and the
09:29:05 company positions, as I recall.
09:29:05 Q. And before your deposition, you asked a colleague
09:29:07 about what was going to happen, correct, with those lots
09:29:10 that had been outside the 2-to-8 range, i.e., that 16-degree
09:29:16 zone; correct?
09:29:17 A. I asked another individual at Liquidia about the
09:29:21 plans for these two lots that we're speaking of, 571 and
09:29:25 572.
09:29:25 Q. Okay. And that individual was Michael Hunter; right?
09:29:28 A. That's correct.
09:29:28 Q. Okay. And you did that in preparation for your
09:29:31 deposition; correct?
09:29:31 A. I did.
09:29:32 Q. Okay. And you so you hadn't known about that apart

09:29:35 from preparing for the deposition; correct?
09:29:36 A. I think -- I think that's correct, yeah.
09:29:44 Q. Okay. Now, would you agree with me that there's no
09:29:48 documentation reflecting the fact that Liquidia is now going
09:29:51 to use it for R & D purposes?
09:29:53 A. There's documentation that the lots were rejected.
09:30:01 The reason for the rejection is indicated in that
09:30:04 documentation, and there's documentation transferring them
09:30:07 out of the GMP storage area to R & D.
09:30:12 Q. So let's look at PTX 19. That's what we were just
09:30:15 looking at with the temperature variation.
09:30:17 A. Yeah.
09:30:18 Q. Let's go to the second page.
09:30:19 A. Mm-hmm.
09:30:19 Q. That's blank; right?
09:30:25 A. At the time this was produced, I see that it's blank.
09:30:28 It's not blank any longer.
09:30:30 Q. Do you know whether Liquidia has ever produced any
09:30:32 documentation or data to United Therapeutics detailing that
09:30:36 this material is not going to be released and used for GMP?
09:30:39 A. I don't know if that's been produced or not.
09:30:42 Q. Okay. When did you find out that the material was
09:30:55 not going to be used for GMP?
09:30:57 A. Well, I found out that it was not going to be used
09:31:02 for GMP as of when I asked the question of Michael Hunter

prior to my deposition.

Q. Okay. Well, as of your deposition -- let's actually pull up your deposition again.

As of your deposition -- can we actually pull up the actual deposition itself.

And let's go to -- so, this is in your -- in redirect after your counsel had identified the fact that what was -- that you had spoken to Mr. Hunter about the -- that it was still in quarantine. And you testified did you discuss the substance -- actually.

So, let's look down at Line 20. And you explained that Liquidia does not intend to use Lot 571; is that right? And that was based on your conversation, again, with Michael Hunter. That goes to the next page.

And then you say Liquidia does not intend to use it.

Can we actually take down the zooms.

And then on Line 6 of the right-hand side here it says, "What is Liquidia going to use it for?" And you say I don't know. And we said is there -- we asked you is there any documentation reflecting that? And you said not at this time, no; right?

A. Yes, I see that all here. That's correct.

Q. And that was truthful testimony at the time?

A. Yes, that's right. We said we are not going it use

it for GMP purposes. I didn't know what it was going to be used for, and there was no documentation at that time reflecting that.

Q. Okay. So -- and you're not aware of any documentation ever having been produced to United Therapeutics with respect to your new testimony today about the fact that it's now not going to be used for GMP and it's now just going to be used for R & D; correct?

A. Well, my previous testimony was it was not going to be used for GMP. That part hasn't changed. I don't know about what documentation has been produced or not produced.

Q. Your previous testimony was also that it was still in quarantine as of October; right?

A. That's correct.

Q. Okay. Now, there's an API supply agreement between LGM and Liquidia; correct?

A. I think I remember being shown a supply agreement as part of my deposition.

Q. So let's look at PTX 115, please. This is the API supply agreement between LGM and Liquidia; right?

A. Yes, I see that.

Q. Okay. Now, this agreement provides that within 45 days, Liquidia can inspect and/or test any batch of Treprostinil that Yonsung sends; correct?

A. Are you referring to a particular point in the

09:33:55 document?
09:33:56 Q. Sure. Let's go look at Section 4.7, which is on
09:33:59 bottom of Page 9, top of Page 10.
09:34:06 Do you see where it says inspection of API?
09:34:08 A. Yes, I see that.
09:34:09 Q. First line reads "Within 45 business days of the
09:34:12 arrival of each batch of API at the designated facility by
09:34:16 purchaser" -- that's Liquidia; right?
09:34:17 A. I believe that's how it's defined. Yes, Liquidia is
09:34:35 purchaser. That's correct.
09:34:36 Q. Okay. So "Within 45 days of the arrival of each
09:34:39 batch of API at the designated facility by Liquidia,
09:34:43 Liquidia shall inspect and/or test each batch of API at its
09:34:47 own cost and expense."
09:34:48 Do you see that?
09:34:49 A. I see that, yes.
09:34:49 Q. Okay. And now, Liquidia never tested the batches
09:34:53 that we just referred to within those 45 days; correct?
09:34:56 A. We did not test those two batches, no.
09:34:59 Q. Okay. But even though Liquidia knew that the batches
09:35:03 were out of spec -- were -- had experienced that temperature
09:35:06 of 16 degrees C; correct?
09:35:08 A. We -- right. We did not. We did not test those two
09:35:13 batches.
09:35:13 Q. So I just want to make sure. You knew when you got

09:35:16 the material that it had gone at 16 degrees C; correct?
09:35:20 A. We knew whatever was indicated in that email and
09:35:24 that -- yeah, from the data logger. Yes.
09:35:26 Q. Right. So well, just turning back quickly to PTX 19.
09:35:33 Go to Page 151. Or Bates number is 151.
09:35:41 A. Yes, so we knew what was in this email.
09:35:43 Q. So, you knew on December 28th, 2020, that this batch
09:35:48 had experienced that temperature of 16 degrees C; correct?
09:35:51 A. Yes, that's here in this email. Yes.
09:35:53 Q. And you if you go to the first page, you received the
09:35:56 stuff on January 7th, about a week -- a little over a week
09:35:59 later; right? A week and a half later; right?
09:36:02 A. Correct.
09:36:02 Q. So before you get the stuff, the batch of the
09:36:07 Treprostinil from Yonsung, you know it's experienced this
09:36:11 temperature of 16 degrees C; right?
09:36:14 A. That's correct.
09:36:15 Q. And so, let's go back to your PTX 115, and we were
09:36:20 just looking at the supply agreement. "Within 45 business
09:36:23 days of the arrival of that batch, purchaser, Liquidia shall
09:36:27 inspect and/or test each batch"; right?
09:36:30 A. I see that here, yes.
09:36:31 Q. But you didn't do that, did you?
09:36:32 A. We did not test those batches.
09:36:34 Q. Okay. Now, if Liquidia had done what this provided,

Liquidia could have determined that the purchaser -- or that it did not conform with the product specifications; correct?

A. Sorry. Can you rephrase the question.

Q. Sure. If Liquidia determined that a batch of the API did not conform to the 2 to 8 degrees or whatever the product specifications were, Liquidia could give notice to Yonsung of that nonconformance; right?

A. It says give supplier notice. I don't know if supplier indicates Liquidia or LGM.

Q. Well, either way, if upon inspecting or testing the API, purchaser, that's Liquidia, determines that a batch of the API does not conform to the product specifications Liquidia shall, within such 45-business-day period give supplier, I think that's LGM, written notice of such nonconformance.

Do you see that?

A. I see that.

Q. So you could have said we're not taking this stuff because it got so hot at 16 degrees C; correct?

A. Presumably, we could have.

Q. Okay. And if you did that, Liquidia could have returned that Treprostinil sodium to Yonsung, and Yonsung would have to have given Liquidia a credit for the batch; correct?

A. I don't see anything here about credit or anything

like that.

Q. Okay. Let's start with the next sentence that starts unless. Do you see that?

Unless supplier objects within 20 business days from notice by purchaser -- again, that's LGM -- objects within 20 business days from notice by Liquidia to the nonconformity, purchaser, Liquidia, will return the non-conforming API to supplier; right?

So you're returning the Treprostinil sodium back to LGM; right?

A. That -- that's what this clause would direct to happen.

Q. Okay. And the next sentence reads "Supplier shall incur all the fright-related expenses and shall issue a credit note for the rejected API"; right?

A. I see that sentence, yes.

Q. Okay. So you could have sent it back and gotten your money back; right?

A. By the way this supply agreement is written, I think that could have happened.

Q. Okay. And then, in fact, they would have been obligated -- Liquidia would have been obligated -- or Yonsung would have been obligated to give you a new batch; right?

A. I don't see Yonsung named here. It talks about

supplier, so I guess LGM Pharma perhaps.

Q. LGM -- LGM, and they're the U.S. supplier for Yonsung; right?

A. That's correct.

Q. And so LGM's sole responsibility shall be to replace any non-conforming as soon as possible, and that's non-conforming API; right?

A. I see that here, yes.

Q. Okay. So they -- you could have said we're sending this back, give us -- give us a credit and let's -- send us a new batch; right?

A. This paragraph seems to suggest that could have been a possible outcome.

Q. Okay. And now, the two batches that we were just talking about, that's about half a million dollars; right? Of material; right?

A. I don't know the cost. I think it might be indicated in some of the documentation, but I don't know off the top of my head.

Q. Okay. But it's -- I think it's -- I'll get back to it.

You agree with me that it's about a hundred grams right?

A. I'm sorry. What are you referring to.

Q. So let's look -- let's look at PTX 19 and go to Bates

149. If now -- if you look, you said the first two were the ones that were going to be used for GMP purposes; correct?

A. Of the three batches represented here, the GMP batches were going to be 120G010 and 120I010.

Q. So it's 50 grams times one each of G and 50 grams two each of I; is that right?

A. That's right.

Q. So it's about 150 grams of this material; correct?

A. That's correct.

Q. And that's about $750,000 worth of material; right?

A. I don't know that.

Q. The documentation will show that, and the material -- this is the stuff, again, that you were going to use for GMP, but you didn't, you put it in quarantine, and now all of a sudden you're saying today that you're just using it for R & D; is that right?

A. That material has now been dispositioned as rejected for GMP and will be used for R & D.

Q. But it had been met for GMP; correct?

A. It was originally ordered and intended for GMP when we received it.

MR. JACKSON: Okay. I want to move to admit the documents I've used with Mr. Kindig, which I believe are PTX 9, PTX 113, PTX 115, PTX 116, 117, 123, 124, 126, 127, 823, and I think that's it.

09:42:11 MR. DAVIES: No objection, Your Honor.

09:42:13 THE COURT: All right. They're all admitted without objection.

09:42:16 (PTX Exhibit Nos. 9, 113, 115, 116, 117, 123, 124, 126, 127, and 823 were admitted into evidence.)

09:42:17 MR. JACKSON: Thank you for your time, sir.

09:42:19 Pass the witness.

09:42:19 THE COURT: Mr. Davies.

09:42:21 MR. DAVIES: Just a few questions.

09:42:21 REDIRECT EXAMINATION

09:42:25 BY MR. DAVIES:

09:42:25 Q. Mr. Kindig, for all of the batches of Treprostinil sodium that counsel walked through with you, did he show you evidence that any of them that were used for human use had experienced temperatures above 8 degrees?

09:42:42 A. No, all the batches we talked about were either below 2 degrees C or didn't contain temperature data in the -- in the files.

09:42:52 Q. Can we go to PTX 3, please. I'm sorry. 103. Oh, I'm sorry. And it's on the screen as well, Mr. Kindig.

09:43:15 And counsel had asked you a number of questions about the -- some of the checked boxes on here including the verified transport conditions box.

09:43:26 A. Yes.

09:43:27 Q. Does anything on this first page of the Receiving

09:43:31 Inspection Report release the material from quarantine for
09:43:34 GMP use?
09:43:35 A. No, it does not.
09:43:36 Q. Are any of these check boxes being completed by a
09:43:40 member of the quality unit?
09:43:41 A. No, they are not.
09:43:43 Q. So, would a quality determination still need to be
09:43:46 made on the quarantined material even with boxes checked on
09:43:49 the first page?
09:43:49 A. Yes, the quality unit when they disposition material,
09:43:54 accounts for all of the information available in the -- in
09:43:57 the receiving file.
09:44:00 Q. Counsel also asked you --
09:44:01 THE COURT: Actually, Mr. Davies, before we go
09:44:03 on.
09:44:05 MR. DAVIES: Yes.
09:44:05 THE COURT: Mr. Kindig, are you -- is your job
09:44:11 in your position to say whether or not you think the two
09:44:16 conditions or the two check boxes that go with verify
09:44:19 transport conditions and verify temperature conditions,
09:44:24 assuming that these are ones where the shipping, you know,
09:44:31 was minus 50 degrees, are the boxes checked correctly?
09:44:36 THE WITNESS: I -- I would take those boxes
09:44:40 being checked to mean the person who received it verified
09:44:43 that it was cold and not necessarily that it meant that they

had gone through all the data at the time that they checked it.

THE COURT: All right. Thank you.

BY MR. DAVIES:

Q. In PTX 3, can we go to Bates number ending 8151.

And there's some emails here, some between LGM Pharma and itself others between LGM Pharma and Liquidia that counsel showed you.

A. Yeah.

Q. Does LGM Pharma make the determination of whether Liquidia can release Treprostinil sodium?

A. No, LGM Pharma does not make that decision.

Q. Does Liquidia rely in any way on LGM's determination on whether or not Treprostinil sodium can be shipped to Liquidia as to whether or not Liquidia can use it for GMP purposes?

A. We wouldn't relay on their determination. We would rely on information they provided us as part of the shipping paperwork like this.

Q. And with the two batches that had been ordered that experienced temperatures above 8 degrees Celsius that counsel told you how expensive they were, did Liquidia throw those batches in the trash?

A. No, they were put in into quarantine initially and have since been dispensed to R & D.

09:46:03 Q. And they will be used for R & D purposes?
09:46:04 A. Yeah, they're labeled for R & D use only.
09:46:07 Q. So Liquidia didn't waste half a million dollars on
09:46:10 those batches?
09:46:10 A. No, it's still material that could be used for
09:46:13 laboratory purposes or process development.
09:46:16 MR. DAVIES: No further questions.
09:46:17 THE COURT: All right. And I have one more
09:46:20 question, Mr. Kindig. And this may have been said, but is
09:46:25 it your understand that LGM is, essentially, a
09:46:27 representative of Yonsung, they are -- and so you're dealing
09:46:31 with them, so to speak, at arm's length?
09:46:34 THE WITNESS: It's my understanding that they're
09:46:36 the U.S.-based supplier that we order through to get things
09:46:42 from Yonsung. I don't know if that answers your question,
09:46:46 but that's how I understand its role.
09:46:48 THE COURT: Well, I guess what I'm wondering is
09:46:50 are they independent of Yonsung? Do you know?
09:46:55 THE WITNESS: I don't know exactly what the
09:46:56 relationship is. I just know that -- that I can't -- yeah,
09:47:00 we can order through them. We -- we can communicate with
09:47:03 them, and they get the material from Yonsung.
09:47:06 THE COURT: Okay. Anything further?
09:47:09 MR. DAVIES: Nothing further, Your Honor.
09:47:10 MR. JACKSON: No, Your Honor. Thank you.

09:47:11 THE COURT: All right. Mr. Kindig, thank you.
09:47:13 You may step down. Watch your step.
09:47:15 THE WITNESS: Okay. Thank you.
09:47:26 MR. MINN: Your Honor, you're about to hear
09:47:28 deposition from Mr. Hamilton Lenox. Mr. Lenox is a 30(b)(6)
09:47:33 witness and also senior vice-president of business
09:47:35 development at LGM Pharma. LGM Pharma is an administrative
09:47:40 intermediary between Yonsung and Liquidia. His testimony
09:47:42 relates to the shipment and storage of Treprostinil sodium
09:47:44 at LG.
09:47:47 THE COURT: All right. Thank you.
09:47:54 MR. DAVIES: We just have a few binders, Your
09:47:57 Honor.
09:47:57 THE COURT: All right.
09:48:04 MR. MINN: May I approach?
09:48:04 THE COURT: Yeah.
09:47:58 (Video playing.)
09:48:25 Q. Please state your full name for the record.
09:48:26 A. Hamilton J Lenox.
09:48:29 Q. How did you prepare for today's deposition?
09:48:30 A. I spent several hours, roughly six or seven,
09:48:33 reviewing the documentation. I also reviewed documentation
09:48:41 when we first received the subpoena and prepared all of the
09:48:44 documentation. And I had also reviewed it when we were
09:48:47 originally planning on the deposition, I believe, in

November.

Q. Who did you meet with in preparing for the deposition?

A. I met, briefly, with Jonathan Davies from Cooley.

Q. How did you decide what email searches to run?

A. With advice from our attorneys about what terms to use and what time periods that were applicable for the subpoena.

Q. And when you say your attorneys, which attorneys do you mean?

A. With Reed Smith as well as with Cooley.

Q. Did you meet with Reed Smith at all in preparing for this deposition?

A. I did not, no.

Q. You're currently employed by LGM; right?

A. Yes, I am.

Q. What's your current job position?

A. My title is senior vice president of business development and operations.

Q. What are your job responsibilities?

A. I manage our business development, marketing, purchasing, sourcing, logistics, and IT functional areas.

Q. LGM is required to handle Yonsung's Treprostinil sodium according to the storage specifications set by Yonsung; right?

09:50:20 A. Correct.
09:50:24 Q. LGM has no control over the contents of Yonsung's
09:50:29 DMF; is that right?
09:50:30 A. Correct.
09:50:34 Q. And you would agree that LGM is not in possession,
09:50:39 custody, or control of Yonsung's drug master file for
09:50:42 Treprostinil sodium; right?
09:50:42 A. Correct.
09:50:46 Q. And you would agree that LGM is not involved in the
09:50:52 development or administration of Liquidia's LIQ 861 drug
09:50:57 product; right?
09:50:58 THE WITNESS: Correct, we are not.
09:51:00 Q. LGM does not control Yonsung's manufacturing process
09:51:04 for Treprostinil sodium; right?
09:51:05 A. LGM has no involvement in the manufacturing process
09:51:11 by Yonsung. Correct.
09:51:14 Q. And LGM does not possess samples of intermediates
09:51:17 from the manufacturers of Yonsung's Treprostinil sodium
09:51:20 before Yonsung's final Treprostinil sodium product, right?
09:51:24 A. Correct. We -- to my knowledge, we have never
09:51:28 possessed intermediates for Yonsung's process and we were --
09:51:34 we did inquire about potential availability of intermediates
09:51:38 and were told that none were available.
09:51:41 Q. You mentioned that LGM had inquired to Yonsung about
09:51:46 potential availability of intermediates previously; right?

09:51:53 A. Yes.
09:51:55 Q. And you said that Yonsung indicated there were no
09:52:00 samples; correct?
09:52:01 A. Correct. Yes.
09:52:04 Q. If Treprostinil sodium intermediate samples were
09:52:08 available from Yonsung, Yonsung would have provided them to
09:52:11 LGM Pharma?
09:52:13 A. I believe so, yes.
09:52:16 Q. You said "typical storage conditions." Has LGM ever
09:52:22 stored Treprostinil sodium for Liquidia at any temperatures
09:52:25 other than between 2 to 8 degrees Celsius?
09:52:28 A. No, we have not. We always store per manufacturers'
09:52:32 storage conditions.
09:52:35 Q. Which are?
09:52:37 A. 2 to 8 degrees Celsius.
09:52:41 Q. Exhibit 4, Mr. Hamilton. What is this document?
09:52:45 A. This looks like storage -- or temperature and
09:52:49 humidity monitoring data from our warehouse in Kentucky for
09:52:53 our refrigerator.
09:52:58 Q. Exhibit 5. What is Exhibit 5?
09:53:00 A. This is additional temperature monitoring for our
09:53:06 refrigerator in our Erlanger, Kentucky, warehouse.
09:53:12 Q. Exhibit 6. And what is Exhibit 6?
09:53:16 A. This is an additional document I reviewed in
09:53:22 preparation, which is temperature monitoring data for our

refrigerator in our warehouse in Erlanger, Kentucky.

Q. Are you aware of any temperature excursions outside of 2 to 8 degrees C for the storage of Treprostinil sodium for Liquidia by LGM at any time?

A. I'm not aware of any temperature excursions while material, Treprostinil sodium API, was in storage at LGM's warehouse.

Q. Exhibit 7. What is LGM 000467 of Exhibit 7?

A. This is a file provided by LGM that shows, to my knowledge, all shipments of Treprostinil sodium API from Yonsung to Liquidia purchased by LGM.

Q. Looking at this document, are you able to identify the last shipment of Treprostinil sodium that was actually received by LGM prior to shipment to Liquidia?

A. Yes, I am.

Q. And what is that -- what are the -- what is that shipment on this document?

A. I believe those are the materials received on December 8th, 2020, that would have been received by LGM and shipped to Liquidia.

It looks like the 6th of January, 2021.

Q. And what were the lot numbers of the Treprostinil sodium that were received in this last shipment?

A. They are TN120C010, TN120G010, TN120I010.

Q. In your preparation for today, did you review any

09:55:53 materials indicating temperature excursions above 8 degrees
09:56:02 Celsius during shipment of Treprostinil sodium from Yonsung
09:56:04 to LGM?
09:56:08 A. Yes, I did.
09:56:18 Q. Do you recall whether the shipment that experienced
09:56:23 that excursion was the last shipment that was received by
09:56:27 LGM from Yonsung?
09:56:30 A. I believe it was, yes.
09:56:35 Q. What lots do you believe were involved in that
09:56:38 shipment?
09:56:39 A. If it was the last shipment that we received, it
09:56:42 would have been the three lots that I originally read out a
09:56:47 few moments ago.
09:56:49 Q. Did LGM provide the lots of Treprostinil sodium to
09:56:59 Liquidia after recognizing there had been a temperature
09:57:04 excursion above 8 degrees during shipment for those batches?
09:57:08 A. We informed Liquidia there had been a temperature
09:57:14 excursion during shipment, and then we did provide that
09:57:18 material to Liquidia, yes.
09:57:22 Q. What determination did LGM make prior to providing
09:57:27 those batches that experienced a temperature excursion to
09:57:32 Liquidia prior to shipment to Liquidia?
09:57:34 A. LGM determined that the material met specifications
09:57:40 for sale to Liquidia and that Liquidia would have the
09:57:46 opportunity to analyze and reject or accept the material.

09:57:51 Q. How was LGM aware that there had been a temperature
09:57:56 excursion during shipment of these last three batches
09:58:01 provided to Liquidia?
09:58:02 A. A data logger had been included within the shipment
09:58:06 by Yonsung. And upon looking at that data, it was indicated
09:58:11 that there had been a temperature excursion.
09:58:15 Q. What is a data logger?
09:58:15 A. A data logger is typically used with cold-chain or
09:58:21 other sensitive shipments, and it can record temperature or
09:58:24 humidity conditions throughout the shipping process.
09:58:29 Q. Do you have any understanding as to future shipments
09:58:36 of Treprostinil sodium for Liquidia, whether data loggers
09:58:40 would be included in the shipments?
09:58:44 A. Yes. Liquidia has requested that data loggers be
09:58:47 included with all shipments of Treprostinil sodium API from
09:58:50 Yonsung, as well as from LGM.
09:58:56 Q. Are you aware of any temperature excursions above or
09:59:00 below 2 to 8 degrees that occurred during storage of
09:59:04 Treprostinil sodium at LGM in the refrigerator?
09:59:07 A. No, I am not.
09:59:10 (Conclusion of video.)
09:59:17 MR. MINN: Again, we would like to move DTX 103,
09:59:23 DTX 104, DTX 105, and DTX 99 into evidence. Thank you.
09:59:31 MR. JACKSON: No objection, Your Honor.
09:59:33 THE COURT: All right. They're admitted without

objection.

(DTX Exhibit Nos. 103, 104, 105 and 99 were admitted into evidence.)

THE COURT: All right. Let's take a morning break of about ten minutes.

DEPUTY CLERK: All rise.

(Recess was taken.)

DEPUTY CLERK: All rise.

THE COURT: All right. Let's be seated. And go ahead, Mr. Pivovar.

MR. PIVOVAR: Thank you, Your Honor. Liquidia calls Mr. John Fuson. Mr. Fuson is a lawyer who practices in FDA regulatory enforcement. Has experience with FDA investigatory matters.

DEPUTY CLERK: Please state an spell your full name for the record.

THE WITNESS: My name is John Fuson. J-O-H-N -- excuse me -- F as in Frank U-S-O-N.

DEPUTY CLERK: Do you affirm that the testimony you are about to give to the Court in the case now pending will be the truth, the whole truth, and nothing but the truth, you do so affirm?

THE WITNESS: Yes, I do.

DEPUTY CLERK: Thank you. Make sure you speak in the microphone.

10:11:25 THE WITNESS: Thank you.

10:11:27 WITNESS, the witness herein, after having been duly sworn under oath, was examined and testified as follows:

10:11:29 DIRECT EXAMINATION

10:11:29 BY MR. PIVOVAR:

10:11:30 Q. Good morning, Mr. Fuson. Can you please state your full name for the record.

10:11:32 A. John Fuson.

10:11:34 Q. And where are you currently employed?

10:11:36 A. I'm a partner at Crowell & Moring in Washington, D.C.

10:11:41 Q. And what is the focus of your practice?

10:11:42 A. I have an FDA regulatory practice. I counsel pharmaceutical, medical device, food manufacturers on compliance requirements under Federal Food, Drug, and Cosmetic Act.

10:11:54 Q. And other than your current law practice, do you have any other experience relevant to FDA regulatory and compliance requirements?

10:12:00 A. Yes, prior to joining Crowell & Moring, I was in the office of chief counsel at the U.S. Food and Drug administration as an associate chief counsel for enforcement.

10:12:09 Q. And can you please briefly describe to the judge some of the experiences that you had while you worked at the FDA

and what your responsibilities were.

A. Sure. It was -- it was my responsibility to counsel the agency on enforcement actions that it was contemplating. I worked with investigators and agency compliance officers during inspections as they were evaluating what regulatory actions to take in response to evidence of noncompliance.

Q. Now, can you please turn to DTX 723 in your binder, Mr. Fuson?

A. Yes.

Q. Now, is that a copy of your CV?

A. Yes, it is.

MR. PIVOVAR: Your Honor, I'd like to offer DTX 723 into evidence.

MR. BURROWBRIDGE: No objection.

MR. PIVOVAR: Your Honor, we offer Mr. Fuson as an expert in FDA regulatory and compliance requirements and procedures, including good manufacturing practices or GMP obligations associated with FDA regulatory -- regulated drug products.

MR. BURROWBRIDGE: No objections, Your Honor.

THE COURT: All right. You may proceed.

(DTX Exhibit No. 723 was admitted into evidence.)

BY MR. PIVOVAR:

Q. Mr. Fuson, you've been asked to respond to

Mr. Matto's opinions in this case; correct?

A. That's correct.

Q. Did you hear Mr. Matto's opinion about how the FDA would view a temperature excursion of Treprostinil sodium above 8 degrees Celsius?

A. Yes, I heard Mr. Matto testify that he would not object to -- the FDA would not object to a temperature storage at 25 degrees Celsius.

Q. And do you agree with his opinion?

A. No, I do not.

Q. Why not?

A. Because Liquidia has a raw materials specification for the storage of Treprostinil sodium that's set for 2 to 8 degrees Celsius, and the FDA would expect Liquidia to follow that raw materials specification.

Q. Can you please turn to DTX 615 in your binder or probably up on the screen here shortly.

And what is shown on DTX 615, Mr. Fuson?

A. This is a section of the good manufacturing practice regulations that are applicable to drug manufacturers in part 211.

Q. What is specifically written in Section 211.80(a) that is relevant to your opinions here?

A. It says here that the drug manufacturers shall have written specifications and procedures for the storage of

10:14:34 handling materials and that, most importantly, that those
10:14:39 written procedures shall be followed.
10:14:41 Q. So, how does this requirement in this one part of the
10:14:45 FDA regulations apply to Liquidia's obligations for the
10:14:51 storage conditions of Treprostinil sodium?
10:14:53 A. So, they have a written specification for
10:14:57 Treprostinil sodium of 2 to 8 degrees Celsius and -- as
10:15:01 required by this regulation, and they have to follow that,
10:15:04 that procedure.
10:15:05 Q. Now, in your review of all of the materials that are
10:15:08 associated with Liquidia's LIQ861 product, is there anything
10:15:15 in those materials that would indicate to you that the FDA
10:15:18 approved Liquidia to use Treprostinil sodium when it's
10:15:21 stored at ambient temperature?
10:15:22 A. No. I don't think they'd even contemplated that
10:15:27 storage. They made no determination.
10:15:28 Q. Right. And what does the specification say about the
10:15:32 storage conditions for Treprostinil sodium?
10:15:33 A. It says that it shall be stored at 2 to 8 degrees
10:15:38 Celsius, and I think protected from light and moisture.
10:15:43 Q. So, is it fair to say that the FDA is going to expect
10:15:45 that the Treprostinil sodium is going to be stored at 2 to 8
10:15:48 degrees Celsius?
10:15:49 A. That would certainly be FDA's expectation.
10:15:51 Q. And when the FDA would be reviewing a violation or a

10:15:54 potential violation -- let me strike that. Start over?

10:15:56 When the FDA is reviewing Liquidia's compliance
10:15:59 with the specification, would it expect that Treprostinil
10:16:03 sodium would be stored between 2 and 8 degrees Celsius?
10:16:06 A. Yes, that would be its expectation.
10:16:08 Q. Did you review any documentation from the FDA on
10:16:12 Liquidia's compliance with the storage obligations as part
10:16:16 of Liquidia's tentative approval by the FDA for LIQ861?
10:16:20 A. Yes, I reviewed the establishment inspection report
10:16:25 that FDA prepared after its pre-approval inspection of
10:16:28 FDA -- or excuse me of Liquidia's manufacturing facility.
10:16:31 Q. All right. Can you please bring up DTX 407.

10:16:34 And is this the FDA establishment inspection
10:16:42 report that you reviewed?
10:16:44 A. Yes, this is the establishment inspection report that
10:16:46 FDA prepared after the pre-approval inspection they
10:16:50 conducted between August 9th and August 13th, 2021.
10:16:54 Q. All right. Can we go to the description of the
10:16:57 manufacturing operation section on Page 3 of this report,
10:17:01 please. Can you please blow it up, the lower part.

10:17:06 Now, how did the FDA confirm Liquidia's
10:17:10 compliance with the storage conditions of 2 to 8 degrees
10:17:14 Celsius protected from light an moisture as set forth in the
10:17:17 specification?
10:17:17 A. Well, so as part of a pre-approval inspection, FDA

would have conducted a walk-through of Liquidia's manufacturing facility. It's notable here that as part of that walk-through, they looked specifically at the refrigeration equipment and noted that the API was stored in a 6-degree Celsius refrigerator.

Q. Right. And they did that could to confirm that Liquidia was complying with the storage requirements and the specification for the drug lot; right?

A. Right. Right. They would have looked at the raw material specification, in preparation for this inspection noted that it was supposed to be stored at 2 to 8 degrees, and they're confirming that in the course of their inspection -- specifically noting that in their inspection report.

MR. PIVOVAR: Your Honor, I would like to move DTX 407 into evidence.

MR. BURROWBRIDGE: No objection.

THE COURT: Admitted without objection.

(DTX Exhibit No. 407 admitted into evidence.)

BY MR. PIVOVAR:

Q. Now, Mr. Fuson, you're familiar with the two Yonsung Treprostinil sodium lots that experienced this temperature excursion during shipping above 8 degrees Celsius that had been talked about in this trial right?

A. Yes, I am.

10:18:18 Q. Now, from an FDA regulatory perspective, can Liquidia
10:18:23 use the Treprostinil sodium lots from Yonsung shipped by LGM
10:18:29 that expose the ambient -- or 16 degrees Celsius
10:18:32 temperature?
10:18:32 A. No, it cannot.
10:18:33 Q. Okay. What would they have to do before they could
10:18:37 use those materials in GMP processing?
10:18:40 A. So in order to use materials that experience an
10:18:43 out-of-specification event, they would need to conduct an
10:18:45 investigation. Liquidia would need to conduct an
10:18:47 investigation into that out-of-specification event. They
10:18:53 would need to marshal evidence sufficient to show that the
10:18:56 out-of-specification event would not negatively impact the
10:19:00 safety, the purity, and the potency of Liquidia's finished
10:19:03 drug product.
10:19:04 Q. From a compliance risk standpoint, what is Liquidia's
10:19:08 safest option in what it can do with the materials that
10:19:11 experience a temperature excursion about above 8 degrees
10:19:14 Celsius?
10:19:14 A. It simply does not use the raw material.
10:19:16 Q. And if they did not use the raw material in GMP
10:19:19 manufacturing, then they wouldn't have the same exposure
10:19:21 that they would have under the FDA risk for compliance;
10:19:26 right?
10:19:27 A. That's right. They would not have to do an

10:19:29 investigation. They wouldn't need to justify to FDA why
10:19:32 they were using material that was out of specification.
10:19:35 Q. Okay. Now, Mr. Fuson, you heard Mr. Matto's
10:19:38 testimony asserting that Treprostinil sodium is stable at
10:19:41 ambient temperatures; right?
10:19:43 A. I did. Yes.
10:19:44 Q. All right. And do you agree with Mr. Matto that the
10:19:47 stability data that he's relying upon is sufficient from an
10:19:50 FDA regulatory perspective for Liquidia to use the
10:19:54 Treprostinil sodium that experienced the temperature
10:19:56 excursions without any ramifications?
10:19:58 A. No, I certainly do not.
10:20:01 Q. And can you explain why Mr. Matto -- the data that
10:20:03 Mr. Matto's relying on would not be sufficient from a
10:20:07 regulatory standpoint to justify its use without further
10:20:11 testing?
10:20:11 A. Sure. So, again, the raw material specification was
10:20:15 2 to 8 degrees. That has significance. FDA expects them to
10:20:19 follow. What they would need to -- you know, the kind of
10:20:22 evidence that they would need -- the problem, I guess, with
10:20:25 the 25-degree stability study is that it's a single
10:20:30 temperature, does not cover the entire range of ambient
10:20:33 temperature.
10:20:34 More importantly, though, what Liquidia needs to
10:20:37 demonstrate is that the finished drug product that they're

10:20:41 manufacturing is not going to be impacted by the
10:20:44 out-of-specification event. And the stability study on the
10:20:48 API doesn't speak to that finished drug product.
10:20:54 Q. Mr. Fuson, can we bring up Page 29 of DTX 232. And I
10:21:01 believe this is the same exhibit as PTX 103. Or 109.
10:21:06 Sorry. Let's go to your binder DTX 232.
10:21:09 Go to page 29.
10:21:15 Were you here when Mr. Kindig testified as to
10:21:19 this declaration earlier today?
10:21:20 A. Yes, I was.
10:21:21 Q. Okay. And what is this declaration?
10:21:26 Like, how would you interpret this from an FDA
10:21:29 regulatory perspective, the impact of this declaration on
10:21:33 what Liquidia can do with materials that experience a
10:21:36 temperature excursion below 2 degrees Celsius?
10:21:39 A. Well, this declaration says that Yonsung, the
10:21:45 manufacturer of the API, is guaranteeing the stability of
10:21:49 its product when it's held at a freezing condition. And so,
10:21:54 you know, this would be -- could be part of, -- you know,
10:21:58 from a regulatory standpoint, could be part of Liquidia's
10:22:01 investigation justifying the use of -- of API that
10:22:05 experienced that temperature excursion.
10:22:08 Q. Right. And in your opinion, have you ever been made
10:22:12 aware of any similar declaration from Yonsung guaranteeing
10:22:16 the quality of Treprostinil sodium above 8 degrees Celsius?

10:22:20 A. No, I'm not aware.
10:22:21 Q. And as between the risk that Liquidia would have
10:22:25 based on the information that you are aware of, is the risk
10:22:28 of them using Treprostinil sodium that's experienced an
10:22:32 excursion above 8 degrees Celsius greater than the risk of
10:22:36 using Treprostinil sodium that's experienced a temperature
10:22:40 excursion below 2 degrees Celsius?
10:22:42 A. Well, from a regulatory standpoint, again, it would
10:22:46 depend, ultimately, on that investigation, but that is
10:22:49 compelling for that investigation. There are other
10:22:51 components that Liquidia needs to consider, which is, you
10:22:54 know, of course, if they do use something that's out of
10:22:56 specification, whether the finished drug product will keep
10:22:59 stability throughout the shelf life, and they don't have
10:23:02 that protection for anything above 8 degrees.
10:23:05 Q. Thank you, Mr. Fuson. I have no further questions at
10:23:08 this time.
10:23:08 THE COURT: All right. Mr. Burrowbridge.

10:23:17 CROSS-EXAMINATION

10:23:18 BY MR. BURROWBRIDGE:
10:23:18 Q. Good morning, Mr. Fuson.
10:23:40 A. Good morning.
10:23:47 Q. Let's look at PTX 30, which is the report you
10:23:50 submitted in this case. And if you could, please, pull up
10:24:01 paragraph 19 of the report.

10:24:03 A. I don't think I have a hard copy of it here, but --
10:24:19 MR. BURROWBRIDGE: May I approach the witness?
10:24:21 THE COURT: Yes.
10:24:31 THE WITNESS: PTX 30, you said?
10:24:31 BY MR. BURROWBRIDGE:
10:24:34 Q. Yes, sir.
10:24:34 Let me know when you're ready.
10:24:40 A. And paragraph 19?
10:24:42 Q. Yes, sir.
10:24:43 A. Yes, I'm there.
10:24:47 Q. You would agree that regulations do not prohibit the
10:24:51 use of out-of-specification drug substance in GMP controlled
10:24:56 manufacturing; correct?
10:24:56 A. That is correct. They -- they do not prohibit its
10:25:01 use so long as you've justified the out of specification.
10:25:05 Q. And if we can look at paragraph 21, please. And in
10:25:26 this -- this is -- these are your words; correct? From your
10:25:29 report?
10:25:30 A. Yes.
10:25:30 Q. Paragraph 21?
10:25:31 A. Mm-hmm.
10:25:32 Q. And you were analyzing 21 CFR Section 211.87;
10:25:39 correct?
10:25:39 A. Yes.
10:25:40 Q. And here, isn't it true that if a manufacturer

10:25:45 chooses to attempt to introduce and use an
10:25:48 out-of-specification drug substance that GMP controlled
10:25:53 manufacturing, it must retest or re-examine as appropriate
10:25:56 for identity, strength, quality, and purity any API exposed
10:26:01 to temperatures that might adversely affect the drug
10:26:04 substance?
10:26:06 A. Yes.
10:26:08 Q. And so, you would agree that in order for a drug
10:26:13 substance to be in spec, it must test within the
10:26:17 specification's criteria; correct?
10:26:19 A. It must confirm that the specifications for the
10:26:27 product have been met, yes.
10:26:29 Q. But specifically, the criteria must be testable;
10:26:33 correct?
10:26:33 A. So, you know, by "testable," it needs to be
10:26:38 monitoring or controlling for the specification. So, that
10:26:43 could be a laboratory test that they would do on
10:26:45 specification, make sure it doesn't have an impurity in the
10:26:48 product that's not specified. But if they're -- you know,
10:26:52 they have other controls, those would include temperature
10:26:56 monitors, to make sure a product is staying within other
10:26:59 specifications like a temperature specification. I would
10:27:01 consider a data logger monitoring a temperature to be a
10:27:07 control, a test, of that specification.
10:27:11 Q. But you would agree that you can't retest

temperature; correct?

In other words -- go ahead.

A. You can review the data. Yes.

Q. You can review the data. But for example, if a company were to ship a lot of a drug substance in 2001, say December in 2001 --

A. Mm-hmm.

Q. -- there's no way to retest the temperature at the time that that shipment was shipped; correct?

A. You can't retest the temperature, right. That's a fact that existed in the past. You can evaluate the product and do other examination of the product that may involve testing to determine whether it's sufficiently stable or is going to negatively impact the finished drug product.

Q. And you said negatively impact. And that relates to your opinion in your report; correct? So the testing is to see if the exposure of temperatures might adversely affect the drug substance; correct?

A. That is correct. You're trying to confirm whether the adverse -- or excuse me -- the out-of-specification event is negatively impacting the finished drug product.

Q. And you were in the courtroom this morning when Mr. Kindig testified; correct?

A. I was, yes.

Q. And he testified that Liquidia's raw material

10:28:16 specification was based on the label; correct?
10:28:20 A. I -- I honestly don't remember specifically whether
10:28:26 he referred to the label. I know that they rely on the
10:28:28 label. I know that the drug master file speaks to the
10:28:31 temperature range.
10:28:33 Q. What in the drug master file speaks to the
10:28:36 temperature range?
10:28:37 A. I believe it's specified in the drug master file.
10:28:40 I'd have to go back and look at the exact documents.
10:28:43 Q. As you sit here today, you don't know what in the
10:28:46 drug master file refers specifically to temperature?
10:28:49 A. It's a 600-page document. I don't know --
10:28:51 Q. You don't know?
10:28:52 A. -- exactly.
10:28:53 Q. Okay. If we can look at PTX 19; again. That's still
10:29:19 your report?
10:29:19 A. Okay.
10:29:20 Q. Your analysis -- as you explained in court and
10:29:22 confirmed by your report, your analysis focuses on
10:29:26 Liquidia's raw material specification; correct?
10:29:28 A. That's correct. Yes.
10:29:31 Q. It does not focus on Yonsung's specification;
10:29:33 correct?
10:29:33 A. Liquidia's responsible for -- yes. It is Liquidia's
10:29:39 raw material specification because Liquidia is the entity

responsible for its finished drug product.

Q. I just want to make sure we're clear. So your analysis focuses on Liquidia's raw material specification; correct?

A. So, the analysis of what Liquidia is obligated to do, what procedure it's supposed to follow, yes, that's based on Liquidia's raw materials specification. Liquidia has the control to write that specification.

Q. And that is the focus of your analysis; correct?

A. That is correct, on that question.

Q. Have you looked the at Yonsung specification?

A. I'm not sure exactly what you mean now by "Yonsung specification," but I've looked at the label and other documents where Yonsung has referred to the 2-to-8-degree Celsius recommendation.

Q. So let's go back to Liquidia's raw materials specification. Okay?

A. Okay.

Q. You agree that Liquidia's raw materials specification has no testing requirement for storage conditions; correct?

A. Liquidia's raw materials specification indicates a storage condition of 2 to 8 degrees Celsius protected from light and moisture. And in the handling procedure, I believe it directs the quality unit to review the documentation relevant to the material. So, you know,

10:31:20 through the -- through the raw material specification and its handling procedure, it is controlling for the temperature of the product.

10:31:30 Q. I understand your testimony, and I appreciate it. Thank you.

10:31:33 But my question is: You agree that there's no testing required for storage conditions in Liquidia's raw material specification; correct?

10:31:42 A. So, again, we're, I guess, discussing a little bit about the meaning of "testing" here. I mean, the testing is the data monitor, the controls that they have to ensure that the raw material specification is met.

10:31:58 Q. You remember being deposed in this case; correct?

10:32:00 A. Yes, I do.

10:32:02 Q. Can we pull up Mr. Fuson's deposition, Page 42 and 43.

10:32:08 So, if we look at Page 42 of your deposition, just to give you context. I'm going to end up on Page 43, but just to make sure has we're clear, on lines 24 and 25, the questioning was about Liquidia's raw materials specification; correct?

10:32:26 A. Yes.

10:32:33 Q. And please feel free to read it at your leisure. I'm going to be asking you about Page 43, lines 10 through 14.

10:32:45 You were asked, "Now, you agree that there's no

testing required for storage conditions; correct?" And that's the question I just asked you in open court.

Your answer during your sworn deposition was that "So on Page 2 of the document that lists testing -- tests that are required, there is no test for storage temperature."

That was your testimony; correct?

A. Right. So I think if we look at the raw materials specification, there is a subsequent page after the -- the first page, I believe, lists the raw -- lists the storage conditions. On the second page, I believe there are a series of tests that specify the various impurities, probably, is what they're looking for or other conditions. I don't -- I don't know all the -- the tests without seeing the document, but there are a series of tests there that are to be conducted.

It is true that there is no test on that list that goes to the storage condition, but that doesn't mean that -- that Liquidia isn't controlling for temperature.

Q. And when you say "storage condition" in your answer right now, you mean the storage temperature; correct?

A. Well, the storage -- the specification refers to 2 to 8 degrees Celsius, yes, and it also refers to protecting from light and moisture.

Q. I'm just confirming that you stand by your testimony

10:34:06 from your deposition; correct?

10:34:07 In your deposition you said that there is no
10:34:09 test for storage temperature, and I'm trying to understand.
10:34:12 That's still your testimony; correct?

10:34:14 A. So, right. But my answer said on Page 2 of the
10:34:19 document that lists the test that I was just describing --
10:34:22 again, I don't remember the exact parameters that were being
10:34:26 tested for there. On that page of the document, there is
10:34:29 not a test listed for storage temperature. But the storage
10:34:36 specification is still set forth on the front page of the
10:34:38 document.

10:34:53 Q. So we'd agree that there's other testing -- - -
10:34:57 there's other testing in the document in the Liquidia raw
10:35:00 material specification; right? You mentioned impurity
10:35:02 testing?

10:35:03 A. Yes. I believe -- again, I don't recall exactly, but
10:35:06 I know that there are a series of -- my recollection is that
10:35:10 there are a series of other specifications on the -- on the
10:35:15 second page of the document, but I -- I don't recall exactly
10:35:18 what they are.

10:35:18 Q. And impurity testing is something that you can test
10:35:21 and retest; right?

10:35:21 A. Yes, it is.

10:35:22 Q. If we look at Page 42 at the top, lines 3 through 5,
10:35:32 you state, "I don't know that the temperature can be tested

10:35:34 and retested, but I don't accept that's the only definition
10:35:39 of out of spec"; correct?
10:35:40 A. That's correct yes.
10:35:41 Q. So, again, you agree with this testimony; correct?
10:35:44 A. I -- I agree that you can't retest temperature that
10:35:47 occurred in the past.
10:35:53 Q. So again, you've looked at Liquidia's raw materials
10:37:02 specification; correct?
10:37:03 A. Yes, I have.
10:37:04 Q. And the specification controlling the Liquidia
10:37:07 Yonsung relationship, though, is a Yonsung specification;
10:37:11 correct?
10:37:11 A. I'm sorry. Can you repeat that question.
10:37:15 Q. There's an API supply agreement between Yonsung and
10:37:19 Liquidia; correct?
10:37:20 A. Yes.
10:37:21 Q. And it's the Yonsung specification that controls that
10:37:25 API supply agreement; correct?
10:37:27 A. No, I -- well, I -- I don't recall specifically.
10:37:35 Q. Can you pull up PTX 115. Section 2.2.
10:37:47 2.2. So this is the API supply agreement. Do
10:38:07 you agree?
10:38:08 A. I -- that's what the front page of the document says,
10:38:12 yes.
10:38:13 Q. And this is referring to the specification that's the

10:38:17 controlling specification between Yonsung and Liquidia;
10:38:21 correct?
10:38:21 A. Yes.
10:38:23 Q. Okay. Can we go to Exhibit B, please, on Page 21 and
10:38:27 22.
10:38:29 This is Yonsung's specification; correct?
10:38:42 A. Yes.
10:38:47 Q. This is not Liquidia's material raw specification;
10:38:50 correct?
10:38:50 A. This is Yonsung's document it appears, yes.
10:38:55 Q. And there's no -- no mention of storage temperatures
10:38:58 on this document; correct?
10:39:06 MR. PIVOVAR: Your Honor, I'm sorry. I've been
10:39:09 looking through the binder that we have from Mr. Fuson, and
10:39:11 I don't find this 115 in here, and I don't know if he has
10:39:15 it, so I just want to confirm that he has access to answer
10:39:18 that question.
10:39:20 THE WITNESS: I was just reading it up there.
10:39:22 MR. BURROWBRIDGE: That's fine.
10:39:23 THE WITNESS: And I don't know if it's here or
10:39:26 not. So, I can read that one without my glasses. I need my
10:39:29 glasses over here.
10:39:30 I do not see -- there's not a temperature
10:39:34 specification on that document. No.
10:39:36 BY MR. BURROWBRIDGE:

10:39:36 Q. And you're aware that the Yonsung specification is
10:39:38 the specification in the DMF; correct?
10:39:41 A. Yes.
10:39:47 Q. And when I say the DMF, I mean Yonsung's DMF that is
10:39:50 incorporated into Liquidia's NDA; correct?
10:39:52 A. It is -- right. The Liquidia NDA incorporates by
10:40:00 reference the drug master file.
10:40:02 Q. Can you please pull up PTX 2020.
10:40:11 A. I'm sorry. You said PTX 2020?
10:40:14 Q. Yes, please. It's Page 469 of the PDF.
10:40:19 A. I don't have that one in this document here.
10:40:21 Q. Can you see it on the screen?
10:40:27 A. Yes.
10:40:35 Q. This is an email from LGM Pharma, correct, Mr. Robert
10:40:39 Hoppes?
10:40:40 A. Yeah, yes, it is an email.
10:40:44 Q. And this email was sent on November 14th, 2019;
10:40:48 correct?
10:40:48 A. Yes, that's the date.
10:40:50 Q. And this email is to Dana Paris at Liquidia; correct?
10:40:53 A. It's to Brad Weitkamp, but Dana Paris is cc'd.
10:41:00 Q. Understood. Thank you for that correction.
10:41:07 This email is Robert Hoppes sending an email
10:41:09 saying Yonsung informed me that currently we do not have
10:41:11 stability testing or stability data for Treprostinil sodium

10:41:14 at freezing temperatures, more specifically, below plus-2
10:41:19 degrees Celsius; correct?
10:41:22 A. Yes, it says that.
10:41:23 Q. And in your direct testimony, you referred to a
10:41:27 declaration from Yonsung; correct?
10:41:28 A. Yes, I did.
10:41:30 Q. And that declaration was essentially Yonsung
10:41:34 guaranteeing the quality of the drug product, and the
10:41:38 Treprostinil sodium API used to formulate the drug product,
10:41:41 below 2 degrees; correct?
10:41:44 A. I believe that's what that declaration says, yes.
10:41:45 Q. And even at freezing conditions; correct?
10:41:47 A. Yes.
10:41:50 Q. And this email confirms that there was no stability
10:41:53 data to support that declaration; correct?
10:41:55 A. That's what this email says, yes.
10:41:59 Q. But you have seen stability data that confirms the
10:42:04 stability of Treprostinil at ambient temperature; correct?
10:42:07 A. Yes, I have.
10:42:09 Q. And when you use the word "ambient temperature" in
10:42:11 this case, what -- what definition did you apply?
10:42:14 A. I believe the Court's applying 15 to 30 degrees.
10:42:21 MR. BURROWBRIDGE: Pass the witness.
10:42:38 Can I please move into evidence PTX 2020 and PTX
10:42:44 115.

10:42:45 MR. PIVOVAR: No objection, Your Honor.
10:42:46 THE COURT: All right. Admitted without
10:42:48 objection.
10:42:48 (PTX Exhibit Nos. 115 and 2020 were admitted
10:42:48 into evidence.)
10:42:50 REDIRECT EXAMINATION
10:42:50 BY MR. PIVOVAR:
10:42:50 Q. Can we please bring up DTX 106.
10:42:53 Mr. Fuson, you were just asked by opposing
10:42:58 counsel some questions about the Yonsung drug master file.
10:43:02 Do you recall that?
10:43:02 A. Yes I was.
10:43:04 Q. And you reviewed parts of the Yonsung drug master
10:43:07 file in rendering your opinions in this case; right?
10:43:09 A. Yes, I did.
10:43:10 Q. Okay. So what is DTX 106 that's shown on the screen
10:43:14 here? Is this the drug master file that you reviewed?
10:43:17 A. This is the drug master file that Yonsung submitted
10:43:20 to the FDA.
10:43:21 MR. PIVOVAR: Your Honor, we would like to enter
10:43:23 DTX 106 into the record.
10:43:25 MR. BURROWBRIDGE: No objection.
10:43:28 THE COURT: So --
10:43:30 MR. PIVOVAR: Can we please go to --
10:43:31 THE COURT: Wait. Wait. The drug master file,

10:43:33 isn't that, like, thousands and thousands of pages?
10:43:36 MR. PIVOVAR: This particular document, Your
10:43:39 Honor, and I apologize, it is exactly 624 pages.
10:43:43 THE COURT: All right. Well, I'm going to ask
10:43:45 that -- I mean, I'll admit it into the record, but which
10:43:52 exact pages we're admitting into the record is something
10:43:56 that I want the parties to resolve. I don't want 600 pages,
10:43:58 and I'm guessing maybe Yonsung doesn't.
10:44:03 MR. PIVOVAR: So why don't we do that. We'll
10:44:05 withdraw that, and I will go to a page --
10:44:07 MR. SUKDUANG: Your Honor, what we'll do at the
10:44:09 end of trial is I'm sure parties have used certain pages of
10:44:12 these massive documents. We'll create a DTX 106A, 106B,
10:44:18 106C, and correlate that with the record so we --
10:44:21 MR. BURROWBRIDGE: We're happy to meet and
10:44:22 confer.
10:44:24 THE COURT: Well, you'll figure it out.
10:44:25 MR. PIVOVAR: Thank you.
10:44:26 BY MR. PIVOVAR:
10:44:27 Q. Can you please go to Page 517 in this document.
10:44:29 Now, Mr. Fuson, do you see on this page there is
10:44:36 the label that Yonsung has for Treprostinil sodium?
10:44:39 A. Yes.
10:44:40 Q. And is this the label that you were referring to that
10:44:43 is incorporated into the NDA?

10:44:44 A. Yes, this is the shipping label.
10:44:46 Q. And what does the Yonsung label say about the storage
10:44:49 condition?
10:44:50 A. It says storage should be kept in a tight container
10:44:55 protected from moisture and light and stored at 2 to 8
10:44:58 Celsius.
10:44:58 Q. And would the FDA expect that Yonsung would be
10:45:01 following the specification for storage conditions in its
10:45:03 label?
10:45:03 A. Yes.
10:45:06 MR. PIVOVAR: No further questions, Your Honor.
10:45:07 THE COURT: All right.
10:45:09 MR. BURROWBRIDGE: One further question.
10:45:10 THE COURT: Mr. Burrowbridge.
10:45:12 MR. BURROWBRIDGE: Thank you, Your Honor.
10:45:12 RECROSS-EXAMINATION
10:45:13 BY MR. BURROWBRIDGE:
10:45:13 Q. Mr. Fuson, this says should be kept in a tight
10:45:17 container protected from moisture and light and stored at 2
10:45:20 to 8 degrees; correct?
10:45:21 A. Yes, it does.
10:45:23 Q. It does not say must be stored at 2 degrees to 8
10:45:28 degrees Celsius; correct?
10:45:29 A. That is correct.
10:45:31 MR. BURROWBRIDGE: Thank you.

10:45:32 THE COURT: All right. Mr. Fuson, thank you.
10:45:34 You may step down. Watch your step.
10:45:37 THE WITNESS: Thank you very much.
10:45:47 MS. KANNAPPAN: Deepa Kannappan for the record.
10:45:48 Your Honor, Plaintiff calls Dr. Jeffrey Winkler.
10:45:50 THE COURT: All right.
10:45:59 MS. KANNAPPAN: Dr. Winkler is a professor of
10:46:00 chemistry at the University of Pennsylvania, and at this
10:46:03 time, he's going to address both non-infringement and
10:46:06 invalidity of the '066 patent back to back, Your Honor.
10:46:10 MR. SUKDUANG: I'm sorry. May I approach?
10:46:11 THE COURT: Yes, sure.
10:46:14 DEPUTY CLERK: Please state and spell your full
10:46:16 name for the record.
10:46:17 THE WITNESS: Jeffrey David Winkler,
10:46:19 J-E-F-F-R-E-Y D-A-V-I-D W-I-N-K-L-E-R.
10:46:26 DEPUTY CLERK: Do you affirm that the testimony
10:46:28 you are about to give to the Court in the case now pending
10:46:31 will be the truth, the whole truth, and nothing but the
10:46:33 truth, you do so affirm?
10:46:34 THE WITNESS: I do.
10:46:34 JEFFREY WINKLER, the witness herein, after
10:46:34 having been duly sworn under oath, was examined and
10:46:36 testified as follows:
10:46:36 DEPUTY CLERK: Dr. Winkler, speak into the

microphone, please.

THE WITNESS: Thank you.

DEPUTY CLERK: Thank you.

DIRECT EXAMINATION

BY MS. KANNAPPAN:

Q. Good morning, Dr. Winkler.

A. Good morning.

Q. Please state your full name for the record.

A. Jeffrey David Winkler.

Q. Where are you currently employed?

A. I'm currently employed at the University of Pennsylvania.

Q. And what is your job title there?

A. I'm the Merriam Professor of Chemistry and undergraduate chair of the chemistry department.

Q. And how long have you been a chemistry professor at U Penn?

A. Since 1990.

Q. Do you have a CV, Dr. Winkler?

A. I do.

Q. Let's turn to DTX 720.

Is this your CV?

A. Yes, it is.

MS. KANNAPPAN: Your Honor, I'd like to offer DTX 720 into evidence.

10:47:39 MR. CARSTEN: No objection, Your Honor.
10:47:40 THE COURT: Admitted without objection.
10:47:40 (DTX Exhibit No. 720 was admitted into evidence.)
10:47:40 BY MS. KANNAPPAN:
10:47:41 Q. Dr. Winkler, would you please briefly describe the classes you teach, particularly as they relate to the synthesis of organic compounds.
10:47:47 A. So, I teach classes in chemistry both at the undergraduate and graduate level. The undergraduate level is introductory organic chemistry. At the graduate level, I teach courses on synthetic methodology, how one makes things, and then applying those reactions to the synthesis of naturally occurring compounds to report biological activity, including active pharmaceutical ingredients.
10:48:14 Q. And please describe the research you've done in your career.
10:48:16 A. So over the course of my career, I've developed chemical reactions, applied them to the synthesis of naturally occurring compounds, and then more recently I've been involved in a number of collaborative exercises with laboratories with the medical school at Penn where we supply the chemistry expertise to problems of biological interest that have been involved in many cases APIs.
10:48:40 Q. And can you describe your industry experience as a

10:48:43 scientist.
10:48:44 A. So since the beginning of my career, I've served as a
10:48:48 consultant to a number of different chemical companies, both
10:48:52 chemical companies and pharmaceutical companies, and I spent
10:48:56 a one-year sabbatical at the drug company at Bristol Myers
10:49:01 Squibb in New Jersey teaching a course and then advising on
10:49:04 process and medicinal chemistry projects there.
10:49:08 Q. Have you ever synthesized an API yourself?
10:49:11 A. Yes, I have.
10:49:11 Q. In what context?
10:49:12 A. Well, I've done that in the context of the natural
10:49:15 product synthesis that we've done. We've also invented a
10:49:18 compound in my lab that's now being developed as an
10:49:21 anti-cancer compound.
10:49:24 Q. Between your teaching research and industry
10:49:26 experience, how many years have you worked on organic
10:49:32 chemistry, chemistry, chemical synthesis and purification,
10:49:37 enantioselective synthesis, biochemistry, process chemistry,
10:49:41 pharmaceutical chemistry, analytical techniques such as
10:49:46 HPLC, identification and quantification of impurities, and
10:49:50 storage of components used in drug product manufacturing?
10:49:53 A. Next year will be my 40th year.
10:49:57 MS. KANNAPPAN: Your Honor, we offer Dr. Winkler
10:49:59 as an expert in the list that I just put in my last
10:50:02 question.

10:50:02 MR. CARSTEN: I don't know that it's been
10:50:05 established that] man stored chemicals for 40 years, but no
10:50:08 objection, Your Honor.
10:50:09 THE COURT: All right. Okay. You may proceed.
10:50:13 BY MS. KANNAPPAN:
10:50:13 Q. Dr. Winkler, before we go on, do you have a pointer
10:50:17 up there?
10:50:17 A. I do.
10:50:18 Q. Dr. Winkler, are you familiar with a compound called
10:50:23 Treprostinil?
10:50:23 A. I am.
10:50:24 Q. What is Treprostinil?
10:50:25 A. Treprostinil is a synthetic molecule that was
10:50:29 designed to mimic the effects of a naturally occurring
10:50:33 compound called prostaglandin.
10:50:35 Q. Are you aware that a company called United
10:50:37 Therapeutics Corporation or UTC is asserting certain patents
10:50:41 on Treprostinil in this case?
10:50:42 A. Yes.
10:50:43 I'm sorry. I meant to say prostacyclin, not
10:50:47 prostaglandin.
10:50:47 Q. And is one of those patents U.S. Patent Number
10:50:51 9,593,066?
10:50:52 A. Yes, it is.
10:50:54 Q. Can you turn to PTX 2. Is this that patent?

10:50:57 A. Yes. It is.
10:50:59 Q. And are you fine with me referring to it as the '066
10:51:02 patent going forward?
10:51:02 A. Yes.
10:51:04 Q. I believe this exhibit is already in evidence.
10:51:07 Dr. Winkler, please describe your understanding
10:51:08 of this patent at a high level.
10:51:10 A. So at a high level, what this patent describes is a
10:51:13 process to prepare Treprostinil that involves a certain
10:51:19 sequence of reactions involving alkylation, hydrolysis, and
10:51:24 salt formation.
10:51:25 Q. And if we look on the first page of this patent at
10:51:28 the Related U.S. Application Data section, when was the
10:51:32 provisional application for this patent filed?
10:51:34 A. The provisional application was filed on
10:51:38 December 17th, 2007.
10:51:41 Q. Have you heard of the term a person of ordinary skill
10:51:43 in the art or POSA?
10:51:44 A. Yes, I have.
10:51:46 Q. What is your understanding of the term?
10:51:47 A. My understanding of the term a person of ordinary
10:51:50 skill in the art is that it's a hypothetical individual who
10:51:54 would be -- who would be familiar with all of the prior art
10:51:58 in this area as of the time of invention.
10:52:03 Q. Have you prepared a demonstrative of your definition

of a POSA?

A. Yes, I have.

Q. Please display DDX 2.1. Is this that demonstrative?

A. Yes, it is.

Q. What is your definition?

A. So the definition that I offer here is two-fold. One is that given the information that's in the '066 patent, that a POSA would have either a master's degree or a Ph.D. in medicinal organic chemistry or a closely related field. And then I offer an alternative definition for a person with a lower level of formal education, a bachelor's degree, but with at least five years of practical experience.

Q. Have you reviewed any other definitions of a POSA for this patent?

A. Yes, I have.

Q. And whether the Court applies those other definitions or your definition here, would your opinions change?

A. No, my opinions would not change.

Q. Let's go back to the patent, JTX 2. The last page. Are you are you aware that UTC is asserting that Liquidia's Treprostinil sodium infringes Claims 1, 2, 3, 6, 8, and 9?

A. Yes, I am.

Q. Do you agree?

A. No, I do not.

Q. At a high level, why not?

10:53:19 A. Well, at a high level, it's my opinion that Liquidia
10:53:26 does not meet the impurities limitation that's in Claims 1,
10:53:30 2, 3 and 6. And then it also does not meet the storage
10:53:37 limitation that's in 8 and then the dependent Claim 9.
10:53:41 Q. And is there also a storage limitation in Claim 6?
10:53:44 A. I'm sorry, yes. In Claim 6 as well.
10:53:47 Q. Let's talk about Claim 1 first. What does Claim 1
10:53:54 cover?
10:53:54 A. So, what Claim 1 covers is a pharmaceutical
10:53:59 composition. If you could highlight that. "A
10:54:07 pharmaceutical composition comprising Treprostinil or a
10:54:10 pharmaceutically acceptable salt thereof." That -- you can
10:54:14 take that away.
10:54:18 Q. Can we just have an unhighlighted version? Thank
10:54:21 you.
10:54:21 And so you said pharmaceutical composition
10:54:23 comprising Treprostinil or a pharmaceutically acceptable
10:54:26 salt thereof?
10:54:27 A. Yes. In the first two lines of the claim.
10:54:29 Q. And then what are the process steps to make that
10:54:32 composition?
10:54:32 A. And the process steps are outlined starting on the
10:54:35 third line, where it says prepared by a process which
10:54:40 involves alkylation and hydrolysis.
10:54:45 Q. And after alkylation and hydrolysis, what's the next

10:54:48 step required by the claim?
10:54:49 A. Forming a salt of Treprostinil by combining the
10:54:52 starting batch with a base.
10:54:54 Q. And after you form a salt, what is required by the
10:54:56 claim?
10:54:57 A. So the next step involves taking the isolated salt
10:55:01 and preparing a pharmaceutical composition comprising
10:55:04 Treprostinil or a salt thereof from the isolated salt.
10:55:09 Q. Earlier when I asked you why you didn't think
10:55:11 Liquidia infringed, you referred to certain impurities
10:55:14 limitations. Can we go to the next highlighted version of
10:55:18 Claim 1.
10:55:19 Can you walk us through the impurities
10:55:21 limitations?
10:55:22 A. Yes. So it turns out that there are very explicit
10:55:26 impurities limitations in Claim 1. And that is -- you can
10:55:30 see, as I've highlighted in yellow it -- the batch, the
10:55:35 starting batch of Treprostinil has one or more impurities
10:55:39 resulting from the prior alkylation and hydrolysis steps.
10:55:45 But there's a very important qualifier at the end that it's
10:55:49 not just impurities resulting or any impurities resulting
10:55:53 from alkylation and hydrolysis steps. The alkylation
10:55:56 explicitly is limited to the alkylation of benzindene triol.
10:56:02 And then there's a further qualification that the level of
10:56:05 one or more of those impurities in the starting batch of

10:56:08 Treprostinil must be lower in the pharmaceutical composition.

10:56:13 Q. Would a POSA consider these highlighted limitations as process limitations or as describing a product?

10:56:20 A. No, they're simply describing the product.

10:56:25 Q. Could any impurity be used to determine infringement of Claim 1?

10:56:29 A. No, I think that the -- a POSA would read this and see that the impurities must result from the prior alkylation and hydrolysis steps. And then more explicitly where the alkylation is the alkylation of the benzindene triol or BTO.

10:56:47 Q. And does Claim 1 require any quantitative purity level for the final Treprostinil or Treprostinil salt made according to the claim?

10:56:56 A. No, it does not.

10:56:59 Q. Let's talk about Liquidia's Treprostinil sodium now.

10:57:02 Also, is your mike far enough away that you can see the screen and talk at the same time?

10:57:06 A. Is the mike working now? Yes. Okay. Great.

10:57:11 Q. Okay.

10:57:12 A. Sorry.

10:57:13 Q. That's okay. Let's talk about Liquidia's Treprostinil sodium now. Who makes Treprostinil sodium for Liquidia?

10:57:19 A. Yonsung.
10:57:21 Q. Do you know the details of the process that Yonsung
10:57:23 uses?
10:57:23 A. Yes.
10:57:25 Q. How do you know those details?
10:57:26 A. I know those details from the -- well, the testimony
10:57:29 that we've heard and also from the drug master file that
10:57:34 Yonsung -- Yonsung submitted to the FDA.
10:57:39 Q. Let's look at DTX 106, which has been put up with
10:57:42 various other witnesses. Does this appear to be a copy of
10:57:45 the open portion of the drug master file that you reviewed?
10:57:48 A. It does.
10:57:49 Q. And if we look at DTX 167, does this appear to be a
10:57:54 copy of the restricted portion of the drug master file that
10:57:57 you reviewed?
10:57:57 A. Yes, it does.
10:58:00 MS. KANNAPPAN: And, Your Honor, I know we've
10:58:01 discussed not entering these entirely in, but for the
10:58:04 moment, I would like to enter them into evidence and we will
10:58:06 parse out which pages are actually referred to.
10:58:10 MR. CARSTEN: I have no objection to that, Your
10:58:12 Honor, as long as you don't --
10:58:14 THE COURT: Right. So it's admitted without
10:58:16 objection.
10:58:18 (DTX Exhibit No. 167 was admitted into

10:58:18 1 evidence.)
10:58:19 2 BY MS. KANNAPPAN:
10:58:19 3 Q. So we talked a little bit about Yonsung and how it's
10:58:21 4 used to make -- how it makes Treprostinil sodium. Have you
10:58:24 5 recreated a demonstrative outlining that process?
10:58:27 6 A. Yes, I have.
10:58:28 7 Q. Display DDX 2.2.
10:58:30 8 Is that that demonstrative?
10:58:31 9 A. Yes, it.
10:58:32 10 Q. Can you walk us through it.
10:58:33 11 A. Sure. So, what I showed here is on the far left, you
10:58:37 12 see the starting material. That's BTO, the benzindene
10:58:41 13 triol. It undergoes three steps here. The first step is
10:58:45 14 alkylation to get TN01. That's the Treprostinil methyl
10:58:50 15 ester. The second step is hydrolysis of TN01 to get TN02.
10:58:54 16 That's the Treprostinil -- sometimes it's called
10:58:58 17 Treprostinil free acid. And this is the starting batch of
10:59:00 18 Claim 1.
10:59:02 19 And then the TN02 undergoes salt formation to
10:59:05 20 deliver Treprostinil sodium. That's the pharmaceutical
10:59:08 21 composition of Claim 1.
10:59:11 22 Q. And what steps of this process are relevant to the
10:59:14 23 impurities limitations of Claim 1?
10:59:16 24 A. So, the impurities which are formed in the alkylation
10:59:21 25 and hydrolysis steps, the levels that are relevant for

10:59:25 Claim 1 are simply the levels of the impurities resulting
10:59:29 from alkylation and hydrolysis of BTO that are present in
10:59:34 TN02, and they must be lower in TN than they are in TN02.
10:59:41 Q. Does Yonsung's process meet these limitations?
10:59:43 A. No, it does not.
10:59:44 Q. Why not?
10:59:46 A. Well, because I've seen no evidence for the presence
10:59:51 of impurities resulting from alkylation and hydrolysis in
10:59:55 the TN02 of Yonsung, and, furthermore, those impurities
11:00:00 being reduced in the Treprostinil sodium product.
11:00:03 Q. And specifically, did you mean impurities resulting
11:00:06 from a particular compound in regard to alkylation and
11:00:11 hydrolysis?
11:00:11 A. Well, in other words, impurity is resulting from the
11:00:15 alkylation and hydrolysis of the benzindene triol.
11:00:18 Q. Dr. Winkler, are you aware that Yonsung's process
11:00:22 includes a step called column chromatography?
11:00:25 A. I am.
11:00:27 Q. What would a POSA expect column chromatography to do?
11:00:28 A. Column chromatography is typically used to purify.
11:00:33 Q. Let's look at DTX 167, which is the closed portion of
11:00:36 the DMF, Page 22.
11:00:39 What step of Yonsung's process are we at?
11:00:44 A. So, this is after the alkylation step. This is TN01,
11:00:53 the formation of TN01 before the hydrolysis step.

11:00:58 Q. And is this the step in which chromatography appears?
11:01:02 A. Yes, it is.
11:01:03 Q. How would a POSA expect this chromatography step to
11:01:07 affect the purity of the TN02 that's generated down the
11:01:12 line?
11:01:12 A. Well, a POSA would have the expectation that the
11:01:15 chromatography would result in purification to a purer
11:01:19 product than if one hadn't done chromatography. And so if
11:01:22 you do chromatography at the end of TN01, a POSA would have
11:01:25 the expectation that the TN02 would be more pure than if one
11:01:30 had not done the chromatography of the TN01 sample.
11:01:35 Q. Why does this matter?
11:01:36 A. Well, it matters because in the Yonsung process with
11:01:41 chromatography, one would expect that the chromatography
11:01:44 would lead to very low levels of impurities resulting from
11:01:48 the alkylation and hydrolysis of the BTO.
11:01:52 Q. And if we turn to the patent again, JTX 2, but Page 6
11:01:56 this time, what does the '066 patent say about column
11:02:00 chromatography?
11:02:00 A. The '066 patent teaches that the purification by
11:02:06 column chromatography is eliminated, and it gives reasons
11:02:09 for the advantages of eliminating the chromatography. You
11:02:15 use less flammable solvent, and less waste is generated.
11:02:16 Q. And are you aware of any inventor testimony on this
11:02:19 patent in this case?

11:02:20 A. Yes, the inventors in their deposition stated that
11:02:25 one of the advantages of this patent was the elimination of
11:02:31 chromatography, and in fact, they went as far as to say if
11:02:34 you added chromatography to this process, I think one of
11:02:37 them called it sheer stupidity.
11:02:42 Q. Dr. Winkler, a few minutes ago you identified four
11:02:46 compounds made in the Yonsung process: BTO, TN01, TN02, and
11:02:50 TN. Does Yonsung measure impurities in all of these
11:02:53 compounds?
11:02:54 A. Yes, they do.
11:02:55 Q. And which of those compounds does Yonsung send to
11:02:58 Liquidia?
11:02:58 A. Just the TN, the last compounds, the Treprostinil
11:03:03 sodium.
11:03:04 Q. Does Liquidia measure impurities in that TN?
11:03:06 A. Yes, they do.
11:03:09 Q. Remind us. Reduction in what impurities in what
11:03:12 Yonsung compound are relevant to Claim 1?
11:03:14 A. So, the only impurities that are relevant to a POSA's
11:03:20 reading of Claim 1 are impurities resulting from the
11:03:24 alkylation and hydrolysis of BTO, and the compounds you want
11:03:30 to test are TN, the Treprostinil sodium, and the TN02, the
11:03:36 starting batch of Treprostinil. So, the level of those
11:03:39 impurities from alkylation and hydrolysis of BTO have to be
11:03:43 lower in TN then they are in TN02.

11:03:46 Q. Do you understand that Dr. Nuckolls and Dr. Toste
11:03:50 have pointed to 15-epi-Treprostinil and total impurities as
11:03:55 evidence of infringement of Claim 1?
11:03:56 A. Yes.
11:03:56 Q. In your opinion, does that evidence establish
11:04:00 infringement?
11:04:02 A. No, it does not.
11:04:03 Q. Let's start with 15-epi-Treprostinil. Why doesn't
11:04:08 Dr. Nuckolls' and Dr. Toste's evidence establish
11:04:10 infringement of Claim 1 for 15-epi-Treprostinil?
11:04:13 A. Well, because 15-epi-Treprostinil is not an impurity
11:04:19 resulting from the alkylation and hydrolysis of BTO, and
11:04:23 that's the requirement of Claim 1 of the patent.
11:04:26 Q. And did -- and what about the levels of
11:04:29 15-epi-Treprostinil? Is that relevant here?
11:04:31 A. Well, the -- if one were to assume that
11:04:36 15-epi-Treprostinil was an impurity resulting from
11:04:40 alkylation and hydrolysis of BTO, which I don't think is
11:04:43 true, if one were to assume that, the levels of
11:04:47 15-epi-Treprostinil in the TN02 compared to the levels that
11:04:52 were observed in TN -- I'm sorry -- in TN compared to TN02,
11:04:57 the differences between those are so miniscule and the
11:05:01 levels themselves are so small that a POSA couldn't reliably
11:05:06 conclude that the level of even that compound had been
11:05:09 reduced.

11:05:10 Q. Let's start with where 15-epi-Treprostinil comes
11:05:13 from. Have you prepared a demonstrative depicting your
11:05:17 understanding of how 15-epi-Treprostinil is formed in
11:05:20 Yonsung's process?
11:05:21 A. I have.
11:05:23 Q. Let's depict DDX2.4.
11:05:25 Is this that demonstrative?
11:05:26 A. It is.
11:05:30 Q. Please describe your understanding of how
11:05:32 15-epi-Treprostinil is formed in Yonsung's process.
11:05:35 A. Okay. So just by way of review, I already showed you
11:05:38 that BTO goes to TN01, goes to TN02. That's the starting
11:05:43 batch. It goes to TN. And it turns out that this molecule
11:05:48 down here in yellow, that's the impurity that we're
11:05:51 describing. That's the 15-epi-Treprostinil. And the point
11:05:55 is that the only way that you can get 15-epi-Treprostinil is
11:05:59 by doing a similar sequence of alkylation and hydrolysis,
11:06:06 but this time starting with 15-epi-BTO, which is a different
11:06:10 molecule than BTO.
11:06:14 Q. And could you jump from the reaction sequence on the
11:06:16 top to the reaction sequence on the bottom?
11:06:19 A. No, I think I put a big X here somewhere. But the
11:06:24 point is -- there should be a big X here. There we go.
11:06:28 Because BTO itself could not be the source of the
11:06:33 15-epi-TN02. BTO becomes TN02. It's 15-epi-BTO which is

11:06:39 different than BTO that becomes 15-epi-TN02.
11:06:45 Q. Are you aware that Dr. Toste and Dr. Nuckolls have
11:06:49 opined that there's this process called epimerization that
11:06:55 could result in 15-epi-TN02 in this process?
11:07:00 A. Yes, I am.
11:07:01 Q. Do you agree?
11:07:02 A. No, I do not.
11:07:03 Q. And just to remind the Court, what is epimerization?
11:07:07 A. So epimerization is when we have three-dimensional
11:07:13 stereochemistry. So that OH group in BTO has a dotted line.
11:07:18 The convention of organic chemistry means that it's going
11:07:21 into the screen. 15-epi-BTO, the OH group is wedged. That
11:07:28 means it's coming out of the screen, and that's what makes
11:07:30 those different molecules. Molecules are only the same in
11:07:34 organic chemistry if they have point-to-point superposition
11:07:38 in three-dimensional space. There's no way that you could
11:07:41 line up these two molecules, and, therefore, we say as
11:07:45 chemists that they're different.
11:07:46 Now, it turns out that the hydroxyl group of
11:07:51 BTO, it's behind the board now. If you pull it off and you
11:07:57 put it back on the front of the board, that's epimerization.
11:08:01 That's changing the stereochemistry of the molecule at a
11:08:04 single position. And basically, what you would have to do
11:08:09 is take BTO and epimerize that stereocenter. You would have
11:08:14 to change dotted to wedge to get 15-epi-Treprostinil.

11:08:19 Q. Are you aware that Dr. Toste relied on an article by
11:08:23 Merritt, et al., to show an example of epimerization that
11:08:27 maybe could be applicable here?
11:08:29 A. Yes, I am.
11:08:30 Q. Let's look at DTX 577. Is this that article?
11:08:38 A. Yes, it is.
11:08:38 Q. And can you briefly describe what this article is.
11:08:42 A. So, this is an article by a group at a chemical
11:08:48 company -- pharmaceutical company that used to exist called
11:08:52 Upjohn by Merritt. And what it describes is, this is a
11:08:58 compound that's related to prostaglandins. This is called
11:09:02 15-methyl prostaglandin E2. And in this molecule, what
11:09:06 Merritt shows is that when treated with acid, that this
11:09:11 15-methyl prostaglandin, with a certain configuration in
11:09:17 carbon 15 where the methyl group is dotted and the OH is
11:09:20 coming forward, flips so that the OH goes back where the
11:09:25 methyl comes forward. In other words, he describes
11:09:28 epimerization of this molecule under acidic conditions.
11:09:33 MS. KANNAPPAN: Your Honor, I'd like to DTX 577
11:09:35 into evidence.
11:09:36 MR. CARSTEN: No objection, Your Honor.
11:09:37 THE COURT: Admitted without objection.
11:09:38 (DTX Exhibit No. 577 was admitted into
11:09:38 evidence.)
11:09:40 BY MS. KANNAPPAN:

11:09:40 Q. In your opinion, would a POSA expect this Merritt reaction to happen with Treprostinil?
11:09:45 A. No.
11:09:46 Q. Have you prepared a demonstrative explaining why not?
11:09:48 A. I have.
11:09:49 Q. Let's put up DDX 2.5.
11:09:51 Is this that demonstrative?
11:09:53 A. It is.
11:09:53 Q. Can you walk us through it.
11:09:54 A. So what this shows you is the difference between the chemical structures of the Merritt compound and Treprostinil, which is shown down here. And the difference that I'd like to point out is that the 15 position in the Merritt compound has an OH group, but that carbon is attached to three other carbons. We call that a tertiary carbon. It's -- that carbon is also attached to -- this double line here is a carbon-carbon double bond. A carbon-carbon double bond next to this carbon means that it is not only tertiary because it has three carbons, it's also called allylic, A-L-L-Y-L-I-C. And what that means is that this OH group of this particular compound is relatively easy to remove and to put back on the other side to effect this epimerization.
11:10:52 If you look at the structure of Treprostinil, you see a very different system because the C15 carbon here,

11:10:59 well, it has an OH group, but now it only has two carbons
11:11:03 attached to it. And it has no carbon-carbon double bond, so
11:11:07 that it's not allylic and it's not tertiary. We call this
11:11:11 secondary and non-allylic, and this molecule would be much
11:11:15 less likely to undergo epimerization than the tertiary
11:11:19 allylic alcohol that's taught in Merritt.
11:11:21 Q. And what is that likelihood?
11:11:23 A. I would say that it's thousands to millions times
11:11:27 less likely to occur.
11:11:29 Q. And specifically, what were the conditions that the
11:11:32 Merritt compound epimerized?
11:11:35 A. So the Merritt compound, if I'm not mistaken, it's in
11:11:39 the paper, but it epimerized under acidic conditions and
11:11:39 elevated temperature.
11:11:46 Q. Did Yonsung test Treprostinil under similar
11:11:47 conditions?
11:11:47 A. Yonsung actually did do testing of Treprostinil under
11:11:53 acidic conditions with heating, and found absolutely no
11:11:56 evidence of epimerization.
11:11:58 Q. So would a POSA believe that epimerization was the
11:12:03 source of 15-epi-Treprostinil in TN02?
11:12:06 A. No. We don't have to go back to the slide, but I
11:12:10 showed two tracks. The first track was BTO going to
11:12:14 Treprostinil. The second track was 15-epi-BTO going to
11:12:19 15-epi-Treprostinil, and a POSA would look at this and

11:12:22 understand that the only source of 15-epi-Treprostinil would
11:12:26 be 15-epi-BTO.
11:12:29 Q. Did Dr. Nuckolls or Dr. Toste provide any documents
11:12:33 demonstrating epimerization of a secondary non-allylic
11:12:37 alcohol like Treprostinil under the conditions of Yonsung's
11:12:42 alkylation and hydrolysis steps?
11:12:44 A. No.
11:12:44 Q. Are you aware of any?
11:12:45 A. No.
11:12:47 Q. Were you in the courtroom when Dr. Nuckolls pointed
11:12:50 to certain batches in which there was no 15-epi in the TN01
11:12:55 but then there was 15-epi in the TN02? Do you recall that?
11:12:57 A. Yes, I do.
11:12:59 Q. How would you explain that?
11:13:00 A. Well, that comes back to how these things were
11:13:06 measured, and these things were measured by HPLC. Now,
11:13:10 remember that in HPLC, you basically have a detector at the
11:13:15 end of the machine that's giving you certain values. And
11:13:18 one of the things that's important when these numbers are so
11:13:21 incredibly small is when you can even detect tiny amounts
11:13:27 that are there. There is a parameter that's referred to as
11:13:31 an LOD, or a limit of detection. And if you're below the
11:13:35 limit of detection, there can be stuff there but you're just
11:13:38 not able to measure it. And so, even though some of these
11:13:43 measurements showed ND, not detected, that doesn't mean that

there was no material there.

Q. And other than limit of detection, are there any other limits that would have been relevant to Dr. Nuckolls' analysis?

A. So, the other thing that's important in HPLC is something called LOQ, which is limit of quantification. What that means is we have enough stuff that you can see it on the HPLC, but it's so tiny -- you know, when you look at the readout of this detector, there's what we call baseline noise. You have to be able to see the peak out of the baseline and that's the signal-to-noise ratio. You have to be able to see that peak out of the noise. That's the limit of detection.

But then you also have to be able to see enough of that peak that you can quantify it, that you can know that it's really .06 percent or .07 percent or .08 percent. There's a limit of quantification that Yonsung established in their HPLC analysis. Again, it was about .047 percent. Below those levels, the numbers don't really mean very much. It means that you're seeing something, but it's not a reliable, quantitative measure.

And then the other issue in HPLC is that there's always going to be error. There's error in all measurements that we do. If I take exactly the same solution and shoot it on the HPLC six times and I look at six different

11:15:13 measurements, I'm going to get a range of values. And
11:15:16 usually good practice would be that I would take the average
11:15:19 of those values and then I would consider the lowest and
11:15:23 highest as sort of the error range that I have among those
11:15:28 measurements. And so, the variation that one would
11:15:34 typically observe in any of these measurements along with
11:15:37 the limits of detection and the limits of quantification are
11:15:41 really important parameters in understanding the differences
11:15:44 between these infinitesimally small numbers.
11:15:48 MR. CARSTEN: Your Honor, I'd like to move to
11:15:50 strike the answer. The first part where he talked about the
11:15:52 data being small, that I elicited from the witness in his
11:15:56 deposition. The remainder about the limits of
11:15:59 quantification and so forth, that's all brand new expert
11:16:04 testimony that's being rendered for the first time at trial.
11:16:09 MS. KANNAPPAN: Your Honor, I can point you to
11:16:10 the deposition testimony where he talks about limits of
11:16:12 detection and that small amounts are hard to reproduce,
11:16:15 which is the limit of quantification.
11:16:17 MR. CARSTEN: Your Honor, that's the stuff I
11:16:18 said -- I get it. I opened the door on that on deposition.
11:16:21 But this other stuff, the limit of quantification and so
11:16:24 forth at the end, that's new.
11:16:28 THE COURT: All right. So I'm going to accept
11:16:31 what counsel just said as, perhaps, talking about the limits

of quantification while perhaps using the term "limit of quantification" and you can move to strike it in the post-trial briefing.

MR. CARSTEN: Very well, Your Honor thank you.

BY MS. KANNAPPAN:

Q. Dr. Winkler if we could put JTX 1 -- or JTX 2, sorry, the patent back up and look at Claim 1.

Did you hear Dr. Nuckolls and Dr. Toste testify that benzindene triol when it's referred to in this claim is actually referring to a batch of benzindene triol?

A. Yes, I did.

Q. Do you agree?

A. No, I don't.

Q. Why not?

A. Well, it seems to me -- I'm trying to read the patent as carefully as I can. What it says here is "Wherein the alkylation is the alkylation of benzindene triol." I know the benzindene triol, and in fact, if I didn't know what benzindene triol was, the patent teaches me. I see chemical pictures of it, and I understand exactly what that molecule is.

If the patent is referring to a batch of something, it refers to it as a batch. Because in fact, if we look at the language on line 3, it says "Providing a starting batch of Treprostinil." So, at that point, I would

11:17:52 understand that I'm working with a batch of material. But
11:17:55 here, it seems to me that the plain reading would be that
11:17:59 we're dealing with the alkylation of a molecule, which is
11:18:03 benzindene triol.
11:18:07 Q. Thank you, Dr. Winkler.
11:18:08 THE COURT: I'm sorry. You would get a batch of
11:18:12 TN from alkylating one benzindene triol molecule?
11:18:16 THE WITNESS: No. I think that what you would
11:18:19 get -- you would get a batch of -- the batch that's being
11:18:26 referred to here is the batch of Treprostinil, right, which
11:18:30 is the starting batch for the formation of the isolated
11:18:34 salt.
11:18:35 THE COURT: Right. But you get that from the
11:18:38 benzindene triol if you do a compilation of alkylation and
11:18:42 hydrolysis.
11:18:42 THE WITNESS: You get that from the alkylation
11:18:43 and hydrolysis of the benzindene triol, yes.
11:18:45 THE COURT: And so, if you are saying that
11:18:49 starting is a molecule, how does alkylation and hydrolysis
11:18:54 get that to then be a batch?
11:18:56 THE WITNESS: Well, maybe I misspoke. What I
11:18:59 mean here is that when they're talking about the alkylation
11:19:03 of benzindene triol, they're talking about that substance,
11:19:09 and that substance only.
11:19:10 THE COURT: Okay. But it's in a batch of that

substance.

THE WITNESS: Well, it's -- what I'm saying is that the batch descriptor I see only referring to Treprostinil. I'm certainly not suggesting that we're alkylating a single molecule of benzindene triol to get the starting batch. What I am saying is that my reading of this is that when this is alkylated, benzindene triol, and that this is referring explicitly and only to the alkylation of benzindene triol.

BY MS. KANNAPPAN:

Q. And specifically -- maybe I can clear it up a little bit -- what is included in a batch of benzindene triol per Dr. Nuckolls' and Dr. Toste's testimony that wouldn't be included in just the term "benzindene triol"?

A. Well, for example, a real batch of -- a bottle of benzindene triol could contain impurities. It could contain 15-epi-BTO. But as a POSA, I wouldn't read that as the molecule that's being claimed in the patent. The claim is starting with the alkylation of benzindene triol and benzindene triol only.

Q. So we talked a little bit about the origins of 15-epi-treprostinil. Let's talk about the levels of that impurity in TN02 versus TN.

If 15-epi-trepostinil was evidence of infringement, which compound in Yonsung's process would you

11:20:40 expect a lower level of 15-epi-Treprostinil in?
11:20:43 A. There would have to be a lower level of
11:20:48 15-epi-Treprostinil in TN compared to TN02.
11:20:52 Q. And were you in the courtroom when Dr. Toste
11:20:55 testified to certain batches in which 15-epi-Treprostinil
11:20:59 was lower in TN?
11:21:01 A. Yes.
11:21:02 Q. And were you in the courtroom when Dr. Toste
11:21:04 testified to certain batches where 15-epi-Treprostinil was
11:21:07 lower in TN02?
11:21:09 A. Yes, I was.
11:21:10 Q. And were you in the courtroom when Dr. Toste
11:21:12 testified to certain batches were, within the same batch,
11:21:17 different measurements of 15-epi-Treprostinil were taken?
11:21:19 A. Yes.
11:21:20 Q. How do you explain those variations?
11:21:24 MR. CARSTEN: Your Honor, I object. This is the
11:21:26 stuff I talked about this morning with the demonstratives
11:21:28 that they said we're not going to use them. They withdrew
11:21:31 that. Now we're just trying to do it without the
11:21:33 demonstratives. This is all brand new testimony. The man
11:21:35 said that Dr. Toste's experimentation was irrelevant. That
11:21:40 was all he said in two paragraphs of his expert report. He
11:21:43 didn't go further. He had the opportunities, and this is
11:21:46 being sprung on us at trial.

11:21:48 MS. KANNAPPAN: Your Honor, if you look at report paragraphs 6 and paragraph 54 in addition to Dr. Winkler's testimony right now that he actually heard Dr. Toste say these things. The explanation is exactly the same, which you'll hear in a second, as what he just said five minutes ago. It's not different explanation than what was elicited at deposition testimony.

11:22:07 MR. CARSTEN: So now, Your Honor, what we're hearing is they got new stuff in, but over my motion to strike, and now we're going to bootstrap around that to get more new stuff in. You know, Your Honor, I object to it.

11:22:18 THE COURT: All right. Well, I'm going to overrule the objection. You can brief it later on.

11:22:23 MR. CARSTEN: Very well. Thank you, Your Honor.

11:22:25 BY MS. KANNAPPAN:

11:22:25 Q. So my question, Dr. Winkler, was how would you explain that variation that Dr. Toste testified to?

11:22:29 A. So, remember, these are tiny differences between really tiny numbers. And so, we come back to how they were measured. They're measured by HPLC. There are issues of limits of quantification of how one can accurately measure really tiny amounts and how reproducible those measures are. And if one imagines the standard error that a POSA would expect for these things, the differences that were described in testimony by Dr. Toste would all -- to a POSA, would all

11:23:08 fit within the level of experimental error so that there was
11:23:12 no clear establishing of a reduction of the impurities, i.e.
11:23:17 the 15-epi-Treprostinil going from TN02 to TN.
11:23:24 Q. Did Dr. Nuckolls or Dr. Toste account for standard
11:23:28 experimental error in their analysis, as far as you were
11:23:31 aware?
11:23:31 A. Not that I am aware of, no.
11:23:34 Q. And do they account for limit of the detection or
11:23:36 quantification in the HPLC values that they looked at?
11:23:38 A. Not that I'm aware of, no.
11:23:43 Q. Given all the data that you've considered and heard
11:23:45 on testimony regarding 15-epi-Treprostinil, what would a
11:23:50 POSA conclude regarding whether 15-epi-Treprostinil in
11:23:55 Yonsung's process is truly lower in TN versus TN02?
11:23:59 A. I think one would not be able to conclude that it
11:24:03 was, in fact, lower.
11:24:05 Q. Why not?
11:24:06 A. Because as I've said, the numbers are so small and
11:24:12 the errors are significant relative to the differences
11:24:16 between those numbers and their absolute levels, that a POSA
11:24:20 wouldn't be able to conclude that the numbers had actually
11:24:24 gone down.
11:24:26 Q. Let's switch to talking about total impurities now.
11:24:31 You understand that Dr. Nuckolls relies on total
11:24:33 impurity measurements between TN02 and TN to show

11:24:37 infringement?
11:24:37 A. I do.
11:24:39 Q. Let's go back to the patent and look at Claim 1
11:24:41 again. At this point, it might be ad nauseam, but can you
11:24:48 remind us, where do the impurities have to result from in
11:24:51 Claim 1?
11:24:51 A. So the impurities must result from the alkylation and
11:24:57 hydrolysis steps, but then there's a very important
11:25:00 qualifier at the bottom which says that the alkylation is
11:25:05 explicitly the alkylation of benzindene triol, so that a
11:25:09 POSA would understand that the only relevant impurities here
11:25:14 are those that result from the alkylation and hydrolysis of
11:25:17 the benzindene triol or the BTO starting compound.
11:25:21 Q. And in contrast, what does total impurities measure?
11:25:25 A. Well, total impurities typically measures everything
11:25:30 in a sample that's not the desired compound.
11:25:34 Q. And what are some examples of impurities that would
11:25:37 be included in total impurities?
11:25:39 A. Well, in a given reaction, for example, if there were
11:25:42 impurities that were present in the reagents, those could
11:25:49 appear in the final product. If there were impurities in
11:25:51 the solvent, those could appear in the final product. If
11:25:55 there were impurities in the starting compound, those could
11:25:59 appear in the product. So, any of those would count as
11:26:03 among the total impurities that could be observed in a given

11:26:07 compound.
11:26:08 Q. Would a POSA consider those impurities that you just
11:26:11 listed to be impurities resulting from all alkylation and
11:26:15 hydrolysis of benzindene triol?
11:26:16 A. No, they wouldn't because the impurities resulting
11:26:20 from alkylation and hydrolysis of benzindene triol would
11:26:25 represent a relatively small subset of this universe of
11:26:30 possible total impurities.
11:26:31 Q. So, Dr. Winkler, if you saw reduction of total
11:26:34 impurities from TN02 to TN01 in a certain batch -- or sorry
11:26:39 from TN02 to TN in a certain batch, would that meet
11:26:43 Claim 1's impurity limitation?
11:26:44 A. No, it wouldn't because if you're reducing total
11:26:48 impurities, you could be reducing some of this other junk,
11:26:52 but the impurities resulting from alkylation and hydrolysis
11:26:57 of BTO could be staying the same or, relatively speaking,
11:27:00 they could even be increasing. But you would have no idea
11:27:03 that just because the total impurities had decreased, you
11:27:09 would have no idea what impact that had directly on the
11:27:14 impurities resulting from alkylation and hydrolysis in BTO.
11:27:17 Q. And do you recall Dr. Nuckolls actually testifying to
11:27:20 a certain batch where that happened, where total impurities
11:27:24 went down, but, for example, 15-epi went up?
11:27:26 A. Yes.
11:27:28 Q. Does Dr. Nuckolls make any attempt to show that

11:27:31 reduction in total impurities is due to reduction in
11:27:34 impurities specifically from alkylation and hydrolysis of
11:27:37 benzindene triol?
11:27:38 A. No, he does not.
11:27:40 Q. Do you also recall that Dr. Nuckolls did a peaks
11:27:46 analysis counting the numbers of peaks that showed up in the
11:27:49 HPLC graph for TN02 versus TN?
11:27:53 A. Yes, I do.
11:27:54 Q. And do you agree with his analysis?
11:27:57 A. Well, I agree that his analysis shows a change in the
11:28:02 number of peaks, but a peak only tells me that something's
11:28:09 there. It doesn't tell me what is there. And so, without
11:28:14 knowing what is there, there is no way that I could know
11:28:18 that a peak results from the alkylation and hydrolysis of
11:28:22 BTO. And so, the analysis that shows a reduction in number
11:28:27 of peaks teaches a POSA nothing about the reduction of
11:28:32 impurities resulting from alkylation and hydrolysis of BTO.
11:28:37 Q. And in fact, in Yonsung's HPLC analysis, was Yonsung
11:28:44 able to identify any specific impurities other than 15-epi
11:28:48 and, I believe, Treprostinil methyl ester?
11:28:52 A. Not that I can remember, no.
11:29:03 THE COURT: So, why don't we take another
11:29:05 ten-minute break, and then we'll continue on until
11:29:08 one o'clock. All right?
11:29:10 DEPUTY CLERK: All rise.

11:29:10 THE COURT: We'll be in recess.

11:29:12 (Recess was taken.)

11:41:06 DEPUTY CLERK: All rise.

11:41:16 THE COURT: All right. Let's continue on.

11:41:24 BY MS. KANNAPPAN:

11:41:27 Q. Dr. Winkler, let's turn back to the patent, JTX 2, and look at Claims 2, 3, and 6.

11:41:39 Do Claims 2, 3 and 6 have the same impurities limitation as Claim 1?

11:41:44 A. Yes, they do.

11:41:45 Q. Why?

11:41:46 A. Because they depend on Claim 1.

11:41:47 Q. And what is your opinion as to whether Liquidia's Treprostinil sodium infringes impurities limitations of Claims 2, 3, and 6?

11:41:55 A. My opinion is the same, that it does not infringe the limitations of those claims.

11:41:59 Q. And, Dr. Winkler, I'd like to turn to your second non-infringement opinion, which is about the storage limitations of Claims 6 and 8. Let's look at Claim 6 first.

11:42:07 Does Claim 6 require storage of isolated salts at ambient temperature?

11:42:13 A. Yes, it does.

11:42:16 Q. Did you consider the Court's construction of the terms "ambient temperature" and "storage" in your analysis?

11:42:18

11:42:21

11:42:23 A. I did.
11:42:25 Q. Let's turn to DI 119, which is the Court's first
11:42:29 claim construction order. What was the Court's construction
11:42:32 of "ambient temperature"?
11:42:34 A. The Court's construction of "ambient temperature" was
11:42:36 room temperature that is in the range of 15 to 30 degrees C.
11:42:41 Q. And your opinion, does Liquidia infringe the storage
11:42:43 at ambient temperature limitation in Claims 6 and 8?
11:42:46 A. No, it does not.
11:42:47 Q. Why not?
11:42:48 A. Because all of the storage documentation that I've
11:42:54 read and the testimony that I've heard is that the
11:42:58 Treprostinil sodium was stored between two and 8 degrees C.
11:43:03 Q. And would a POSA understand 2 to 8 degrees C to be
11:43:06 ambient temperature under the Court's construction?
11:43:08 A. No.
11:43:09 Q. And what construction did the Court apply for
11:43:12 "storage"?
11:43:12 A. For "storage," the Court applied plain and ordinary
11:43:16 meaning.
11:43:17 Q. And what is the plain and ordinary meaning of
11:43:20 "storage"?
11:43:20 A. Well, for the plain and ordinary meaning of
11:43:25 "storage," what I did was to go to the Hawley's Chemical
11:43:29 Dictionary, which is a standard reference in chemistry.

11:43:34 Q. Let's look at DTX 135.

11:43:37 Is this an excerpt from the 2007 edition of
11:43:43 Hawley's Condensed Chemical Dictionary?

11:43:44 A. It is.

11:43:44 MS. KANNAPPAN: Your Honor, I'd like to offer
11:43:45 DTX 135 into evidence.

11:43:47 MR. CARSTEN: No objection, Your Honor.

11:43:48 THE COURT: All right. Admitted without
11:43:50 objection.

11:43:50 (DTX Exhibit No. 135 was admitted into
11:43:52 evidence.)

11:43:52 BY MS. KANNAPPAN:

11:43:52 Q. If we go to Page 3. What is Hawley's definition of
11:43:55 "storage"?

11:43:55 A. So I thought this was a great definition to use of
11:43:58 "storage" because it's quite clear, I think. It says that
11:44:02 storage is any method of keeping raw materials, chemicals,
11:44:06 food products, and energy while awaiting their use,
11:44:10 transportation, or consumption. So, it clearly
11:44:15 differentiates storage from use and storage from
11:44:17 transportation.

11:44:19 Q. Did any of UTC's experts in this case agree with your
11:44:23 understanding of the plain and ordinary meaning of store
11:44:26 stored?

11:44:26 A. Yes.

11:44:26 Q. Who?
11:44:27 A. Dr. Scheidt.
11:44:29 Q. Let's turn back to the patent, JTX 2. Look at
11:44:33 Claim 8.
11:44:34 Does Claim 8 also require storage at ambient
11:44:36 temperature?
11:44:37 A. Yes, it does.
11:44:39 Q. And if we put up Claim 6 and 8 at the same time or
11:44:43 just pull it out -- you can go back. That's fine.
11:44:46 In Claim 6 and 8, is a salt stored before or
11:44:49 after making the composition?
11:44:51 A. So, in both Claim 6 and Claim 8, the storage takes
11:44:57 place before the preparation of the pharmaceutical product.
11:45:06 Q. Do you understand that the Patent Trial Appeal Board
11:45:09 also defined storage?
11:45:10 A. Yes, I am.
11:45:11 Q. What was the PTAB's construction?
11:45:12 A. The PTAB's construction was that storage was at
11:45:18 ambient temperature for a period, I think, of at least three
11:45:20 months.
11:45:21 Q. Did Dr. Nuckolls provide any evidence that Liquidia
11:45:26 or Yonsung stores Treprostinil sodium salt for three months
11:45:31 at ambient temperature?
11:45:32 A. Not that I saw, no.
11:45:35 Q. Are you aware that Dr. Nuckolls actually provided his

11:45:37 1 own definition of storage along the lines of "storage" means
11:45:41 2 "storage"?
11:45:41 3 A. Yes, I am.
11:45:43 4 Q. And based on your review of Dr. Nuckolls' analysis,
11:45:46 5 what duration of time would be storage under his definition?
11:45:51 6 A. If one considers simply that storage is storage, it
11:45:56 7 could be any period of time. It could be a second or a
11:45:58 8 minute.
11:45:59 9 Q. Do you agree?
11:45:59 10 A. No, I don't.
11:46:01 11 Q. Why not?
11:46:01 12 A. Because I think the plain meaning of "storage" and
11:46:05 13 the term that I applied from the dictionary is that we're
11:46:08 14 putting something away awaiting use and that that would
11:46:11 15 be -- to a POSA would clearly indicate that a matter of
11:46:16 16 seconds wouldn't count.
11:46:19 17 Q. And under Hawley's definition that you used, would a
11:46:23 18 POSA understand standard processing times between process
11:46:26 19 steps to be storage?
11:46:27 20 A. No. Because again, the thing I like about Hawley's
11:46:31 21 is it clearly differentiates between awaiting use and use.
11:46:36 22 If the material is being used in some way, then it seems to
11:46:40 23 me that Hawley's makes clear that that's not storage.
11:46:44 24 Q. Okay. Let's walk through specific storage
11:46:46 25 documentation, some of which you might have seen through

11:46:49 previous witness testimony. Let's look at the open portion
11:46:51 of the DMF, which is DTX 106, specifically Page 517.
11:47:07 What does this page say about the storage
11:47:10 temperature of Yonsung's Treprostinil sodium?
11:47:12 A. So, what it says here is stored at 2 to 8 degrees C.
11:47:19 Q. And what is the full storage instruction?
11:47:23 A. The full storage instruction is "should be kept in a
11:47:25 tight container protected from moisture and light and stored
11:47:28 at 2 to 8 degrees C."
11:47:31 Q. And you heard some testimony or questions that maybe
11:47:35 the word "should" might mean optional. In your opinion,
11:47:38 would a POSA understand these storage conditions to be
11:47:41 optional?
11:47:42 A. No, I think in my laboratory, for example, if we
11:47:45 received a chemical or reagent and it had those kind -- that
11:47:49 kind of label on it, we would know that this is a material
11:47:53 which would be stored under refrigerated conditions.
11:47:56 Q. And what would happen if you didn't do that?
11:47:58 A. Well, if you didn't store it as recommended on the
11:48:02 label, then one would risk compromising the material. And
11:48:06 you would have no longer have certainty that the material
11:48:09 would -- would be stable or what it was supposed to be.
11:48:14 Q. Let's look at some of the certificates of analysis,
11:48:16 also in the DMF, for example at Page 448. What does the
11:48:23 Certificate of Analysis say about storage of Treprostinil

11:48:26 sodium?
11:48:26 A. So at the bottom, it clearly states the storage
11:48:29 condition should be kept in a tight container, protected
11:48:33 from moisture and light, and stored at 2 degrees C to 8
11:48:37 degrees C.
11:48:38 Q. What's the approval date of this document?
11:48:40 A. The approval date of this document is November 11th,
11:48:45 2019.
11:48:46 Q. Let's look at Page 450 of the DMF. What is this
11:48:50 document?
11:48:50 A. This document is a Certificate of Analysis for a lot
11:48:55 of Treprostinil sodium.
11:48:56 Q. And what's the approval date of this document?
11:48:59 A. And the approval date of this document is
11:49:02 January 22nd, 2020.
11:49:04 Q. And what does this document say about storage of
11:49:07 Treprostinil sodium?
11:49:07 A. I think it's exactly the same. It says should be
11:49:10 kept in a tight container, protected from moisture and
11:49:13 light, and stored at 2 degrees C to 8 degrees C.
11:49:17 Q. Based on the documents you've considered in this
11:49:19 case, have you seen any information indicating that Yonsung
11:49:23 intentionally does not store Treprostinil sodium at 2 to 8
11:49:27 degrees Celsius?
11:49:28 A. I'm sorry. Could you repeat the question.

11:49:29 Q. Sure. Based on the documents you've considered in
11:49:32 this case, have you seen any information indicating that
11:49:36 Yonsung does not store Treprostinil sodium at 2 to 8 degrees
11:49:39 Celsius?
11:49:39 A. No, I have not.
11:49:41 Q. Let's look at DTX 236 and 237 side by side. What are
11:49:48 these documents?
11:49:48 A. So, these documents are the results of measurements
11:49:53 of the temperatures of refrigerators that were used for the
11:49:57 storage of Treprostinil sodium.
11:49:58 Q. And what do the graphs on these documents depict?
11:50:01 A. What the graphs depict is temperature ranges of
11:50:05 function of time.
11:50:06 Q. And what temperature range was the Treprostinil
11:50:11 sodium here stored at in these two fridges?
11:50:13 A. So, this -- the Y axis, the vertical axis, is
11:50:18 temperature degrees C, and it looks like the numbers hover
11:50:21 around 5 or 6 degrees C.
11:50:24 Q. And do you see that spike in the middle of both
11:50:27 graphs?
11:50:27 A. I do.
11:50:28 Q. What is that spike?
11:50:29 A. My understanding is that that spike is a calibration
11:50:33 point to guarantee the accuracy of the measurement, and that
11:50:39 during that spike, the Treprostinil sodium was not being

stored in the refrigerator.

Q. So, what do these graphs tell a POSA about the way that Treprostinil sodium is stored?

A. So, I think they just reinforce my opinion that the storage of this material was consistently between 2 and 8 degrees C. In fact, it looks like an even tighter range in the data that's shown here.

MS. KANNAPPAN: Your Honor, I'd like to offer DTX 236 and 237 into evidence.

MR. CARSTEN: No objection, Your Honor.

THE COURT: Admitted without objection.

(DTX Exhibit No. 236 and DTX Exhibit No. 237 were admitted into evidence.)

BY MS. KANNAPPAN:

Q. So based on the documents you've considered in this case -- can we leave it up? Thank you.

And actually, do you see it says printed by Michael Hunter on both documents at the bottom? It's a little small.

A. I do see that.

Q. Okay. And do you know where Michael Hunter works?

A. I -- I think he works at Liquidia.

Q. So based on the documents you've considered in this case, have you seen any information indicating that Liquidia doesn't store Treprostinil sodium at 2 to 8 degrees Celsius?

11:51:48 A. No, I have not.
11:51:49 Q. Dr. Winkler, are you aware that Yonsung's
11:51:52 Treprostinil sodium sometimes is shipped through an
11:51:54 intermediary called LGM?
11:51:56 A. Yes, I am.
11:51:57 Q. And what conditions does LGM store the Treprostinil
11:52:00 sodium?
11:52:00 A. My understanding is that LGM uses those same
11:52:04 conditions, that it is refrigerated between 2 and 8 degrees
11:52:07 C.
11:52:08 Q. How do you know that?
11:52:09 A. I know that from the testimony that we heard today
11:52:12 and also from the documents that I've reviewed.
11:52:15 Q. So based on the documents that you've considered in
11:52:17 this case, have you seen any information indicating that LGM
11:52:21 does not store Treprostinil sodium at 2 to 8 degrees
11:52:24 Celsius?
11:52:24 A. No, I have not.
11:52:26 Q. We've talked about how Yonsung, LGM, and Liquidia
11:52:30 store Treprostinil sodium. Now let's talk about shipment
11:52:32 between the three companies. Do you have an understanding
11:52:34 of what conditions Treprostinil sodium is shipped from
11:52:38 Yonsung to LGM or LGM to Liquidia or Yonsung to Liquidia?
11:52:42 A. Yes, I am.
11:52:46 Q. What is your understanding?

11:52:47 A. My understanding is that the temperatures during
11:52:51 those shipments are also in refrigerated conditions.
11:52:53 Q. And, Dr. Winkler, are you actually aware that UTC
11:52:57 provided Treprostinil sodium to one of its experts,
11:53:01 Dr. Smyth?
11:53:01 A. I am.
11:53:02 Q. Do you recall when that material was shipped?
11:53:04 A. I think it was fairly recently, last year maybe. I
11:53:11 think it's on the document.
11:53:13 Q. Okay. And do you remember under what conditions that
11:53:16 Treprostinil sodium was shipped to Dr. Smyth?
11:53:19 A. The material was shipped to Dr. Smyth in -- under
11:53:24 cold-pack conditions.
11:53:25 Q. Would a POSA understand cold-pack conditions to be
11:53:29 ambient temperature?
11:53:29 A. No.
11:53:29 Q. Why not?
11:53:30 A. Well, the cold pack is called cold pack because it's
11:53:34 cold, so it's refrigerated at temperatures lower than
11:53:37 ambient.
11:53:39 Q. If a -- if UTC shipped Treprostinil sodium under
11:53:43 cold-pack conditions, how would a POSA store that material
11:53:46 after it was received?
11:53:47 A. Well, I think that the standard practice is that a
11:53:51 POSA would store material under the conditions that were

either stated on the label or under the conditions under which it was received. So, if we received samples refrigerated at 0 or it's refrigerated at minus 78, that's how we would store it.

Q. Okay. So, are you aware that Dr. Nuckolls has pointed to various steps between Yonsung and Liquidia as evidence of storage at ambient temperature despite these specifications?

A. Yes, I am.

Q. And, specifically, are you aware that he pointed to a step in Yonsung's storage process as evidence of storage at ambient temperature?

A. Yes.

Q. Let's turn to DTX 399. What is this document?

A. This is a batch production record from Yonsung.

Q. Dr. Winkler, do you read Korean?

A. No, I do not.

Q. So did you review a translated version of this document?

A. I did.

Q. Could we have DTX 413.

Is this a translated version of the previous document?

A. It is.

MS. KANNAPPAN: Your Honor, I'd like to offer

DTX 399 and DTX 413 into evidence.

MR. CARSTEN: No objection, Your Honor.

THE COURT: Admitted without objection.

(DTX Exhibit No. 399 and DTX Exhibit No. 413 were admitted into evidence.)

BY MS. KANNAPPAN:

Q. So let's go to Page 12 of this translated version and specifically this step that Dr. Nuckolls pointed to.

Do you understand that Dr. Nuckolls pointed to this particular step in the process as evidence of storage at ambient temperature?

A. I am aware, yes.

Q. Do you agree?

A. No, I do not.

Q. Why not?

A. Well, it clearly states refrigerated here.

Q. And what would refrigerated mean to a POSA?

A. Refrigerated, to a POSA, would mean somewhere in the range of 2 to 8 degrees C.

Q. Would a POSA understand refrigerated to mean ambient?

A. No.

Q. And are you aware of any translation issues that Dr. Nuckolls had with this document?

A. Yes, I am.

Q. Turn to DTX 053. Is this an example of a document

11:55:49 that Dr. Nuckolls relied on that had a translation error?
11:55:52 A. Yes.
11:55:54 MS. KANNAPPAN: Your Honor, I'd like to offer
11:55:56 DTX 053 into evidence.
11:55:58 MR. CARSTEN: Objection.
11:55:59 THE COURT: How?
11:56:00 MS. KANNAPPAN: I'll explain in a second. I can
11:56:04 offer it again after we walk through the questions.
11:56:04 THE COURT: Why -- you know, I don't read Korean
11:56:07 either.
11:56:08 MS. KANNAPPAN: That's fair, Your Honor.
11:56:09 THE COURT: Sorry.
11:56:10 BY MS. KANNAPPAN:
11:56:11 Q. So if we go to page 31 of this document, does this
11:56:17 appear to be in English now, Dr. Winkler?
11:56:19 A. It does appear to be in English.
11:56:21 Q. Is this the same document as the original document in
11:56:24 the translation?
11:56:25 A. Yes.
11:56:25 Q. Okay. So let's look at this page of the translation
11:56:29 that Dr. Nuckolls relied on and then the original Korean
11:56:33 document. And let's blow up the same step on both.
11:56:36 I know you said earlier you don't read Korean;
11:56:39 right, Dr. Winkler?
11:56:40 A. I do not.

11:56:41 Q. So how can you tell this was mistranslated?
11:56:43 A. Well, if I look at the Korean text on top, you can
11:56:47 see that there's a parenthetical on the first line and a
11:56:52 parenthetical on the second line. But if I look at the
11:56:54 English translation that Dr. Nuckolls used, there's a
11:56:58 parenthetical on the first line that has the same Q C 002-01
11:57:03 as on the -- as on the first line of the Korean, but the
11:57:08 parenthetical on the second line appears to be missing in
11:57:10 the English translation.
11:57:12 Q. And, Dr. Winkler, are you aware of what that
11:57:15 parenthetical translates to?
11:57:16 A. So I've been advised by counsel that this
11:57:20 parenthetical in Korean actually means refrigerated.
11:57:22 Q. And does that correspond to the refrigerated that you
11:57:24 showed in the previous document?
11:57:25 A. Yes, it does.
11:57:27 MS. KANNAPPAN: Your Honor, I'd like to admit
11:57:29 DTX 053 into evidence.
11:57:31 THE COURT: So, you know, advice by counsel,
11:57:37 being that counsel is certified, you know, this seems to be
11:57:41 the outside his expertise. It's just repeating hearsay. If
11:57:45 it's important, then somebody who's qualified to testify
11:57:49 about translations from Korean to English should be the one
11:57:54 who's presenting this. So I'm going to sustain what I take
11:57:57 to be the objection here.

11:57:59 MR. CARSTEN: Thank you, Your Honor.

11:57:59 MS. KANNAPPAN: Your Honor, actually can we put up DTX 413. And the same step. Or actually let's go to the last page of this -- this exhibit.

BY MS. KANNAPPAN:

Q. Dr. Winkler, what does this page say?

A. This page is from TransPerfect, and it says that they're globally certified under various standards to do translation --

Q. Okay. And --

A. -- from Korean to English.

Q. And if we go to Page 12 of this document, which is what we were looking at earlier, and we look at that step H5, how is has second parenthetical translated?

A. So, what we can see clearly here is that the second parenthetical that's been refrigerated to explicitly state refrigerated.

Q. So is that a separate basis for how you understand the mistranslation issue?

A. Yeah, so on the basis of seeing this, in the -- in the correctly translated document, my conclusion is that the characters that were in the parenthetical in Korean must correspond to this word refrigerated.

Q. And Dr. Nuckolls -- Dr. Winkler --

A. Please.

11:59:14 Q. -- are you aware that Dr. Nuckolls pointed to certain
11:59:18 batches of Treprostinil sodium that reached above 8 degrees
11:59:21 during shipping?
11:59:22 A. Yes, I am.
11:59:25 Q. And in your opinion, do those batches establish that
11:59:28 Liquidia infringes Claim 6 or 8 of the '066 patent?
11:59:32 A. No, they do not.
11:59:33 Q. Why not?
11:59:34 A. Well, because my understanding is that those batches
11:59:37 were never used to prepare pharmaceutical product.
11:59:42 Q. And how do you know that?
11:59:42 A. I know that from Jeffrey Kindig's testimony today in
11:59:47 Court and also from the documents that I reviewed.
11:59:51 Q. Why does it matter that Liquidia doesn't or hadn't
11:59:54 prepared a pharmaceutical product from those batches?
11:59:56 A. Well, my reading of the claim language is that the
12:00:00 claim language refers to a pharmaceutical product or a
12:00:03 pharmaceutical composition. And so that they haven't used
12:00:08 this material to do that.
12:00:09 Q. And specifically what does -- what is the sequence of
12:00:13 preparing that pharmaceutical product compared to storage?
12:00:16 A. So, the -- the preparation of the pharmaceutical
12:00:18 product in the patent language comes after the storage step.
12:00:24 Q. And if we look at DTX 232, which has been shown to
12:00:28 other witnesses, and go to page, this is -- go to page 29.

12:00:36 Have you reviewed this page, Dr. Winkler?
12:00:38 A. I have.
12:00:39 Q. What is it?
12:00:40 A. So, it's a declaration letter from Yonsung that's
12:00:43 essentially guaranteeing the stability of the API, in this
12:00:49 case the Treprostinil sodium, if the temperature -- if there
12:00:54 are temperature excursions below 2 degrees C.
12:00:57 Q. And to your knowledge, has Yonsung provided any
12:00:59 similar guarantee of quality of Treprostinil sodium if it's
12:01:03 shipped above 8 degrees?
12:01:05 A. Not that I've seen, no.
12:01:08 Q. And, Dr. Winkler, are you aware that Liquidia
12:01:12 converts the Treprostinil sodium it receives from Yonsung
12:01:16 into a dry-powder?
12:01:18 A. I am.
12:01:19 Q. And are you aware that Dr. Nuckolls points to certain
12:01:22 step in his -- Liquidia's process as evidence of
12:01:25 infringement of Claim 8?
12:01:27 A. Yes.
12:01:29 Q. Let's turn to DTX 204. Do you recognize this
12:01:34 document?
12:01:34 A. I do.
12:01:35 Q. What is it?
12:01:36 A. This is a description of the manufacturing process
12:01:41 for Liquidia '861 inhalation patent.

12:01:46 MS. KANNAPPAN: Your Honor, like to offer DTX 204 into evidence.

12:01:49 MR. CARSTEN: No objection, Your Honor.

12:01:51 THE COURT: All right. Admitted without objection.

12:01:52 (DTX Exhibit No. 204 was admitted into evidence.)

12:01:53 BY MS. KANNAPPAN:

12:01:53 Q. If we turn to the second page. And blow it up a little so we can see it.

12:01:57 What does -- what is Liquidia's process called?

12:02:02 A. So Liquidia's the process here is called PRINT process.

12:02:06 Q. And what are the steps in that process?

12:02:09 A. The steps are enumerated here. The first step is the preparation of an aqueous stock solution. The second step is the preparation of the engineered particles. The third step is the dry collection of the engineered particles as the bulk powder. The fourth step is the drying and packaging of the bulk powder. And then the fifth step is the encapsulation of the bulk powder into capsules. And the sixth step involves blister packaging and assembly of the commercial drug product kit.

12:02:11 12:02:15 12:02:20 12:02:22 12:02:25 12:02:28 12:02:32 12:02:37 12:02:41

12:02:43 Q. Let's put up the language of Claim 8 next to this disclosure. Does Liquidia's use of Treprostinil sodium in

12:02:47

12:02:52 the PRINT process meet the storage limitation of Claim 8?
12:02:55 A. No, because the storage is before in Claim 8. If we
12:03:01 go to line 57 there, the storage of the Treprostinil salt at
12:03:08 ambient temperature is taking place before the preparation
12:03:12 of the pharmaceutical product because it clearly states here
12:03:15 that that happens, the preparation takes place after
12:03:18 storage. And the preparation is enumerated in these steps
12:03:22 here leading to the formation of the bulk of Liquidia '861
12:03:27 inhalation powder.
12:03:29 Q. And, Dr. Winkler, are you aware that Dr. Nuckolls has
12:03:33 pointed to -- I'm sorry. One second.
12:03:44 MS. KANNAPPAN: Your Honor, I neglected to enter
12:03:46 DTX 232 into evidence, which was the last exhibit that we
12:03:50 were referring to. This is the Receiving Inspection Report
12:03:55 with the declaration letter.
12:03:56 MR. CARSTEN: I thought that was in through the
12:03:59 last witness.
12:04:01 MS. KANNAPPAN: You're right.
12:04:02 MR. CARSTEN: But I'm not entirely sure. If it
12:04:04 hasn't been, I have no objection.
12:04:05 THE COURT: All right. Well, it's admitted
12:04:08 without objection.
12:04:09 (DTX Exhibit No. 232 was admitted into
12:04:09 evidence.)
12:04:09 BY MS. KANNAPPAN:

12:04:10 Q. Sorry. We were talking about Claim 8 verse the PRINT process, Dr. Winkler. Would a POSA understand the steps 1 through 4 on the left side to be storage within the meaning of Claim 8?

12:04:21 A. No.

12:04:22 Q. And why not?

12:04:23 A. Well, remember, I go back to the Hawley's definition. In the Hawley's definition, what it says is that we're storing if we're waiting use. So when the -- when the Treprostinil salt is being stored awaiting use, it's being used in Step 1 when one prepares the aqueous stock solution. So from Step 1 on, I considered these to be steps involved in preparing the pharmaceutical product. In other words, in which it's being used. So these are the steps that take place after the storage of the Treprostinil salt.

12:05:03 Q. Dr. Winkler, are you aware that Dr. Nuckolls pointed to dry box that was used at Step 1 -- and specifically if we can put up PDX 2.30 from Dr. Nuckolls.

Do you remember seeing this slide?

12:05:19 A. I do.

12:05:22 Q. And would you understand what Dr. Nuckolls has highlighted as storage under a Claim 8?

MR. CARSTEN: Your Honor, I object. I specifically asked the witness at his deposition about this document and he pretended he didn't even know what AM and PM

meant on it, so this is a brand new opinion.

MS. KANNAPPAN: Your Honor, I can point you to the deposition testimony where counsel specifically asked about the dry box limitation and --

THE COURT: He just said he did.

MS. KANNAPPAN: I am sorry.

THE COURT: He just said he did.

MS. KANNAPPAN: Sorry. That he asked about the dry box limitation and Dr. Winkler testified as to whether that would be storage or not. And also, Dr. Nuckolls offered this for the first time yesterday. We didn't object because we didn't want to waste the Court's time, but that is partly also why Dr. Winkler didn't put it in his rebuttal report because it wasn't in Dr. Nuckolls's opening report.

And so just out of fairness, Your Honor, we would ask that he be able to address the demonstrative that was put in front of this Court yesterday. I am not going to enter it into evidence.

MR. CARSTEN: It doesn't matter if she enters it into evidence or not. You know, I specifically asked the man what is this. He said I don't -- I can't read these -- these notations. I asked him what is AM and PM? He said I don't know. I could guess in certain contexts, but in this context I'd be reticent to hazard hazards a guess.

You know, I understand that there's an effort

here to try to backfill things, but when I specifically asked the man about an exhibit at his deposition and he says I don't know, I don't know, I think it's a little far afield to now say, oh, now, you're an expert on it, Your Honor. I object.

MS. KANNAPPAN: Your Honor, I can point to a specific page.

THE COURT: Why don't you put the page on the record and then we'll have an adequate basis for you to brief in post-trial.

MR. CARSTEN: Very well. Thank you, Your Honor. Apologies for taking the Court's time on this.

THE COURT: It's all right. What's the page?

MS. KANNAPPAN: It's page is 158, Your Honor.

THE COURT: That's of an expert report or at a deposition?

MS. KANNAPPAN: Of the deposition transcript, Your Honor.

THE COURT: Okay.

MS. KANNAPPAN: I think it goes onto 59.

THE COURT: All right. Well, go ahead.

MS. KANNAPPAN: Okay.

BY MS. KANNAPPAN:

Q. So, Dr. Winkler, I was asking if you remember seeing this demonstrative in Dr. Nuckolls' presentation.

12:07:22 A. I do.
12:07:23 Q. And would you understand these disclosures to be
12:07:28 storage under ambient temperature?
12:07:30 A. No, I wouldn't.
12:07:31 Q. Why?
12:07:32 A. Well, for two reasons. The first reason is that my
12:07:37 understanding is that the Treprostinil sodium, which had
12:07:41 been stored between 2 and 8 degrees is being put in a dry
12:07:45 box at ambient temperature to initiate Step 1 of the PRINT
12:07:52 sequence that we've seen before.
12:07:54 A POSA would understand that a refrigerated
12:07:56 material would have to be calibrated to room temperature so
12:08:01 that it could be used and, in fact, so that it could be
12:08:04 opened without compromising the material. Sometimes you
12:08:09 take something out of a refrigerator and you put it out at
12:08:13 room temperature, you can see beads of moisture on the
12:08:15 bottle. That's what we're -- what's being avoided here by
12:08:18 going into the dry box. That's one thing.
12:08:21 The other thing is that when I looked more
12:08:23 carefully through this document, what I saw is that there
12:08:27 actually are, I think, 17 different operations that are
12:08:34 going on in the dry box. So it's not simply being stored
12:08:38 there, but this is actually representing the initiation of
12:08:42 Step 1 of the PRINT process.
12:08:44 Q. And specifically, what is this number where the

12:08:50 initial time stamp is?
12:08:52 A. I'm sorry. 2-2.
12:08:54 Q. And the number where the final time that Dr. Nuckolls
12:08:58 pointed to was?
12:08:59 A. Step 2-17.
12:09:02 Q. So roughly how many steps happened in those three
12:09:04 hours?
12:09:04 A. So there are -- there are roughly 15 discrete
12:09:09 operations that are taking place during these three hours.
12:09:12 Q. And, Dr. Winkler, are you aware that Dr. Nuckolls
12:09:14 also pointed to hold times between steps 1, 2, and 3 of the
12:09:19 PRINT process as evidence of storage within the scope of
12:09:22 Claim 8?
12:09:22 A. Yes.
12:09:24 Q. Do you agree?
12:09:24 A. No, I don't.
12:09:26 Q. Why not?
12:09:26 A. Because I think these would all be steps that would
12:09:30 be part of the use of the Treprostinil sodium that was --
12:09:36 that's the starting material for this process.
12:09:44 Q. Are you aware that Dr. Nuckolls -- if we can put back
12:09:47 up the six steps of the PRINT process, the previous one --
12:09:53 are you aware that Dr. Nuckolls opined that only steps 5 and
12:09:56 6 of this process are preparing a pharmaceutical product
12:10:01 within the claim meaning of Claim 8?

12:10:03 A. Yes.
12:10:06 Q. Do you agree?
12:10:07 A. No, I don't.
12:10:08 Q. Why not?
12:10:08 A. Well, because I think what we're really doing here is
12:10:12 starting with Treprostinil sodium and that material is being
12:10:18 processed, is being changed, to develop the Liquidia '861
12:10:23 inhalation powder that's really present and sort of final
12:10:28 material, if you will, at the end of Step 4. That bulk
12:10:33 Liquidia '861 inhalation powder at the end of Step 4 on the
12:10:39 slide is then simply being put into capsules and then
12:10:44 blister packaging being done. At that point, I think a POSA
12:10:47 would understand that the chemistry of the material is
12:10:53 unchanged and that one has, essentially, the product or
12:10:57 prepared at the end of Step 4.
12:11:03 Excuse me. That -- another way -- Step 5 and
12:11:05 Step 6, really, are just sort of packaging of the material
12:11:08 that's been prepared in Step 4.
12:11:11 Q. In sum, what is your opinion on whether the batches
12:11:15 shipped above 8 degrees are evidence of infringement of
12:11:17 Claim 6 and 8?
12:11:18 A. I think they are not evidence of infringement of
12:11:25 Claim 6 or Claim 8.
12:11:26 Q. Why not?
12:11:26 A. Because they were never used to prepare a

12:11:28 pharmaceutical product.
12:11:30 Q. And is there anything in that step H5 of Yonsung's
12:11:34 process that provides evidence of infringement of Claim 6 or
12:11:37 8?
12:11:37 A. No, because when we go through the correct
12:11:41 translation, we see that that material is, in fact,
12:11:44 refrigerated, so it was kept between 2 and 8 degrees. And
12:11:48 so, in that case, it's my opinion that it would not infringe
12:11:53 the storage at ambient temperature limitation.
12:11:55 Q. And is there anything in Liquidia's PRINT process
12:11:58 that provides evidence of infringement of particularly
12:12:01 Claim 8?
12:12:02 A. No.
12:12:03 Q. And why not?
12:12:04 A. Well, again, the PRINT process involves the use of
12:12:08 the stored Treprostinil sodium salt, and so by my
12:12:14 understanding of "storage" based on Hawley's, none of the
12:12:17 steps or none of the times in between the different steps of
12:12:21 the PRINT process would constitute storage of Treprostinil
12:12:26 sodium.
12:12:29 Q. Thank you, Dr. Winkler. Let's transition to talking
12:12:31 about validity, now, of the '066 patent.
12:12:33 In your opinion, are the asserted claims of the
12:12:36 '066 patent valid?
12:12:37 A. It's my opinion that they are not valid.

12:12:41 Q. Have you prepared a demonstrative outlining why not?
12:12:43 A. I have.
12:12:44 Q. Let's put up DDX 2.11.
12:12:48 Is this that demonstrative?
12:12:51 A. It is.
12:12:51 Q. Please summarize your opinions on why you believe the
12:12:53 asserted claims of this patent are invalid.
12:12:55 A. So, I, basically, present three opinions here, or
12:12:59 three bases for my opinion that the claims are invalid. The
12:13:05 first is my opinion is that the product-by-process claims
12:13:09 are invalid. And I say that the product-by-process claims
12:13:14 are invalid because the '066 patent claims the same product
12:13:19 that had already been made by a publicly known process. And
12:13:23 that refers specifically to Claims 1, 2, 3, 6 and 9.
12:13:27 The second opinion that I offer on the
12:13:30 invalidity of the '066 patent has to do with the lack of
12:13:34 written description of the reduction in impurities. And
12:13:38 it's my opinion that the inventors were not in possession of
12:13:42 the "a level of one or more impurities found in the starting
12:13:47 batch of Treprostinil is lower in the pharmaceutical
12:13:50 composition" limitation of Claim 1. And that refers to
12:13:56 Claim 1 and also to the dependent Claims 2, 3, and 6.
12:14:00 And then, finally, I think that the claim -- the
12:14:05 patent is invalid because of the indefiniteness of the
12:14:09 storage limitation. And that refers specifically to Claims

12:14:14 6, 8 and the dependent Claim 9.
12:14:18 Q. Let's start with your product-by-process opinion. At
12:14:22 a high level, please explain why you believe that Claims 1
12:14:27 through 3, 6, and 9 are invalid product-by-process claims?
12:14:31 A. So, the reason that I think that the
12:14:36 product-by-process claims are invalid is that they're
12:14:40 claiming the exact same product that had been already made
12:14:43 by a publicly known process.
12:14:47 Q. And so, specifically, are you going to be comparing
12:14:49 two different processes as part of your opinion?
12:14:52 A. I am.
12:14:52 Q. So before we get too far into that opinion, have you
12:14:55 prepared a demonstrative laying out the terminology you will
12:15:00 be using to compare the two processes?
12:15:02 A. Yes, I have.
12:15:03 Q. Let's look at DDX 2.12. Is that your demonstrative?
12:15:06 A. Yes, it is.
12:15:06 Q. And what terminology will you be using?
12:15:09 A. So, the terminology that I'm going to be using to
12:15:12 compare these two different processes are I'm going to refer
12:15:16 to the publicly known process. That's also called the
12:15:19 Moriarty process, because it was disclosed in 2004. It's
12:15:23 also referred to as the Chicago process in various
12:15:27 documents, and it's also simply called the former process.
12:15:30 This publicly known 2004 process makes Treprostinil, which

12:15:36 has the code UT-15 from United Therapeutics.

12:15:41 The process of the '066 patent is referred in
12:15:45 various documents as the Silver Spring process or the
12:15:50 process according to the invention. And this process also
12:15:54 makes exactly the same molecule, which is Treprostinil code
12:15:58 name UT-15.

12:16:03 Q. Okay. Let's get into your analysis now. Let's go
12:16:06 back to the patent. Could you briefly describe your
12:16:08 understanding of product-by-process claim?

12:16:12 A. So, my understanding of a product-by-process claim is
12:16:16 that it claims a product and it claims that product being
12:16:21 prepared by a certain process.

12:16:22 Q. And what is your understanding of the validity of a
12:16:25 claim that might claim a different process, but claims a
12:16:31 known product?

12:16:31 A. My understanding of a product-by-process claim, where
12:16:36 claims are to a previously known product but by a new
12:16:39 process that that claim was not valid.

12:16:44 Q. And if we're looking at the patent, which claims are
12:16:48 product-by-process claims?

12:16:50 A. The product-by-process claims that we're referring to
12:16:58 here are Claims 1, 2, 3, 6 and 9.

12:17:05 Q. And what is the product claimed by these claims?

12:17:08 A. The product that's claimed is the pharmaceutical
12:17:11 composition, which is Treprostinil or a pharmaceutically

12:17:15 acceptable salt thereof for Claims 1, 2, 3, and 6. And for
12:17:21 Claim 9, it's the pharmaceutical product that's claimed by
12:17:26 the process of Claim 8.
12:17:28 Q. And is Claim 9's pharmaceutical product similarly
12:17:31 comprising Treprostinil or a pharmaceutically acceptable
12:17:34 salt thereof?
12:17:35 A. Yes, it is.
12:17:37 Q. Do any of these claims recite any specific overall
12:17:41 impurity of the claimed product?
12:17:43 A. No, they do not.
12:17:45 Q. Do any of these claims recite any numerical impurity
12:17:49 profile of the claimed product?
12:17:50 A. No, they do not.
12:17:53 Q. Do any of these claims require commercial scale
12:17:56 production?
12:17:56 A. No, they do not.
12:17:59 Q. And was Treprostinil actually in any FDA-approved
12:18:03 product by the time the '066 patent was filed?
12:18:05 A. Yes, it was.
12:18:06 Q. What product?
12:18:07 A. Remodulin.
12:18:09 Q. And do you know if processes for synthesizing
12:18:15 Treprostinil were known before the '066 patent was filed?
12:18:16 A. Yes.
12:18:19 Q. Let's turn to DTX 258 and blow up the title.

What is this document, Dr. Winkler?

A. So I had mentioned in my overview in the Moriarty process, there is Moriarty. And this is the Moriarty disclosure in 2004 in the Journal of Organic Chemistry where he describes the synthesis of UT-15 which is, again, the United Therapeutics code for Treprostinil.

Q. Is this -- this paper, was it published before the '066 patent was filed in 2007?

A. Yes, it was.

MS. KANNAPPAN: Your Honor, I'd like to offer DTX 258 into evidence.

MR. CARSTEN: No objection, Your Honor.

THE COURT: Admitted without objection.

(DTX Exhibit No. 258 was admitted into evidence.)

BY MS. KANNAPPAN:

Q. Dr. Winkler, let's go to Page 8 of this document. What is the process for synthesizing Treprostinil described in this Moriarty article?

A. So what Moriarty does is to disclose starting with a molecule that he calls triol 34. That's actually the benzindene triol or BTO. He describes the alkylation and then he describes the hydrolysis to deliver UT-15, which is compound seven, and we've already said the UT-15 is the code, the United Therapeutics code, for Treprostinil.

12:19:54 Q. Let's look at the last page of Moriarty. And I know
12:19:59 it's really small on here, but at a high level, what does
12:20:02 this page describe?
12:20:02 A. So this last page, the bold line there gives the
12:20:06 chemical name of Treprostinil UT-15, and below that in the
12:20:13 next column is a detailed recipe, a detailed experimental
12:20:17 procedure, for the final step. So what it describes is the
12:20:20 final compound is UT-15. That's Treprostinil.
12:20:25 Q. And so, if we're looking at this right-hand column
12:20:29 disclosure, does Moriarty provide the purity of the final
12:20:32 UT-15?
12:20:33 A. Yes, he does. It's on the third to the last line.
12:20:37 Q. And what is that purity?
12:20:38 A. 99.7 percent.
12:20:41 Q. Let's go back to the patent. Last page. Can the
12:20:48 product claimed by these product-by-process claims be
12:20:51 Treprostinil?
12:20:51 A. Yes. It says here clearly that the pharmaceutical
12:20:56 composition can comprise Treprostinil or a pharmaceutically
12:21:01 acceptable salt thereof.
12:21:02 Q. So it doesn't have to be it a salt?
12:21:04 A. So it does not have to be a salt. It could just be
12:21:08 Treprostinil or, as we described, the Treprostinil free
12:21:10 acid.
12:21:11 Q. And how does the Treprostinil claimed by the '066

12:21:14 patent compare to the Treprostinil made by Moriarty?
12:21:16 A. It's the exact same substance.
12:21:20 Q. Let's look to Page 11 where Example 6 of the patent
12:21:24 starts. What is Example 6 disclosing?
12:21:26 A. What Example 6 discloses is a comparison of the
12:21:31 former process, that's the Moriarty process or the Chicago
12:21:37 process, with a working example of the process according to
12:21:40 the '066 patent.
12:21:45 Q. And how do you know that the former process relates
12:21:46 to the Moriarty article?
12:21:47 A. I know that by my examination of this and also from
12:21:53 the 393 IPR in which I was a witness.
12:21:59 Q. And are you aware of inventor testimony on this
12:22:02 topic?
12:22:02 A. Yes.
12:22:03 Q. And what did that inventor testimony say?
12:22:06 A. And the inventor testimony corroborated that,
12:22:09 supported that, the former processes described in the '066
12:22:12 is the Moriarty process.
12:22:14 Q. And did UTC use both the Moriarty process and the
12:22:18 process in the '066 patent to make Treprostinil?
12:22:21 A. Yes, they did.
12:22:22 Q. Let's go to DTX 627. Dr. Winkler, what is this
12:22:28 document?
12:22:28 A. So, this is an optimization report for the formation

of their API of UT-15 in Silver Spring.

Q. And what does this document describe?

A. So, what it describes is the -- well, it's an optimization report for the Silver Spring process. And --

Q. Sure.

MS. KANNAPPAN: Sorry, Your Honor. I'd like to offer DTX 627 into evidence.

MR. CARSTEN: No objection, but I believe it's 627A.

MS. KANNAPPAN: Correct.

THE COURT: Okay. So it's admitted as 627A.

(DTX Exhibit No. 627A was admitted into evidence.)

BY MS. KANNAPPAN:

Q. Dr. Winkler, per the first paragraph of this document, where did UTC use the former Moriarty process?

A. UTC used the former Moriarty process in the Chicago, Illinois, facility.

Q. When did UTC use the Moriarty process in Chicago?

A. They began using it in 1997, and then in 2007, they closed the Chicago facility and moved the manufacturing process to Silver Spring, Maryland.

Q. Is -- and what process did UTC use in Silver Spring, Maryland?

A. So in Silver Spring, Maryland, they switched from the

12:23:48 Chicago process to the Silver Spring process, which is the
12:23:51 process of the '066 patent.
12:23:54 Q. And if we turn to DTX 646, what is this document?
12:23:58 A. This is a letter from UTC to the FDA.
12:24:07 MS. KANNAPPAN: Your Honor, I'd like to offer
12:24:08 DTX 646 into evidence.
12:24:10 MR. CARSTEN: No objection, Your Honor.
12:24:11 THE COURT: Admitted without objection.
12:24:12 (DTX Exhibit No. 646 was admitted into
12:24:13 evidence.)
12:24:13 BY MS. KANNAPPAN:
12:24:14 Q. If we turn to Page 4 of this document. Do you see a
12:24:17 section where -- that's titled Chemistry Manufacturing and
12:24:22 Controls?
12:24:23 A. Yes, I do.
12:24:23 Q. And some questions under that?
12:24:24 A. I do.
12:24:27 Q. Let's turn to DTX 619. Does this document appear to
12:24:32 be UTC addressing some of those questions that we saw in the
12:24:35 previous document?
12:24:35 A. Yes, it does.
12:24:37 MS. KANNAPPAN: Your Honor, I'd like to offer
12:24:39 DTX 619 into evidence.
12:24:40 MR. CARSTEN: No objection, Your Honor.
12:24:41 THE COURT: Admitted without objection.

(DTX Exhibit No. 619 was admitted into evidence.)

BY MS. KANNAPPAN:

Q. If we go to Page 6 of this document. What is this page depicting?

A. So, what this page shows is a schematic of a comparison between the two processes. The former process, the Chicago process or the Moriarty process, it starts with BTO. It gives an alkylation product that here is described as the nitrile, and then on hydrolysis it forms UT-15 or Treprostinil that I'll highlight here in yellow.

And then the new manufacturing process for UT-15 starts with the same starting material with BTO. Alkylation and hydrolysis gives UT-15. And then that material can be treated with a base -- if you don't want to highlight anything -- that material is treated with a base to give the diethanolamine salt, which I'm treating with acid. Leads to the final product. Let's highlight that in yellow. No, over on the left. On the left is the UT-15, and that's the same exact UT-15 as was formed in the former process.

Q. And so if you were just to summarize in simple terms the main differences between the two processes, what would they be?

A. The main difference between the two processes is that in the new process in Silver Spring, they take the UT-15

12:26:08 intermediate, prepare a salt, and finally form the final
12:26:13 product Treprostinil.
12:26:15 Q. Are there any differences in the chemical structures
12:26:18 drawn at the end of those two processes?
12:26:20 A. No, they are the exact same.
12:26:22 Q. And if we go to the next page of this document. Does
12:26:26 the new process eliminate any steps from the former process?
12:26:29 A. Yes, it does.
12:26:31 Q. What step?
12:26:31 A. It eliminates the step of column chromatography.
12:26:35 Q. And if we look at Page 8, what did UTC say is the
12:26:40 reason they eliminated column chromatography?
12:26:42 A. Well, what it states here, is that they eliminated
12:26:46 column chromatography because it was too cumbersome and that
12:26:50 it would require voluminous amounts of solvents if scaled
12:26:54 up.
12:26:55 Q. Do you understand that UTC has taken the position
12:26:58 that the product made by these two processes is structurally
12:27:01 or functionally different?
12:27:02 A. I am aware of that, yes.
12:27:07 Q. Is there -- in your opinion, is there any structural
12:27:10 difference between the UT-15 produced by both processes?
12:27:14 A. No, there is no structural difference.
12:27:16 Q. And how do you know that?
12:27:17 A. Well, I know that because they're the same molecule,

12:27:21 Treprostinil, and that both of these materials prepared in
12:27:27 Chicago and in Silver Spring were both -- were both used to
12:27:32 prepare Remodulin.
12:27:35 Q. So is there any functional difference between the two
12:27:37 products of these processes?
12:27:39 A. I'm sorry?
12:27:41 Q. Is there any functional difference between the two
12:27:44 products of these processes?
12:27:45 A. No, there is no functional difference between the
12:27:47 two.
12:27:47 Q. And how do you know that?
12:27:48 A. Well, I know that because that's what was represented
12:27:50 to the FDA.
12:27:52 Q. Let's take a look at that. If we go to DTX 619,
12:27:57 which I believe has already been offered into evidence and
12:28:00 Page 10. What did UTC tell the FDA about the purity
12:28:03 profiles of the two products?
12:28:05 A. So, what UTC told the FDA is that the drug substance
12:28:11 prepared by the revised route of synthesis, that's the
12:28:14 Silver Spring material, right, is of equivalent purity to
12:28:20 the batches produced by the current synthesis route, that's
12:28:23 the Chicago and Moriarty process, particularly with respect
12:28:26 to purity. So I think a POSA would read this and conclude
12:28:30 that the purities of these two materials were the same, and
12:28:35 one would expect that they would behave -- would be

12:28:38 functionally equivalent.
12:28:40 Q. Have you seen any documents from UTC where the --
12:28:43 where they told the FDA that the Treprostinil made by the
12:28:46 new process is functionally different from the Treprostinil
12:28:50 made by the former process?
12:28:51 A. No.
12:28:53 Q. Have you seen any documents where UTC told the FDA
12:28:56 that the Treprostinil made by the new process is more
12:29:00 efficacious than the Treprostinil made by the Moriarty
12:29:03 process?
12:29:03 A. No.
12:29:04 Q. Have you seen any documents where they told the FDA
12:29:07 that one product was safer than the other?
12:29:12 A. No.
12:29:13 Q. Dr. Winkler, did you do a comparison of the purity
12:29:15 profiles of the products made by these two processes?
12:29:18 A. I did.
12:29:19 Q. Let's go back to DTX 627 and look at Page 7.
12:29:25 Dr. Winkler, what is this page showing?
12:29:27 A. So what this page -- what this page is showing is a
12:29:31 summary of testing data for the UT-15 for the Treprostinil
12:29:38 that was prepared in Chicago. And it actually summarizes
12:29:42 data from 96 different batches of material.
12:29:46 Q. Does this document provide levels of allowable
12:29:50 impurities and total related substances for the Chicago

12:29:54 product?
12:29:54 A. It does.
12:29:56 Q. If you can blow that up.
12:29:57 Is this that disclosure?
12:29:59 A. It is.
12:30:00 Q. And at the risk of having you read every single line
12:30:03 into the record, let's just look at the comparison in the
12:30:07 Silver Spring process. If we go to the same document, two
12:30:10 pages up, what do these pages depict?
12:30:12 A. So, what these pages show is basically analogous
12:30:17 information. It's testing data for UT-15, but you can see
12:30:20 that that's now prepared by the Silver Spring process.
12:30:23 Q. And on the second page of this table, do you see a
12:30:26 list of allowable impurities in the Silver Spring product?
12:30:29 A. I do.
12:30:30 Q. Can we blow that up.
12:30:31 And if we put those two allowable impurities
12:30:34 disclosures side by side, how do they compare?
12:30:37 A. So the limitations for impurities in the Chicago
12:30:41 process and the Silver Spring process were exactly the same.
12:30:46 Q. Let's go to DTX 151.
12:30:49 What is this document, Dr. Winkler?
12:30:53 A. So this is a Certificate of Analysis for a sample of
12:30:58 Treprostinil that was prepared by UTC.
12:31:04 Q. And what process was used to make this UT-15?

12:31:07 A. This is from 2020, and you can see that it's coming from Silver Spring.

MS. KANNAPPAN: I'd like to offer DTX 151 into evidence.

MR. CARSTEN: No objection, Your Honor.

THE COURT: Admitted without objection.

(DTX Exhibit No. 151 was admitted into evidence.)

BY MS. KANNAPPAN:

Q. And if we put -- sorry, do you see on this Certificate of Analysis a similar disclosure of allowable impurities?

A. I do.

Q. If we blow that up and put that side by side with the Chicago impurities that we looked at a few minutes ago, how do these compare?

A. So, what -- it's a little confusing. These are exactly the same impurities, but the order in which they're listed is a little different.

Q. So based on the certificates of analysis that you reviewed from the prior Moriarty Chicago process and the new '066 Silver Spring process, how do the products compare?

A. They're the same.

Q. Now, there's another measurement on these two documents that we're looking at. It's the row below. It

says assay HPLC. Can we blow that up.

Dr. Winkler, in the Chicago specification, which was on the right side of your screen at the top, what was the allowable assay range?

A. So this is from the Chicago page, and what it says is that it has to be not less than 97 percent and not more than 101 percent.

Q. And what's the similar specification for the 2020 Silver Spring Certificate of Analysis?

A. And in Silver Spring, that corresponding limitation is not less than 98 percent and not more than 102 percent.

Q. So what is the difference between these two?

A. The difference is one percent.

Q. Now, let's look at what was actually measured for assay HPLC values in the Chicago batches. What was the minimum?

A. So the minimum value that was measured in Chicago was 98.9 percent.

Q. And what was the maximum?

A. And the maximum was 100.3 percent.

Q. Do these numbers fall within the new 2020 Certificate of Analysis's, 98 to 102 percent range?

A. Yes. So certainly these two numbers, both the minimum and maximum obtained in Chicago, fall within this new HPLC limitation for Silver Spring.

12:33:27 Q. So, how would a POSA understand the one percent change in assay HPLC range in the specifications?
12:33:34 A. With respect to the differences between the material in Chicago and the material in Silver Spring, no difference at all.
12:33:44 Q. And are you aware that UTC actually pointed to this 1 percent difference in an argument to the Patent Trial and Appeal Board?
12:33:51 A. I am.
12:33:52 Q. And what was the board's opinion on that issue?
12:33:54 A. The board rejected that.
12:33:56 THE COURT: So, yeah. Yeah.
12:33:59 MS. KANNAPPAN: Okay. I'll move on, Your Honor.
12:34:01 MR. CARSTEN: Thank you, Your Honor.
12:34:02 BY MS. KANNAPPAN:
12:34:02 Q. Other than these UTC documents, did you review any batch data on the purity profiles on the Chicago versus Silver Spring products yourself?
12:34:10 A. Yes, I did.
12:34:11 Q. Where did you get that data from?
12:34:13 A. I got that data from the 393 IPR from Dr. Williams, who was a UTC expert in that case.
12:34:24 Q. Let's go to that data. If we go to DTX 664. What is this document?
12:34:32 A. This is a declaration by Robert Williams in his

12:34:36 support of UTC in that IPR.
12:34:40 Q. So Dr. Williams was -- who was he an expert for?
12:34:43 A. For UTC.
12:34:44 Q. And if we go to Page 2 of this document, where is the
12:34:49 batch data you referred to?
12:34:51 A. The batch data that I referred to is in these
12:34:54 appendices, A and B.
12:34:56 MS. KANNAPPAN: Your Honor, I'd like to offer
12:34:58 DTX 664 into evidence.
12:34:59 MR. CARSTEN: Your Honor, this is material back
12:35:01 from the old 393 IPR. We had a motion in limine about this.
12:35:05 It seems like they're just using it as a proxy for somehow
12:35:09 explaining what the old process provided, in which case I
12:35:12 think that doesn't run afoul of motion in limine one. So no
12:35:16 objection on that basis.
12:35:18 THE COURT: Okay. Your non-objection is
12:35:21 approved.
12:35:23 Go ahead.
12:35:23 (DTX Exhibit No. 664 was admitted into
12:35:25 evidence.)
12:35:25 BY MS. KANNAPPAN:
12:35:25 Q. Did you prepare a demonstrative explaining your
12:35:28 analysis of this data, Dr. Winkler?
12:35:29 A. I did.
12:35:31 Q. Let's display DDX 2.13. Is this one of those

12:35:36 demonstratives?
12:35:36 A. It is.
12:35:37 Q. So how many Chicago batches did you analyze?
12:35:39 A. 46.
12:35:40 Q. And do you list the exhibits that you relied on from
12:35:44 which you got this data?
12:35:45 A. I do.
12:35:46 Q. And where do you list it?
12:35:47 A. At the bottom left.
12:35:51 MS. KANNAPPAN: Your Honor, I'd like to offer
12:35:52 the exhibits that are listed at the bottom left in evidence,
12:35:55 DTX 072 and DTX 658.
12:35:57 THE COURT: I'm sorry. What kind of things are
12:35:59 those exhibits?
12:36:00 MS. KANNAPPAN: They have the certificates of
12:36:02 analysis where these values come from.
12:36:06 MR. CARSTEN: Your Honor, I think I'd like to
12:36:09 take a look at them and we can meet and confer about them.
12:36:11 I don't know how voluminous they are. I don't want to load
12:36:14 you down with stuff. It sounds like he's going to testify
12:36:16 to what this is.
12:36:17 THE COURT: Yeah, I mean, why don't you do that.
12:36:24 I take it this is a summary of what all those documents
12:36:28 show; right?
12:36:29 THE WITNESS: That's correct.

12:36:31 MR. CARSTEN: It seems like 1,006 might be an
12:36:34 appropriate remedy here.
12:36:35 THE COURT: Yeah. Why don't you all talk about
12:36:37 it. He's going to continue to testify, but my preference
12:36:40 would be that you agree that this is the only document that
12:36:43 needs to be admitted for this point. But, you can talk
12:36:46 about it once amongst yourselves and see what you can come
12:36:50 up with.
12:36:50 Go ahead.
12:36:51 MS. KANNAPPAN: Thank you, Your Honor.
12:36:51 BY MS. KANNAPPAN:
12:36:52 Q. Dr. Winkler, did you exclude ten batches from your
12:36:54 analysis?
12:36:54 A. I did.
12:36:55 Q. Why did you do that?
12:36:55 A. I excluded ten batches because when they were working
12:36:59 out this process, the initial batches are sometimes called
12:37:03 development batches where they're kind of just working
12:37:06 things out. And so the purities that are obtained in those
12:37:09 initial batches are typically not -- not thought to be
12:37:13 reliable. So I removed them from my analysis and really
12:37:16 only considered once they had things working -- worked out.
12:37:20 Q. Did UTC's expert Dr. Williams similarly exclude those
12:37:24 same ten batches?
12:37:25 A. Yes, he did.

12:37:26 Q. And what was the average purity that both you and
12:37:29 Dr. Williams got for these batches?
12:37:30 A. The average purity that I calculated was
12:37:34 99.7 percent.
12:37:38 Q. And how does your calculated value compare to the
12:37:41 Moriarty publication we were talking about a few minutes
12:37:44 ago?
12:37:44 A. It's the same value that Moriarty published in 2004.
12:37:48 Q. And if we go to the next page of your demonstrative,
12:37:52 have you considered the average purity of the Silver Spring
12:37:55 batches?
12:37:56 A. Yes, I have.
12:37:57 Q. What was that purity?
12:37:58 A. That purity was also 99.7.
12:38:02 Q. And did you do the calculation for the Silver Spring
12:38:05 batches yourself?
12:38:05 A. No, I simply used the calculation that Dr. Williams
12:38:08 had performed.
12:38:11 MS. KANNAPPAN: And similar issue here, Your
12:38:12 Honor. The documents that are on the bottom left are
12:38:16 actually Dr. Williams' calculation. Is it okay to enter
12:38:19 those into evidence?
12:38:20 THE COURT: Why don't we do the same thing, see
12:38:22 if you really need to.
12:38:23 MR. CARSTEN: Your Honor, this is the

demonstrative that I objected to earlier in the day as well, so we can talk this through.

THE COURT: All right.

BY MS. KANNAPPAN:

Q. And are you aware that Dr. Williams did an analysis of specific individual impurities measured in this batch data?

A. Yes.

Q. What would a POSA attribute any differences in individual impurities to?

A. The individual impurities, remember, are going to be very tiny amounts. And so, the variations in those impurities from batch to batch, I think one would attribute simply to inter-batch variations.

Q. And are you aware that in this proceeding, Dr. Fawzi did a similar reanalysis of the same data about specific individual impurities?

A. Yes, I am.

Q. And assuming Dr. Fawzi's impurity calculations are correct, did UTC inform the FDA about these impurity differences?

A. Not that I am aware of, no.

Q. Did UTC tell the FDA that the Treprostinil made by this new process was more pure than the Treprostinil made by the old process?

12:39:34 A. Not that I am aware of, no.
12:39:37 Q. And remind us. What did UTC tell the FDA about the
12:39:40 comparative impurities of the products?
12:39:43 A. Well, in the document that we looked at before, they
12:39:46 said that the purity of the material from the '066 was the
12:39:50 same as it got from the previous process of Moriarty.
12:39:55 Q. So in your opinion, would a POSA understand the
12:39:57 differences that Dr. Fawzi points to in individual
12:40:01 impurities to impart any structural or functional
12:40:05 differences between the two products?
12:40:06 A. No.
12:40:08 Q. Why not?
12:40:09 A. Well, because the miniscule levels of impurities that
12:40:14 Dr. Fawzi was analyzing, first of all, they're very, very
12:40:18 small, and there's been no indication that at those
12:40:22 concentrations that any of those impurities would impart any
12:40:27 functional difference to the compound in terms of efficacy,
12:40:31 toxicity, or any other consideration.
12:40:33 Q. Any biological activity at those levels?
12:40:35 A. There's no biological activity that I'm aware of at
12:40:39 those levels.
12:40:40 Q. In summary, what is your opinion on whether the
12:40:43 product of the publicly known Moriarty Chicago process is
12:40:47 the same as a the products claimed by Claims 1, 2, 3, 6, and
12:40:53 9 of the '066 patent?

12:40:55 A. My opinion is that they're structurally and
12:40:59 functionally the same.
12:41:01 Q. Okay, Dr. Winkler. Let's talk about your next
12:41:05 invalidity opinion, which is the reduction of impurity
12:41:08 limitations of Claim 1 lacking written description. We'll
12:41:11 just look at Claim 1 of the patent.
12:41:15 And do you do you see the limitation in blue?
12:41:17 A. I do.
12:41:19 Q. Dr. Winkler, harkening back to our infringement
12:41:22 discussion, what was the comparison that UTC had to do to
12:41:28 demonstrate infringement of the limitation in blue?
12:41:31 A. So what UTC had to do was to demonstrate that the
12:41:37 level -- that the level of impurities resulting from
12:41:41 alkylation and hydrolysis of BTO was lower in the
12:41:45 pharmaceutical composition than it was in the starting batch
12:41:48 of Treprostinil.
12:41:49 Q. And specifically, what compounds was it comparing?
12:41:53 A. I think I just said comparing the impurities
12:41:58 resulting from alkylation and hydrolysis of BTO in the TN
12:42:06 versus the TN02. In other words, in the Treprostinil salt
12:42:10 versus the Treprostinil free acid.
12:42:13 Q. And does the '066 patent provide information to make
12:42:16 that same comparison in its process?
12:42:17 A. No, it does not.
12:42:21 Q. Does the '066 patent identify any impurities after

12:42:26 1 alkylation of BTO?
12:42:27 2 A. No, it does not.
12:42:29 3 Q. Does the '066 patent identify any impurities after
12:42:33 4 hydrolysis?
12:42:33 5 A. No, it does not.
12:42:36 6 Q. And do you know if the inventors actually measured
12:42:40 7 impurities after alkylation or hydrolysis?
12:42:42 8 A. Well, in fact, I know that they didn't because their
12:42:47 9 testimony was that their invention was not testing materials
12:42:52 10 throughout the different steps of the reaction process.
12:42:57 11 Q. And why did they not do that?
12:42:58 12 A. Because I think their idea was that they were going
12:43:02 13 to -- it was going to be purified in the salt formation, so
12:43:05 14 they didn't have to look at the purity levels or impurities
12:43:10 15 in the -- in either of the reactions leading up to the final
12:43:14 16 salt.
12:43:18 17 Q. And does the '066 patent identify any impurities
12:43:21 18 after salt formation?
12:43:21 19 A. No, it does not.
12:43:24 20 Q. Does the '066 patent provide any comparison of
12:43:27 21 impurities between the starting batch and the final
12:43:31 22 pharmaceutical composition?
12:43:32 23 A. No, it does not.
12:43:34 24 Q. So what is your opinion as to whether the patent
12:43:37 25 conveys that the inventors had possession of this reduction

12:43:40 in impurities limitation?
12:43:41 A. I think the lack of that information tells a POSA
12:43:46 clearly that they did not have possession of the limitation
12:43:49 of demonstrating that the level of impurities resulting from
12:43:53 alkylation and hydrolysis of BTO was lower in the
12:43:58 pharmaceutical -- in the pharmaceutical composition than it
12:44:03 was in the starting batch of Treprostinil.
12:44:06 Q. Let's now turn to talking about what is disclosed in
12:44:09 the patent. I apologize because we're going to just have to
12:44:13 walk through each of the examples so that we can cover what
12:44:18 Dr. Scheidt has argued.
12:44:19 So let's look at Examples 1 through 6 starting
12:44:21 with Example 1.
12:44:22 Are you aware that Dr. Scheidt points to various
12:44:26 lines in Examples 1 through 6 as disclosures of generation
12:44:29 and reduction of impurities resulting from alkylation and
12:44:32 hydrolysis of BTO?
12:44:33 A. I am.
12:44:36 Q. If we look at Example 1, what does Example 1
12:44:38 describe?
12:44:38 A. Example 1 teaches exactly what's in the title there,
12:44:43 the alkylation of benzindene triol. So what you see on the
12:44:46 left is the chemical structure BTO, and on the right is the
12:44:50 structure of the alkylation product, the -- what's called
12:44:54 the benzindene nitrile.

12:44:56 Q. If we look at the paragraph disclosure under these
12:45:00 structures, does the patent disclose measurement of any
12:45:03 impurities after the alkylation step?
12:45:05 A. No, it does not.
12:45:10 Q. And what does it describe of that last step?
12:45:14 A. It simply says that the crude benzindene nitrile,
12:45:20 crude product was used in the next step without any
12:45:22 purification.
12:45:23 Q. Does the statement identify any specific impurities
12:45:27 resulting from alkylation of benzindene triol?
12:45:29 A. No, it does not.
12:45:31 Q. And just a foundational question. You understand
12:45:33 that Dr. Scheidt is UTC's expert but might testify later in
12:45:38 trial; correct?
12:45:39 A. That is correct.
12:45:41 Q. And are you aware that Dr. Scheidt points to the fact
12:45:44 that the patent discloses that the triol is light brown as
12:45:49 opposed to clear as a disclosure that there were impurities
12:45:54 from alkylation of BTO?
12:45:56 A. Yes.
12:45:56 Q. Do you agree?
12:45:57 A. No.
12:45:57 Q. Why not?
12:45:58 A. Well, there's nothing in the patent that teaches me
12:46:03 what the color of pure benzindene nitrile is. So, I can --

12:46:07 I could guess what that is, but I don't know. It could be
12:46:10 that it's light brown. If it's not light brown, if it's
12:46:14 colorless and the light brown color is an indication of
12:46:18 impurity, there's nothing about the descriptor "light brown"
12:46:22 that tells me that the light brown material is the result of
12:46:28 the alkylation of BTO as opposed to, for example, an
12:46:33 impurity in the alkylating agent or an impurity in the
12:46:37 solvent or coming from anywhere else.
12:46:40 Q. And do you see at line 30 there's a sentence about
12:46:42 the progress of the reaction being monitored by TLC?
12:46:46 A. Yes, I do.
12:46:48 Q. What is TLC?
12:46:49 A. TLC is thin layer chromatography. It's a common
12:46:55 technique that we use in the laboratory for exactly this
12:46:57 purpose, to monitor the progress of a reaction.
12:47:00 Q. And how is TLC being used in this patent?
12:47:03 A. So the TLC would be being used to monitor the
12:47:08 disappearance of the starting material and the appearance of
12:47:11 the product.
12:47:12 Q. Would a POSA understand from this sentence disclosure
12:47:14 that TLC was used to identify or measure impurities?
12:47:18 A. No.
12:47:19 Q. Why not?
12:47:20 A. Well, because the impurities that we've been
12:47:23 describing are obtained in such low levels that a POSA would

know that they would not be visible by TLC. There wouldn't be enough of them to -- TLC is a plate -- it's on a plate of glass. It would be too -- would be too little of the materials for you to be able to see them.

Q. And do you know if the inventors actually used TLC to identify or measure impurities?

A. They did not.

Q. How do you know he that?

A. From the inventor testimony at deposition.

Q. And remind us. Did the inventors measure impurities at this step at all?

A. They did not.

Q. Let's look at Example 2 next. What does -- what reaction is disclosed at Example 2?

A. So Example 2 is the second step of the process. It's the hydrolysis of the benzindene nitrile that's shown in the -- on the left upper left there. That's the alkylation product. And it's now being hydrolyzed to give this molecule, and this is actually the chemical structure of the Treprostinil.

Q. So would that Treprostinil that you just pointed to, is that the starting batch as it's referred to in Claim 1?

A. Yes, it is.

Q. Does Example 2 provide the purity of this starting batch?

12:48:38 A. No, it does not.
12:48:39 Q. And do you see the table at the top of Example 2's
12:48:43 disclosure.
12:48:44 A. I do.
12:48:44 Q. And there's a note below it?
12:48:46 A. Yes.
12:48:48 Q. What does that note say?
12:48:49 A. The note says that this weight, in other words, the
12:48:53 starting weight of the benzindene nitrile that's used in the
12:48:58 hydrolysis reaction, this weight is based on 100 percent
12:49:02 yield from the previous step. It is not an isolated yield.
12:49:05 Q. Are you aware that Dr. Scheidt points to this note as
12:49:08 evidence that impurities introduced in the previous step
12:49:11 were not removed prior to the hydrolysis step?
12:49:14 A. Yes.
12:49:15 Q. And how would you understand what this note
12:49:18 discloses?
12:49:18 A. Well, all this note discloses is that they're using a
12:49:24 theoretical number for the weight of the benzindene nitrile
12:49:28 for the mass of benzindene nitrile that's being used in this
12:49:32 reaction. They're not actually weighing it. They're just
12:49:34 saying that if all of the BTO was transformed to benzindene
12:49:39 nitrile, they would have gotten 1,397 grams.
12:49:43 Q. And in fact, what does this note assume about the
12:49:46 purity of the compounds listed there?

12:49:48 A. Well, it's assuming that the material is in fact, all
12:49:55 benzindene nitrile.
12:49:58 Q. Do you see at column 11, line 14, a similar
12:50:03 disclosure in this example about the progress of the
12:50:05 reaction being monitored by TLC?
12:50:07 A. I do.
12:50:08 Q. And would a POSA understand this disclosure as
12:50:10 identifying any specific impurities resulting from this
12:50:12 step?
12:50:13 A. No.
12:50:14 Q. And why not?
12:50:15 A. Well, for the same reason as the last example that we
12:50:18 looked at. The amounts of impurities that we've been
12:50:21 describing in these reactions are so small that a POSA would
12:50:26 know that they couldn't be observed by TLC.
12:50:28 Q. And do they mention the fact they used TLC to observe
12:50:31 impurities in this step?
12:50:33 A. They did not.
12:50:34 Q. And if we look at line 46 of this column, do you see
12:50:38 a disclosure that the filtrate at the end of this step is
12:50:41 pale yellow?
12:50:42 A. Yes, I do.
12:50:43 Q. Would a POSA understand this color disclosure as
12:50:46 evidence of impurities resulting from alkylation and
12:50:50 hydrolysis of BTO?

12:50:51 A. No.
12:50:52 Q. Why not?
12:50:52 A. Well, because again, all we have here is a pale
12:50:57 yellow solution. So, if the Treprostinil is itself
12:51:02 colorless, then the pale yellow solution is something that's
12:51:06 not Treprostinil. But we don't know from reading this
12:51:11 whether that pale yellow material is resulting from the
12:51:16 alkylation and hydrolysis of BTO or whether it's some other
12:51:19 garbage that got in the flask. It could be an impurity in
12:51:23 one of the reagents. There have been multiple reagents now
12:51:26 through these two steps. It could be from one of the
12:51:29 solvents. A POSA would have no idea, looking at just pale
12:51:32 yellow color, that that represents -- that that's an
12:51:37 indication of the presence of impurities resulting from
12:51:41 alkylation and hydrolysis of BTO.
12:51:45 Q. Finally, do you see in the same last paragraph of
12:51:49 Example 2 the rest of that sentence where it says the
12:51:53 filtrate was reduced to a involve 35 to 50 -- or sorry -- so
12:51:58 35 to 40 liters by evaporation in vacuum for direct use in
12:52:03 the next step?
12:52:03 A. Yes, I do.
12:52:05 Q. Does this disclose an amount of impurities resulting
12:52:08 from alkylation and hydrolysis of BTO, if any, that were
12:52:12 carried over into the next step?
12:52:14 A. No, it certainly doesn't.

12:52:15 Q. And remind us. Did the inventors measure impurities
12:52:18 after hydrolysis at all?
12:52:20 A. Not per the deposition testimony that I saw. No.
12:52:25 Q. Let's talk about Example 3 next. What reaction is
12:52:30 disclosed here, Dr. Winkler?
12:52:31 A. So here, the pale yellow solution which is the
12:52:36 starting batch in this sequence is being treated with a base
12:52:43 with diethanolamine to form the salt to form the
12:52:49 Treprostinil diethanolamine salt.
12:52:51 Q. And if we look at Column 12 -- sorry. Does Example 3
12:52:55 provide the purity of the resulting Treprostinil
12:52:59 diethanolamine salt?
12:53:00 A. Of the resulting Treprostinil diethanolamine salt.
12:53:05 Q. Yeah.
12:53:05 A. No, it does not.
12:53:06 Q. And if we look at the note that's now on the screen
12:53:09 below the table in Column 12.
12:53:11 A. Yes.
12:53:12 Q. What does this note say?
12:53:13 A. This note says that the weight of the Treprostinil
12:53:18 that's being used in salt formation is based on a
12:53:22 100 percent yield from benzindene triol. It's not an
12:53:25 isolated yield. The Treprostinil was carried from the
12:53:29 previous step and ethanolamine solution is used as such for
12:53:34 this step. So remember, if you have a pale yellow solution,

12:53:36 you don't really know exactly how much Treprostinil is in
12:53:39 there. And that's why they're using this theoretical number
12:53:43 of 1,464 that comes from knowing exactly how much BTO was
12:53:49 used at the very beginning and then imagining that it all
12:53:53 was completely alkylated and all was completed hydrolyzed.
12:53:58 Q. And what does this note assume about the purity of
12:54:00 these compounds?
12:54:01 A. Well, again, it's based -- they're saying that it's
12:54:04 based on 100 percent yield. So you would only get 1,464
12:54:08 there if the material is Treprostinil and nothing but --
12:54:13 Q. So what would that number of purity be for us --
12:54:15 A. So it would be 100 percent.
12:54:17 Q. -- laymen.
12:54:17 I'm sorry. Can you say it again?
12:54:18 A. So it would be 100 percent.
12:54:19 Q. Let's talk about Example 4 next. What is disclosed
12:54:26 in Example 4?
12:54:27 A. Example 4 is sort of a purification of the salt that
12:54:34 was made with Example 3. So, it's preparing a heptane
12:54:39 slurry of the Treprostinil diethanolamine.
12:54:42 Q. And if we look at the table at the bottom of that
12:54:44 column, what does that table convey to a POSA?
12:54:47 A. So what that table conveys is a measurement of purity
12:54:52 of the Treprostinil diethanolamine as determined by HPLC.
12:54:57 Q. Does this table provide any information on

impurities?

A. No, it does not.

Q. So do we have any information on whether impurities resulting from alkylation and hydrolysis of BTO were reduced with the salt formation?

A. We do not.

Q. If we go to Example 5. What is this example disclosing?

A. So what this example is disclosing is taking the purified Treprostinil diethanolamine salt and treating it with acid to regenerate the Treprostinil itself, the Treprostinil carboxylic acid.

Q. If we look at column 14, line 47. Do you see that the patent discloses that the Treprostinil, the crude Treprostinil, is an off-white solid?

A. Yes.

Q. Are you aware of a compound that can be pale yellow or white but with the same purity?

A. Yes.

Q. Give me an example of such a compound.

A. Well, an example of a compound that's been described at high purity levels as being either off-white or pale yellow is Treprostinil sodium itself.

Q. And are you aware that Dr. Scheidt points to this disclosure as evidence that impurities from the prior

12:56:17 alkylation and hydrolysis steps were removed?
12:56:19 A. Yes.
12:56:20 Q. Does this reference to an off-white Treprostinil --
12:56:25 crude Treprostinil solid tell you anything about whether or
12:56:30 which impurities from the prior alkylation and hydrolysis
12:56:35 steps were removed?
12:56:36 A. No.
12:56:38 Q. Let's talk about Example 6 now, and that's the last
12:56:41 example in the patent. Remind us. What is this example
12:56:44 showing?
12:56:45 A. So, again, this is the example where they compare the
12:56:49 former process (the Moriarty process/Chicago process), with
12:56:53 the process of the '066 patent.
12:56:57 Q. And if we look at all that -- all those steps in a
12:57:00 little bit of a blow up. At what step of the new process --
12:57:05 so the on column on the right -- is the starting batch of
12:57:10 Treprostinil formed?
12:57:11 A. The starting batch of Treprostinil, according to this
12:57:14 new process, is formed in Step 30.
12:57:19 Q. And at what step of the new process is the final
12:57:23 pharmaceutical product formed?
12:57:24 A. So the final product is formed in Step 51 in the new
12:57:30 process.
12:57:31 Q. And what do steps 52 and 53 convey?
12:57:33 A. 52 and 53 are just the characterization of 51. In

other words, they give a percent yield and they give the purity.

Q. What steps' compounds would a POSA compare to see if there was a reduction in impurities as claimed in Claim 1?

A. So, to meet the limitation of Claim 1, you would have to compare the impurity level of the material that was prepared in Step 51 in the working example of the -- of the '066. We'd have to compare the -- the material from Step 51 with the material from Step 30.

Q. Does the patent, in fact, provide any purity at Step 30 to do that comparison?

A. No, in fact, the -- the Treprostinil is not even isolated. It's just in solution.

Q. Are you aware that to get around this, Dr. Scheidt instead compares the former process compound at Step 51 and the new process compound at Step 51?

A. I am.

Q. Would a POSA understand that to be the relevant comparison for the reduction of impurities limitation of Claim 1?

A. No, because the material that's in Step 51 of the -- of the old process is not the material that's being used to prepare the material in Step 51 of the new process. So, the material, the Step 51 material, UT-15, from the former process is different and was not used as the starting batch

12:59:15 for the '066.
12:59:16 Q. And in fact, what is one difference in the way that
12:59:23 the Step 51 compound of the former process was produced
12:59:30 compared to the -- the intermediate starting batch of the
12:59:34 new process?
12:59:35 A. Well, we talked about this already. Right. There
12:59:38 are two big differences between these processes, are that
12:59:41 the old process uses chromatography after the alkylation
12:59:46 step. That's been removed in the new process.
12:59:48 And the second difference is the salt formation
12:59:51 which takes place in the new process that did not take place
12:59:55 in the Chicago process but more -- in terms of the UT-15
01:00:00 that's in Step 51 of the former process, the big difference
01:00:04 is that UT-15 underwent column chromatography, but the
01:00:11 Treprostinil batch in Step 30 of the new process never
01:00:14 underwent column chromatography. So, those -- those would
01:00:18 represent, I think, to a POSA significant differences.
01:00:21 Q. And in particular would a POSA expect differences in
01:00:24 impurities, though?
01:00:25 A. Yes.
01:00:27 Q. Why is that?
01:00:28 A. Well, because, again, we said that the purpose of
01:00:32 chromatography is to purify, is to remove impurities, so
01:00:35 there would be -- impurities removed by column
01:00:37 chromatography in the former process for the preparation of

01:00:41 the UT-15. That would not have been removed in the material
01:00:47 that forms the starting batch of the working example.
01:00:51 Q. And finally, Dr. Winkler let's turn to column 17,
01:00:55 line 29. And do you see the sentence that's highlighted on
01:01:00 your screen?
01:01:01 A. I do.
01:01:03 Q. And are you aware that Dr. Scheidt points to this
01:01:05 sentence as disclosing that the inventors have possession of
01:01:08 the reduction of impurities limitation of Claim 1?
01:01:11 A. Yes.
01:01:12 Q. Do you agree?
01:01:13 A. No.
01:01:13 Q. Why not?
01:01:14 A. Well, because what this sentence says is that the
01:01:17 impurities carried over from the intermediate steps are
01:01:22 removed during carbon treatment and salt formation. It does
01:01:24 not say that the impurities that are specifically resulting
01:01:30 from the alkylation of BTO and hydrolysis are being removed.
01:01:38 And it gives me no indication of what impurities are present
01:01:45 and are being reduced in the course of this process or by
01:01:50 how much.
01:01:51 Q. And where it says impurities carried over from
01:01:55 intermediate steps, what are some example of intermediates
01:01:58 that could have been carried over from the intermediate
01:02:00 steps that don't fall within the scope of Claim 1?

01:02:03 A. Well, we've talked about these already. In other
01:02:09 words, there could be impurities in the reagents. There
01:02:12 could be impurities in the solvents. There could be
01:02:14 impurities in the starting materials, all of which would be
01:02:18 carried over from these steps but would not result from the
01:02:22 alkylation and hydrolysis of the BTO.
01:02:27 Q. And in fact, just to ask you one more time,
01:02:30 Dr. Winkler, per your review of the inventor testimony, did
01:02:33 the inventors ever measure the supposed impurity removal?
01:02:38 A. They did not.
01:02:40 Q. In sum, does the '066 patent disclose anywhere a
01:02:44 reduction in impurities resulting from alkylation and
01:02:48 hydrolysis of benzindene triol between a starting batch or
01:02:52 Treprostinil and a post-salt formation pharmaceutical
01:02:55 composition?
01:02:55 A. No, it does not.
01:02:58 Q. And before we move on, let's look back at the first
01:03:00 page of this patent. Doctor, what is the title of this
01:03:18 patent on the top right? Top left, sorry.
01:03:21 A. The title of the patent is Process to Prepare
01:03:24 Treprostinil, The Active Ingredient in Remodulin.
01:03:28 Q. Is that the same Remodulin we were talking about
01:03:30 earlier that was used or that was made by the Moriarty
01:03:33 Chicago process?
01:03:34 A. I'm sorry. Could you repeat your question?

01:03:41 Q. Sure. Is that Remodulin that's referred to here the
01:03:44 same Remodulin that was made by the Moriarty Chicago
01:03:48 process?
01:03:48 A. Yes.
01:03:52 THE COURT: All right. So should we break for
01:03:54 lunch here?
01:03:55 MS. KANNAPPAN: We can, Your Honor, but the last
01:03:57 section is very short, so it's up to you.
01:03:58 THE COURT: Okay. Let's break for lunch. All
01:03:58 right.
01:04:03 MS. KANNAPPAN: I see you don't trust us.
01:04:03 THE COURT: So, we'll start again at 2 o'clock.
01:04:09 DEPUTY CLERK: All rise.
01:49:45 (Recess was taken.)
01:58:49 DEPUTY CLERK: All rise.
01:58:57 THE COURT: All right. Let's be seated and --
01:59:01 oh, here you are. Okay. Ready to go.
01:59:05 BY MS. KANNAPPAN:
01:59:07 Q. Dr. Winkler, I'd like to now turn to your final
01:59:09 invalidity opinion, that the term "storage" in Claim 6 and 8
01:59:13 is indefinite. And what is the basis for your opinion?
01:59:17 A. The basis, broadly, for my opinion is that two
01:59:22 different Courts have now defined this in very different
01:59:26 ways.
01:59:27 Q. And have you prepared a demonstrative listing these

different definitions?

A. I have.

Q. Let's go to DDX 2.15.

Can you briefly describe what you have depicted on this demonstrative?

A. So what I show here is that in the PTAB proceeding, "storage" was defined as being at ambient temperature for at least three months, while this Court has defined "storage" as its plain and ordinary meaning.

Q. And where did the PTAB get the three months from?

A. The PTAB, as you can see below there, determined that based on the applicant's statements during the prosecution of the '623 application, which was the parent of the '066, they determined that it required storage for a period of at least three months.

Q. And under the Court's "plain and ordinary meaning" construction, what competing definitions have you seen in this case?

A. So, this is where I used Hawley's definition. It's quoted here as any method of keeping raw materials, chemicals, food products, and energy while awaiting use, transportation, or consumption.

And I note here that Dr. Scheidt, one of UTC's experts, agreed with me in that definition. And Dr. Nuckolls offered an independent, but yet different,

02:00:49 definition that "storage" means storage without limitation,
02:00:52 without time limitation.
02:00:54 Q. Are there scenarios in which a POSA would be
02:00:58 practicing storage under one of these definitions but not
02:01:01 the others?
02:01:01 A. Yes.
02:01:02 Q. And does the '066 patent provide a POSA with any
02:01:05 definition of "storage" that clarifies these competing
02:01:09 definitions?
02:01:10 A. No, I don't think so.
02:01:11 Q. So would a POSA have reasonable certainty as to the
02:01:16 scope of "storage" as it's used in Claim 6 and 8, such that
02:01:21 they would know how to avoid infringing the claim?
02:01:24 A. In my opinion, they would not.
02:01:27 MS. KANNAPPAN: Your Honor, no further questions
02:01:28 at this time.
02:01:29 THE COURT: All right. Are you going have any
02:01:30 more on this indefiniteness argument?
02:01:32 MS. KANNAPPAN: Not if there's no cross on it,
02:01:34 Your Honor.
02:01:35 THE COURT: All right. Well, that's one of the
02:01:39 most frivolous indefiniteness arguments I've ever heard.
02:01:42 No offense to you, Doctor, just I don't think
02:01:46 anyone makes these things up.
02:01:47 And so I would certainly, if this were a jury

trial, never let this go to the jury.

But in any event, go ahead, Mr. Carsten.

MR. CARSTEN: I can eliminate a piece of my cross-examination outline, Your Honor. Thank you.

Thank you, Your Honor.

CROSS-EXAMINATION

BY MR. CARSTEN:

Q. Good afternoon, Dr. Winkler.

MR. CARSTEN: May I approach with a binder, Your Honor?

THE COURT: Sure.

THE WITNESS: Good afternoon.

MR. CARSTEN: Now, Your Honor, I regret to tell you that my cross-examination binders have gone missing, so what you've got is the expert report and the deposition. I'm going to try to stick with the universe of materials that my co-counsel used on direct with the witness. We'll see where that gets us.

BY MR. CARSTEN:

Q. Okay. Good afternoon, Dr. Winkler.

A. Good afternoon.

Q. I'm Doug Carsten. I don't think we ever met in person. I've only seen you through a video screen on Zoom depositions, I think.

I'd like to walk through your direct testimony.

And you started with infringement. Now, you testified on direct in connection with your infringement opinion -- you had an aside about a thing called column chromatography. Do you remember that?

A. I remember discussing column chromatography, yes.

Q. I want to make it clear, you -- you're not saying the claim excludes column chromatography; right?

A. I think that the claim, essentially, does exclude column chromatography.

Q. So, I thought that I heard from your mouth earlier today that you had two non-infringement opinions, one being impurities and the other being storage. Are you now saying that the inclusion of column chromatography is a third basis for non-infringement?

A. I think you -- you just asked me, if I remember correctly, whether I thought column chromatography was included in the patent; is that correct?

Q. No, I thought I'm asking you, is -- does the claim, the claims of the patent that you opined upon earlier --

A. Yes.

Q. -- do they exclude column chromatography?

A. My reading of the claims of the '066 is that they do not include column chromatography.

Q. And I'm asking you: Do you have a non-infringement position or opinion that you're expressing here today that

the inclusion of column chromatography in Yonsung's process renders that process and that product non-infringing?

A. Well, the opinions that I offered in terms of non-infringement related to the two issues that I've discussed earlier today. It is also my opinion that column chromatography is not part of the '066.

Q. Well, I understand that. But you're not offering that as a separate basis for non-infringement; right?

A. I am not offering that as a separate basis for non-infringement.

Q. Okay. Thank you.

Now, when you were talking about column chromatography earlier, you said that the column chromatography in connection with Yonsung's process makes their material, at a certain stage, more pure. Do you remember that?

A. I -- I don't remember exactly what I said, but it's certainly my opinion that column chromatography -- column chromatography typically leads to purification, yes.

Q. Right. Now, I do remember what you said. I wrote it down, in fact. I was listening quite carefully, sir. You said "more pure." You don't believe that column chromatography results in absolute purity, do you?

A. I do not think that column chromatography typically results in complete purity, know. I think that column

chromatography typically results in the reduction of impurities.

Q. Now, let's turn -- thank you for all that. Now let's turn to your opinion relating to impurities in terms of your infringement opinions. Okay?

A. Yes.

Q. Okay. In your view, it is only impurities that result directly from the alkylation of BTO that count for purposes of infringement under the claim; is that right?

A. Impurities that result from the alkylation and hydrolysis of BTO, yes. That's correct.

Q. Now, there was -- you've been here all the time of trial; right? You've heard every witness, pretty much?

A. Pretty much, yes.

Q. There's been discussion about a 15-epi-BTO compound. Do you remember that?

A. Yes, I do.

Q. 15-epi-BTO is a BTO; isn't it?

A. Well, there's only one BTO. BTO is BTO. That's benzindene triol. 15-epi-BTO is a different compound. It's epimeric with BTO at the 15 position.

Q. 15-epi-BTO is a benzindene triol, right?

A. I guess I would say that it is -- it could be referred to as a benzindene triol, but I certainly wouldn't -- would not consider it to be the benzindene triol that's

02:07:36 described in Claim 1.
02:07:37 Q. Now, you looked through various certificates of
02:07:42 analysis of Yonsung batches in connection with your work in
02:07:47 this case; correct?
02:07:48 A. I have. Yes.
02:07:50 Q. Right. And I think you testified that you had
02:07:53 considered some certificates of authenticity in connection
02:07:57 with BTO, along with the other TN01, TN02, and TN in
02:08:04 connection with your work in the case; is that right?
02:08:06 A. That's correct.
02:08:06 Q. And you saw evidence that the BTO starting material
02:08:10 that was used by Yonsung contained amounts of 15-epi-BTO in
02:08:16 it; right?
02:08:17 A. I did.
02:08:18 Q. So, let me get this -- so let me just set the stage.
02:08:22 All right. So, let's assume that I'm chemist working in
02:08:27 Yonsung laboratory.
02:08:28 A. Okay.
02:08:28 Q. I'm going to follow the recipe to make TN.
02:08:33 A. Yes.
02:08:33 Q. I'm going to start with BTO; right?
02:08:39 A. Yes.
02:08:39 Q. And I'm going to alkylate it; yes?
02:08:41 A. Okay.
02:08:42 Q. And I'm going to hydrolyze it; yes?

02:08:44 A. Yes.
02:08:45 Q. And then I'm going to do a salt formation; right?
02:08:48 A. That's correct.
02:08:50 Q. Okay. The starting point of that, I'm going to go
02:08:53 and I'm going to grab a bottle that's labeled BTO; right?
02:08:56 A. Correct.
02:08:57 Q. And I'm going to pour a certain amount that I have
02:08:59 into a flask or whatever reaction vessel that I'm going to
02:09:02 use; right?
02:09:05 A. Yes.
02:09:05 Q. When I pour that in, I'm not just pouring 100 percent
02:09:10 little molecules that look like the structures of the BTO
02:09:14 that we've talked about; right?
02:09:15 A. There certainly could be impurities in the bottle of
02:09:20 BTO that somebody would use, yes.
02:09:23 Q. It's not could be, sir. You know for sure that there
02:09:26 are in connection with your work in the case; right? You
02:09:28 just told me you look the at the COAs.
02:09:30 A. In the COAs for the BTO that I examined, there were
02:09:33 impurities, yes.
02:09:35 Q. Okay. So you know that when you start -- the chemist
02:09:40 starts the process, they're starting with a batch of BTO in
02:09:42 the real world that -- poured into that reaction vessel;
02:09:46 right?
02:09:46 A. Yes.

02:09:47 Q. Okay. They do the alkylation, so they add an alkylating agent and run that reaction; right?
02:09:50
02:09:53 A. Correct.
02:09:53 Q. Okay. They do whatever work-up and chromatography purification techniques and steps are specified in the process; right?
02:09:59
02:10:04
02:10:05 A. I'm sorry. Which process are we talking about?
02:10:07 Q. I'm the chemist at Yonsung.
02:10:10 A. At Yonsung, yes.
02:10:11 Q. Right?
02:10:11 A. Yes.
02:10:12 Q. And then they go ahead, and they do the hydrolysis; right?
02:10:17
02:10:17 A. Correct.
02:10:18 Q. In order to do the hydrolysis, they start the hydrolysis with the material, impurities and all, that resulted from the alkylation and its workup; right?
02:10:20
02:10:24
02:10:29 A. Correct.
02:10:30 Q. Okay. And then they end that process behind hydrolysis --
02:10:34
02:10:35 A. Excuse me. Including the chromatography, if it is in Yonsung.
02:10:39
02:10:39 Q. Yes. Yes.
02:10:43 And then they take that, and that is the starting batch, to use the parlance of the claim; right?
02:10:46

A. The material that was obtained from the alkylation and hydrolysis of the BTO.
Q. Yes.
A. Yes.
Q. That's the starting batch?
A. That could certainly be the starting batch, yes.
Q. It's your opinion that is the starting batch, isn't it?
A. It's my opinion that the starting batch is Treprostinil and that the alkylation and hydrolysis of the BTO at Yonsung leads to the formation of Treprostinil. Yes.
Q. And the Treprostinil is generated and made in the hydrolysis step; right?
A. Correct.
Q. Okay. So we're on the same page.

Now, the judge had a question for you about a batch. You never take a bottle of just chemical structures, 100 percent of them, and do a reaction in real life; right?
A. I'm afraid I don't completely understand your question.
Q. You start with a batch every time that you're going to do a reaction; right?
A. You start with a bottle or sample of whatever the starting material is. That's correct.
Q. And that bottle or sample or whatever you're going to

02:12:04 do, it contains impurities; right?
02:12:06 A. Typically, it does, yes.
02:12:10 Q. So, it's not like you start with a single molecule of
02:12:13 BTO and you end up with a starting batch; right?
02:12:16 A. I don't -- I don't think one of -- well, in the kind
02:12:20 of work that I do, one doesn't start with single molecule.
02:12:23 That's certainly true.
02:12:24 Q. Organic chemists don't play in the area of single
02:12:27 molecules. They play in the area of -- well, medicinal
02:12:31 chemists, for example, don't play in the area of single
02:12:34 molecules. They play in the area of making quantities of
02:12:37 material that have more than one molecule; right?
02:12:39 A. Typically, that's correct. Yes.
02:12:41 Q. Okay. Thank you.
02:12:42 Now, you talked about epimerization. I probably
02:12:52 said that wrong.
02:12:55 Epimerization; right?
02:12:56 A. Epimerization.
02:12:57 Q. Epimerization. Thank you for that.
02:12:59 And you cited a document by -- a publication by
02:13:03 a fellow named Merritt; right?
02:13:04 A. Yes, I did.
02:13:05 Q. Okay. Now, I think on direct you said that it would
02:13:09 be -- that based upon structural differences between the
02:13:18 Treprostinil and the molecule that Merritt was studying,

that it would be far less likely for epimerization to occur; right?

A. That's correct.

Q. And you said it would be thousands to millions times less likely; right?

A. That's correct.

Q. Okay. Now, if it were a thousands times less likely and it happened in that amount, you would expect for 100 percent sample to see .1 percent; right?

A. If a thousandth of the material underwent that process, then you would see -- you could see .1 percent. That's correct.

Q. And you relied upon some experimentation that you saw in connection with work that Yonsung had done about exposing their sample of Treprostinil or precursor to some acid; correct?

A. Correct.

Q. And they didn't necessarily observe any epimerization product, according to you; right?

A. Well, in my analysis of that data, what I saw was that they looked at treatment of Treprostinil sodium with acid under two different reaction conditions and saw, essentially, no increase in the amount of the 15-epi-Treprostinil impurity, which I would take as -- I think a POSA would take as an indication that under the

02:14:52 conditions, under acidic conditions, at elevated
02:14:56 temperatures -- and remember that the alkylation and
02:14:58 hydrolysis that we're talking about did not involve acid
02:15:04 treatment of elevated temperatures. But even under -- under
02:15:08 an elevated -- at elevated temperatures, one did not observe
02:15:12 epimerization in the Treprostinil. That was the conclusion
02:15:14 from the outset of the study.
02:15:16 Q. Understood. Now, you didn't analyze yourself a
02:15:20 sample of Treprostinil and determine -- and subject it to
02:15:26 acidic conditions and determine for yourself whether it
02:15:28 epimerized; right?
02:15:28 A. No, I didn't, but you have a summary.
02:15:30 Q. And you didn't take a sample of Treprostinil and
02:15:33 expose it to basic conditions and see it if it epimerized
02:15:37 did you?
02:15:37 A. No, although Yonsung did expose to base as well and
02:15:41 showed there was no epimerization.
02:15:42 Q. Okay. Although you did see examples in the data in
02:15:46 the certificates of analysis where 15-epi went from being
02:15:51 not detected to being detected in the next step; right?
02:15:54 A. We -- I certainly did see those examples, but I think
02:15:58 as I mentioned before, this issue of not detecting a
02:16:02 material doesn't mean that it's not there. It simply means
02:16:05 that it was below the limit of detection in that particular
02:16:10 assay. And so that doesn't mean that the material that's

found down the line is coming out of nowhere or is necessarily the result of a epimerization, but it could still be and should still be derived from some -- some small amount of 15-epi-BTO.

Q. Now, you have your reports in front of you there, Doctor? In the white binder?

A. Yes, I have opening, rebuttal, reply, and then supplemental.

Q. All right. If you turn in your rebuttal report to Page 23.

A. Yes.

Q. You have a sentence here that says in -- I'll just read it to you. "Thus, Dr. Toste's discussion of HPLC sensitivities as it relates to 15-epi-Treprostinil is not relevant to the claim limitation requiring impurities resulting from alkylation of BTO and hydrolysis of the resulting compounds."

Do you see that?

A. I do.

Q. That's your testimony and you stand by it; right?

A. I do.

Q. So the HPLC sensitivities are just not relevant; right?

A. No, I don't think that's what I'm saying here. What I am saying is that his discussion of HPLC sensitivity as it

relates to the 15-epi-Treprostinil is not relevant to the claim limitation. And then I -- I say see Section 5A above.

Q. Let's turn to storage. Your understanding or definition as you applied it in this case is based upon the Hawley disclosure at DTX 135; is that correct?

A. I don't remember the number, but it's certainly the Hawley's definition, yes.

Q. Okay. And essentially, your opinion is "storage" means awaiting use, awaiting transportation, or awaiting consumption; correct?

A. That -- that paraphrases what I -- the definition -- I don't remember the words explicitly, but that's the gist of it, yes.

Q. You can't think of some way that doesn't capture your opinion, does it, the way I phrased it?

A. I think what I just said was I think that captures the gist of it, yes.

Q. Okay. You said "the gist." I'm making sure that it is -- it is essentially your opinion; right?

You don't see a real problem with agreeing that your opinion is that "storage" means awaiting use, transportation, or consumption; right?

A. If I could see the Hawley's definition, but that sounds right to me. I just don't want to say something that's not accurate.

02:19:39 Q. So, you want to make sure that you mimic the
02:19:42 definition of storage in Hawley directly; right?
02:19:51 Okay. I think we've got it.
02:19:52 Any method --
02:19:53 And thank you to the clerk and to my colleague
02:19:55 for getting ELMO back on track.
02:19:58 "Any method of keeping raw materials, chemicals,
02:20:01 food products, and energy while awaiting use,
02:20:03 transportation, or consumption"; right?
02:20:05 A. That's correct.
02:20:06 Q. Okay. And that was DTX 135.
02:20:13 Now, let me ask you this: In your opinion of
02:20:17 "storage," if I -- if I pack a box in a cold room and it
02:20:32 sits there, that's awaiting use, awaiting transportation, et
02:20:37 cetera, right?
02:20:37 A. It could be.
02:20:40 Q. Well, it's just sitting in a cold room, so that's
02:20:43 being stored at reduced temperature; right?
02:20:46 A. If it's in a cold room, I am assuming it would be
02:20:49 stored at reduced temperature, yes.
02:20:50 Q. Now, I take that box. I put it on a plane, not under
02:20:53 any cold conditions, and that plane flies from Korea to
02:21:00 Memphis, Memphis, Tennessee; okay?
02:21:03 A. Okay.
02:21:04 Q. It's received in Memphis, Tennessee, and it gets put

in a cold refrigerated room.
A. Okay.
Q. According to you, that was stored at refrigerated temperature under your definition; right?
A. I would say that by my definition, that material was stored until it was transported. And the storage conditions that you're describing were at subambient temperature. Yes.
Q. Okay. So, the transportation part of that doesn't count as far as you can tell. It was still stored at reduced temperature?
A. It was stored at reduced temperature before it was transported in the scenario that you are describing --
Q. Right.
A. -- according to the Hawley's definition, which I support.
Q. Right. And so by the same token, I could pack something at reduced temperature, put it in a pan, for example, at reduced temperature and then put it in an oven and bake it to 300 degrees, take it out, and I could put it in a refrigerator and, again, it would be stored at reduced temperature; right?
A. I think we -- when you were done with the first two steps that you did, if you took the final product and you refrigerated it, then I would say that that final product was being refrigerated -- was being stored at refrigerated

temperature, yes.

Q. Right. It doesn't matter what happens during the transportation or during the use so long as it's at reduced temperature first and reduced temperature after it's stored at reduced temperature.

A. Well, I think we're conflating two different things here. I think one of the things that I really like about the Hawley's definition is kind of an on/off switch. In other words, if it's a awaiting use, if it's awaiting transportation, it's being stored. If it's being used, if it's being transported, it's not being stored.

Q. You saw temperature trackers relating to the transportation between Korea and the United States for Yonsung's Treprostinil product; correct?

A. I did.

Q. And you pointed to documents -- let me show you one. This is from DTX 106 in evidence. Let me just show you that. I'm trying to be square with you.

DTX 106; yes?

A. Yes.

Q. You're familiar with this?

A. I am.

Q. I'm going to try to give you a page that you looked at with your counsel. You see there -- I can zoom in a little more -- should be kept in a tight container prepared

02:23:58 -- protected from moisture and light and stored at 2 degrees
02:24:01 to 8 degrees C (long-term storage).
02:24:05 Do you see that?
02:24:05 A. I do see that.
02:24:06 Q. Okay. Now, this says long-term storage; right?
02:24:15 A. It says long-term storage, yes.
02:24:18 Q. And it says "should be stored"; right?
02:24:21 A. That's -- it says should be kept.
02:24:24 Q. Yeah, should be kept.
02:24:25 Now, you, despite the list of things that you
02:24:31 were qualified as an expert for, one was not reading FDA
02:24:35 documents; correct?
02:24:36 A. That is correct.
02:24:37 Q. Okay. Now, let's turn to validity, if we could.
02:25:16 You're not saying that the Moriarty publication invalidates
02:25:29 the claims of the patent -- the '066 patent here, are you?
02:25:33 A. Well, I think what I'm saying is that my opinion is
02:25:40 that the product-by-process patent claims are not valid
02:25:44 because they describe the same compound, that is
02:25:50 Treprostinil in UT-15, prepared by a different process than
02:25:55 the previously described process, which is the Moriarty
02:25:58 process. And that the two materials that are prepared by
02:26:02 these two different processes are structurally and
02:26:06 functionally the same. That's my opinion.
02:26:08 Q. Right. So, you're not relying upon the Moriarty

publication. You're relying upon compound -- a compound that you say was publicly known that uses a process similar to the Moriarty process; is that right?

A. I don't think I made that differentiation in my mind. I think what I -- what I think I testified to this morning was that the Treprostinil prepared by the Moriarty process, which is outlined in this publication and as practiced in the Chicago facility, gave Treprostinil that was structurally and functionally the same as a material that was produced in Silver Spring.

Q. Okay. Well, bear with me a minute, sir. I just want to get the right slide up here.

You say in your summary slide, DDX 2.11, the '066 patent claims are the same product -- or claims the same product as made as a publicly known process; right?

A. Yes.

Q. And I remember you talking about the Chicago process.

A. Correct.

Q. Okay. And something called the Moriarty process or the former process; right?

A. Correct.

Q. Okay. Now, the Moriarty reference -- sorry, it's DTX 258, is the version that was admitted. That doesn't say that it was adopted by United Therapeutics for preparation of UT-15 for Remodulin; right?

02:28:09 A. Well, the -- the testimony that I heard from the
02:28:15 inventors was that the process that was used to prepare the
02:28:20 UT-15 for Remodulin in Chicago was the Moriarty process.
02:28:25 Q. And those -- that testimony that you're referring to,
02:28:29 that was marked as highly confidential; correct?
02:28:36 A. I don't remember.
02:28:38 Q. Okay. The inventor testimony that you rely upon for
02:28:44 that came years after 2007; isn't that right?
02:28:47 A. The inventor testimony in this case certainly came
02:28:56 years after 2007. That's correct.
02:29:04 Q. And you relied upon a document that was a
02:29:10 confidential internal UT document to determine what years
02:29:15 the so-called Chicago process was taking place; right?
02:29:19 A. Again, I'm embarrassed to say, but I don't remember
02:29:25 what the markings were on the documents that I looked at. I
02:29:28 certainly looked at documents that indicated that the
02:29:32 Chicago process or Moriarty process was the one that was
02:29:36 being used to prepare the UT-15 for Remodulin in the Chicago
02:29:40 facility.
02:29:52 Q. My notes demonstrate to me, and I could be wrong, but
02:29:55 you relied upon DTX 627A.
02:30:00 A. It looks kind of fuzzy.
02:30:02 Q. Oh, it's very fuzzy, and I apologize for that. There
02:30:05 it goes.
02:30:05 A. Yes.

02:30:06 Q. This is the document you relied upon to determine
02:30:08 what times various processes were used in connection with
02:30:14 United Therapeutics making UT-15 for its products; correct?
02:30:19 A. It is. This and the testimony of inventors.
02:30:24 Q. Right. And this document is highly confidential?
02:30:26 A. This document is marked highly confidential. That's
02:30:30 correct.
02:30:30 Q. And you have no reason to doubt that it's an internal
02:30:32 confidential UT document, do you?
02:30:34 A. I -- I actually don't know anything about the exact
02:30:37 status of the document other than what I just read here now.
02:30:50 Q. So, you relied upon testimony that was taken in
02:30:53 litigation from inventors who were employed at the time or
02:31:00 consulting for UT and this document in order to establish
02:31:05 that the Moriarty process was making the Remodulin, the
02:31:10 Treprostinil in Remodulin in the dates that we just
02:31:13 discussed; right?
02:31:14 A. Well, that's not really true because I've read the
02:31:18 Moriarty paper. The Moriarty paper appeared in the American
02:31:23 Chemical Society journal in 2004. Looking at the procedure
02:31:27 of the Moriarty paper, I was able to look at the Chicago
02:31:31 process and see that they were the same reactions.
02:31:35 Q. Well, you only knew it was the Chicago process
02:31:39 because you had looked at UT's internal documents; correct.
02:31:45 A. I don't think so. I think it's in Example 6 of the

patent.

Q. And the priority date at issue here, sir, is December 17th, 2007; correct?

A. Correct.

Q. And so you're talking about using the specification of this patent, Exhibit 6 -- I'm sorry, Example 6, in order to confirm that a prior process was actually being used; correct?

A. Well, what -- just to be clear, what I'm saying is that based on the inventor testimony, I understand that the Chicago process, the former process here, was the Moriarty process. And looking at the Moriarty publication, I can see that it was the same reagents under the same conditions, essentially, as is -- the former process that's described here.

Q. And you learned that from the internal UT highly confidential document, the deposition testimony from UT-affiliated individuals who were inventors, and from the specification of the '066 patent; correct?

A. I think that's correct. I think it's those three places.

Q. Okay. I think you had -- well, I'll move on.

You pointed to a document that --

Sorry, I can't help myself. I'm going to go back. Strike that.

So, you're unaware of anyone, aside from someone internal to UT before 2007, doing any work on the purification or purity of Treprostinil; correct?

A. Could you repeat that, please.

Q. Sure. Let me rephrase. It was a bad question. I apologize.

You're saying that the publicly available product from Treprostinil -- from United Therapeutics, the Treprostinil product Remodulin, that's the reason why a person of ordinary skill in the art would have understood that the '066 patent is invalid, knowing that it was the Chicago process; right?

A. I think what I'm saying is that the product that's obtained in the Silver Spring process is the same product prepared by a different process as was taught in the Moriarty publication in 2004.

Q. So, now you're saying that it's not the Chicago process, it's the publication that is giving rise to your invalidity concern; right?

A. No, that's not what I'm saying. What I'm saying is my understanding is that the Chicago process practiced the Moriarty synthesis. The Moriarty synthesis was disclosed publicly in 2004 with a 99.7 purity level, and it was that process that, my understanding is, was adopted by UTC. My understanding of the product-by-process claim and the

02:35:28 invalidity in the product-by-process claim is that if it
02:35:31 claims a product that was already known, and Treprostinil
02:35:34 was already known, by a different method and yet there's no
02:35:38 structural or functional difference in the product, then
02:35:41 that product-by-process claim becomes invalid based on the
02:35:46 fact that it was a previously known compound, a previously
02:35:49 known product, that had been prepared by a different
02:35:53 process. In this case, the process being the Moriarty
02:35:55 synthesis.
02:35:56 Q. Okay. You're unaware of anyone, apart from Moriarty,
02:36:01 having actually publicly done the steps that are disclosed
02:36:08 in the Moriarty publication before 2007; right?
02:36:11 A. I'm not sure of the answer to that question because
02:36:24 there was an earlier publication on the synthesis of
02:36:28 Treprostinil by Aristoff, and in that Aristoff publication,
02:36:35 I just can't remember, sitting here, whether he practiced
02:36:39 alkylation and hydrolysis of the benzindene triol or, in
02:36:43 fact, whether the benzindene triol was an intermediate in
02:36:47 his synthesis. But there's at least one other synthesis of
02:36:50 Treprostinil of which I'm aware that would have taken place
02:36:54 before 2007 and, in fact, I'm almost certain before 2004.
02:36:58 Q. And it's true, isn't it, sir, that a person of
02:37:03 ordinary skill in the art who was interested in knowing how
02:37:05 United Therapeutics was making, for commercial purposes, its
02:37:10 products before 2007 would look at the literature and find

02:37:15 1 at least two syntheses reported of Treprostinil synthesis;
02:37:21 2 correct?
02:37:22 3 A. I think that is correct.
02:37:24 4 Q. Okay. Now, you -- you testified earlier about --
02:37:30 5 based on DTX 619. I think this was -- you submitted this as
02:37:34 6 some of the interactions between UT and FDA. Do you
02:37:37 7 remember that?
02:37:37 8 A. Yes, I do.
02:37:39 9 Q. All right. And I think you turned to Page 10. I
02:37:51 10 hope you turned to Page 10.
02:37:52 11 A. That looks right.
02:37:53 12 Q. Right. And it's for the -- let me blow this up just
02:37:56 13 a little bit.
02:37:57 14 And you relied upon this to say that -- you
02:38:03 15 relied upon this to say that UT told the FDA that the Silver
02:38:11 16 Spring stuff was equivalent to the -- equivalent quality to
02:38:16 17 the old Chicago stuff; right?
02:38:18 18 A. That the drug substance batch prepared by the Silver
02:38:23 19 Spring root of synthesis was of equivalent quality to the
02:38:26 20 batches produced by the current synthetic group, yes.
02:38:29 21 Q. Right. Now, that doesn't say it's the same. It says
02:38:32 22 equivalent quality; right?
02:38:34 23 A. It says of equivalent quality, particularly with
02:38:44 24 respect to the purity profile. Yes.
02:38:46 25 Q. Right. Now, you understand that FDA criteria

02:38:53 specifications are listed as minimal thresholds; right?
02:38:58 A. I'm not an expert in FDA requirements.
02:39:02 Q. You just put up a half a dozen documents from the FDA
02:39:06 saying, see, this shows they're same, this shows they're
02:39:09 same, this shows they're same. Now you're saying you're not
02:39:12 an expert on that?
02:39:13 A. No, what I'm saying is reading this as a POSA, what I
02:39:16 read is that the release data for the batch prepared by the
02:39:19 revised group, which I understand to be the Silver Spring
02:39:23 group, is of -- that UTC told the FDA that the batch
02:39:31 prepared by the revised group was of equivalent quality to
02:39:35 the batch prepared by the Chicago group with respect to the
02:39:38 purity profile. That's what I took from that document.
02:39:42 Q. Okay. Now, you say "as a POSA reading this." You're
02:39:47 saying as a POSA reading this in 2007?
02:39:52 A. What I'm saying is that in my plain reading of this
02:39:56 document, that was the conclusion that I drew.
02:39:59 Q. Now, you know this is a highly confidential document
02:40:02 reflecting communications between UT and the FDA; right?
02:40:07 A. I see it marked as highly confidential, yes.
02:40:09 Q. And a person of ordinary skill in the art, all they
02:40:11 wanted to look at this, they couldn't have found this;
02:40:14 right?
02:40:19 A. Well, again, I was trying to make a determination
02:40:20 whether the material that was prepared in Silver Spring as a

02:40:24 chemist -- that's what I am -- that the material in Silver
02:40:28 Spring and the was structurally and functionally the same.
02:40:31 And I have this letter from UTC to the FDA saying that they
02:40:35 are the same. That they have -- or that they're --
02:40:39 equivalent purities, and so that was the -- that was what I
02:40:43 took from that document.
02:40:45 Q. Now, let's turn to that just a little bit. This is
02:40:48 the very next page in the same document. This is page 11 of
02:40:52 15 of DTX 619. Let me -- sorry. Wrong way. Let me zoom
02:40:57 out so you can establish that.
02:40:58 Do you see that?
02:40:59 A. I do.
02:41:02 Q. Okay. Now, this is a table, Table 5, historical
02:41:09 release testing data and ranges. Do you see this?
02:41:11 A. Historical release testing data and ranges for
02:41:16 commercial -- yes, I do.
02:41:18 Q. Okay. Now, this talks about the impurities, the
02:41:22 purity profile. And that's identified down at the bottom by
02:41:25 the impurities by HPLC; correct?
02:41:27 A. Yes.
02:41:32 Q. I just highlighted that so we can all be on the same
02:41:35 page, literally, of where we are. Do you see that?
02:41:37 A. Yes.
02:41:38 Q. All right. Now, these specifications, these are all
02:41:43 written in the context of being not more than. Do you see

that?
A. I do.
Q. And "not more than" is a minimum threshold specification; right?
A. That's correct.
Q. And so, when they talk about equivalent quality, they may be saying that -- they may be saying that both the old lots and the new lots met each of these minimum quality thresholds. In that sense, they were equivalent; correct?
A. Well, again, I would have to go back to the exact wording on the previous page, but the --
Q. There it is.
A. Right. And what it said was that they're of equivalent quality, right, with respect to purity profile. So that's what I concluded from that sentence.
Q. But, again, you're not an FDA expert here?
A. I am not an FDA expert.
Q. Right. Okay.
Okay. This is the 627A. You used this with your counsel on your direct examination. This is where you obtained the information about when to -- the Chicago process was used and when the Silver Spring process was used; right?
A. That's correct.
Q. Okay. You also turned with your counsel to Page 7

02:43:37 for release data. Now, this is awful small, but you
02:43:49 remember talking with your counsel about this page, don't
02:43:52 you, sir?
02:43:52 A. I do.
02:43:54 Q. Okay. And again, this specification of impurities,
02:44:02 it's written as not more than -- correct?
02:44:08 A. That's correct.
02:44:09 Q. And so those are minimum thresholds?
02:44:12 A. That's my understanding, yes.
02:44:14 Q. Now, in order to assess that these compounds, that
02:44:25 these products are the same, you didn't look at any
02:44:31 published information as of the priority date about what the
02:44:37 -- about what the purity looked like for the -- what you
02:44:41 called the Chicago process and the Silver Spring process;
02:44:44 right?
02:44:45 A. I'm sorry. I don't think I understand your question.
02:44:49 Q. I thought that you had gone through with your counsel
02:44:53 a whole number of certificates of authenticity, COAs, and
02:44:59 used that to derive information pertaining to the purity
02:45:03 from Chicago and the purity from Silver Spring; right?
02:45:07 A. That's correct.
02:45:08 Q. Okay. And let me put one of those up for you.
02:45:25 Here's DTX 151. Do you see that?
02:45:28 A. DTX 151, yes.
02:45:32 Q. And this is one of those certificates of

authenticity -- or certificates of analysis --

Excuse me.

A. Yes.

Q. -- that you relied upon with counsel?

A. Yes, I think it is.

Q. Okay. And it's marked highly confidential; right?

A. Yes, it is.

Q. So, a person of skill in the art would not have had access to the purity information as of 2007 from which you'd make the conclusion that the Chicago process and the Silver Spring process were the same; correct?

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

Q. Okay. If you don't know, you don't know. I understand that. And I appreciate your forthrightness, sir.

I apologize, sir.

Now, this page -- let me put this up. Let me show you where I'm getting it from. This is 627A, so this is the same document we looked at before. This is where you derived Chicago versus Silver Spring; right?

A. Yes.

Q. Okay. I'm going to go back to the page that I just had up there, one of the pages that I just had up there. And this is -- what is the right page? This is the summary 2000-2006 the Chicago site.

Do you see that?

02:47:09 A. That's correct.
02:47:09 Q. Okay. And what -- there's some data in here about
02:47:14 minimum purity, maximum purity, and average purity.
02:47:17 Do you see that?
02:47:18 A. I'm afraid I'm not sure where you are.
02:47:22 Q. Fair enough. It's awfully small. I'm going to try
02:47:26 to zoom it in a little bit, and maybe I can gesture a bit to
02:47:29 try to help. It's a five-column table; right?
02:47:32 A. Five-column table, yes.
02:47:34 Q. And I'm at Page 7 of DTX 627A the first column says
02:47:40 test.
02:47:43 A. The first column says test, yes.
02:47:45 Q. Second column says specification.
02:47:46 A. Yes. I see that.
02:47:47 Q. Third says minimum.
02:47:48 A. Yes.
02:47:49 Q. Fourth is maximum.
02:47:50 A. Yes.
02:47:50 Q. Fifth is average; right?
02:47:52 A. Yes.
02:47:54 Q. This is a highly confidential UT document that was
02:47:57 submitted to the FDA; correct?
02:47:59 A. I think so, yes.
02:48:01 Q. Now, you relied upon this document in order to
02:48:04 determine what the purity profile of the Chicago process

was; correct?
A. I did rely on this document, yes.
Q. And you did no independent testing in order to determine what the purity profiles were from the Moriarty process; correct? You relied upon these documents?
A. The only -- I relied on those documents and the 99.7 percent purity that was published in the Moriarty paper.
Q. Fair enough. Thank you for raising that. Yeah, so the 99.7 percent purity from Moriarty, here it's marked as DTX 58, but this is the Moriarty paper; right?
A. It is.
Q. Okay. And you're relying upon -- I apologize for my chicken scratch on here, sir.
You're relying upon the -- Page 13 of the exhibit in the right-hand column, the purity of 99.7; right?
A. I'm not sure what page that is, but it -- but that is the location of the purity level that I'm relying on. Yes.
Q. Yeah. It's Page 13.
A. Okay. Thank you.
Q. Great. That Moriarty paper doesn't say anything about the impurity profile. It just gives a total purity value; right?
A. It just gives a purity value. That's certainly true.
Q. Now, you said Moriarty is the same as '066 or Silver

02:49:37 Spring; right? That was your testimony?
02:49:38 A. My testimony was that the product that's prepared by
02:49:43 the Moriarty process or the Moriarty publication is, in my
02:49:49 opinion, structurally and functionally the same as the
02:49:53 material that was prepared by the Silver Spring process.
02:49:56 Yes.
02:49:57 Q. Now, you haven't done any experiments to try to
02:50:00 assess whether the alkylation or hydrolysis impurities in
02:50:05 Moriarty are reduced when you do a salt formation step;
02:50:10 right?
02:50:10 A. I've made -- I am afraid I don't understand your
02:50:21 question. If I -- if your question was did -- did I
02:50:25 personally test to see whether the Moriarty alkylation and
02:50:30 hydrolysis process followed by salt formation would lead to
02:50:34 a reduction in the impurities, the answer is no. No, I
02:50:38 never did that.
02:50:38 Q. Thank you, sir. I appreciate that.
02:50:40 I -- counsel -- well, let's shift over to -- I
02:50:59 can't help myself. You put up a slide DDX 2.13; right?
02:51:08 You remember this?
02:51:09 A. I did.
02:51:11 Q. You remember this, Doctor?
02:51:13 A. I do.
02:51:13 Q. Okay. Now, this data on DDX 2.13, that's based off
02:51:23 of certificates of analysis that are confidential to United

02:51:27 Therapeutics as of 2007; correct?
02:51:29 A. That's correct.
02:51:30 Q. Okay. And we'll hear more about that tomorrow from
02:51:38 Dr. Fawzi. Let's switch over to written description, if we
02:51:44 could.
02:51:45 This is the '066 patent, the reason you're
02:51:57 sitting where you are; right?
02:51:58 A. Yes, it is.
02:51:59 Q. Okay. Now, counsel walked you through written
02:52:03 description. She walked you through a whole bunch of
02:52:05 examples that talked about color. Do you remember that?
02:52:08 A. I do.
02:52:10 Q. And your opinion on that is, well, you can't tell
02:52:14 from color unless you know what the real color of the
02:52:17 compound is, essentially; correct?
02:52:19 A. Well, there were two parts in my analysis of color.
02:52:23 The first part was that the color of a product doesn't
02:52:26 really tell you anything unless you know what the color of
02:52:29 the pure product would be in terms of whether there are
02:52:33 impurities present or not.
02:52:34 And the second part of my opinion was that if I
02:52:37 see a colored impurity, I have no idea what that material
02:52:42 is. And I don't know what the origin would be of a
02:52:45 particular color of impurity. That's my opinion.
02:52:48 Q. I understand. Okay.

Now, at the end of that analysis, counsel -- and apologies for the orange highlighting here. This is my copy.

This is column 17 of the '066 patent. Are you with me?

A. It is.

Q. Counsel put up a section that I've highlighted in yellow here. It says "The impurities carried over from intermediate steps (i.e. alkylation of triol and hydrolysis of benzindene nitrile) are help removed during the carbon treatment and the salt formation step."

Do you see that?

A. Yes.

Q. Now, you say that a person of ordinary skill in the art would not understand or would not read that to mean that the amount of impurities from, among other things, the alkylation of triol and hydrolysis of benzindene nitrile steps are lower after salt formation; correct?

A. No, that's not what I said. What I said was that my reading of this sentence, and the way that I think a POSA would and should read this sentence, is that it states that the impurities carried over from intermediate steps are removed during carbon treatment and the salt formation step. Okay.

And then it further, right, limits, i.e.,

alkylation of triol and hydrolysis of benzindene nitrile. Now, I think there's a very specific limitation here with respect to the impurities in the reaction. I think it's very important that the impurities that have to be lowered in Claim 1 must result in the alkylation and hydrolysis of BTO. I think that's the plain reading of Claim 1, frankly, in my opinion.

Now, what this sentence says is that the impurities that are carried over from the intermediate steps are removed. It doesn't tell me; right? It identifies what steps they're talking about. But it does not explicitly teach me that what's being removed are the impurities resulting from alkylation and hydrolysis of the BTO. They could be impurities in the alkylation reagent. They could be impurities in the hydrolyzing reagent. They could be impurities in any of those solvents. Those would all qualify to a POSA as impurities carried over from the intermediate steps. And yet, they have nothing to do with the alkylation and hydrolysis -- or excuse me. They have nothing together do with impurities that are resulting from the alkylation and hydrolysis of the BTO molecule. And that's the differentiation that I think is really critical to make here.

Q. I hear what you're saying. I respectfully disagree.

You agree with me that the word "triol" there,

that refers to benzindene triol, BTO; right?
A. My assumption is that is correct that that is what it refers to, yes.
Q. And that's what a person of skill in the art would understand that reference to triol means, BTO; right?
A. I think what a POSA would clearly see reading this is that the intermediate steps that are being described are the alkylation and hydrolysis reactions. What this sentence does not call out to me is that the impurities that are being removed are impurities that result directly from the alkylation and hydrolysis of the BTO molecule. And I think that's a critical differentiation here. Because for example, if there was an impurity in one of the reagents, that would be an impurity carried over from the intermediate steps. And yet, that has nothing to do with the alkylation and hydrolysis of BTO or with impurities that come from the alkylation and hydrolysis of BTO, in my opinion.
Q. Understood. Let's go back to the fellow that we left in Korea at Yonsung who's trying to make Treprostinil and make his bosses happy. Okay? He started with that bottle of BTO that had impurities in it. He went ahead and ran the alkylation reaction and got a batch at the end of that which had impurities in it; correct?
A. There could be impurities in it, yes.
Q. There will be impurities in it; right?

02:57:19 A. In what?
02:57:19 Q. In the batch that he -- that results from that
02:57:22 alkylation step; correct?
02:57:25 A. Well, there are impurities in, essentially, any
02:57:30 reaction. So there should be impurities in that reaction,
02:57:33 yes.
02:57:33 Q. You can't think of a single reaction, an organic
02:57:37 reaction, sitting here today, that doesn't generate
02:57:39 impurities; correct?
02:57:41 A. I think, as a general rule, one would say that there
02:57:44 are impurities generated in all reactions.
02:57:47 Q. Okay. Now, so this fellow has got his little sample
02:57:52 of benzindene -- in this case, it would be the ester; right?
02:57:58 Because he's in Yonsung. He's doing the Yonsung process.
02:58:01 And he takes that impure sample, and he puts it
02:58:04 into the next reaction, which is the hydrolysis reaction;
02:58:08 right?
02:58:08 A. Correct. After chromatography.
02:58:12 Q. And then he goes ahead and he says, all right, I'm
02:58:20 going to do the salt formation step.
02:58:23 A. Okay.
02:58:23 Q. And he comes out -- and he does an assay impurity,
02:58:27 and he comes out with 99 percent pure. Okay?
02:58:30 A. Yes.
02:58:31 Q. He takes it to his boss and he says, "Boss, I did

what you asked me to do. I've got 99 percent pure salt-formed Treprostinil." Okay?

A. Yes.

Q. His boss says, "That's no good. You got one percent of impurities in it."

Would the boss be satisfied if he responded by saying, "Don't worry, Boss. I'm pretty sure that there are no impurities that are derived directly from the alkylation and hydrolysis of benzindene triol"?

A. I am afraid I don't understand the point of your question.

Q. Okay. I understand.

Let's turn back to Exhibit 6, which is the last thing that you -- among the last things, I think, that you walked through with your counsel.

Now, let me get this straight. Right. So Chicago process, you say, is the same as -- in terms of the product, Chicago process same as Silver Spring process; right?

A. The product that's obtained. My opinion is that the product that's obtained in the Chicago process is structurally and functionally the same as the product that's obtained in the Silver Spring process.

Q. All right. And you just went through now -- this is the former process on the left; right? Starting at

Column 15, Example 6.

A. I'm sorry. That's way too fuzzy for me.

Q. Oh, boy. Sorry. It's small print as well.

A. No, there's no way I could read it.

Q. But you have JTX 2, the '066 patent, in your book somewhere.

A. Let me look for it.

Q. That might be helpful for you, Doctor.

A. Yes.

Q. So, now, your testimony, this is something you relied upon to determine Chicago process from Silver Spring; right?

A. I'm sorry.

Q. This Example 6.

A. Yes.

Q. Former process.

A. Yes.

Q. And working example of the process according to the claim, the present invention. This is one of the things you pointed to when I asked you how you knew what Chicago process was versus what's new process; right?

A. Yes.

Q. Okay. So the left is the former process; right?

A. That is correct.

Q. And the right is what you call the new process?

A. The right is the Silver Spring process or the '066

process, yes.

Q. Okay. And now, there were some questions in terms of written description about is there anything that tells you about matching up the compounds of 51; right? Remember this?

A. I don't understand what you mean by "matching up at 51."

Q. If you turn to the following column, at 51, there's UT-15 under the old process; right?

A. Yes.

Q. And there's UT-15 under the working example process here; right?

A. That's right.

Q. And your counsel asked you if you could compare those; right.

A. Correct.

Q. And you said, no, you can't compare them. They're different; right?

A. Well, no. What I said was -- and let me try to explain this. My understanding of the limitation of Claim 1 is that the pharmaceutical composition must have a lower level of impurities resulting from alkylation and hydrolysis than the starting batch. What I was saying during my testimony was that one cannot use, and I think Dr. Scheidt implied this, that one cannot use the material from line --

from Step 51 of the former process and compare that to the product from the final -- from the -- from the '066 process. That's not the limitation of Claim 1.

The limitation of Claim 1 is that you have to look at the impurity levels of impurities resulting from alkylation and hydrolysis of BTO in the material at Step 30 of the new process and compare that to the material in Step 51. That was my testimony.

Q. Got it. And your testimony was the material in the old process at Step 30 was going to be significantly different because it had undergone a column?

A. The material at the old process in Step 51. Is that what you said? I didn't hear what you just said. I'm sorry.

Q. The material in the old process at Step 30.

A. Well, the material in the old process in Step 30 has undergone chromatography.

Q. Right.

A. Whereas the material at Step 30 in the new process has not undergone chromatography.

Q. Right. And you testified on your direct that the exposure to that chromatography, the fact that that chromatography was done, made those significant -- provided significant differences with differing impurities; correct?

A. Well, no. What I said was that if one does

chromatography in the Yonsung process or in the Moriarty process, that what's going to happen is that a POSA would have the expectation that that chromatography would be reducing impurities. And, therefore, if I compare that material to the starting batch of Treprostinil in the -- in the new process, in the '066, I would expect that there would be impurities that had been removed by chromatography in the old process that would still be present in the starting batch of the new process.

Q. And yet, between the old process and the new process, for purposes of obviousness, you say they're the same; right?

A. Well, for -- for purposes of the validity of the patent -- I thought we were talking about validity. In the -- maybe I'm getting confused.

But my opinion is that the material that's prepared by the Chicago process and the material that's prepared by the Silver Spring process are structurally and functionally the same.

Q. I understand. Thank you.

MR. CARSTEN: No further questions. Pass the witness.

THE COURT: All right.

MS. KANNAPPAN: No redirect, Your Honor.

THE COURT: All right. Doctor, you're done.

You can step down.

THE WITNESS: Thank you.

THE COURT: Watch your step.

THE WITNESS: Thank you very much.

MR. SUKDUANG: Your Honor, we're going to play two videos that will close out with respect to the '066.

THE COURT: Okay.

MR. SUKDUANG: And then after that, our case transitions to the '793.

THE COURT: Okay.

MR. MINN: Your Honor, you will hear deposition testimony from Dr. Hitesh Batra. He is 30(b)(6) witness and associate vice president for R & D at UTC. His testimony will relate to non-infringement and invalidity of the '066 patent. Thank you.

THE COURT: All right.

(Video playing.)

Q. Good morning, Dr Batra. My name is Santa Sukduang. And you also understand that you have been noticed for your deposition in your personal capacity; is that right?

THE WITNESS: That's right.

Q. When you discussed the API manufacturing, did it concern API manufacturing of Treprostinil free acid?

A. Yeah. We make Treprostinil as well as Treprostinil salt.

Q. And when did UTC implement these chemical processes to form the Treprostinil diethanolamine salt?

A. I would not have the exact date, but my expectation is sometime after 2007, we started doing this process, based on the research that was carried out before 2007, all developmental work that culminated into this science and this beautiful process. So we implemented some time after 2007, 2008 time, we started to -- you know, making these batches using this process.

Q. So Dr. Batra, I'm going to mark as Batra Exhibit Number 1 a document identified as United Therapeutics Corporation's Responses and Objections to Liquidia Technology Incorporated's Rule 30(b)(6) Notice of Deposition.

And do you also understand that you've been identified to be the corporate witness with respect to topics 24 through 26, subject to UTC's objections?

A. I do.

Q. I'd like to mark as Batra Exhibit Number 2 the CV of Hitesh Batra.

Dr. Batra, is Exhibit 2 a copy of your CV?

A. That's my old CV. Yes.

Q. What is your current title?

A. My current title is AVP of chemical R & D and API manufacturing.

Q. Is AVP assistant vice president?
A. Associate vice president.
Q. What are your current remember responsibilities as AVP?
A. I am involved in, you know, planning and strategizing the API operation, including over the chemical R & D process. Definitely helping in designing and developing the chemical processes of the API molecules here at UTC. So provide my input and direction to the groups who are working on production as well as the chemical R & D.
Q. Okay. Does that API include Treprostinil?
A. That's correct.
Q. So Dr. Batra, Exhibit Number -- it should be Number 6 -- is a copy of the '066 patent?
A. Okay.
Q. Great. And you're a named inventor on the '066 patent?
A. I see my name. Yes, I am.
Q. Dr. Batra, you have in front of you Exhibit 9, U.S. Patent Number 8,497,393?
A. That's right.
Q. And you are a named inventor on this patent; is that right?
A. That's right.
Q. So, with respect to the general chemical processes of

alkylation, hydrolysis, forming the salt, and then reconverting it back to the Treprostinil acid that you just discussed that UTC uses, are those processes the ones that are disclosed in the '066, '901, and '393 patents?

THE WITNESS: That's my understanding.

BY MR. SUKDUANG:

Q. Dr. Batra, I'd like to mark as Batra Exhibit Number 10 a document titled, "Silver Spring Process Optimization Report for the Conversion of UT-15C Intermediate to UT-15 API (Treprostinil)."

Do you know what this document is, Dr. Batra?

A. Yeah. As the title explains, it's the optimization report for the conversion of UT-15C intermediate to UT-15 API Treprostinil. That's a developmental report, 01194.

Q. Do you see on the first page, on the introduction, the first sentence says, "United Therapeutics Corporation (UT) has manufactured UT-15 (Treprostinil) API, the active ingredient in Remodulin, in its Chicago, Illinois, facility since 1997."

Do you see that?

A. That's right.

Q. To make commercial UT-15, did UTC use the process reflected in the '066 and '901 patents in its Chicago facility?

A. Not to my knowledge.

Q. Did UTC implement the process in the '066 and '901 patents to make Treprostinil commercially when it moved to Silver Spring?

A. That is my understanding, yes.

Q. Have you heard about in UT -- within UTC that the process used in the Chicago facility to make Treprostinil commercially as the Moriarty process? Have you heard that within the company?

A. I've heard all kinds of terms. That might be one of the terms, yes. Moriarty's process.

Q. So, we talked about the alkylation of the triol to form the benzindene nitrile.

Do you recall that?

A. I do recall.

Q. And my understanding is that you said there's no need to assay the benzindene nitrile because your process can take the crude nitrile and carry it through to the final formation of the diethanolamine salt; is that correct?

A. So we don't do that at the nitrile step. But we do, down the road, confirm that our process is working the way we want.

Q. Okay. So you don't assay at the nitrile step. That was my question. Very simple. Do you assay for impurities after formation of the UT-15 intermediate prior to salt formation?

THE WITNESS: I would not call that as a -- you know, just checking the levels, but there is a method in our process where we check if our reaction is complete or no, and we assay against our starting material and check how does our product look on TLC, which is called thin layer chromatography. So, in another form, we do check the progress of the nitrile intermediate through some means.

BY MR. SUKDUANG:

Q. And the TLC, you check to see if the reaction has been completed; correct?

A. Yeah. It gives you an idea of your reaction completion and, if you may see some impurity, they will show up on TLC, also.

Q. Does TLC allow to you identify specifically what those impurities are?

THE WITNESS: You can use TLC in general if you have that as a part of your process. But we don't do it.

BY MR. SUKDUANG:

Q. UTC does not use that as part of the process; correct?

A. Correct. Right.

Q. So when you say you don't need to assay at the nitrile stage because of your process, that means you don't use HPLC assay at the nitrile stage?

A. To my knowledge, we don't need it, and we don't do

it.

Q. Okay. After hydrolysis to the formation of the Treprostinil free acid, before salt formation, does UTC need to perform an HPLC assay of the Treprostinil free acid prior to salt formation?

THE WITNESS: Your question is does UTC need? No, UTC doesn't need.

BY MR. SUKDUANG:

Q. Okay. Because UTC does not need to perform HPLC assay after the formation of the Treprostinil free acid, but before salt formation, does that mean UTC does not perform HPLC at that step?

THE WITNESS: Yeah, since you don't need it, we are getting it crude solution for the salt formation. You don't need it.

Q. I'd like you to go back to Exhibit 6, which is the '066 patent.

A. Okay. Exhibit 6.

Q. In Column 9, towards the bottom, starting around line 46, starts the examples.

Do you see that?

A. That's right.

Q. And Example 1 is alkylation of benzindene triol; is that right?

A. That's right.

Q. And the resulting product is a benzindene nitrile; is that right?

A. That is right.

Q. I'm asking you. Doesn't your process allow for column chromatography after the benzindene nitrile formation?

THE WITNESS: Based on the document I'm looking and the patent I'm looking, based on the process we are carry, we do not use column chromatography in making our API which is Treprostinil -- from Treprostinil diethanolamine salt.

Q. Now, you testified earlier that you're always improving the process. The goal is to try to make the best, cleanest, prettiest, "beautifulest" product you could make. Wouldn't adding column chromatography enhance the purity of the product, assuming I do it right? Wouldn't that be a motivation to do that if your goal is to really make the best, purest product you can?

THE WITNESS: That is a crappy way to look at any process. You want to remove column chromatography, not introduce column chromatography in general. But if I have better options available other than column chromatography, I would use better options, like I mentioned. It's environment-friendly. It's efficient. It's safe. It gives you good quality. Why would I resort to the choice of

column if I have better option?

BY MR. SUKDUANG:

Q. So looking at your process, would someone, a chemist looking at your process here, would they not want to introduce column chromatography after benzindene nitrile formation?

THE WITNESS: I give this process the way it is, and it is giving the desired purity the way we want. If somebody is trying to introduce a column after look looking at this process, it is nothing but a sheer stupidity.

BY MR. SUKDUANG:

Q. Can you turn to Column 15.

A. Column 15.

Q. Column 15 is Example 6 comparison of the former process and a working example of the process according to the present invention?

A. That's right.

Q. And on the right side of the column is a working example of the process according to the present invention.

Do you see that?

A. That's right.

Q. And the middle column says, "former process."

Do you see that?

A. That's right.

Q. Would that be the process from the Chicago facility?

THE WITNESS: Yeah, I would assume that one, meaning it says former process. I don't know how close is it to the former process that we carry in Chicago? Most likely yes.

(Conclusion of video.)

MR. MINN: Your Honor, we would like to enter into evidence DTX 707, DTX 623, DTX 138, PTX 219, and JTX 2.

MR. CARSTEN: No objection, Your Honor.

THE COURT: All right. Admitted without objection.

(DTX Exhibit Nos. 138, 623, and 707 were admitted into evidence. JTX Exhibit No. 2 was admitted into evidence. PTX Exhibit No. 219 was admitted into evidence.)

MR. CHEEK: Your Honor, you will now hear deposition testimony from Dr. Sudersan Tuladhar. Dr. Tuladhar is a named inventor of the '066 patent and a senior scientist at UTC. His testimony relates to the invalidity of the '066 patent.

(Video playing.)

Q. Thank you for taking time to speak with us to today. Could you please state your full name for the record.

A. My full name is Sudersan Tuladhar.

Q. Do you have Exhibit 4 pulled up, Dr. Tuladhar?

A. Yeah, I see that.

Q. Okay. Great.

Are you an inventor on this patent?

A. Yes.

Q. This is U.S. Patent Number 9,593,066?

A. Yes.

Q. Do you recognize this reaction at the end of Example 1?

A. Example 1 is the salt formation, yes.

Q. For Example 1 in Column 9?

A. Column 9, example -- oh, okay. Now, I'm down there. Yes.

Q. So -- so which reaction is this?

A. This is alkylation of phenolic oils.

Q. Did you ever identify any impurities that resulted from this specific step?

A. No. In this case, no.

Q. So, did you ever conduct analysis on the benzindene triol and the benzindene nitrile after it to determine if any impurities would result from this step?

A. Actually, the benzindene triol, potassium carbonate, those are the things we buy from the competitor, and we use it as such without purification. We use as we -- as we get it.

Q. Could we turn to Example 2. It's on that same column.

A. Same column. Example 2. Okay.

Q. Yep. And so what -- what reaction is shown here?
A. This is a hydrolysis of a nitrile.
Q. So, going back to impurities, did you identify any impurities that resulted from this step?
A. No.
Q. So from both the alkylation and hydrolysis steps, did you identify any impurities that result from these steps?
A. No.
Q. Did -- did UTC, even outside of Example 1 and 2, ever identify any impurities that resulted from these steps?
A. No. In this case, the impurity generated from the reagent, not from the compound.
Q. Okay. And for -- for hydrolysis, out -- outside of Example 2, did UTC ever identify any impurities that result from this step?
A. No.
Q. Okay. Can you identify any impurities that result from the alkylation step.
A. No.
Q. Did -- did UTC identify any impurities that result from the prior alkylation step?
A. No.
Q. So outside of the -- the examples in this patent, did -- did UTC ever identify any specific impurities that resulted from these steps?

03:23:16 A. No.

03:23:21 THE VIDEOGRAPHER: The time is 11:29 a.m. We're back on the record.

03:23:24 Please proceed, counsel.

03:23:26 Q. I'd like to turn to Example 6.

03:23:30 A. Example 6. Example 6, yes.

03:23:40 Q. Okay. So this compares the former and the new process; right?

03:23:49 A. Yes.

03:23:52 Q. Does the former process use alkylation of the benzindene triol?

03:23:56 A. Yes.

03:23:57 Q. And the -- the new process, does that use alkylation of the benzindene triol?

03:24:04 A. Yes.

03:24:09 Q. And the -- the former process uses hydrolysis of the benzindene nitrile; correct?

03:24:14 A. Yes.

03:24:17 Q. And the new process also uses hydrolysis of the benzindene triol -- nitrile, right?

03:24:23 A. Yes.

03:24:28 Q. But in Step 12, the former process uses an alkyl -- or a column chromatography step after alkylation, correct?

03:24:35 A. Yes. Yes.

03:24:37 Q. And in the new process, no column chromatography step

is used?

A. Yes. No column, yes.

Q. And in the former process, the Treprostinil free acid is isolated as a solid?

A. Yes.

Q. And in the -- the new process, the Silver Spring process, the Treprostinil free acid is not --

A. Yes.

THE WITNESS: In the case of our old process, we eliminated some of the impurity in the column. In the new process, we carry on until the hydrolysis steps until the salt formation.

Q. But in terms of the primary differences between the new and the former process, would that be the elimination of column chromatography --

A. Yes.

Q. -- and the elimination of the isolation step?

MS. WU: Same objection.

THE WITNESS: Yes.

Q. Do the products have the same or different impurity profiles?

A. More pure.

Q. Which is more pure?

A. In the new process.

Q. Does the product from the new process have a

different impurity profile from the product made by the old process?

THE WITNESS: More purer means, yes, better -- better profile is better in the new process.

(Conclusion of video.)

MR. SUKDUANG: There were no exhibits to be entered with that.

THE COURT: All right. So, why don't we take a 15-minute break, and we'll come back at 20 minutes to 4:00 to finish up for the day.

MR. CARSTEN: Thank you, Your Honor.

DEPUTY CLERK: All rise.

(Recess was taken.)

DEPUTY CLERK: All rise.

THE COURT: All right. Please be seated.

And let's continue.

MR. DAVIES: Your Honor, Defendants call Nicholas S. Hill.

UNIDENTIFIED SPEAKER: Your Honor, we also have copies of the demonstratives if you want them.

THE COURT: That's not necessary. Thank you.

DEPUTY CLERK: Please state and spell your full name for the record.

THE WITNESS: Nicholas, N-I-C-H-O-L-A-S. S, middle initial. Hill, H-I-L-L.

DEPUTY CLERK: Do you affirm that the testimony you are about to give to the Court in the case now pending will be the truth, the whole truth, and nothing but the truth, you do so affirm?

THE WITNESS: I do so affirm.

NICHOLAS HILL, the witness herein, after having been duly sworn under oath, was examined and testified as follows:

DEPUTY CLERK: Thank you. So make sure you speak into this microphone right here on the computer as best you can.

THE WITNESS: Thank you.

Good afternoon, Your Honor.

THE COURT: All right. Make sure you speak up. All right.

THE WITNESS: Okay.

DIRECT EXAMINATION

BY MR. DAVIES:

Q. Good afternoon, Dr. Hill?

A. Good afternoon.

Q. Can you please state your full name for the record.

A. Nicholas S. Hill.

Q. And where are you currently employed, Dr. Hill?

A. I work in Boston at Tufts Medical Center affiliated with Tufts University School of Medicine.

03:41:05 Q. And what's your current position?
03:41:06 A. I am chief of the division of pulmonary care and
03:41:12 sleep medicine as well as a professor of medicine at the
03:41:15 medical school.
03:41:15 Q. And how long have you been in that role?
03:41:17 A. This is my 21st year.
03:41:18 Q. And what are your responsibilities in that role?
03:41:21 A. I oversee the -- the business management of the
03:41:26 division with my business manager, and I supervise some
03:41:32 three dozen doctoral-level faculty members, the educational
03:41:37 program for medical students, residents, and fellows and
03:41:40 also our research program.
03:41:43 Q. In your current position, do you treat patients?
03:41:45 A. Yes, I do.
03:41:47 Q. For how many years have you been treating patients
03:41:50 suffering with various types of pulmonary hypertension?
03:41:54 A. About 40.
03:41:55 Q. And how many patients with pulmonary hypertension do
03:41:58 you currently manage?
03:41:59 A. Roughly 150.
03:42:01 Q. And how many are managed by your group overall?
03:42:03 A. About 600.
03:42:04 Q. Do you have a CV?
03:42:06 A. Yes, I do.
03:42:07 Q. Can we bring up DTX 721. And it should also be in

your binder, if you prefer, Dr. Hill, or you can look at the screen.

A. I see it on the screen.

Q. Is this a copy of your CV?

A. Yes, it is.

Q. Does it accurately reflect your credentials?

A. I think so.

MR. DAVIES: I'd like to offer DTX 721 into evidence.

MR. JACKSON: No objection, Your Honor.

THE COURT: Admitted without objection.

(DTX Exhibit No. 721 was admitted into evidence.)

BY MR. DAVIES:

Q. Dr. Hill, when did you graduate from medical school?

A. In 1975.

Q. And after that, did you perform an internship and residency?

A. Yes, I did.

Q. And after residency, did you complete any additional training?

A. Yes, I did.

Q. And what was that?

A. I did a year of cardiovascular medicine training in Worcester, Massachusetts, at U Mass and also three years of

pulmonary medicine training at Boston University.

Q. Do you have experience working on clinical trials?

A. Yes.

Q. Have you worked on clinical trials for treatments of various types of pulmonary hypertension?

A. Yes, I have.

Q. And about how many clinical trials have you participated in for pulmonary hypertension drugs?

A. Many dozens over the years.

Q. Of the currently available treatments for the various forms of pulmonary hypertension, would have you worked on clinical trials for -- or how many have you worked on clinical trials for?

A. I worked on clinical trials involving all of the currently available medications.

Q. Have you participated in clinical trials with Liquidia?

A. Yes, I have.

Q. Have you also participated in clinical trials with United Therapeutics?

A. Yes, I have.

Q. Are you currently working with United Therapeutics on any clinical trials?

A. Yes, I'm currently site principal investigator on one of the -- their active trials.

MR. DAVIES: Your Honor, we offer Dr. Hill as an expert in internal medicine, pulmonary disease, critical care medicine, and the treatment of pulmonary hypertension.

MR. JACKSON: No objection, Your Honor.

THE COURT: All right. You may proceed.

BY MR. DAVIES:

Q. Dr. Hill, you've offered opinions on the '793 patent in this case?

A. Yes, I have.

Q. Can we bring up JTX 3.

And, Dr. Hill, is this the '793 patent that you've offered opinions on in this case?

A. Yes, it is.

MR. DAVIES: Your Honor, I'd like to move JTX 3 into evidence.

THE COURT: I thought that was already done, but if it's not, it's admitted without objection.

MR. DAVIES: I apologize. Thank you, Your Honor.

(JTX Exhibit No. 3 was admitted into evidence.)

BY MR. DAVIES:

Q. If you look at the cover page, what's the date of the earliest application associated with this '793 patent?

A. May 15th, 2006.

Q. And is this the date that you applied for offering

your opinions as a POSA in this case?

A. Yes, it is.

Q. Can you please turn to the claims on the last page of the patent.

And at a high level, what is Claim 1 generally directed to?

A. It is a method of treating pulmonary hypertension with the Treprostinil or a pharmacologically acceptable salt thereof by inhalation.

Q. And we'll come back to the patent, but before that, I'd like to provide the Court with a little bit of background about pulmonary hypertension.

What is pulmonary hypertension, Dr. Hill?

A. It's high blood pressure in your lungs.

Q. In general, is pulmonary hypertension a chronic condition?

A. Yes, it is.

Q. And what are the symptoms of pulmonary hypertension?

A. The main symptom is shortness of breath on exertion. People are often -- are fatigued as well. And they may have exertional chest pain or dizziness or even syncope in more advanced cases.

Q. Is PH -- or if I say PH throughout the day, Doctor, will you understand me to be referring to pulmonary hypertension?

A. I will, and I should say that syncope refers to fainting.

Q. Is PH a single condition, Dr. Hill?

A. No, it's not.

Q. Are there different diseases that make up pulmonary hypertension?

A. Yes, there are.

Q. About how many?

A. Well, there are many diseases, but they have been lumped into five different groups.

Q. And have you prepared a demonstrative that describes those five groups?

A. Yes, I have.

Q. Can we bring up DDX 3.1, please.

And is this that demonstrative, Doctor?

A. It is.

Q. Can you please describe this to the Court.

A. Right. So what we're looking at here on the left, we list the five different groups. And they share the commonality of all having elevation of the blood pressure in your lungs. And the schematic on the right is to illustrate how these different groups are caused.

So, I should point out that the schematic -- the illustrator took some license in that in order to illustrate how the various vessels interrelate with each other, the

vessels have been extracted from the lungs, and the lung is shown here. Ordinarily, these vessels are inside the lungs. You wouldn't be able to see most of them without a microscope, frankly.

But what the schematic is illustrating is the flow of blood through the pulmonary circulation. So if we imagine blood entering the right heart from the systemic veins, which are conducting the blood that has delivered oxygen to the body's tissues and hence is blue, and the first chamber it comes to is the right atrium, and it helps to fill up the right ventricle to pump blood into the pulmonary arteries. And then into the very small vessels, the capillaries, where gas exchange occurs and oxygen is taken up from the small air sacs in the substance of the lung where it pinks up, as shown by the redder color, then goes through the pulmonary veins into the left heart up and then pumped out into the rest of the body oxygenated.

Now, the schematic is helpful in characterizing the causation of the various groups. Group one, which includes pulmonary arterial hypertension, is referring to a form of pulmonary hypertension where the main problem is in the so-called precapillary vessels where the vessels must -- the wall -- the smooth muscle, the wall of the vessels, constricts and the vessels thicken, narrowing the channels and making it more difficult for the right heart to pump

blood through. So it increases the pressure to maintain flow into those vessels and into the capillary bed and, hence, into the pulmonary veins.

And group two has a very different causation because there, the primary problem is the left ventricle. Now, the left ventricle gets into trouble sometimes because the muscle of the left ventricle weakens so it becomes harder to contract or the walls of the left ventricle stiffen and it becomes harder to fill. It takes more pressure to stretch out the ventricle and get adequate blood in there for filling.

And either way, the pressure filling the left ventricle goes up in the pulmonary veins, and this is reflected back through the capillaries and into the arteries where the pressure goes up, and that is what causes the pulmonary hypertension of group two.

Now, group three, there is damage to the lungs by a number of different conditions, but the end result for the pulmonary circulation is the pulmonary precapillary vessels get damaged and they -- some of them are destroyed. The resistance to flow from the right ventricle goes up, and, once again, the right ventricle has to pump at higher pressure, causing the pulmonary hypertension.

Then group four is a condition where blood clots accumulate in those precapillary vessels and pulmonary

arteries, and over time, there's more and more blockage to flow, and the right ventricle has to pump harder and at higher pressures to maintain the flow, causing the pulmonary hypertension.

And finally, there's a group five, a miscellaneous category, where conditions that don't fit well into these other four categories are classified.

Q. And, Dr. Hill, when were these five groups first established?

A. In 1998.

Q. And where were they established and by whom?

A. It was a meeting of international pulmonary hypertension experts held in Evian, France, and they deliberated on these -- how to classify pulmonary hypertension and came up with these five groupings.

Q. Are these groups still in use today?

A. They are.

Q. Have there been any changes to the groups since they were first established in 1998?

A. There have been minor changes, but nothing substantial. We still use these five groups.

Q. Do the descriptions in your demonstratives reflect the groupings as of about May 2006?

A. They do.

Q. Dr. Hill, can you turn to DTX 385 in your binder.

Derrick, can you bring that up. Maybe blow up the top to start.

And Dr. Hill, what is this document at DTX 385?

A. Well, this group of international experts on pulmonary hypertension has convened every five years since that 1998 meeting. And this is the report from the 2003 meeting, which would -- would have been relevant to the 2006 date we're focusing on. And this was a subgroup of -- at the meeting of experts who met to re-examine the clinical classification, and that is what is contained in this document.

MR. DAVIES: Your Honor, I'd like to offer DTX 385 into evidence.

MR. JACKSON: No objection, Your Honor.

THE COURT: All right.

(DTX Exhibit No. 385 was admitted into evidence.)

BY MR. DAVIES:

Q. Can we turn to -- it should be exhibit Page 2 of DTX 385. There's a table there.

What does the table show, Doctor?

A. Well, what we're looking at here, it's a little hard to make out, but if you look at the numbers to the far left here, those are the major groupings. You can see group one, pulmonary arterial hypertension; and group two, pulmonary

venous or that left-heart disease form, and so forth. So we get the five groupings. As I said, there's many entities that cause pulmonary hypertension, and they have been, then, subgrouped in each of these major five groupings.

Q. Have you prepared a demonstrative that shows the number of pulmonary hypertension patients that fall into each of these five groups?

A. Yes, I have.

Q. Can we bring up DDX 3.2, please.

And is this that demonstrative, Doctor?

A. Yes, it is.

Q. And can you explain this demonstrative to the Court?

A. Yeah, this is a study that was done on almost 5,000 patients that were referred to a center for echocardiography or cardiac ultrasound, and they proved to have elevated estimated pressures by echo where the -- the authors subsequently categorized these 5,000 patients with elevated pressures into the five different groups getting at their causation.

And as you can see, by far, the most prevalent group is group two, that group with left-heart disease is the primary cause leading to the increased filling pressures on the left side of the heart.

Group three, the lung disease form was second at 10 percent.

And then the group one, for which all the medications we have available today have been approved, was just under five percent.

And then 4 and 5, relatively small prevalence as well.

Q. Is there a publication that provides the percentages that you used in this demonstrative, Doctor?

A. Yes, there is.

Q. Can we please go to DTX 398.

And what is DTX 398?

A. This is the front page of an issue of the American Journal of Respiratory and Critical Care Medicine that contains the abstracts that were presented at the American Thoracic Society meeting in 2007.

MR. DAVIES: Your Honor, I'd like to offer DTX 398 into evidence.

MR. JACKSON: No objection.

THE COURT: Admitted without objection.

(DTX Exhibit No. 398 was admitted into evidence.)

BY MR. DAVIES:

Q. Can you turn to Page 14. There should be an abstract in the lower right-hand corner.

And, Dr. Hill, could can you describe what's shown here.

A. Well, this is the study from which the bar graph we just showed you, where the data were obtained, and we -- if we look at their little table in the lower right-hand corner here, you can see that there are almost 500 PH patients, about 10 percent of the 5,000. And although they didn't number the groups specifically, you can see left-heart disease, which is the group two, and there's the almost 80 percent prevalence.

And then lung disease, group three, shown here.

Chronic thromboembolic pulmonary hypertension, group four.

Pulmonary arterial hypertension in group one, and then unknown in group five.

And I should point out that congenital heart disease is usually lumped in group one, and so we have added that and the pulmonary arterial hypertension together to get that 4.2 percent we showed for group one.

Q. Would this same breakdown of patients into the various groups of pulmonary hypertension have existed as of May 2006?

A. Yes.

Q. And is this breakdown of the patient population between the groups consistent with your own practice?

A. Yes.

03:56:29 Q. Can we go back to your demonstrative, DDX3.1?

03:56:37 And I want to focus on the group two patients
03:56:42 that you have on the chart. Do all group two patients
03:56:45 suffer solely from left-heart defects?
03:56:48 A. No, they don't.
03:56:49 Q. What is the group of group two patients called who
03:56:54 suffer from solely left-heart defects?
03:56:56 A. They are called isolated group two pulmonary
03:57:01 hypertension.
03:57:03 Q. And is there a term you use to refer to those
03:57:06 patients who have the defect in addition to a left-heart
03:57:09 defect that fall within group two?
03:57:11 A. Yes. That's referred to as combined pre- and
03:57:15 post-capillary pulmonary hypertension.
03:57:17 Q. And how do the combined pre- and post-capillary
03:57:20 patients differ from the isolated group two patients?
03:57:24 A. Well, as I mentioned with the isolated, the problem
03:57:28 is the left heart and the buildup of pressure in the
03:57:32 pulmonary veins that is reflected through the capillaries
03:57:35 and pulmonary arteries. And the increase in the pulmonary
03:57:38 artery pressure is roughly equivalent to the increase in the
03:57:43 left-heart filling pressure, so that is pretty much entirely
03:57:47 responsible for the increase in the pulmonary artery
03:57:49 pressure.

03:57:50 When you have pre and post, what happens is the

these precapillary vessels undergo changes that are actually similar to what I described for group one, which is that the vessels constrict and the walls thicken and the channels narrow, and they pose an additional resistance that increases the pulmonary arterial pressure even more than would be the case with isolated, and that high pressure is associated with more morbidity and mortality because of those higher pressures.

Q. What percent of the group two patients are isolated group two patients?

A. The estimates vary, but they're generally in the range of 25 percent to a third.

Q. I'm sorry. Was that the isolated?

A. Oh, I'm sorry.

Q. Yeah. I can ask the question again so it's clear.

A. Yeah.

Q. So in group two, what percent of group two patients are isolated group two patients?

A. They are majority. Generally in the range of two-thirds to 75 percent.

Q. And then would the remainder of those patients be the pre and post combined patients in group two?

A. That's correct.

Q. Okay. So then across all pulmonary hypertension patients, what percent are isolated group two patients?

A. Roughly 50 percent or slightly more.
Q. I'd like to turn now to some of the available treatments for pulmonary hypertension patients. Do you recall what compound is used in Claim 1 of the '793 patent?
A. It's Treprostinil.
Q. In 2006, was Treprostinil an approved treatment for any of the groups of pulmonary hypertension?
A. Yes, it was.
Q. And what was the name for that product?
A. Remodulin.
Q. And how was the Remodulin administered?
A. It could be administered subcutaneously. Approved by the FDA by that route in, I believe, 2001. And it could also be administered intravenously. That route of administration approved in 2004.
Q. And in 2006, by 2006, what was Remodulin approved to treat?
A. Group one pulmonary hypertension.
Q. Are you familiar with the term "prostacyclin"?
A. Yes, I am.
Q. And is Treprostinil a prostacyclin?
A. It is.
Q. Were there any other prostacyclins that were approved for treatment of any of the PH groups in May of 2006?
A. Yes.

04:00:19 Q. And what were they?
04:00:21 A. Well, there was epoprostenol administered
04:00:26 intravenously that had been approved in 1995. And then
04:00:29 there was iloprost, brand name Ventavis, which was approved
04:00:36 for inhalation in 2004.
04:00:39 Q. And those two products that you just mentioned,
04:00:42 iloprost and epoprostenol, what groups were they approved to
04:00:45 treat?
04:00:46 A. Group one.
04:00:48 Q. How were prostacyclins thought to work in pulmonary
04:00:52 hypertension patients?
04:00:53 A. Mainly by vasodilating the pulmonary vessels, and the
04:01:00 term "vasodilation," of course, the "vaso" refers to
04:01:04 vessels. The "dilation" refers to widening of the vessel
04:01:09 due to relaxation of the muscle in the vessel wall.
04:01:15 Q. I'd like to turn now to the definition you applied in
04:01:18 your opinions, and in offering your opinions, did you do so
04:01:21 from the perspective of a POSA?
04:01:23 A. Yes, I did.
04:01:24 Q. Okay. And have you prepared a demonstrative that
04:01:26 sets out the POSA you applied?
04:01:28 A. I have.
04:01:29 Q. Can we, please, bring up DDX 3.3.
04:01:32 A. Yes. A POSA would have a medical degree with a
04:01:36 specialty in pulmonology or cardiology plus at least two

years of experience treating patients with pulmonary hypertension as an attending, including with inhaled therapies or an equivalent degree or experience.

Q. And is that the definition of a POSA that you applied in offering your opinions on the '793 patent?

A. Yes, it is.

Q. Are you aware that some of UTC's experts have offered different definitions?

A. Yes, I am.

Q. Would your opinions be different if the Court adopted one of UTC's experts proposed definitions?

A. They would not.

Q. I'd like to turn back now to the '793 patent, JTX 3. And if we could go back to the claims and specifically Claim 1.

Do you see Claim 1 refers to a method of treating pulmonary hypertension?

A. Yes, I do.

Q. And have you formed an opinion on how a POSA would understand the term "pulmonary hypertension" as it's used in Claim 1 of the '793 patent?

A. "Pulmonary hypertension" as used, as far as I can tell in the patent, and would be used as a general term by a POSA comprises all the five different groups. It refers to the -- any condition where the -- there's an elevation of

the pulmonary pressure, pulmonary pressures.

Q. And those five groups you referred to, those are the five groups that we've been discussing earlier?

A. That's correct.

Q. Okay. Was there anything in the patent that informed that opinion?

A. Yes.

Q. Can we turn to Column 1 at Line 41.

Go down. Yeah.

Can you blow that up a little, Derrick?

And how, if at all, did this portion of the patent impact your opinion?

A. Well, as you can see, the first sentence says that pulmonary hypertension may occur due to various reasons, and the different entities of pulmonary hypertension were classified, based on clinical and pathological grounds, in five categories according to the latest WHO convention. And they're referring to that Journal of American College of Cardiology article from 2004 that we had shown earlier. It's one of the exhibits.

Q. And that would have been DTX 358, the Simonneau article that we looked at earlier that's referenced here?

A. That's right. And I think this demonstrates that we're talking about pulmonary hypertension as a broad group, including those five groupings.

Q. Dr. Hill, do you understand that Dr. Waxman has taken the position that "pulmonary hypertension" as used in the '793 patent is limited to just group one pulmonary hypertension?

A. Yes, I'm aware of that.

Q. And do you agree with that opinion?

A. No, I don't.

Q. Did anywhere in the patent inform your decision that pulmonary hypertension in the patent is not limited to just group one PH?

A. Well, I think that the statement we were just looking at here is one of those bits of evidence, but there also are a couple of examples included in the patent.

Q. Can we start with Example 1 at Column 8, beginning at line 58.

And what's described in Example 1, generally, Doctor?

A. Example 1 is an open-label study on acute safety, tolerability, and hemodynamic effects of inhaled Treprostinil delivered in seconds.

Q. And can you turn later in the same example to column 9, and let's start at line 36 through line 50.

And what's described here?

A. Well, in this paragraph, the authors give us the total number of patients in this example, denote that they

had moderate to severe precapillary pulmonary hypertension, thus, pulmonary hypertension arising from the pulmonary artery is damaged or thickened. And also, some of the demographics and the hemodynamics, "hemodynamics," of course, meaning "hemo" for blood and "dynamics" for pressures and flow. So basically the blood pressure flows in the pulmonary circulation and then we have the disease etiologies in the last sentence.

Q. And what does disease etiology refer to?

A. Those are the causes of the types of precapillary pulmonary hypertension in the patients included in the study, and these included the idiopathic PAH, which is a group one entity. And then chronic thromboembolic hypertension or CTEPH, as it's commonly referred to, which is the group four.

And then pulmonary fibrosis, which is a lung condition, and hence that's a group three.

Q. So are there PH patients included in Example 1 other than or in addition to group one PAH?

A. Yes, groups 3 and 4.

Q. And you pointed to the term, I think, Doctor, precapillary pulmonary hypertension.

A. Yes, I did.

Q. Okay. If you go back to Claim 1 of the patent, does Claim 1 of the patent refer to precapillary pulmonary

hypertension?

A. No, it doesn't. It just gives a general term, pulmonary hypertension.

Q. So is Claim 1 limited to precapillary pulmonary hypertension?

A. It doesn't appear so.

Q. Can we now go to Example 2 in the patent. It should be Column 12, line 1. Sorry, Derrick.

Let's go to Example 2, Column 12, line 1.

And what is Example 2, Doctor?

A. This is three different investigations of the effects of inhaled Treprostinil on pulmonary hemodynamics and gas exchange in severe pulmonary hypertension.

Q. And then if we continue on down in the same example, there should be a Table 3 beginning at Column 13.

And, Doctor, what does Table 3 show?

A. These are -- these are these three different studies looking at different conditions, and it gives the demographics of these -- patients in them as well as the hemodynamics. And these patients that we just highlighted in yellow give the causes, which it turns out are the same as in Example 1, specifically idiopathic PAH group one entity, chronic thromboembolic pulmonary hypertension, group four, and pulmonary fibrosis, group three.

Q. Are any of the patients in this example group two

patients?

A. It -- no, they're -- there don't appear to be any.

Q. And how do you know that?

A. Well, in this case, we have hemodynamics, and the differentiation between group one and group two are made partly on hemodynamic definitions. Now, it turns out -- this PAWP stands for pulmonary artery wedge pressure, and that's a measure of the filling pressure of the left ventricle. And the accepted definition is if that wedge pressure is higher than 15 millimeters mercury, that's considered elevated and places the patient into group two.

Now, if you look at the individual numbers here, which are a little hard to make out in the figures, all of them are well below that 15, and that means that these are all non-group two patients. Essentially, all of them.

Q. Based on your review of the patent and other than the general term "pulmonary hypertension," does the patent include any specific reference to treatment of group two patients?

A. No, it doesn't.

Q. Does it include any specific reference to administration of any drugs to group two patients?

A. No, it doesn't.

Q. In 2006, would a POSA have understood the plain and ordinary meaning of "pulmonary hypertension" to include all

04:10:54 five groups?
04:10:54 A. Yes.
04:10:58 Q. I'd like, now, to turn to your opinions on invalidity
04:11:02 in this case. And we'll turn first to enablement, Doctor.
04:11:07 A. Yes.
04:11:07 Q. Have you formed an opinion as to whether the '793
04:11:12 patent enables a POSA to practice the claimed method for
04:11:14 treating group two patients?
04:11:15 A. I have formed an opinion.
04:11:18 Q. And what is that opinion?
04:11:19 A. That it provides no enablement for treating patients
04:11:26 with group two pulmonary hypertension.
04:11:27 Q. In 2006, was there any evidence that Treprostinil
04:11:31 would treat any group two patients?
04:11:33 A. No, there wasn't.
04:11:35 Q. In 2006, was there any evidence that any prostacyclin
04:11:39 would work in group two patients?
04:11:42 A. No, there wasn't.
04:11:42 Q. In 2006, was there any evidence that any group one
04:11:46 pulmonary hypertension treatment would work in group two
04:11:49 patients?
04:11:50 A. No, there wasn't.
04:11:51 Q. And what's your basis for that opinion?
04:11:53 A. Well, as I said, I've been practicing or caring for
04:12:01 pulmonary hypertension patients for almost 40 years, so that

goes back to 1982, so I was around well before 2006. I long had an interest in how you manage people with group two. And I know that there were no reports that would have told a POSA how to treat those patients using any PH -- PAH-specific medications.

Q. Can you turn to DTX 358 in your binder.

A. Yes.

Q. And is this one of those publications, Doctor, that you just referenced?

A. Yes.

Q. And what is this publication?

A. This is a randomized control trial of epoprostenol therapy for congestive -- severe congestive heart failure, and the trade name of epoprostenol, which was used in this study, was Flolan, so it was the Flolan International Survival Trial. That's where they got the acronym FIRST.

Q. And is this published in the Journal of the American -- American Heart Journal? I'm sorry.

A. That's correct. 1997.

MR. DAVIES: Your Honor, I'd like to offer DTX 358 into evidence.

MR. JACKSON: No objection.

THE COURT: Admitted without objection.

(DTX Exhibit No. 358 was admitted into evidence.)

04:13:13 BY MR. DAVIES:
04:13:13 Q. And if you turn to the abstract, can you generally
04:13:16 describe this study for the Court, Doctor?
04:13:17 A. Yes. This was a randomized, controlled trial where
04:13:21 471 patients received the epoprostenol infusion for standard
04:13:29 care. And the bottom line is that there was an excess
04:13:36 mortality in this trial, and it was stopped early.
04:13:42 Q. Why was it stopped early?
04:13:44 A. An excess mortality.
04:13:45 Q. And what do you mean by excess mortality?
04:13:48 A. More people died in the treatment group than in the
04:13:51 control group, so the so-called data monitoring safety
04:13:54 committee stopped it for safety reasons.
04:13:54 Q. And did this study include patients with group two
04:13:58 pulmonary hypertension?
04:14:00 A. It did.
04:14:00 Q. And how do you know that?
04:14:03 A. Well, you know, it's not mentioned in the patient
04:14:08 characteristic part because this preceded the development of
04:14:12 that world symposium where the groupings were worked out.
04:14:17 So, 1997, this was published, but based on the definition of
04:14:25 pulmonary hypertension, we can deduce that these were pretty
04:14:29 much all group two patients. If we go to Figure 1 --
04:14:33 Q. Okay. Can we go to Figure 1, please.
04:14:36 And how do you draw that conclusion from

Figure 1?

A. Well, if we can enlarge this a little bit. So what's shown here are the hemodynamics of the patients in this study. Now, all of them had to do -- have a wedge pressure of 15 or greater to get in. So, that tells us they had a wedge high enough to be in group two, all of them.

But then it's a question of was the mean pulmonary artery pressure, which is shown here, high enough to warrant the diagnosis of pulmonary hypertension? And at the time this study was done, the definition based on hemodynamics of somebody with pulmonary hypertension they had to have a mean pulmonary artery pressure of 25 or greater, so that would be right here in this chart. And you can see up here in the middle here, this is the average pressure. It's about 38. So that means the average patient was well above that cut-off, and the lower part of the little box there is the 25th percentile, so that means 75 percent had over that level which is about 28. So, more than 75 percent of these patients had to have group two pulmonary hypertension by the definition as of 2006.

Now, one other thing I want to point out here is that these hemodynamics were obtained at the start of the study when they did what's called a dose-ranging trial with the epoprostenol. And what they did was start off at a low dose -- you know, a two would be a low dose, and then they

04:16:19 did a dose-ranging trial where you can see they go up to 2, 4, 6 level, and then the MTD is the maximum dose achieved. And, this would have taken place over a few hours.

Now, what you can see is over time here, over these few hours, there's a general trend down. So the mean pulmonary artery pressure dropped down, and that was statistically significant in this study. The wedge pressure dropped down. The pulmonary vascular resistance dropped down. These were all significant changes, and they would be considered improvements. So the authors were quite surprised by this excess mortality that they found in the study, but I think it shows that an acute vasodilator that looks promising does not necessarily translate into an effective therapy. If we could go to the last --

Q. And, Doctor, before you go on to mention improvements, those are improvements in hemodynamics?

A. Yes.

Q. Can you go to Page 8 of 11. In summary, it starts at the bottom of page 8 continuing on to Page 9.

And, Doctor, what's described here?

A. Well, let's -- yeah, here we go. So in summary, despite what they felt would be evidence of -- in the preliminary clinical evidence of benefit, which I was just talking about, they found increased mortality rates and no evidence of improved quality of life. So, it was a negative

trial, and it raised concern about harm using this treatment approach in people with this kind of pulmonary hypertension.

Q. So, what would this say to a POSA about using a prostacyclin in group two pulmonary hypertension patients?

A. Be extremely cautious.

Q. Can we turn to DTX 345.

And what is DTX 345, Doctor?

A. This is the prescribing information for Ventavis, which is the trade name for another prostacyclin, iloprost, which is administered by inhalation.

Q. And when was Ventavis approved?

A. 2004.

Q. And what is the date of the label?

A. 2005.

MR. DAVIES: Your Honor I'd like to offer DTX 345 into evidence.

MR. JACKSON: No objection.

THE COURT: Admitted without objection.

(DTX Exhibit No. 345 was admitted into evidence.)

BY MR. DAVIES:

Q. What is Ventavis?

A. Ventavis is this prostacyclin iloprost that's administered by inhalation.

Q. As of May 2006, were there any other inhaled

04:18:54 prostacyclins approved in the U.S. other than iloprost?
04:18:58 A. There were not.
04:18:59 Q. What was Ventavis approved to treat?
04:19:01 A. Group one pulmonary hypertension.
04:19:03 Q. Can we turn to Page 6 and focus on the last
04:19:09 paragraph, the warning section.
04:19:10 And what does this mean, Doctor?
04:19:15 A. Well, it says should signs of pulmonary edema occur
04:19:20 when inhaled iloprost is administered in patients with
04:19:24 pulmonary hypertension, the treatment should be stopped
04:19:26 immediately. This may be a sign of pulmonary venous
04:19:29 hypertension.
04:19:29 And the relevance to the concern in group two is
04:19:34 that this pulmonary hypertension, the theory is that if you
04:19:39 open up the precapillary vessels and allow more blood to
04:19:44 flow through into the capillaries and then into the
04:19:49 pulmonary veins, it could increase the pulmonary venous
04:19:51 pressure, the pressure filling the left heart, and that
04:19:55 increase in the capillaries can cause leakage of fluid into
04:20:00 the gas exchanging areas of the lungs, interfering with
04:20:04 oxygenation and creating a potentially life-threatening
04:20:08 situation.
04:20:08 Q. And in 2006, what would this portion of the Ventavis
04:20:12 label that we're looking at have led a clinician to believe
04:20:15 about using inhaled prostacyclins in group two patients?

04:20:19 A. Be extremely cautious.
04:20:21 Q. And why?
04:20:21 A. Because of that concern. If you increase the
04:20:25 pulmonary venous pressure as a consequence of dilating the
04:20:30 precapillary vessels, you could induce pulmonary edema.
04:20:35 Q. Can we go to DTX 383. And blow up the top part,
04:20:43 please, Derrick.
04:20:44 And, Doctor, what is DTX 383?
04:20:48 A. This is a review article published in Current
04:20:51 Cardiology Reviews in 2015 on pulmonary hypertension types
04:20:58 and treatments.
04:21:00 MR. DAVIES: Your Honor, I'd like to admit DTX
04:21:02 383 into evidence.
04:21:04 MR. JACKSON: No objection.
04:21:06 MR. DAVIES: And can we please go to Page 5 and
04:21:08 look at the heading WHO groups 2 through 4.
04:21:11 (DTX Exhibit No. 383 was admitted into
04:21:11 evidence.)
04:21:11 MR. DAVIES: Blow that up, Derrick.
04:21:14 Q. And, Doctor, what conclusions can you draw from this
04:21:16 review?
04:21:17 A. Well, the conclusion I would draw is the same as the
04:21:21 conclusion the authors drew, and if we can enlarge the last
04:21:27 sentence.
04:21:37 So, what it says is there are no randomized

04:21:40 controlled trials to support the benefit of group one
04:21:43 PAH-specific therapies in group two, and they also mention
04:21:47 group three, and there are potential risks, including
04:21:50 worsening pulmonary edema in group two disease. So, that,
04:21:55 you know, just solidifies that concern.
04:21:59 Q. Between 2015 and today, have there been any
04:22:02 developments that would alter your view and the view of the
04:22:06 authors in this paper regarding the use of group one
04:22:08 therapies in group two patients?
04:22:11 A. Not to my knowledge, no.
04:22:14 Q. Dr. Hill, do you recall earlier talking about
04:22:17 isolated and pre- and post-combined group two patients?
04:22:21 A. Yes.
04:22:22 Q. So I'd like to start first with the isolated group
04:22:25 two patients. And can you just remind us how many PH
04:22:29 patients are isolated group two patients.
04:22:31 A. 50 percent or somewhat greater.
04:22:35 Q. And in 2006, would a POSA with the information in the
04:22:39 patent, the '793 patent, have believed that inhaled
04:22:43 Treprostinil could be used to treat isolated group two
04:22:46 patients?
04:22:46 A. I don't believe so.
04:22:47 Q. And why not?
04:22:48 A. Well, first of all, the -- there's nothing, as I
04:22:55 mentioned, that offers any guidance in the patent or in the

04:23:00 preexisting literature. And just from a conceptual point of
04:23:07 view, it really doesn't make any sense because we're talking
04:23:10 about a condition where the pressure is filling the left
04:23:13 ventricle up. It caused pulmonary venous hypertension.
04:23:17 Then that gets transmitted across the capillaries and into
04:23:20 the pulmonary arteries and the effect of those increases of
04:23:24 pressures will distend the vessels.
04:23:27 And if you administer Treprostinil, the aim of
04:23:32 which is to distend the vessels more, I don't think it would
04:23:35 have any effect, and it would not provide any benefit.
04:23:39 Q. I'd like to ask you now about the pre and post
04:23:41 combined group two patients. So, in 2006, would a POSA have
04:23:47 believed that an inhaled Treprostinil could be used to treat
04:23:51 combined pre- and post-capillary PH patients, group two PH
04:23:57 patients?
04:23:57 A. Well, I think there would be a rationale there.
04:24:00 Q. And what is that potential rationale?
04:24:03 A. Well, as I mentioned when we went over the first
04:24:06 schematic, the pathology, the constriction in the remodeling
04:24:13 that you see in pre- and post-capillary, you know, in the
04:24:18 precapillary vessels is similar to that you see in group
04:24:21 one. And you could imagine that an agent that vasodilates
04:24:27 like inhaled Treprostinil could open up those vessels a bit
04:24:31 and lead to easier flow of blood through them.
04:24:36 Q. Does the '793 patent include any description of

04:24:39 treating any group two patient?
04:24:41 A. No, it doesn't.
04:24:42 Q. Does the '793 patent include any description of
04:24:46 administering Treprostinil to any group two patient?
04:24:47 A. It does not.
04:24:48 Q. And when we looked at the patents earlier, neither of
04:24:52 the patents included group two patients, did they?
04:24:54 A. The examples.
04:24:56 Q. Examples, I'm sorry. Yes.
04:24:58 A. That's correct.
04:25:00 Q. Given -- they did include some forms of PH, though;
04:25:04 correct?
04:25:05 A. Several groupings, yes.
04:25:06 Q. And what were those three groupings?
04:25:08 A. They were group 1, 3 and 4.
04:25:10 Q. And given that the examples mention at least some
04:25:14 groups of PH, would that have provided guidance to a POSA
04:25:17 for treatment of group two pulmonary hypertension patients?
04:25:20 A. No, it wouldn't.
04:25:21 Q. Why not?
04:25:22 A. Well, there -- as I pointed out, you know, there were
04:25:28 no group two patients discernable in that group, either
04:25:34 according to their listing or the hemodynamics that they
04:25:37 presented. And group two pulmonary hypertension has a very
04:25:41 different pathophysiology than the precapillary group 1, 3,

and 4. So, you couldn't look at what happened in these examples and deduce anything about how to treat group two.

Q. Does the '793 patent provide any information that would address these safety concerns you discussed earlier?

A. No, it doesn't.

Q. In the -- in the pre- and post-combined patients, you mentioned that there may be a rationale for why inhaled Treprostinil might work.

A. Correct.

Q. Would you, nonetheless, still have safety concerns as of May 2006?

A. Yes, I would.

Q. In 2006, how predictable would a POSA have found developing inhaled Treprostinil to treat group two pulmonary hypertension?

A. Virtually unpredictable.

Q. Do you have any opinion as to the amount of experimentation a POSA would have had to conduct to be able to treat group two pulmonary hypertension with inhaled Treprostinil?

A. Yes, I do.

Q. And what is that?

A. I think it would have required a lot of experimentation.

Q. What types of experimentation, in your mind, would

have been needed?

A. Well, I think you'd have to stop -- start at square one because you know, we have nothing in the literature to establish feasibility of this approach. We have nothing in the literature to establish the safety of this approach. So you have to start out with very carefully selected patients, work out a protocol with their safety in mind. So you'd have to start off very low levels, monitor these patients very carefully, and just determine in kind of a phase one and early-type study that it is -- there is a potential feasibility and that it's reasonably safe.

And then you'd have to go on to a larger trial, where you would get more patients to establish safety and to determine whether there's some efficacy before you could go to the large trials that would be necessary to convince the -- rather, the clinical community and eventually the FDA that it's worth, you know, labeling a drug to treat that entity.

Q. You're familiar with TYVASO; right?

A. I am.

Q. And TYVASO is an improved inhaled form of Treprostinil?

A. Yes, it is.

Q. And is that approved for treatment of some groups of pulmonary hypertension?

A. It is.
Q. And what is it approved to treat?
A. It's approved to treat group one pulmonary hypertension, which was in 2009. And then just last year in 2021, it was approved to treat group three pulmonary hypertension.
Q. Is TYVASO approved to treat group two?
A. No, it's not.
Q. Do you use TYVASO with your patients?
A. I do.
Q. About what percentage of your patients currently use TYVASO?
A. Roughly 5 to 10 percent.
Q. Are any of your patients that you use TYVASO with group two patients?
A. No.
Q. Can we bring up DTX 388.
And what is DTX 388, Doctor?
A. This is the prescribing information for TYVASO.
Q. And what's the date on this prescribing information?
A. I believe it's 2005.
Q. If you look in the lower right-hand corner there, it mentions a revised date.
A. Oh, yeah. The revision is 2021.
MR. DAVIES: Your Honor, I'd like to offer DTX

388 into evidence.

MR. JACKSON: No objection.

THE COURT: It's admitted without objection.

(DTX Exhibit No. 388 was admitted into evidence.)

BY MR. DAVIES:

Q. Today, is there any prostacyclin that's approved for treatment of group two?

A. No, there's not.

Q. Today, is there any group one therapy that's approved for treatment of group two pulmonary hypertension?

A. No, there's not.

Q. To summarize, Dr. Hill, what is your opinion on whether a POSA, even with the patent, could practice a method of treating the full scope of pulmonary hypertension including group two without undue experimentation?

A. I think they would not be able to practice the use of inhaled Treprostinil on patients with group two, especially the isolated version, and it would take a considerable amount of experimentation to get to that point.

Q. Dr. Hill, I'd like to turn now to your written description opinion on the '793 patent. Have you formed an opinion as to whether a POSA reading Claim 1 of the patent would believe that the inventors actually possessed a method of treating isolated group two with inhaled Treprostinil?

04:30:45 A. Yes, I have such an opinion.
04:30:47 Q. And what is that opinion?
04:30:48 A. I don't think a POSA would have believed that the
04:30:53 patent possessed a way of treating patients with isolated
04:30:59 group two pulmonary hypertension.
04:31:00 Q. And why don't you believe that?
04:31:02 If you could just speak up a little bit --
04:31:03 A. Oh, sorry.
04:31:04 Q. -- Doctor.
04:31:05 A. There is nothing offered in the patent that provides
04:31:12 any guidance, and it would take an undue amount of
04:31:19 experimentation to get to that point.
04:31:23 Q. And the '793 includes no description of any group two
04:31:26 patients treated with Treprostinil; correct?
04:31:29 A. That's correct.
04:31:29 Q. Given your answers, do you believe the inventors of
04:31:32 the '793 patent actually possessed a method of treating
04:31:35 isolated group two with inhaled Treprostinil?
04:31:37 A. I don't.
04:31:38 Q. Can you turn back to the claims of the '793 patent,
04:31:42 Derrick.
04:31:44 Can we focus -- Derrick, that's great.
04:31:50 Do Claims 4, 6, 7, and 8, in your opinion, also
04:31:53 require a method of treating pulmonary hypertension that
04:31:56 we've been discussing in Claim 1?

A. Yeah, they refer back to Claim 1. And you know, they all would be relying on the method the -- claimed in Claim 1.

Q. So the opinions that you've just offered, Doctor, with respect to Claim 1 would apply, for the same reasons to Claim 4, 6, 7 and 8 with respect to the full scope of pulmonary hypertension?

A. That's correct.

MR. DAVIES: I have no further questions at this time, Your Honor.

THE COURT: All right. Cross-examination.

MR. JACKSON: May I approach, Your Honor?

THE COURT: Sure.

MR. JACKSON: I'm not sure these are really going to be necessary, but.

DEPUTY CLERK: Thank you.

MR. JACKSON: I apologize. Sorry.

DEPUTY CLERK: Thank you.

MR. JACKSON: I apologize.

CROSS-EXAMINATION

BY MR. JACKSON:

Q. Good afternoon, Doctor.

A. Good afternoon.

Q. Now, in this case, you offered, -- you had provided expert reports; correct?

04:33:46 A. I'm sorry. We haven't met.
04:33:47 Q. I'm sorry. My name is William Jackson. I represent
04:33:51 United Therapeutics.
04:33:52 A. Yeah, I know who you represent, but I hadn't met you.
04:33:54 I'm sorry. Nice to meet you, Mr. Jackson.
04:33:56 Q. Nice to meet you.
04:33:58 Now, you provided expert reports in this case;
04:34:05 correct?
04:34:05 A. Yes, I did.
04:34:05 Q. And those expert reports, at least on the validity
04:34:08 side, do you recall that you had two? You had the opening
04:34:11 and then you had a reply; right?
04:34:13 A. Yes.
04:34:15 Q. Is that correct?
04:34:16 A. Yes.
04:34:17 Q. And in the opening and the reply, you had a bunch of
04:34:24 opinions about obviousness; is that right?
04:34:27 A. Yes.
04:34:27 Q. Do you recall that?
04:34:28 You're not offering those today; correct?
04:34:30 A. That's correct.
04:34:35 Q. And so, the only opinions you're offering are on
04:34:38 written description and enablement; correct?
04:34:40 A. That's correct.
04:34:47 Q. So is it -- so it's your view that the patent claim

that is directed to the use of Treprostinil to treat pulmonary hypertension, where pulmonary hypertension includes isolated postcapillary group two, would be invalid for lack of written description or enablement; correct?

A. That's correct.

Q. Would you agree that a patient can be in multiple groups?

A. Yes, I would.

Q. And would you agree that you personally have administered Treprostinil to some patients in group two; correct?

A. Yes, I have.

Q. Successfully; right?

A. Not so successfully, but I have.

Q. And would you agree that there's a rationale for using a vasodilator like Treprostinil in people in group two with both pre- and post-capillary hypertension?

A. Yes, I would.

Q. And you have seen some patients with mixed group one and group two actually respond to some of these medications, correct?

A. That's correct.

Q. And would you agree that a POSA in 2006 would have known not to give Treprostinil or any vasodilator to a pure postcapillary group two pulmonary hypertension patient?

04:36:20 A. I think that's fair.
04:36:23 Q. In fact, I think your deposition you might -- you
04:36:27 were asked whether it would be stupid for someone to give a
04:36:30 pure group two postcapillary pulmonary hypertension patient
04:36:34 a vasodilator such as Treprostinil, and you said it would;
04:36:39 correct?
04:36:39 A. Yeah, I'm usually very cautious about referring to
04:36:43 any of my colleagues in that way, but in this particular
04:36:46 situation, that's probably apt.
04:36:49 Q. Okay. So now I'd like to show you what's been marked
04:36:52 as PTX 64. Can we open that up.
04:36:54 I'm happy if you want to use your binder, but
04:37:01 it's also on your screen if that helps.
04:37:07 A. So, this is a United States Patent. Is that what I'm
04:37:11 looking at?
04:37:11 Q. Yes. And it's -- it ends in '494. Do you see that?
04:37:15 A. Yes, I do.
04:37:18 Q. Okay. So it's a patent number -- patents usually
04:37:20 go -- are usually referred to by their last three digits.
04:37:23 This is Patent Number '494 for this case; right?
04:37:26 A. Yes.
04:37:26 Q. Okay. And this is a patent that includes Liquidia as
04:37:29 the applicant; correct?
04:37:31 A. That's correct.
04:37:32 Q. Now, if you turn to Column 1 of the patent, and look

04:37:36 at Line 63, please.
04:37:46 A. This is in Column 1, did you say?
04:37:49 Q. Yeah. And if we can pull it up on the screen.
04:37:52 Column 1, Line 63.
04:37:55 A. Yes.
04:37:59 Q. While we're doing that, I'm going to move admission
04:38:01 of PTX 64.
04:38:04 MR. DAVIES: No objection, Your Honor.
04:38:06 THE COURT: Admitted without objection.
04:38:08 (PTX Exhibit No. 64 was admitted into evidence.)
04:38:09 BY MR. JACKSON:
04:38:09 Q. Okay. Now, we looked at Line 60 to 66 there. Do you
04:38:12 see that?
04:38:14 And it reads PAH. That's pulmonary arterial
04:38:18 hypertension; right?
04:38:18 A. Yes.
04:38:19 Q. PAH is part of a larger classification for pulmonary
04:38:22 hypertension, which is divided into five groups based on
04:38:25 World Health Organization (WHO) criteria designated as WHO
04:38:31 groups 1 through 5. And that's what you were talking about
04:38:34 earlier; correct?
04:38:34 A. That's correct.
04:38:35 Q. And then it says, "PAH, pulmonary arterial
04:38:41 hypertension, is used to describe exclusively WHO group
04:38:44 one"; right?

04:38:44 A. I don't agree with that.
04:38:48 Q. But that's what the patent says; right?
04:38:50 A. That's what the patent says. Yes, sir.
04:38:52 Q. Okay. And then it says, "Pulmonary hypertension is
04:38:54 used to describe the remaining four groups, WHO groups 2
04:38:59 through 5, and also when referring to all five groups
04:39:01 collectively."
04:39:02 Do you see that?
04:39:02 A. Yes.
04:39:03 Q. So, at least for the purpose of this patent, the
04:39:06 patent describes pulmonary hypertension as all five groups;
04:39:11 right?
04:39:11 A. Yes.
04:39:12 Q. Okay. Now, you spent a couple of minutes with
04:39:15 Mr. Davies talking about hemodynamics. Do you recall that?
04:39:17 A. I do.
04:39:20 Q. Now, is hemodynamics the way blood flow -- it's the
04:39:27 calculation of the way the blood flows through the body. Is
04:39:29 that fair?
04:39:30 A. Yeah. I gave a -- a definition, but "hem-" refers to
04:39:36 blood. And "dynamics" refers to pressures and flows. So
04:39:40 it's basically blood pressure and flows.
04:39:42 Q. And so pulmonary hypertension is problems in those
04:39:46 blood flows, especially in the pulmonary system, which is
04:39:49 the heart and the lungs; right?

04:39:50 A. Yeah, and specifically high blood pressure.
04:39:52 Q. Okay. So, hemodynamics is the study of the blood
04:39:56 flow, and pulmonary hypertension is the constriction of the
04:40:00 ability to -- for that blood to flow through the heart and
04:40:04 lungs; right?
04:40:04 A. Right. It's constriction and thickening of the
04:40:08 vessels that narrows the channels.
04:40:10 Q. Okay. So let's come back to the patent. Would you
04:40:12 agree that looking at this definition of pulmonary
04:40:16 hypertension, this definition of pulmonary hypertension
04:40:19 would include isolated postcapillary group two pulmonary
04:40:23 hypertension?
04:40:24 A. This is a very broad definition, so, yeah.
04:40:30 Q. Okay. Now, can you go to Page 63, Column 77, of the
04:40:38 patent, where it says we claim.
04:40:39 A. This is count what? I am sorry.
04:40:41 Q. Sorry. Just all the way at the end of the patent
04:40:44 where it says "we claim." Do you see it?
04:40:49 I think it's a long patent -- I think it's
04:40:52 Column 77. It should be on Bates ending in 973.
04:40:57 A. Yeah. Yes, I see it.
04:40:59 Q. Are you with me?
04:41:02 Okay. It says "we claim." Do you see that?
04:41:02 A. I see it.
04:41:02 Q. And it says, "We claim a method for treating a

patient, comprising: Administration of a dry-powder composition comprising from about 100 micrograms to about 300 micrograms Treprostinil or a pharmaceutically acceptable salt thereof to a patient by inhalation using a dry-powder inhaler over one to four breaths to treat pulmonary hypertension."

Did I read that right?

A. You did.

Q. Okay. And so that, to treat pulmonary hypertension, that includes group two pulmonary hypertension; right?

A. By the way they're using the terms, yes.

Q. Including isolated group two pulmonary hypertension; right?

A. They don't exclude it, so, yes.

Q. Okay. And so there -- this is claiming a method of treating that -- all those types of pulmonary hypertension with Treprostinil; right?

A. Yes.

Q. Okay. And so to the degree that your concern about using Treprostinil to treat pulmonary hypertension in the '793 patent is because Treprostinil shouldn't be used to treat that group, those same concerns apply to here; right?

A. They do.

Q. Okay.

MR. JACKSON: I have nothing further. Thank you

for your time, Dr. Hill.

THE WITNESS: Okay. Thank you.

THE COURT: Anything further?

MR. DAVIES: Just a couple things, Your Honor. Just really quick.

REDIRECT EXAMINATION

BY MR. DAVIES:

Q. Dr. Hill, you responded to counsel that you had administered Treprostinil to a group two patient. When did you do that?

A. That was about ten years ago.

Q. Why did you do that?

A. This was a patient who had been allergic to sildenafil, which is one of the PH drugs that I had been using, and there was some evidence that accumulated around that time suggesting that sildenafil might be helpful. This man had severe functional limitation, and as a compassionate use of the medication -- he had combined pre- and post-pulmonary hypertension, very severe, I very cautiously started him on inhaled Treprostinil.

Q. Did that evidence suggesting that it might be helpful come out after May 2006?

A. Yes, it did.

Q. Counsel asked you a question about mixed group one and group two --

04:43:32 A. Yes.
04:43:33 Q. -- pulmonary hypertension. What did you understand
04:43:36 counsel to refer to by mixed group one and group two?
04:43:39 A. Well, there are mixed forms of pulmonary
04:43:44 hypertension. The classification system is not perfect, and
04:43:47 there are patients who do not fit neatly into any one
04:43:50 category. So, this requires adjudication by experts to
04:44:00 agree on something like this.
04:44:02 But that kind of patient would have less filling
04:44:10 pressure elevation on the left side and more precapillary
04:44:15 resistance with very high pressures in the pulmonary
04:44:19 circulation. But there are such patients, and they're
04:44:23 actually -- you know, people talk about combined group 1 and
04:44:27 2, and then combined group 2 and 1 where the group two is
04:44:32 the predominant. But what we try to do when we treat these
04:44:36 patients is identify the predominant pathology and go after
04:44:40 that.
04:44:40 But with some of these patients, the
04:44:44 precapillary component is quite substantial, and so in those
04:44:49 kinds of patients, we might try one of the medications
04:44:53 that's approved for group one.
04:44:56 MR. DAVIES: No further questions, Your Honor.
04:44:58 THE COURT: All right.
04:44:59 MR. JACKSON: Nothing further, Your Honor.
04:45:00 THE COURT: All right, Dr. Hill.

THE WITNESS: Thank you.

THE COURT: You can step down, and watch your step. Okay.

THE WITNESS: Thank you, Your Honor.

MR. SUKDUANG: Your Honor, given the time, we have another live witness, our last live witness, Dr. Gonda, which will definitely go over past 5:00, but we do have a deposition video that would take us to about five, if you'd like us to play that and then start tomorrow. It depends on how you'd like to proceed.

THE COURT: Well, it's your case. How would you like to proceed?

MR. SUKDUANG: I think we play the transcript. It will get us to 5 o'clock.

THE COURT: That would be fine.

MS. CAZAKOFF: Your Honor, we will now hear deposition testimony from Dr. Lewis Rubin, who's a former clinical development consultant to UTC and a named inventor on the '793 patent. And his testimony relates to the scope of his collaboration with UTC.

(Video playing.)

LEWIS RUBIN, the witness herein, after having been duly sworn under oath, was examined and testified as follows:

Q. Good morning, Dr. Rubin. Good morning.

Is Rubin Exhibit Number 7 a copy of your current CV?

A. Yes.

Q. Why do patients all over the world come to see you with respect to pulmonary circulation disorders?

A. Well, it's been something that I've been involved in since 1977. It's a long time. I've published, as you can see from my Curriculum Vitae, quite extensively. I've edited books, specifically, on the pulmonary circulation. I've been either the principal investigator or steering committee member for all of the drugs currently approved by the U.S. Food and Drug Administration to treat pulmonary hypertension, including the first one.

I've served as a consultant to the federal government, the FDA, the NIH, the Veterans Administration, for foreign countries, United Kingdom, Canada, Australia, and others. And so I'm well-known as one of the world's experts in this disease, in this field.

Q. Are there different classifications of patients with pulmonary arterial hypertension?

A. There are different classifications of etiologies. There's one generally accepted classification of etiology, and then there are sort of minor differences between some of the others, but there's one consensus, generally accepted classification.

Q. And then what would you call that general consensus of classification of the etiology of pulmonary arterial hypertension?

A. Well, currently, I would call it either the European Respiratory Society classification or the World Symposium classification. The two are virtually identical and, not surprisingly, were generated by consensus of the world's experts.

Q. You mentioned you've worked on every FDA-approved drug for PAH; is that right?

A. That's correct.

Q. Okay. Under the umbrella of PH, pulmonary hypertension, other than PVH and PAH, are there any other manifestations that would fall under that umbrella?

A. Well, I wouldn't say "manifestations." I would say etiologies or conditions, again, according to the classification.

So classification very simply is -- number one is pulmonary arterial hypertension, PAH, and then the subclassification lists a number of different disease processes that cause PAH.

Number two is pulmonary hypertension due to left-heart disease and that, in general, causes pulmonary venous hypertension, but it's not the only cause of pulmonary venous hypertension. It's the most common, but

it's not the only one.

And then group three is chronic lung diseases that can cause pulmonary hypertension, emphysema, pulmonary fibrosis, those sorts of things, cystic fibrosis.

Group four is chronic thromboembolic pulmonary hypertension. So blood clots that are chronic that plug up the vasculature in the lungs and cause the back pressure to be elevated. That's intrinsic clots within the lungs.

And group five is a grab bag of miscellaneous causes, less common diseases that can be associated with pulmonary hypertension.

Q. Dr. Rubin -- I'm marking as Rubin Exhibit Number 8, a document titled "United Therapeutics Corporation Moderator Martine Rothblatt, November 1, 2007." It has Bates numbers UTC-SAND-REM00242621 through 24236.

Do you recall seeing this document before?

A. I don't, specifically, recall seeing it, but I can't exclude the possibility that I have. It's a long time ago.

Q. And do you recall providing statements at that teleconference?

A. I do recall providing statements.

Q. Okay moving on, it says, "It was just over four years ago today that Dr. Rubin and I had what was for both of us one of the most satisfying lunches ever."

Do you see that?

A. Yes.
Q. So four years from November 1, 2007, would have been around November 1st, 2003?
A. Yes.
Q. It says, "We closed down a restaurant in La Jolla, patiently explaining to me that the best and most logical way to deliver Treprostinil, our active ingredient, was through inhalation."
Do you see that?
A. Yes.
Q. When you had the initial meetings in 2003, was the prospect of using a metered dose inhaler discussed?
A. Yes, they were both -- alternative modes of delivery were discussed at -- certainly, they were discussed at the luncheon meeting in Ohio, and I believe were either discussed at the New York meeting or certainly a number of times subsequent to that over the course of the clinical development of inhaled Treprostinil.
Q. What about the use of a dry-powder inhaler?
A. I recall it being mentioned. I recall bringing up to Rothblatt, that given the limitations of inhaled iloprost, which were improved upon by nebulized Treprostinil, but still not quite as convenient and effective as it could be, that there would be other methodologies of delivery that could be very useful down the road. And, you know, those

included metered dose inhalers, soft-mist inhalers, and dry-powder, and those were discussed, and I think she said that those would be down the road.

Q. Could you use a solution in a dry-powder inhaler?

A. No, they're completely different. Solution is a formulation that includes liquid. The medication in this case is put into solution to create a solution of a certain amount or concentration to be used to deliver through a delivery vehicle that is designed to deliver particles in a mist, particles of a certain size delivered through a mist to the patient. So that could be a nebulizer. It could be a soft mist or a metered dose inhaler. They all would use the same principle of creating a breathable, hydrated formulation of the drug.

Dry-powder inhaler has no water or other carrier solution. It is simply particles of drug that have been formulated such that the particles would contain a specified amount of drug and would be deliverable through a device directly to the lungs without requiring it to be put in any kind of solution whatsoever.

Q. While you were working with UT, did you ever work on an inhaled powder formulation of Treprostinil?

A. No, not with UT. Subsequently I did with two companies.

Q. What is a "single event"?

A. It means a single treatment event. A period of time during which the delivery of the full dose of medication required to achieve the treatment is made.

Q. Is -- the work that you did with UT on the Phase III clinical trial for inhaled Treprostinil, do you recall how many times a day a patient had to take the drug?

A. Four.

Q. Four times a day?

A. Correct.

Q. Is that -- is each integral time a "single event" as you're describing here?

A. Yes. For a simple analogy, let's say you're taking blood pressure medicine four times a day, and you have to take two pills four times a day. Each event is one of those intervals when you take the medication, and the taking of the two pills is the event.

Q. So two pills would be a "single event"?

A. Correct.

Q. Would -- the "single event," could it also be a dose?

A. The event includes a dose, but a dose itself is not an event. For example, you know, if the dose is 10 milligrams and you need to take 10 milligrams four times a day, then the event is the taking of 10 milligrams each time four times a day.

If it were just the dose and if you took it at

8:00 a.m. and then you decided you couldn't remember. You took it at 10:00 am and you took another one cause you felt like it at noon, that would each be an event. But that's not accurate.

It means a single treatment event. A period -- a period of time during which the delivery of the full dose of medication required to achieve the treatment is -- is made.

Q. Can you turn to Exhibit 5, which is the '793 patent.

A. Okay.

Q. And do you see there is a number one, a Claim 1?

A. Yes.

Q. If you read Claim 1, Claim 1 doesn't indicate to take the drug multiple times a day, does it?

A. No, it does not.

Q. Do any of Claims 2 through 8 indicate taking the drug more than a single event?

A. They do not.

Q. Could you, Dr. Rubin, could you pull out Exhibit 21, which I think you have in front of you?

A. Yes.

Q. And can you please turn to the page at the bottom that begins LR, and it's LR 000166. Let me know when you're there.

A. Yup.

05:02:45 Q. And this document spans five pages, it ends in LR000170; is that right?
05:02:52 A. Yes.
05:02:55 Q. And on this page, do you see a signature by a Lewis J. Rubin, M.D.?
05:02:58 A. Yes.
05:03:02 Q. Is that your signature?
05:03:04 A. Yes, it is.
05:03:05 Q. And is the date September 24, 2003?
05:03:06 A. Yes.
05:03:09 Q. And is the cosignatory from Lung Rx, Inc.?
05:03:11 A. Yes.
05:03:18 Q. And is that Martine Rothblatt?
05:03:18 A. Yes.
05:03:22 Q. And is it dated September -- well -- 30th, 2003?
05:03:23 A. Yes.
05:03:28 Q. Could you turn to the first page of this agreement, LR000166?
05:03:31 A. Yes.
05:03:35 Q. And is this titled the service -- "services agreement"?
05:03:38 A. Yes.
05:03:39 Q. And is this between yourself and Lung Rx?
05:03:43 A. Yes.
05:03:43 Q. And do you see a paragraph 9, "ownership"?
05:03:44
05:03:48
05:03:51

A. Yes.

Q. And it says, "Patents and trade secrets. Dr. Rubin eight agrees to properly disclose, grant, and assign to Lung Rx all right, title, and interest in and to any patentable or unpatentable inventions, discoveries, and ideas which are made or conceived in whole or part on behalf of Dr. Rubin in the course of or any -- or as a result of the services performed under this agreement."

Okay. And this provision in paragraph 9 was signed in September 2003; correct?

A. Yes.

Q. And do you remember counsel directed you to some patent assignments, documents, in the questions that he asked you today?

A. Yes.

Q. And do you recall those were dated in 2006; correct?

A. Yes.

Q. That's three years after you were required to assign, at least in UT's view, all your inventions and trade secrets to them?

A. Well, all inventions and trade secrets that were generated during the time of this agreement. Not anything prior to that.

(Conclusion of video.)

MS. CAZAKOFF: Your Honor, just for the record,

I'm Brittany Cazakoff.

And at this time, we would like to enter into evidence DTX 687, PTX 174 and DTX 530.

MR. JACKSON: No objection, Your Honor.

THE COURT: All right. Admitted without objection.

(DTX Exhibit Nos. 687 and 530 were admitted into evidence.)

(PTX Exhibit No. 174 was admitted into evidence.)

MR. SUKDUANG: Your Honor, I think that would close for today, and then we'll have one more live witness tomorrow, Dr. Gonda, and one more short video. And then we'll pass the case off to UT.

THE COURT: All right. And what are you all expecting to do tomorrow when it's your turn?

MR. JACKSON: Well, we have the infringement witness that we had.

THE COURT: Yeah. What's that person's name?

MR. JACKSON: Dr. Waxman.

THE COURT: Okay.

MR. JACKSON: Aaron Waxman, and then we have several other experts who will go afterwards.

THE COURT: All right. And those other experts are who?

05:06:20 MR. JACKSON: Dr. Fawzi, Dr. Scheidt,
05:06:28 Dr. McConville, Dr. Clark, and Dr. Smyth.
05:06:31 THE COURT: All right. That should get us
05:06:37 through tomorrow.
05:06:37 MR. JACKSON: Thank you, Your Honor.
05:06:37 MR. SUKDUANG: And just for a note, because of
05:06:40 Dr. Waxman's availability we talked about earlier, he's
05:06:43 going to do his infringement and then invalidity, if I
05:06:47 understand correctly. And then Dr. Hill is going to come
05:06:50 back and do his response to infringement.
05:06:54 THE COURT: Oh, okay.
05:06:54 MR. SUKDUANG: And then the rest of UT's
05:06:57 witnesses are going to go after that.
05:06:59 THE COURT: All right. So basically -- okay I
05:07:03 get it.
05:07:03 So, Dr. -- I think it was Waxman. He's going to
05:07:05 start off tomorrow?
05:07:06 MR. SUKDUANG: No. Well, do you want him to
05:07:08 start off tomorrow?
05:07:09 MR. JACKSON: We can work that out.
05:07:11 THE COURT: Yeah, yeah.
05:07:11 MR. JACKSON: But Dr. Waxman will provide both
05:07:13 his validity and his infringement opinions tomorrow, and
05:07:19 Dr. Hill will come back for the response to the infringement
05:07:22 piece.

05:07:22 THE COURT: All right. Why don't you work that
05:07:24 out.
05:07:24 MR. JACKSON: Thank you. Thank you, Your Honor.
05:07:25 THE COURT: All right. Well, thank you. We'll
05:07:27 be in recess.
05:07:28 DEPUTY CLERK: All rise.
(Court was recessed at 5:07 p.m.)
I hereby certify the foregoing is a true and accurate transcript from my stenographic notes in the proceeding.

/s/ Heather M. Triozzi
Certified Merit and Real-Time Reporter
U.S. District Court.