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 I

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

Monday, March 28, 2022
8:30 a.m.
Bench Trial

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

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*** PROCEEDINGS ***

08:29:17 DEPUTY CLERK: All rise. Court is now in session. The Honorable Richard G. Andrews presiding.

08:29:24 THE COURT: All right. Good morning. This is

United Therapeutics vs. Liquidia. Are you ready to go, Plaintiff?

MR. CARSTEN: We are, Your Honor.

THE COURT: All right. Well, then, let's go.

MR. CARSTEN: May I proceed, Your Honor.

THE COURT: Yeah.

MR. CARSTEN: Good morning, and may it please the Court. This is, like so many other cases that Your Honor has had before, a Hatch-Waxman case. We are asking the Court to find Liquidia's proposed inhalation product infringes two of United Therapeutics's patents. You'll hear from three current or former UTC employees. You'll hear first from Patrick Poisson.

THE COURT: I'm sorry, Counsel. Who are you.

MR. CARSTEN: My name is Doug Carsten, Your Honor --

THE COURT: Okay.

MR. CARSTEN: -- on behalf of United Therapeutics.

You'll hear from Mr. Patrick Poisson, who will talk about UTC, how it was formed around the Treprostinil molecule as a treatment for pulmonary hypertension. Now, pulmonary hypertension is different from the hypertension we commonly think of. Pulmonary hypertension is hypertension in the vasculature, the blood vessels, between the heart and

the lung. It is rare. It is progressive, and it is often fatal.

You'll hear from Mr. Bunce, the global regulatory executive vice president of United Therapeutics to talk about the regulatory implications, and you'll hear from Dr. David Walsh, who's retired. He's a named inventor, and he'll be talking about some of the chemistry that's at the heart of one of the patents at suit. Let's talk about those two patents.

The two patents you'll be hearing about over the next several days, Your Honor, are the '066, what we call the synthesis patent, and the '793, what we're calling the inhalation patent. Since the Court's time is precious, I'd like to dive right in, starting with the synthesis patent.

Liquidia is challenging the validity of the '066 synthesis patent. Now, they've done that before, Your Honor, by filing an IPR. The PTO rejected that challenge and did not institute the IPR. Liquidia rolls out the same arguments here in the hopes that under an even higher burden of proof, they will succeed where they failed before the Patent and Trademark Office.

The '066 patent claims a process, and a product by that process, that improves the impurity profile and stability of the produced Treprostinil product, allowing for storage at ambient temperature. Drs. Fawzi and Scheidt,

each with decades of experience, will address Liquidia's assertions. Dr. Fawzi will help the Court understand why Liquidia's prior art-based assertions fail, and Dr. Scheidt will address Liquidia's various Section 112 positions.

Dr. Fawzi explain how the primary reference, a publication by Dr. Moriarty, taught a highly pure synthesis of Treprostinil free acid, 99.7 percent pure, according to that paper, leaving no motivation for a person of ordinary skill in the art to want to improve it. And the secondary reference, a patent publication by Ken Phares, is silent about impurities altogether. Similarly, neither of those references talk about stability or storage at ambient room temperature. Dr. Fawzi will also explain how the product-by-process claims of the synthesis patent import structural and functional improvements over the prior Moriarty-described compounds. At bottom, Liquidia tries to turn the '066 patent into an academic exercise, not the real-world, inventive solution to real-world chemical problems.

Turning to Liquidia's Section 112 arguments, Dr. Scheidt will help the Court understand how the '066 patent and specifications describe the claimed invention and enable a person of ordinary skill in the art to make and use the claimed invention. The reduction of impurities and improved stability of the resulting product are disclosed to

the world for companies like Liquidia to use, but only after the expiration of the patent. That's the quo in the quid pro quo UTC obtained what it obtained this patent.

Turning to infringement, here's Claim 1 of the '066 patent. Now, I've got a number of things highlighted here, but at bottom, it comes down to one thing. They're saying, the argument is, that we must provide a starting batch of Treprostinil having one or more impurities resulting from prior alkylation and hydrolysis steps, wherein said alkylation -- reading from the bottom now, Your Honor, is alkylation of benzidine triol. Liquidia, through its hired expert, Dr. Winkler, narrowly reads the claims to make this blackboard chemistry, not real-world chemistry taking place in laboratories.

Dr. Winkler reads the claims to require that the only impurities -- only those impurities that are derived directly from the two-dimensional structure that you can put on a blackboard of a benzidine triol counts for purposes of the claim. That isn't how real-world chemistry works.

And by doing so, Dr. Winkler reads the word "steps" right out of the claim. Dr. Nuckolls will explain that there is no such thing as a hundred percent pure in chemistry laboratories and that the process that Liquidia's chosen supplier uses, a real-world process, not a 2D process drawn on a chalkboard, falls squarely with in the scope of

the claims, both product-by-process and process.

Dr. Nuckolls will show by virtue of analyzing the data supplied by that supplier that the claimed reduction of impurities happens whether you count by virtue of looking at the impurity percentages or if you count by looking at the number of impurities.

However you slice it, Liquidia infringes.

And Liquidia infringes the storage claims as well. Liquidia and its manufacturer store it isolated Treprostinil at ambient temperature at various times between the time it's made in Korea and its use by Liquidia to manufacture Liquidia's infringing product in the United States.

Here's temperature logging data, and Dr. Nuckolls will explain how temperature-tracking data captured during the journey from Korea to the United States established that Liquidia infringes these storage-at-ambient temperature claims. You can see it at the beginning of the chart. It's in the ambient temperature zone. You can see at the end of the zone it's at the ambient temperature zone. This tracking data applies to batches that were actually used to support Liquidia's new drug application.

And Mr. Matto will testify that there are such things as excursions, and under the approval that Liquidia seeks, Liquidia is able to use batches that are shipped with

excursions into the ambient temperature zone for purposes of making products in the future.

Now, Liquidia has said we're going to quarantine these batches that do this. We're not going to use them. We'll use them for R & D. But that's not the legal test for infringement. The test for infringement rises and falls on what it is that Liquidia is seeking approval from the FDA to do and to use. It is not an undocumented self-serving promise saying our word for it that we're not going to use it.

Turning to the inhalation patent, Drs. Waxman and McConville will help the Court understand the basis for this fundamental UTC patent an inhaled Treprostinil to treat pulmonary hypertension.

Dr. Smyth will explain, in contrast to Liquidia's armchair experts, how he took the '793 patent and by using 2006 knowledge made Treprostinil dry powder that demonstrated suitable properties to carry forward in only three weeks. And Drs. Waxman and McConville will explain how none of Liquidia's alleged prior art teaches the dose limitations of the asserted claimed and certainly not the dose limitations in a dry powder form.

Turning to infringement, like most Hatch-Waxman cases, the infringement inquiry rises and falls on what Liquidia seeks approval to do. Here, the claims require

administration of a single of a therapeutically effective single-event dose in a particular dosage range delivered in one to three breaths. And Dr. Waxman will explain how Liquidia's patient instructions direct patents to directly infringe the claim to the '793 patent, the dosage, the breaths, the single dose.

Now, Liquidia tries to add a strict requirement that you can only do one dose a day. Those words appear nowhere in the claim. In fact, it is a comprising claim. Multiple doses a day are within the scope of the claim, and that opened the reading of the word "comprising" out to manufacture a made for litigation, non-infringement argument.

At the end of the presentation of evidence, Your Honor, UTC will respectfully request that the Court find UTC's patent valid and infringed by Liquidia's proposed product. We look forward to presenting our evidence to you.

THE COURT: Thank you, Mr. Carsten.

MR. SUKDUANG: May I approach, Your Honor?

THE COURT: Yes, sure.

MR. SUKDUANG: Good morning, Your Honor. Good morning. Sanya Sukduang on behalf of Liquidia.

I'd like to start out by giving you a little bit of information about Liquidia. Liquidia is not a generic drug manufacturer. They're a brand-name pharmaceutical

company that has used their proprietary print technology to bring new products to the market. Their first product is Yutrepia, otherwise another known as LIQ861, which you might hear throughout the course of the trial. Yutrepia is the very first dry-powder inhaled Treprostinil therapy for the treatment of pulmonary arterial hypertension. Liquidia filed an NDA, not an ANDA, and they received approval, tentative approval, on November 2021. And the only last step before patients can get this novel therapy is completion of this litigation.

Now, UTC has a collaboration with a company called MannKind. And UTC and MannKind, despite having these patents for decades, have just filed or filed an NDA themselves for a dry-powder formulation. Now, the UTC MannKind collaboration, they filed their NDA after Liquidia, and they have yet to receive FDA approval for their drug. So, both companies realize that the real issue here is benefit to the patients. Both companies want to get their products to the market, and Liquidia was there first.

Now, I mentioned the print technology, and the print technology is going to come up during the course of trial. And the print technology is a proprietary technology developed by Liquidia. It takes the Treprostinil and puts it into solution with other components so the Treprostinil is no longer isolated. It's in solution. And they pour the

solution into these molds, the ones that we have up in red, and then they compress those folds to push out the water, dry them, and you end up with these particles that you see on the right-hand side. They look like pollen shaped, and they pick pollen shapes specifically because they have better aerodynamic properties in order to inhale the dry-powder drug and get it into the lung. And they collect those particles, store them in a 2- to 8-degree refrigerator, and then when ready, they put them in capsules, blister pack them, and send them off to patients to use in the drug.

The components of Yutrepia are really going to be a game changer for pulmonary arterial hypertension patients. On the right-hand side, you'll see UTC's drug. It's called TYVASO. And it's an inhaled solution of Treprostinil. And they use a nebulizer, and the nebulizer takes the solution, makes it a mist, and actually pushes the drug into the patient's mouth through a mouthpiece. The patient just needs to inhale.

It is handheld, but not very portable. It's about 15 to 20 pieces that you have to clean regularly, and when you travel, you have to put it into, like, a small dog carrier type of bag to carry around with you.

Yutrepia is a dry powder inhaler, and I've got one right here. This is what it is. It can fit in your

pocket. You get blister packs that are -- that are sealed in foil, and when you need to take the drug, the patient just opens up the device, drops the capsule in, pushes the two buttons which puncture the capsule, and you inhale. That's how it works. You put it in, and you can go on your way.

This is actually pretty critical for pulmonary arterial hypertension patients. They're already pretty homebound. It's a very serious disease and often fatal. Just think about when you're exercising, if you're really exercising hard and get to a point where you cannot catch your breath. That is the life of a PAH patient. They have difficulty -- if I had to drop something off to Your Honor, difficulty walking these steps, difficulty walking up a flight of stairs. And so, to get these medications so they're portable, so they can take them, really is going to change their life.

We talked about the disease a little bit, but I want to give you a little bit more idea about how it's defined. The '793 patent, which is UTC's patent, is a great example of this. They tell you that pulmonary hypertension can result in heart failure or death. They tell you that pulmonary hypertension is comprised five different entities, and those five different entities are defined by the World Health Organization, WHO, and these are five categories of

Ph that everybody understands, that all the skilled artisans use, and doctors and patients, when they're diagnosed, fall within certain categories.

What we have here is the five groups by the WHO. Now pulmonary hypertension, arterial hypertension, falls within group one. And as you can see, it's about 4, 4 and a half percent of all PAH patents -- excuse me -- PH patients fall within group one. Group two is the largest group by far. About 78 percent of all PH patients fall within group two. Group one, PAH is an orphan disease. Group two is not.

Now, you'll hear from UT's expert, Dr. Waxman, that the claims to pulmonary hypertension are limited just to group one. That's clearly not the case. The specification says pulmonary hypertension. As we saw, the patent actually describes all five groups.

I'd like to turn to the substance of the matter. And first, infringement. And there are two separate infringement issues, the first I've got identified in green. The claims of the '066 patent require impurities resulting from prior alkylation and hydrolysis, and it's not just high alkylation. The claims specifically requires alkylation of benzidine triol. So when you read the claim, the impurities that result from this process come from the alkylation of the benzidine triol, hydrolysis of that resulting product,

and then you add a base to make a salt. Pretty basic chemistry. Then, the claim requires you to compare the starting batch, which is Treprostinil, against the final pharmaceutical composition, in this case, UTC is pointing to Liquidia's salt Treprostinil sodium.

We do not meet that comparison limitation because all of the impurities that UTC points to do not result from the alkylation of BTO. We put on the top here some nomenclature that you're going to hear during the course of the case. BTO is benzidine triol. TN01 is one of Yonsung, which is Liquidia's manufacturer of API, they have an intermediate TN01. That intermediate TN01 undergoes hydrolysis to form TN01, which is Treprostinil, or in the claim, the starting batch, and then finally they take Treprostinil, add a base to make TN, or Treprostinil sodium or the pharmaceutical composition of Claim 1. So that's the nomenclature.

And that caret pointing larger to TN02 is what UT's claim is supposed to do. The impurities from alkylating this BTO and hydrolysis of the TN01, the impurities here have to be higher from this step then the impurities here. What UT points to is total impurities, and their expert, Dr. Nuckolls, relies on the total impurities. Well, the total impurities are all the impurities that are not tied to the alkylation of BTO. And in fact,

Dr. Nuckolls cannot point to any impurity, whether it's total impurity analysis, that derives from this step.

UTC's other expert Dr. Toste, points to a different impurity. It's called 15-epi-Treprostinil. 15-epi-Treprostinil is derived not by this scheme up top. There's another compound called 15 BTO. It's an impurity that you can find in the starting material. All the experts agree that 15-epi-BTO is not BTO. It's a completely separate compound. And so when you take by 15-epi-BTO, conduct alkylation of a different compound, not BTO, you end up with 15-epi-Treprostinil.

Okay. Those sets of impurities are not within the scope of the limitations. And even if you were to consider those impurities, the evidence shows that the levels of these impurities we're talking about are so small, less than one percent, and in often cases it's 0.1 percent less. All these impurities are measured by a process called HPLC, and HPLC has natural variation. The '066 patent itself shows the differences you can get testing Treprostinil using the same HPLC method. What UT's experts failed to do was consider this standard deviation, this natural error, and they're saying these small changes, essentially from .01 to .06, is something that falls within the scope of the claim, and it doesn't. They're just too small. It just falls within the error.

08:51:45 The other argument, Your Honor, refers to the
08:51:52 storage limitation of the claims, and the Court construed
08:51:56 "storage" to have its plain and ordinary meaning. The --
08:51:59 both sides' experts have applied that. There's a dispute
08:52:02 between them as to what the plain and ordinary meaning is of
08:52:04 storage, but nonetheless, the temperature here is critical.
08:52:08 It's 15 to 30 degrees C in terms of the storage condition.
08:52:14 The DMF by Yonsung clearly and unambiguously says that that
08:52:20 product is stored at 2 to 8 degrees C. It is shipped to the
08:52:24 United States to Liquidia. Liquidia receives it. Its raw
08:52:30 materials specifications, its operating procedures when they
08:52:33 receive the materials says store it at 2 to 8 degrees.
08:52:37 There is no intervening time where this material is not
08:52:40 stored at 2 to 8 degrees, and that's because both parties
08:52:44 have told the FDA this is what we do. This is the product
08:52:50 that we have, and this is how we control it.
08:52:52 Now, UT's experts are going to rely on two
08:52:56 batches that were shipped from Korea to the United States
08:53:00 that were out of specification. The temperature went to
08:53:03 16 degrees. Those batches -- those batches have not and
08:53:08 will never be used by Liquidia. Now, you heard today, well,
08:53:13 that's not the standard for infringement. It's the standard
08:53:16 for infringement of this claim because the claim requires
08:53:20 that you store the salt at ambient temperature before you
08:53:25 make the pharmaceutical composition. In Claim 8, you store

the salt at ambient temperature and then you make the pharmaceutical composition. We never made and never will make any pharmaceutical composition of this material because it is out of spec. Because we will never make a pharmaceutical composition and none of their experts have said a pharmaceutical composition has been made from this material, those batches cannot meet Claim 6 and 8.

Additionally, you saw slides about various time points traveling, using UTC -- excuse me Liquidia's print process. Again, that is processing the material. That's the print process to make the particles. This claim requires time points. You store it then you use it. UTC points to evidence of using Treprostinil to make the particles as evidence of storage at ambient temperature. Essentially, Your Honor, they say you take milk out of your refrigerator. You store it in your refrigerator. You put it on the counter. Now that it's on the counter and I'm using it to pour it into my cereal so I can have breakfast in the morning. That's storage, when I put it back on the counter. That's not storage. You don't store your milk on the counter while you're using it. You store it in the refrigerator. And so when you listen to the testimony from UTC's experts, it will be during process steps, not storage steps.

I'd like to turn to the issue of invalidity, and

I've highlighted in yellow the preamble of Claim 1. It's a pharmaceutical composition comprising Treprostinil or a pharmaceutically acceptable salt thereof. Claims 1, 2, 3, 6, and 9 are product-by-process claims, and as the Court is aware a product-by-process claim, the product is not valid if it claims -- if it's not novel or it's not nonobvious. It's on old product, it's invalid. Even if the process used to make it is new, and this process isn't new. But the product is not new, and the reason why we know that is because the pharmaceutical composition can either be Treprostinil free acid or Treprostinil salt. That's all that's required.

UT has been making Treprostinil for decades. They had a product called Remodulin, and Remodulin is a solution of Treprostinil that you administer by intravenous or subcutaneous. It treated pulmonary hypertension but it's just a different route of administration. They made that Treprostinil starting in the 2000s using a process developed by a professor, Dr. Robert Moriarity. Dr. Robert Moriarty was hired by UTC to find a better synthesis process for their product for Remodulin, and he published it. And all they did was take benzidine triol, alkylate it, conduct the hydrolysis step, and you end up with Treprostinil, known as UT-15. So you'll see UT-15 throughout the course of the case. And the purity of this Treprostinil is 99.7 percent.

That's the product Remodulin. That's the process that they used to make it, and UT did this in their Chicago plant.

Now, in the 2006-2007 time frame, UT moved their Treprostinil manufacturing facility from Chicago to Silver Spring, Maryland, and when they did that, they did two things. They added a salt step, adding a base to make a Treprostinil salt, and specifically Treprostinil diethanolamine, and they removed column chromatography, a purification step in the intermediate. The reason why they did that is because Silver Spring, Maryland, has different environmental concerns than Chicago, Illinois, so they had to take that into consideration and try to remove some solvents that they used that might be carcinogenic.

That process moved to Silver Spring is exemplified in the '066 patent. And the title of the '066 patent is a Process to Prepare Treprostinil, the Active Ingredient in Remodulin. So, the Treprostinil that they make in Silver Spring in the '066 patent is Treprostinil free acid Treprostinil. Same chemical structure. There is nothing different. The purity is the same. When they presented this to the FDA, they did not tell the FDA our product is now more pure. They did not say our product is more safe. They did not say our product is less toxic. In fact, they told the FDA that the purity using this '066 process is of equivalent to the purity of the Moriarty

process in 2000 -- the 2000 time frame. The products are the same because the products are the same. The product-by-process claims of the '066 patent are invalid.

Now, because it's product-by-process claim UTC's experts want to argue that there's a structural or functional difference in the product of the '066 versus the product of Moriarty Chicago. And they use Dr. Fawzi. He's their expert on this issue. And Dr. Fawzi takes data that was already considered by the Patent Trial Appeal Board, already considered by the Federal Circuit and rejected, and said there that there's an impurity profile difference between the '066 patent, Treprostinil, and the prior Treprostinil that UT used to make. Well, the problem is Dr. Fawzi's analysis is just a rehash of data that was already considered by all the experts, including Liquidia's expert, Dr. Winkler, who is an expert in the '393 IPR and an expert here, rejected by those tribunals, and his data -- and he will he testify that it's the exact same analysis. Excuse me. The same data where he tries to do a different mathematical analysis.

That doesn't happen. It doesn't create a structural functional difference. And even if you considered it, the important thing to remember is that these minor numerical differences that Dr. Fawzi identifies, nowhere and at to time did UT go to the FDA and say, look,

these minor differences make us different, FDA. They didn't. They told explicitly that the purity profile of these two products are equivalent. And therefore, the product-by-process claims are invalid.

Going to the whereby level, we talked about this for non-infringement with respect to comparing the impurity profile of the starting batch of Treprostinil against the purity profile of the pharmaceutical composition. Now, UT can't establish infringement of this claim because the impurities they point to from Liquidia and Yonsung don't meet that limitation. The problem they're having is also one of their own making. The claim requires you to compare a starting batch purity and a final pharmaceutical composition purity.

When you look at the specification of the, '066 patent, none of the examples identify any impurity. None of the examples identify the purity of the intermediate starting batch. All you have is the purity of the final composition. When you don't have the purity of the intermediate starting batch, when you don't tell a POSA what impurities are specifically going to be reduced, there is actually no possession, no possession, of this claim limitation, and, therefore, the claims of the '066 patent are invalid for lack of written description support.

Now, how do we know that there's no data? Well,

the inventors testified to that. The inventors testified that with this new process that they implemented, they can do it in a one step or a one pot kind of concept, where you start with benzidine triol and you go all the way through until you make your final salt. You don't isolate any intermediates as solids. You only isolate at the very end, and when you take it from step A to step B, without entering any intervening isolations, they testified that we never tested the impurity in the middle. They didn't do it. They said we don't need to do it because our invention -- and this is really what they think their invention is -- is just purifying by a salt purification step.

So, again, because there's no information in the patent itself that allows a skilled artisan to understand that the inventors actually possessed this specific limitation where you compare the starting batch to the final batch, the claims lack written description support.

Finally, Your Honor, we have arguments of invalidity regarding the storage limitation. Okay. Now, this Court has construed "storage" to be its plain and ordinary meaning. And within that, UT's experts have one idea of storage. Storage is storage. And Liquidia's expert, Dr. Winkler, has his own definition from all his chemical dictionary. Some of UT's experts agree with Dr. Winkler. Some of UT's experts disagree with

09:03:00 Dr. Winkler, but you've got different constructions.

09:03:05 Importantly, the PTAB construed this same term
09:03:10 to require at least three months of storage at ambient
09:03:15 temperature; right? That is a minimal requirement. At
09:03:18 least three months. So, a POSA will not have reasonable
09:03:22 certainty as to whether they can infringe these stored
09:03:26 limitations because there could be a scenario where a
09:03:29 company stores Treprostinil for one month at 16 degrees.
09:03:35 That may infringe under the Court's construction, but that
09:03:38 would not meet the PTAB's construction of the same term that
09:03:41 requires three months of storage. And therefore, because
09:03:45 there's no reasonable certainty as to the scope of the
09:03:47 claim, Claim 6 and 8 are invalid as indefinite.

09:03:51 Now I'd like to move to the '793 patent, and we
09:03:57 discussed this in the beginning. The '793 patent is a
09:04:00 method patent. It's a method of treating pulmonary
09:04:03 hypertension by administering a therapeutically effective
09:04:06 single-event dose, and you'll inhale a formulation of
09:04:09 Treprostinil to do that. The parties' experts do not
09:04:14 dispute that a single-event dose is one dose. Okay. The
09:04:18 specification of the '793 patent supports only giving a
09:04:23 single dose. All of the examples in PH patients in the '793
09:04:30 patent received only a single dose, not multiple dosing.

09:04:35 UT wants this comprising term to carry pretty
09:04:39 heavy weight. They want to say it can include multiple

steps, multiple dosing. Well, comprising cannot be used as an open-ended term that reads out a limitation within the claim, which is single-event dose. And the reason why Yutrepia or '861 doesn't infringe is because you cannot give Yutrepia as a single dose per day. Because of the state of the disease, you give this three to five times daily. That's how you take the drug. Doctors and patients will never use a single-event dose of Yutrepia, and the information that Liquidia provides in their label tells doctors and patients to use three to five times a day. Never do they say use a single-event dose.

Now, UT recognizes this, and, again, they mentioned the comprising claim that's supposed to read out the single-event dose. But they also point to different information to establish that there's a therapeutic effect with Yutrepia with a single-event dose. They want to argue that therapeutic effectiveness is based on a change in what's called hemodynamic data. Now, pulmonary hypertension, as I mentioned is essentially high blood pressure. And when you give certain drugs, you can change the pressure in the arteries. And those changes are hemodynamic data. Okay. But a change in hemodynamic data will not necessarily lead to a therapeutic effect. In fact, when doctors and patients evaluate whether a drug is being effective to treat the pulmonary arterial hypertension, they

look at factors as how they feel, how they function, and if they live, if they survive, because it is a fatal disease. So if a patient has a change in hemodynamic data but they can't walk up the stairs any better, they have to stop halfway through because they can't catch their breath, they can't play with their children or grandchildren even though there may be a change in hemodynamic data, that is not a therapeutic effect.

That is what all the skilled artisans look at. There's actually no data in our label related to hemodynamic changes. UT will point to no data on our dry-powdered, inhaled Treprostinil formulation for hemodynamic changes. What UT wants to point to is their own product, which is a liquid formulation, and they say because Treprostinil in a liquid formulation produces hemodynamic changes then Treprostinil in a dry-powder formulation will also provide that. Okay. You can't compare those two types of solutions. And when UT does, they use a form of Treprostinil, TYVASO, that requires nine breaths, and they compare nine breaths of TYVASO to our product. The claim is limited, however, to one to three breaths. So even the data that they rely on for hemodynamic changes is of nine breaths, not one to three breaths. And so that data on hemodynamic change does not establish that we infringe. And UT does not has not asserted a Doctrine of Equivalents

09:08:04 1 infringement argument saying nine breaths is equivalent to
09:08:07 2 one to three breaths.
09:08:10 3 Finally on validity, I mentioned before
09:08:14 4 pulmonary hypertension is all five categories. Treprostinil
09:08:21 5 does not work for group two. How group two -- how the
09:08:26 6 disease comes up with group two is in a manner that these
09:08:30 7 types of drugs just are not effective for. Now, Dr. Waxman,
09:08:35 8 UT's expert has taken the extraordinary position that
09:08:40 9 pulmonary hypertension doesn't mean group two, doesn't mean
09:08:43 10 group three, four or five. It's limited just to group one,
09:08:48 11 pulmonary arterial hypertension okay. That is not the plain
09:08:51 12 and ordinary meaning of the term. That's not how POSAs use
09:08:54 13 it. And moreover, the examples of the patent, Examples 1
09:08:57 14 and 2, test patients beyond group one. So, the
09:09:03 15 specification, not only in the beginning where they describe
09:09:07 16 pulmonary hypertension, recognizes it's a broad term, but
09:09:10 17 the actual examples cover more than a single group. Because
09:09:15 18 the claims do not enable and do not describe the full scope
09:09:21 19 of treating pulmonary hypertension as that term is
09:09:24 20 understood, that those -- the claims of the '793 patent are
09:09:28 21 invalid.
09:09:28 22 Finally, the formulation that's talked about in
09:09:32 23 this claim can be either a solution of Treprostinil or a
09:09:38 24 dry-powder formulation of Treprostinil. The patent has two
09:09:43 25 lines about powder formulations. One is you can use a

dry-powder inhaler and two is, you put a powder in a dry-powder inhaler. That's it. There's no examples of making a dry-powder formulation. There's no information as to what excipients you would you say in a dry-powder formulation, there's no formulation of testing a dry-powder formulation in any type of patient. The inventors also testified that during the time period the prior art, the priority date, while they were working with United Therapeutics, they never tried dry-powder formulations of Treprostinil. They were focused solely on solutions.

Why is powder formulations now included in this claim? Because Liquidia filed their NDA on January 27th, 2020. On January 31st, 2020, after seeing that, UT took their old patent that was all directed to solutions, filed the patent claim to powder formulations, did expedited prosecution at the PTO to get the claims, and this claim, if you recall, Your Honor, was added a few months after this litigation had started. This is purely an attempt by UT to cover subject matter that their inventors did not describe, that their inventors do not enable, that their inventors simply never worked on in order to stop patients from getting a new therapeutic that's going to change their lives.

So, on the terms -- excuse me. With respect to the powder formulations, there's no written description to

support. The inventors didn't possess it. And also, it would require undue experimentation, given the specification, as well as the knowledge of the skill in the art as of 2006 to actually make a Treprostinil dry powder formulation that would be suitable to treat a patient with pulmonary arterial hypertension.

I mentioned some of our experts. They're here, and I know we sent up pictures earlier in the week. Dr. Jeff Winkler is going to be talking about invalidity and non-infringement of the '066 patent. Dr. Nuckolls is going to be talking about invalidity and non-infringement of the '793 patent. Dr. Igor Gonda will be talking about invalidity of the '793 patent, and Mr. Fuson is going to be addressing UT's expert Mr. Matto, who originally was talking about what FDA requirements and, oh, even though your specifications that you sent to the FDA say that you can store at 2 to 8 degrees, you can ignore that. That's Mr. Matto's opinion. You can ignore all that we told the FDA. Mr. Fuson will address those issues.

We thank you for your time. If you have no questions, Your Honor, we'll turn over the case.

THE COURT: All right. Well, let's keep going.

MR. PIVOVAR: Your Honor, may I address the Court, please?

THE COURT: All right. Who are you.

MR. PIVOVAR: My name is Adam Pivovar, Your Honor. I represent the defendant.

THE COURT: I'm sorry. Adam who.

MR. PIVOVAR: Pivovar.

THE COURT: Okay.

MR. PIVOVAR: Your Honor, before we embark on witnesses, we have a pretty profound objection to new exhibits that the plaintiff wants to introduce through their experts that were never previously disclosed. And we would like to resolve that before we go into this.

And just, to give you an inkling of what some of these new exhibits are, one is called PTX 2083. The first time that we received that exhibit from Plaintiffs was last night at 5:00 p.m., And then the they intend to use that, we found out an hour and a half later, with one of their experts, Your Honor. And we believe that there are a number of exhibits that Plaintiffs have identified to us as part of their disclosures that are not actually anything that was ever disclosed in their expert reports.

If I can just --

Apparently, the auto focus is not working, Your Honor. I apologize. Thanks.

But anyhow, Your Honor, the disclosures that we received last night included the exhibits that they intend to go through with their experts. There are a number of --

I think the total is right around 15 that were never disclosed in connection with the expert reports or in connection with any of the actual exhibits -- or I'm sorry the opinions that the experts have. And we believe that you should resolve this dispute and our objection before the experts actually go on the stand, if we may.

THE COURT: And did you say PTX 2083?

MR. PIVOVAR: That's one of them, Your Honor, yes.

THE COURT: Does Plaintiff know what the other ones are that Mr. Pivovar is talking about?

MS. WU: Yes, Your Honor. Plaintiffs did object to four exhibits.

THE COURT: Okay.

I'm sorry. Ms. Pivovar is --

MS. WU: Defendants. Yes, Your Honor. Defendants have objected to four exhibits that are summary exhibits under FRE 1006. The particular exhibit that's referenced --

THE COURT: Okay. So, he just said 15. Is four part of the 15, or as far as you know, there are only four?

MS. WU: I'm only aware of four exhibits that have been objected to that are summary.

THE COURT: And basically all four are your opinion summary exhibits under Rule 1006?

MS. WU: Yes, Your Honor.

THE COURT: All right. What do you have to say about that, Mr. Pivovar?

MR. PIVOVAR: Your Honor, just to be clear, so what we have are four exhibits that were never cited in any of the expert reports, that they're trying to introduce all four of those through Mr. -- Dr. Nuckolls and two of those through Mr. Matto. We know that they were never actually cited in any of those expert reports. So these documents were not created or produced to --

THE COURT: Well, I understand that. But if they're based on underlying information that's been produced, unless there's some objection that you don't have a chance to, like, figure out the accuracy of them, then --

MR. PIVOVAR: Your Honor, it's that and also -- so for Mr. Matto, they never disclosed a number of exhibits that are just documents, that are new to his report. And then with respect to these other exhibits that we have, they are not simply a compendium of existing data. They are --

THE COURT: Well, so --

MR. PIVOVAR: Yeah.

THE COURT: -- maybe if somebody has a copy, and I'm sorry. I don't know what your name is, either.

MS. WU: Huiya Wu.

THE COURT: Ms. Wu, do you have copies of these

four exhibits that you saw are summary exhibits?

MS. WU: Your Honor, may I approach.

THE COURT: Sure.

Are these exhibits what you're handing up here?

MS. KANNAPPAN: Yes, Your Honor.

THE COURT: Okay.

MR. CARSTEN: May we have a copy, Your Honor.

THE COURT: I think I do.

MR. CARSTEN: We don't have one yet.

MS. KANNAPPAN: Your Honor.

THE COURT: I'm sorry. Who are you?

MS. KANNAPPAN: For the record, Deepa Kannappan, also for Liquidia.

And just to make the record clear, the four exhibits are PTX 2083, PTX 1584, PTX 1589, and PTX 1590. And they actually fall into three categories that I think might be helpful to talk briefly about that. The first category, PTX 2083, and there's two demonstratives that actually basically just take the top summary and put it into the demonstrative. Those are PDX 2.16 and PDX 2.17. That underlying exhibit was served at 5:00 p.m., as my co-counsel was saying. It contains a new opinion with that data about levels of a certain impurity that Dr. Nuckolls never offered. Rather, those documents were used for a different opinion and now they're being repurposed for an opinion that

he never offered in his reports. And it relies on batches and data that weren't in the paragraph that counsel tried to point us to yesterday to say that this is where it was disclosed.

Similar issues for the second category which is PTX 1584 and then used in PDX 2.15. They're 19 rows, I believe, of batch data, and only the first row was disclosed in Dr. Nuckolls's opinion and at least five weren't cited for any opinion, much less that particular piece of opinion.

And the third category is PTX 1589, 1590, that correspond to PDX 2.28 and 2.29 where none of those batches except for two were ever identified in Dr. Nuckolls's reports as going into ambient temperature.

And so all these things, Your Honor. It's not a simple summary of what was in the reports. They're adding new bases.

THE COURT: What do you have to say about this?

MS. WU: Yes, Your Honor. I'll try to take these this turn. With regard to -- with regard to PTX 2083, these -- this is a summary document categorizing the epi-impurities these were disclosed in a couple of places.

THE COURT: So before we get to that, the actual form of the four exhibits 2083, 1584, 1589, 1590, they were actually produced for the first time last night?

MS. WU: The -- the two -- 2083 was produced

yesterday. The other three were served on March 4th.

THE COURT: March 4th. All right.

Do you, Liquidia, agree that the other three were served on March 4th.

MS. KANNAPPAN: No, Your Honor at least two of them were corrected and so served on March 11th. It's a little messy.

THE COURT: Well, in any event. Go ahead, Ms. Wu.

MS. WU: So in terms of 2083, this is a summary that we wanted to use with Dr. Nuckolls. The underlying data that you see in the tabular form was presented in a slightly different form, in kind of pros form, in Dr. Nuckolls's expert report, his reply report paragraph 28. I don't know if we can.

MS. KANNAPPAN: It's in your binder.

THE COURT: Okay. So here's the thing. If he presented it in slightly different form in his expert report, why doesn't he present it again today in that slightly different form and then that resolves the issue?

MS. WU: Well, it's just tabular versus words. If Your Honor takes a look at reply paragraph 28, you can see all the same data is presented. So it was fully disclosed.

THE COURT: Okay. Hold on a minute. Is this

09:22:16 the last thing that's in this? I've got something that says
09:22:20 it's -- hold on. Okay. Yes, I see a long list of stuff.
09:22:29 MS. WU: Correct, Your Honor. It's a little
09:22:31 messy in the report, so we put it in tabular form in this
09:22:34 exhibit, and the second page of the exhibit, you can see all
09:22:37 the source material that was referenced is the same source
09:22:40 material that's in paragraph 28.
09:22:42 THE COURT: Okay. I got you there, Ms. Wu.
09:22:45 Is it the same source material?
09:22:47 MS. KANNAPPAN: No, Your Honor. They've added
09:22:49 at least three batches, and it's being offered for a
09:22:51 different opinion, Your Honor.
09:22:52 THE COURT: Well, I mean, it's a chart. The
09:22:56 different opinion, if there is a different opinion.
09:23:06 MS. WU: If I may, Your Honor, it's the same
09:23:08 opinion Dr. Nuckolls explained, the amounts of the
09:23:11 epi-impurity in these batches. The three other batches
09:23:15 aren't missing. They were disclosed in the opening report.
09:23:19 As you can -- you'll see in paragraphs 92 to 95 of the
09:23:23 opening report, there is the disclosure of this exact
09:23:28 information, the epi-impurity.
09:23:39 THE COURT: All right. And what do you have to
09:23:41 say about the 1584, and 1589, and 1590.
09:23:48 MS. WU: With regards to those three, we agree
09:23:51 that there were corrections served with 1589 and 1590 on

March 11th. I believe that someone on our team noticed a typographical error and fixed those.

THE COURT: I'm not too worried about March 4th versus March 11th.

MS. WU: Yes, Your Honor, so with regard to the impurity peaks, that's at PTX --

THE COURT: Wait. Wait. So hold on, Ms. Wu.

So you agree that these were served on March 11th in the corrected form. And you say they're a summary, Ms. Wu, of a voluminous data somewhere. Why is it that you say this is not a summary and voluminous data.

MS. KANNAPPAN: I believe we're talking about 1589. Do I have that right, Your Honor.

THE COURT: Or 1584.

MS. KANNAPPAN: So 1584, only the first row was disclosed at all for that opinion. So it's notice a summary of data that was anywhere.

THE COURT: All right. What do you have to say about that, Ms. Wu?

MS. WU: Your Honor, as you can see from some of the boxes on our side of the courtroom, there were a lot of batch records, and so what Dr. Nuckolls did, as he stated in paragraph 40 of his opening report, is to note that the examples he cites are exemplary. For example, when I cite to certain batch records, QT Test Sheet and COA, the same

analysis applies to other similar documents which have not been directly cited. And so, in his reply report, he goes through an impurities peaks analysis. The underlying document, some of them have been cited for other purposes, but clearly he sets forth not only here, but, again, in his reply report. Let me find that cite for you.

Reply report paragraph 24, he writes while this analysis explicitly refers to batch TN0I117. I'm sorry, Your Honor, I --

THE COURT: All right. I'm having trouble reading this number.

As far as I'm concerned, it's pretty easy. He can do the batch that he disclosed in his report at Page 24. He can't do the rest of the batches now with all this detail.

MS. WU: Your Honor, though, he explicitly writes in paragraph 24 that this exact analysis applies to other batches.

THE COURT: Well, he can say. He can say that. But I'm not going to take all this other data that's being produced pretty late.

MS. WU: The data wasn't produced -- I mean, first of all, this is the defendant's data.

THE COURT: The form of the chart is produced pretty late. All right. So, he can say what he can say

based on the one thing. He can say it applies to everything else.

MS. WU: So, Your Honor, if I understand correctly, this -- some of this -- some of these batches, the underlying documents are actually coming in already beyond this summary.

THE COURT: A pile of batches evidence, just it means nothing to me. So, I don't really care whether it's coming in or not. If you want to move all the boxes from your side of the courtroom to my side of the courtroom, that's fine, but it's pointless.

MS. WU: Your Honor, that's not my -- I just want to make sure I you understand your ruling because he does talk about some of the underlying batch records in his testimony. Separately, he also addresses the summary document. I just want to make sure that the underlying documents that he's talking about, that he can --

THE COURT: If he talked about them in his report, it's not a problem. If he didn't talk about them in his report, and I don't think saying the same analysis applies to other batches as well means he can talk about all kinds of other things, that's not an improper disclosure in my opinion.

MS. WU: Yes, Your Honor. Again, can I just take one moment to explain what the --

09:27:50 THE COURT: Yeah sure.

09:27:51 MS. WU: So if you could take a look at reply
09:27:54 paragraph -- reply paragraph 22.

09:27:58 THE COURT: Okay.

09:27:59 MS. WU: And this is where he analyzes the
09:28:01 amounts of impurities in four different batches and you can
09:28:07 see those four blue bars.

09:28:09 THE COURT: I do see it.

09:28:10 MS. WU: So what he does is he counts the number
09:28:12 of impurities of these four types of batches in one batch.
09:28:17 And he says, you can go ahead and count the batches, the
09:28:21 number of impurities in each of the batches, in the same
09:28:23 way. So, that's what he meant by paragraph 24. So he's not
09:28:30 doing anything different. He's counting the number of
09:28:33 impurities in each of these batches and all -- and that's
09:28:36 what this summary Exhibit 1584 endeavored to summarize
09:28:42 because we certainly didn't want to fill your courtroom with
09:28:44 boxes of exhibits.

09:28:45 THE COURT: All right. Well, I'm going to allow
09:28:47 him to give the same analysis he gives in the report, but
09:28:51 I'm not going to admit these exhibits that include lots and
09:28:58 lots of details that he didn't say in his report.

09:29:02 MS. WU: Yes, Your Honor. I think I understand
09:29:04 that he can talk about the exact the number of impurity
09:29:08 peaks but not the other stuff. Is that --

09:29:10 THE COURT: I don't really know what's in his
09:29:12 report, but certainly paragraph 22, he seems to have
09:29:15 something that says number of impurity peaks relating to
09:29:18 four different things. So he can say that because he's
09:29:21 already said it once.
09:29:23 MS. WU: Okay.
09:29:24 THE COURT: So, you know, basically, I think --
09:29:33 so, on the assumption that PTX 1584 is representative of
09:29:38 what this dispute is about, I'm going to sustain the
09:29:46 defendants' objections to the summary exhibits that, as far
09:29:51 as I can see -- that 1548 and 1589, and I'm going to -- I'm
09:30:02 going to sustain the objection to 2083 based on the fact
09:30:06 that it was provided last night.
09:30:08 Are there other exhibits that I need to address?
09:30:11 MS. KANNAPPAN: Just on the list, it's 1590.
09:30:13 It's the same issues.
09:30:15 THE COURT: And thank you. I meant to say
09:30:16 that --
09:30:17 MS. KANNAPPAN: Sorry.
09:30:17 THE COURT: -- but my brain didn't match my
09:30:19 mouth.
09:30:21 MS. KANNAPPAN: No, Your Honor that's it. The
09:30:23 corresponding demonstratives would those also similarly
09:30:27 be --
09:30:27 THE COURT: It's hard for me to say. If the

demonstratives have the same thing as in the chart, that's fine. Maybe they're in a different way. Often demonstratives are. But to the extent that the demonstratives rely on exhibits that I'm excluding, and he doesn't have some other basis for saying the same thing, then yes.

MS. KANNAPPAN: Thank you, Your Honor.

MS. WU: Your Honor, I don't think I got a chance to talk about 1589 and 1590 because that's different from the impurity analysis. That is as shown.

THE COURT: Okay. Well, go ahead, talk about 1589 and 1590.

MS. WU: Okay. So in terms of the these two exhibits, they intended to summarize shipping details that are in voluminous shipping records, and the two exhibits are similar. One refers to batches that were referred to in Liquidia's NDA, and the second refers to shipping information of other batches. And so, Dr. Nuckolls, in his report, referred to the shipping records and temperature in the shipping records. The summary exhibits summarize those temperatures, and that is -- that is how we complied.

THE COURT: So where in your report is it -- is wherever it is that you say he's summarizing?

MS. WU: He starts -- one place he talks about receiving inspection reports, because he discusses these

repeatedly, is at 163.

THE COURT: That's the opening report?

MS. WU: In the opening report, yes, Your Honor. He explains what it is and he talks about, in particular, in paragraph 165, the shipment, the temperature during shipment.

THE COURT: Well, he refers to two manufacturing lots. Is that what you're referring to.

MS. WU: Yes, Your Honor.

THE COURT: And are there other manufacturing lots, as there appear to be?

MS. WU: In his reply paragraph 46, he talks about a couple different lots.

THE COURT: Well, so whatever it is that -- whatever lots he actually talks about in his two different reports, you know, I'll let you use them for that, but if he's talking about other lots that he doesn't talk about in his reports, you need to remove them.

MS. WU: Even if talks about other lots in talking about temperature, we can't discuss that. Is that my -- is that correct?

THE COURT: You can have him say whatever it is he said in the reports, but I don't want to see data that's not in the reports.

MS. WU: Yes, Your Honor, I think I understand.

09:33:38 THE COURT: All right. So have we resolved
09:33:40 that? I think.
09:33:43 MS. KANNAPPAN: Yes, Your Honor.
09:33:43 THE COURT: Okay. Charge the 25 minutes we just
09:33:46 spend doing that to the plaintiff.
09:33:48 Are we ready to go?
09:33:50 MR. PIVOVAR: I am sorry, Your Honor, there's
09:33:52 another dispute. So those were the ones with respect to
09:33:54 Dr. Nuckolls. We also have a similar dispute with respect
09:33:57 to Mr. Matto, who's a proffered expert for today. And I
09:34:03 think you've already --
09:34:04 THE COURT: What kind of expert is he?
09:34:05 MR. PIVOVAR: He is -- well, I would defer to
09:34:08 the plaintiff on how they would characterize his expertise.
09:34:12 THE COURT: All right. I looked at the -- well,
09:34:15 go though the names.
09:34:17 MS. WU: He's an FDA regulatory expert.
09:34:20 THE COURT: Okay. All right. Thank you, that's
09:34:21 helpful. Yes.
09:34:22 MR. PIVOVAR: Okay. So what we received, and if
09:34:26 I may approach, Your Honor, I actually, since -- I have a
09:34:29 list of all the exhibits they cited and where we have some
09:34:31 issues, just to make it easier for you to describe them.
09:34:34 THE COURT: All right.
09:34:41 MR. PIVOVAR: So, Your Honor, when we received

09:34:43 the plaintiffs' list of exhibits for use with Mr. Matto, we
09:34:48 went through it, and what we saw were PTX 25, 37, 105, 116,
09:34:56 117, 118, 125 and 128 were all new exhibits that are not
09:35:00 cited anywhere in either his opening report --
09:35:03 THE COURT: Well, so.
09:35:05 MR. PIVOVAR: Yes.
09:35:05 THE COURT: The Pretrial Order states there were
09:35:09 a long list of exhibits. Were these things not on the
09:35:12 exhibit list, then?
09:35:13 MR. PIVOVAR: So, these were -- I believe these
09:35:16 were on the exhibit list, but they're going to use Mr. Matto
09:35:19 as an expert to sponsor them. These are nowhere in any of
09:35:23 his expert reports. He has no opinions that rely on them,
09:35:26 and our concern is that this is new evidence either to
09:35:29 support old opinions that was never disclosed or new
09:35:31 evidence to support new opinions that we haven't heard
09:35:33 before.
09:35:34 THE COURT: All right.
09:35:35 MR. PIVOVAR: And --
09:35:36 THE COURT: What does your side say about this?
09:35:39 MS. WU: Your Honor, we do not plan to use
09:35:41 Mr. Matto to sponsor those exhibits. I'm not sure the scope
09:35:46 of the objection, but we're -- we're not planning to have
09:35:49 him sponsor these.
09:35:50 THE COURT: So in other words, these things that

I don't know whether you have them highlighted in red, list of -- that I have, he's not going to mention these things?

MS. WU: He does -- he does reference, I believe, the PTX 37, at least in his deposition. Do we have that in his cross binder report?

So at least in his deposition, he was questioned about that, and this has to do with how Liquidia handles --

THE COURT: So, were you planning -- you just said he's not going to sponsor these things. Does that mean he's going to testify about them or not? If he's not going to testify about them, then I don't care.

MS. WU: I believe he will be testifying about PTX 37. We're looking for where it was discussed during his deposition and report.

THE COURT: Right.

MS. WU: In terms of the receiving reports, I know that there were at least two of these that he cited explicitly.

THE COURT: So, wait. Ms. Wu, you started off by saying he's not going to sponsor any of these. Are these going to be in evidence before he gets on the stand or --

MS. WU: That's my understanding, Your Honor.

THE COURT: Okay. And so -- and, Mr. Pivovar, is your objection that he's never mentioned these things before in his life or what?

09:37:22 MR. PIVOVAR: Yes, Your Honor. And if we could
09:37:25 actually pull up the opening report of Mr. Matto, and I'm
09:37:29 going to use this as an example for the receiving lots that
09:37:33 begin around PTX 116.
09:37:37 THE COURT: All right.
09:37:37 MR. PIVOVAR: While he brings that up, I think
09:37:53 we can do this maybe orally, so I have Mr. Matto's opening
09:37:56 expert report. It is ten pages. During the meet and
09:37:59 confer, we asked where were these documents disclosed. It's
09:38:02 not that much. And we couldn't get anything.
09:38:04 And what Mr. Matto's opening expert report says,
09:38:08 Your Honor, is this: I have been provided certain
09:38:12 documentation relating to a temperature excursion that
09:38:15 occurred during the shipment of three batches of Yonsung
09:38:20 Treprostinil sodium from South Korea to U.S. around
09:38:25 Christmas 2020. It cites --
09:38:27 THE COURT: Do you think these are those things
09:38:28 he was exposed to?
09:38:30 MR. PIVOVAR: These are not those things, and
09:38:32 that's the point, and they're saying there's three batches.
09:38:34 And it's one document because that one document covers all
09:38:37 three batches because there's a shipping report that shows
09:38:40 there's three different packages shipped in the same
09:38:44 container. And when I deposed him, I asked him
09:38:48 specifically --

MS. WU: Your Honor, I think to short circuit this, we'll just talk about the ones that Mr. Pivovar has talked to Mr. Matto about and not any other receiving inspection reports.

THE COURT: All right. That doesn't seem like that big of a deal. So, all right. That resolves the matter. Charge this time to the defendant.

All right. Go ahead.

MR. JACKSON: Good morning, Your Honor. William Jackson for United Therapeutics.

THE COURT: Sorry. Is that Mr. Jackson?

MR. JACKSON: It is. United Therapeutics calls Patrick Poisson to the stand.

MR. JACKSON: May I approach, Your Honor?

THE COURT: Yes.

DEPUTY CLERK: Please stated and spell your full name for the record.

THE WITNESS: It's Patrick Poisson. It's spelled P-A-T-R-I-C-K P-O-I-S-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: I do.

DEPUTY CLERK: Please make sure you speak into

the microphone.

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

THE WITNESS: I do.

MR. JACKSON: May I proceed?

THE COURT: Yes.

DIRECT EXAMINATION

BY MR. JACKSON:

Q. Good morning, Mr. Poisson.

A. Good morning.

Q. Could you please introduce yourself to the Court and spell your name for the court reporter.

A. Sure. My name is Patrick Poisson. It's spelled P-A-T-R-I-C-K P-O-I-S-S-O-N.

Q. And where do you work?

A. I work at United Therapeutics.

Q. And is United Therapeutics go by any other name?

A. It's commonly referred to as UT or UTC.

Q. And what is your title?

A. I'm executive vice-president of technical operations.

Q. And what do you do in that role?

A. I oversee manufacturing, quality, and regulatory affairs.

Q. And how long have you worked at UTC?

09:41:31 A. 13 years.
09:41:33 Q. Before being the employed by UTC, did you have any
09:41:36 interactions with the company?
09:41:37 A. I did.
09:41:38 Q. And what were those?
09:41:39 A. I worked for a company that was doing contract work
09:41:44 for UTC.
09:41:47 Q. On any particular drug or any particular product?
09:41:50 A. Yes, it was inhaled Treprostinil.
09:41:55 Q. And so what was your first role at UTC?
09:41:58 A. I was head of sterile and biologics manufacturing in
09:42:03 Silver Spring.
09:42:04 Q. And how long were you in that position?
09:42:06 A. Approximately five years.
09:42:09 Q. Now, over the course of your career, your entire
09:42:12 career, have you had any experience working on inhalation
09:42:14 drug products?
09:42:15 A. I have. Pretty much my entire 30-year career has
09:42:18 involved manufacturing, developing respiratory product.
09:42:23 Q. And can you give me a couple of examples?
09:42:25 A. Sure. So, the first products I worked on were
09:42:32 Pulmozyme, a product for cystic fibrosis while I was at
09:42:36 Genentech, and then I moved on to a number of other
09:42:39 products. Tobi, which was the second product approved for
09:42:42 cystic fibrosis, and a number of different asthma and COPD

09:42:47 products.
09:42:48 Q. And have you done any teaching with respect to how to
09:42:51 make inhaled drug products?
09:42:52 A. I do. I'm a frequent industry speaker on the
09:42:58 manufacture of sterile respiratory products and requested by
09:43:02 FDA on occasion to come to the FDA facilities and teach
09:43:06 their reviewers on how to make respiratory inhalation
09:43:10 products.
09:43:11 Q. Now, we've mentioned United Therapeutics. What
09:43:15 exactly does United Therapeutics do?
09:43:17 A. So United Therapeutics develops and commercializes
09:43:20 drug products and medical devices to treat various diseases.
09:43:24 Q. Is there any particular set of diseases that United
09:43:27 Therapeutics has focused on?
09:43:28 A. Focused on mainly pulmonary hypertension, rare
09:43:32 diseases -- we do have a product for neuroblastoma as well.
09:43:40 Q. Now, in your more than a dozen years at UTC, have you
09:43:43 come to learn how UTC was founded?
09:43:45 A. Yes.
09:43:46 Q. And how was UTC founded?
09:43:48 A. So, Martine's daughter, Genesis, was diagnosed with a
09:43:55 form of pulmonary hypertension at a very young age.
09:43:58 Q. Can I pause. Martine. Who's Martine?
09:44:00 A. Martine is our CEO, Martine Rothblatt.
09:44:05 And it's a very serious disease, often fatal

09:44:10 over time. And there were very limited options for her at
09:44:16 the time to treat her daughter. So, she took it upon
09:44:19 herself to pursue finding a medicine that could either
09:44:25 prolong her daughter's life or even cure it.
09:44:28 Q. And so, what drug therapy or solution did United
09:44:35 Therapeutics first focus on?
09:44:36 A. So ultimately, Martine was able to gain rights to the
09:44:41 compound Treprostinil, and that has been the basis of many
09:44:45 of the products that we developed and commercialized.
09:44:49 Q. And how did UTC originally synthesize the
09:44:53 Treprostinil molecule?
09:44:55 A. So when she acquired the rights to it, it was from a
09:44:59 company called Burroughs, which was a fairly large
09:45:03 pharmaceutical company that's, through acquisitions, is now
09:45:08 part of GSK today. And Burroughs told her she was going to
09:45:16 have to find someone to make that compound for her. It was
09:45:19 something they didn't want to make. It was too hard to make
09:45:22 at scale.
09:45:22 So, she went and located a company in Chicago
09:45:27 that thought they could do it, and it took a lot of work,
09:45:30 and they figured out how to do it. And that company was
09:45:36 eventually acquired by United Therapeutics in 1999, so since
09:45:42 that time, Treprostinil has been made by United Therapeutics
09:45:46 internally.
09:45:47 Q. And did --

09:45:48 MR. SUKDUANG: Your Honor, just a lodge an objection. Mr. Poisson didn't join the company until 2009.

09:45:54 THE COURT: It's just background. Overruled.

09:45:58 BY MR. JACKSON:

09:46:00 Q. Did UTC ever seek to improve that synthesis process?

09:46:04 A. Yes.

09:46:04 Q. I want to show you what's been marked as JTX 2. Do you recognize this document?

09:46:09 A. Yes, I do.

09:46:10 Q. And what is it?

09:46:11 A. That's what we call the '066 patent.

09:46:12 Q. And is that -- what does the '066 patent involve?

09:46:18 A. It involves a technique for synthesis of Treprostinil.

09:46:22 Q. You also in addition to the -- is that patent at issue in this case?

09:46:29 A. Yes.

09:46:33 Q. Okay. You also -- are there any other patents at issue in this case as well?

09:46:34 A. Yes.

09:46:39 Q. And I want to show you what's been marked as JTX 3. Do you recognize this document?

09:46:40 A. I do.

09:46:46 Q. And what is it?

09:46:47 A. That's what we call the '793 patent or the

09:46:54 Treprostinil for inhalation patent.
09:46:56 Q. And do you understand that that's also at issue in
09:46:58 this case?
09:46:59 A. I do.
09:47:00 Q. How was the technology in the '793 patent developed?
09:47:03 A. It was developed as a collaboration between UT and
09:47:08 some physician researchers in Germany.
09:47:12 Q. And what was that -- what did that collaboration
09:47:16 involve?
09:47:16 A. It involved figuring out how to deliver an inhaled
09:47:21 version of Treprostinil effectively to a PH patient.
09:47:27 Q. And who -- do you know any inventors there listed
09:47:32 under 72?
09:47:34 A. I know their names.
09:47:35 Q. Okay. Do you know who came up with which portions of
09:47:37 the invention?
09:47:38 A. I can't tell you exactly who did what.
09:47:42 Q. Was it a collaboration, then?
09:47:43 A. Yeah, it was certainly a group effort.
09:47:45 Q. Now, why did UTC pursue an inhaled form of
09:47:49 Treprostinil?
09:47:49 A. Well, the approved form of Treprostinil, which is --
09:47:55 was Remodulin is an injection. And developing an inhalation
09:48:03 product would lower the burden on the patient to be able to
09:48:07 take the product, so it's an easier way to take

Treprostinil.

Q. And do you know what the first product or what the first inhaled product was?

A. For Treprostinil?

Q. Yes.

A. Yes, it was TYVASO.

Q. And what type of inhaled product is that?

A. It was an inhaled solution.

Q. And do you know why an inhaled solution was pursued at that time?

A. So, the particular researchers in Germany that we were collaborating with were very familiar with using nebulization to deliver Treprostinil. So, through that experience, we leveraged that to bring TYVASO to market through the clinical studies.

Q. Did UTC also consider other forms of inhaled Treprostinil?

A. Yes.

Q. And what other forms did UTC consider?

A. So there's other methods for inhalation. There's metered dose inhalers, there's dry-powder forms, there's soft mist. So, all of them -- all those were on the board, and various discussions and testing happened to determine what to go forward with. There was a sense of urgency because we wanted to get an alternative method for taking

09:49:35 Treprostinil on the market, and there was evidence that being able to start people on Treprostinil earlier was a big advantage for the patient. It prolonged life.

MR. JACKSON: Your Honor, I move to admit JTX 2 and 3.

MR. SUKDUANG: No objection.

THE COURT: Admitted without objection.

(JTX Exhibit No. 2 and JTX Exhibit No. 3 were admitted into evidence.)

MR. JACKSON: And I pass the witness.

THE COURT: All right.

Cross.

CROSS-EXAMINATION

MR. SUKDUANG: Just briefly.

BY MR. SUKDUANG:

Q. Mr. Poisson, do you remember being deposed by my colleague in this case?

A. I do.

Q. And do you recall being deposed regarding conception and reduction to practice and who came up with the idea for how formulation of the '793 patent?

A. Yes, I do.

Q. And do you recall being asked who came up with the dry-powder concept and you said I don't recall?

A. I do.

09:50:28 Q. And do you also -- are you also aware that you were
09:50:31 asked was UT attempting to prepare a dry-powder formulation
09:50:35 as of 2006, and you said don't you don't believe so?
09:50:38 A. I can't say one way or the other. I don't have any
09:50:42 knowledge as to the status of 2006.
09:50:47 Q. So just so you're clear, you don't know whether, as
09:50:51 of 2006, UT was working on a dry-powder formulation of
09:50:55 Treprostinil?
09:50:55 A. I do not know.
09:50:58 Q. And you don't know, as of 2006, whether any of the
09:51:01 inventors of the '793 patent actually were working on
09:51:05 dry-powder formulations of Treprostinil, isn't that correct?
09:51:07 A. That's correct.
09:51:08 MR. SUKDUANG: No further questions, Your Honor.
09:51:10 THE COURT: All right. Any redirect?
09:51:13 MR. JACKSON: No, Your Honor. Thank you.
09:51:16 THE COURT: Okay. Mr. Poisson, you may step
09:51:20 down. Thank you very much. Watch your step.
09:51:26 MR. JACKSON: Your Honor, the next witness is --
09:51:30 we're doing Mr. Kindig, who is a Liquidia executive. We're
09:51:35 doing it by excerpts of his video deposition.
09:51:39 THE COURT: Okay.
09:51:49 (Video playing.)
09:51:53 Q. Good morning, Mr. Kindig. Can you state your name
09:51:55 for the record.

09:51:57 A. My name is Jeffrey Kindig.
09:52:00 Q. You have also been designated as the corporate
09:52:02 witness on Topic 18; correct?
09:52:04 A. That's correct.
09:52:09 Q. That topic reads, "Storage and holding conditions at
09:52:14 every step of the manufacturing process for Liquidia's NDA
09:52:17 product and its API, including the storage conditions which
09:52:21 documents identify those storage conditions and the reasons
09:52:25 for those storage conditions."
09:52:26 Did I read that correctly?
09:52:30 A. Yes, that is what this document says.
09:52:33 Q. What is the active ingredient in LIQ861?
09:52:39 A. Treprostinil sodium.
09:52:45 MR. SUKDUANG: Your Honor, may I just pause it
09:52:46 for a second? I realized I need to bring the binders of the
09:52:51 exhibits that are going to be admitted through --
09:52:54 THE COURT: All right. Thank you.
09:53:06 (Video playing.)
09:53:16 Q. Treprostinil sodium is a Treprostinil salt; correct?
09:53:21 A. Treprostinil sodium API is a salt of Treprostinil,
09:53:24 yes.
09:53:26 Q. You understand you're designated as a corporate
09:53:32 witness on the issue of the active ingredient in Liquidia's
09:53:37 NDA product?
09:53:38 A. I do.

09:53:42 Q. The API Liquidia purchases from Yonsung is a
09:53:47 Treprostinil salt?
09:53:48 A. Treprostinil sodium of salt, yes.
09:53:52 Q. Mr. Kindig, do you have Exhibit 2?
09:53:55 A. I have just opened it, yes. Yeah.
09:54:00 Q. Do you recognize this document?
09:54:02 A. I recognize it as a section from our NDA,
09:54:10 Section 23P.
09:54:10 Q. Do you see under Section 1.1 on the first page,
09:54:19 that's LIQ1538, "Stability of the drug substance
09:54:26 Treprostinil sodium has been studied by the manufacturer,
09:54:30 Yonsung Fine Chemicals, Limited, and data are included in
09:54:33 the Yonsung DMF Number 27680."
09:54:38 Do you see that?
09:54:39 A. I see that sentence, yes.
09:54:46 Q. If further goes on to state, "Although the assigned
09:54:49 long-term storage condition is typically 2 to 8 degrees
09:54:52 Celsius, the accelerated data reported at 25 degrees
09:54:57 Celsius/60 percent RH relative humidity for six months show
09:55:01 no change in the drug substance attributes tested."
09:55:05 Do you see that?
09:55:06 A. Yes, I see that sentence.
09:55:10 Q. The next sentence reads, "Specifically, the related
09:55:13 substances show no increase in drug-related degradation when
09:55:18 stored at 25 degrees Celsius/60 percent RH when protected

09:55:22 from light."

09:55:23 Do you see that?

09:55:23 A. Yes.

09:55:26 Q. And finally, "The six-month, 25 degrees

09:55:31 Celsius/60 percent RH data for Treprostinil sodium shows

09:55:34 excellent solid state stability in support of controlled

09:55:38 room temperature storage of LIQ861 drug product."

09:55:43 You see that?

09:55:44 A. Yes.

09:55:47 Q. So, here, Liquidia is telling the FDA that the drug

09:55:50 substance, the Treprostinil sodium, has excellent solid

09:55:57 state stability at room temperature over six months; right?

09:56:03 The Witness: I see that's what the sentence

09:56:05 says, yes.

09:56:07 Q. You see there's a Table 2.3.P-4, Critical Process

09:56:13 Parameters for LIQ861 Inhalation Powder Manufacturing?

09:56:17 A. I see that here, yes.

09:56:20 Q. Looks -- in general, there are six manufacturing

09:56:26 steps.

09:56:27 You see that?

09:56:28 A. I see that here, yes.

09:56:34 Q. Step 1 is "Preparation of the aqueous stock

09:56:38 solution"; is that right?

09:56:39 A. That's what it says, yes.

09:56:41 Q. Step 2 of the manufacturing process for LIQ861 is

"preparation of engineered particles (particle fabrication)"; right?

A. That's what this says, yes.

Q. Step 3 of the manufacturing process for LIQ861 is "dry collection of engineered particles as bulk LIQ861 inhalation powder"; right?

A. Correct.

Q. Step 4 of the manufacturing process for LIQ861 is "dry and packaging of bulk LIQ861 inhalation powder"; right?

A. Correct.

Q. Step 5 of the manufacturing process for LIQ861 is "drug product priming packaging - encapsulation of bulk LIQ861 inhalation powder in HPLC capsules"; right?

A. Correct.

Q. Step 6 of the manufacturing process for LIQ861 is "drug product secondary packaging - blister packaging and assembly of commercial drug product kit"; right?

A. That's correct.

Q. The inactive ingredients in the bulk powder are trehalose dihydrate polysorbate 80, L-Leucine, sodium citrate dihydrate, sodium chloride, and water; is that right?

A. Those are the components that are used to produce the bulk powder.

Q. Liquidia takes the Treprostinil sodium from Yonsung

and the other components we just went through to produce the bulk powder; right?

The Witness: Yes.

Q. Do you see there's a flow chart for Step 1 of Liquidia's manufacturing process?

A. Yes, I see that.

Q. And there's a box that reads, "Hold time: NMT 71 hours."

Do you see that?

A. I see that box, yes.

Q. Okay. NMT means no more than?

A. It -- yeah, it is defined in the footer of the figure as not more than. Yes, I see that.

Q. At the end of Step 1 of Liquidia's manufacturing process for bulk powder, the aqueous solution containing Treprostinil sodium can be held for almost three days at room temperature; correct?

The Witness: That's what this says, yes.

Q. All right. Let's move on to the next page of LIQ29616. Step 2, "Preparation of engineered particles."

Do you see that?

A. I see this, yes.

Q. So, based on this flow chart, do you agree that Liquidia takes the formulation containing Treprostinil sodium, puts it on a film, and at the end of Step 2, puts

10:00:02 that film into a bag?

10:00:09 The Witness: Generally, yes, that's what occurs here.

10:00:11 Q. Do you agree that the film containing the formulation containing Treprostinil sodium can be held in a bag for up to 18 hours at room temperature?

10:00:25 The Witness: That's what it says here in this document, yes.

10:00:33 Q. Okay. All right.

10:00:35 Step 3 is the "dry collection of engineered particles as bulk LIQ861 inhalation powder"; correct?

10:00:46 A. That's what it says here, yes.

10:00:51 Q. And can you describe what that step entails?

10:00:53 A. Generally, this step is the step at which the particles that had been produced and were still on PET substrates from the previous step get removed from the PET substrate and into a powder form and get packaged in a bag with desiccants.

10:01:23 Q. And the powder that's formed from Step 3, containing Treprostinil sodium, is held in a bag for up to 88 hours at room temperature; correct?

10:01:39 The Witness: The powder that was produced from the stock solution to which Treprostinil sodium was added is held for not more than 88 hours, yes.

10:01:55 Q. At room temperature?

10:01:56 THE WITNESS: It, again, doesn't specify here.
10:01:58 I -- to the best of my knowledge, it is at room temperature.
10:02:02 Q. The materials from steps one through three can be
10:02:05 held up to a week or so at room temperature; right?
10:02:14 THE WITNESS: Yes.
10:02:19 Q. What is Exhibit 6?
10:02:20 A. I don't know what this is. I've not seen this
10:02:24 before. Let me look.
10:02:29 Based on the headers, it appears to be part of
10:02:32 our NDA submission. The content appears to be executed
10:02:37 batch records.
10:02:38 Q. Let's start on the first page. It states "executed
10:02:43 batch record - 18004 - LIQ861 - PK."
10:02:53 You see that?
10:02:54 A. Yes, I see that.
10:02:55 Q. And it was used for both stability studies and for
10:03:03 clinical use; correct?
10:03:05 A. That's what this says, yes.
10:03:08 Q. The particles of the formulation made from
10:03:13 Treprostinil sodium are put in bags and stored at room
10:03:20 temperature until the next step; correct?
10:03:23 THE WITNESS: The LIQ861 bulk powder formulation
10:03:28 particles are put into bags and stored at room temperature,
10:03:31 held at room temperature, until the next step.
10:03:36 Q. Right. Do you see that it's a batch record for batch

18008 - LIQ861 - PK?

A. That's what this appears to be, yes.

Q. Batch 18008 was used for stability studies?

A. That is what it says here, yes.

Q. Do you have Exhibit 39?

A. Yes.

Q. What is a receiving inspection report?

A. So when material arrives at Liquidia, this report is filled out to indicate what the material is, manufacture a lot number, the various questions you see on the page. And then it gets assigned a Liquidia lot number that is unique for that shipment, that receipt.

Q. So Liquidia lot number 00572 correlates with Yonsung lot number T N 120I010.

THE WITNESS: Yes. It appears that, to be the case from had document.

Q. You see Exhibit 40?

A. Yes.

Q. You see that it appears to be a similar collection of documents starting with the receiving inspection report?

THE WITNESS: I see that it starts with a similar looking receiving inspection report, yes, for a different lot.

Q. So, for Exhibit 40, the lot is Liquidia number L IQ 00571, and that corresponds with Yonsung lot T N 120 G 010?

10:05:39 A. Yes, that's what is reflected here.
10:05:44 Q. Do you consider materials under quarantine to be
10:05:47 materials being stored?
10:05:49 THE WITNESS: I would say materials are being
10:05:52 stored while they are in quarantine, yes.
10:05:55 Q. Do you see that according to this data logger, that
10:06:03 on or around December 13th, it appears that the temperature
10:06:08 log was above 8 degrees Celsius?
10:06:13 A. I see that. Yes, I see that that is what is
10:06:20 apparently reflected here.
10:06:21 Q. And the data logger states that the high temperature
10:06:27 was 16.7 degrees Celsius.
10:06:31 Do you see that?
10:06:33 A. In the logger result section, yes, I see that.
10:06:41 Q. Based on the graph in Exhibit 40, do you agree that
10:06:47 the isolated Treprostinil sodium was not stored at
10:06:53 refrigerated conditions between December 13th, 2020, and
10:07:03 December 24th, 2020?
10:07:07 THE WITNESS: This graph says to me that it was
10:07:09 not shipped between 2 and 8 during that period of time that
10:07:14 you specified.
10:07:15 Q. During the period of December 13th, 2020, through
10:07:20 December 24, 2020, Yonsung's Treprostinil sodium was being
10:07:28 shipped at ambient temperature; right?
10:07:34 THE WITNESS: It was being shipped at the

temperatures reflected here up to 16.7 C.

Q. Do you have Exhibit 41?

A. Yes.

Q. Exhibit 41, a part of Liquidia's original NDA submission?

A. From the headers, that appears to be true, yes.

Q. It appears to be Section 2.3.S, quality overall summary for drug substance.

Do you see that?

A. Yes.

Q. The drug substance is Treprostinil sodium from Yonsung?

A. Correct.

Q. Do you see that there is a reference to Yonsung Type II drug master file 27680 in the section?

A. Yes, I see that reference.

Q. Are you aware of any lots of Treprostinil sodium that have not been released from quarantine?

A. Yes, I am.

Q. Do you know whether Liquidia intends to use those lots?

THE WITNESS: There are two lots still quarantined. We do not intend to use them.

(Conclusion of video.)

MR. JACKSON: Your Honor, Plaintiffs move

admission of Exhibits PTX 66, PTX 70, PTX 71, PTX 103, PTX 104, and PTX 105 which were used in the deposition.

MR. SUKDUANG: We have no objections. There's some -- in the binder, there's different exhibits than what was entered, so I think the binders need to come back and the right exhibits need to happen.

THE COURT: Well, so why don't you try to work those things out between yourselves.

MR. SUKDUANG: But no objection to the exhibits.

THE COURT: But the exhibits are admitted.

MR. JACKSON: Thank you, Your Honor.

(PTX Exhibit No. 66, PTX Exhibit No. 70, PTX Exhibit No. 71, PTX Exhibit No. 103, PTX Exhibit No. 104, PTX Exhibit No. 105 were admitted into evidence.)

MR. JACKSON: Plaintiffs now call Todd Battistoni by video as well.

THE COURT: All right.

(Video playing.)

Q. So please states your full name for the record.

A. Todd Battistoni.

Q. How many lots piqued your interest in terms of how long they had stayed in quarantine and prompted you to talk to Mr. Hunter?

A. Two.

Q. And what did Mr. Hunter tell you about why those lots

still in quarantine?

A. That the information we received from LGM described a temperature excursion for the shipment of those lots. The lots went outside of the required shipping temperature range. And that -- that caused us to pause and question the release.

Q. So, am I understanding correctly that for both of these lots that were quarantined, they were quarantined because there was a temperature excursion in this leg of shipment from Yonsung to LGM in the U.S.; is that correct?

A. That is my understanding, yes.

Q. Did Mr. Hunter tell you what the disposition of these two lots would be?

A. So officially, I will be the final arbiter of the disposition, which is why I started asking questions. So --

Q. Makes sense.

A. -- as head of quality. Our intent is to not use these lots for GMP purposes.

Q. And why is that?

A. Because this excursion violates the manufacturer's recommended storage condition and shipping condition. And per our contract, when that happens, you know, we are -- we are not technically -- not legally required to accept them. In addition, you know, being outside of the temperature

range represents a quality of risk that we're not willing to take.

Q. Sure. So it sounds like you're saying that, you know, as head of Q A, the intent for these two lots that are -- have that temperature excursion outside of the recommended storage condition, your current intent is to not use the lots for GMP purposes; is that right?

A. That's correct.

Q. Okay. So, in your current role then, is it, ultimately, your decision as to whether or not to use the API that has excursions?

THE WITNESS: Well, from a -- from a -- "responsibilities" as defined by FDA regulation, it is my decision to make -- any decision generally, any problem with product quality, it's my decision, ultimately, to make.

Q. Okay. So you would be the ultimate arbiter. It's not by committee or vote or any other mechanism?

A. I am accountable to make the final decision, yes.

Q. And then this is as to GMP purposes; right?

A. That's correct.

THE WITNESS: That's correct.

Q. So, I think you had mentioned earlier that your current role is as head of quality assurance; is that right?

A. That is correct.

Q. Is that your formal title?

10:13:31 A. My formal title is vice president of quality.

10:13:39 (Conclusion of video.)

10:13:41 MR. JACKSON: Thank you, Your Honor. Plaintiffs now call Dr. Colin Nuckolls to the stand.

10:13:53 THE COURT: All right.

10:13:54 MR. JACKSON: May approach just with copies of transcripts that we just used?

10:13:58 THE COURT: Sure.

10:14:30 DEPUTY CLERK: Please states and spell your full name for the record.

10:14:32 THE WITNESS: Colin Peter Nichols C-O-L-I-N, P-E-T-E-R, N-U-C-K-O-L-L-S.

10:14:38 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?

10:14:46 THE WITNESS: I do.

10:14:46 DEPUTY CLERK: Thank you. Just make sure you speak into the microphone.

10:14:49 THE WITNESS: Okay.

10:14:49 COLIN NUCKOLLS, the witness herein, after having been duly sworn under oath, was examined and testified as follows:

10:14:55 DEPUTY CLERK: Could he have a laser pointer?

10:15:07 MR. CARSTEN: I have one for the witness, Your

Honor, a laser pointer. May I approach?

THE COURT: Sure.

MR. CARSTEN: Thank you.

(Discussion held off the record.)

DIRECT EXAMINATION

BY MS. WU:

Q. Good morning, Dr. Nuckolls. Where are you currently employed?

A. At Columbia University in New York.

Q. What's your position?

A. I'm the Sheldon and Dorothea Butler professor.

Q. Do you specialize in any particular field?

A. My group is interested in organic chemistry and reaction chemistry to prepare new and unusual molecules and materials.

Q. Do you have a couple binders in front of you?

A. No, I do not.

MS. WU: May I approach, Your Honor?

THE COURT: Yes.

BY MS. WU:

Q. Could you please take a look at PTX 510.

A. I'm there.

Q. Do you recognize this document?

A. Yes, that's my CV.

Q. Does this CV accurately reflect your experience and

10:17:04 accomplishments?
10:17:05 A. Yes, it does.
10:17:06 MS. WU: Your Honor, at this time, I tender
10:17:08 Dr. Nuckolls as an expert in the field of organic synthesis
10:17:10 and reaction chemistry.
10:17:12 MR. SUKDUANG: No objection.
10:17:13 THE COURT: All right. You may proceed.
10:17:15 BY MS. WU:
10:17:16 Q. Dr. Nuckolls, have you worked with counsel to prepare
10:17:18 slides to assist in your testimony today?
10:17:20 A. Yes, we did.
10:17:22 Q. What opinions are you offering today?
10:17:24 A. I'm offering the opinion that Liquidia infringes the
10:17:28 '066 patent.
10:17:29 Q. From what perspective did you evaluate infringement
10:17:32 of the '066 patent?
10:17:33 A. If you go to the first slide, I evaluated this
10:17:38 through the lens of a POSA, which would be the person of
10:17:42 ordinary skill in the art. That would either be a chemical
10:17:43 engineer or process research chemist with three to
10:17:46 five years of experience in API and drug manufacturing or a
10:17:49 master's degree in chemistry or chemical engineering who
10:17:52 collaborated with individuals having three to five years of
10:17:54 experience in API drug manufacturing.
10:17:57 Q. Can you explain, generally, the invention of the '066

10:18:00 patent?
10:18:00 A. It's a method of -- an improved method of preparing
10:18:06 prostacyclin derivatives such as Treprostinil by making
10:18:10 salts of them and providing materials of higher purity.
10:18:16 Q. What claims did you evaluate?
10:18:18 A. If you could go to its next slide, I have a
10:18:22 demonstrative on that. So I -- there were two independent
10:18:25 claims, Claim 1 and Claim 8. And from Claim 1, there were
10:18:29 three dependent claims, Claims 2, 3 and 6. And one
10:18:33 dependent claim from the independent Claim 8, Claim 9.
10:18:37 MS. WU: Your Honor, I realize I neglected to
10:18:40 hand up a copy of the slides. May I do that now?
10:18:42 THE COURT: Sure.
10:18:58 MS. WU: These slides reflect our pre-objection
10:19:03 ruling, so I will try to navigate around them.
10:19:07 THE COURT: Thank you.
10:19:08 BY MS. WU:
10:19:09 Q. Can you explain with respect to impurities what's
10:19:12 required by Claim 1.
10:19:13 A. Sure. If you go to the next slide. So, the Claim 1
10:19:20 requires that you have a starting batch of Treprostinil in
10:19:23 and one or more of the impurities that resulted from the
10:19:26 prior alkylation hydrolysis steps, and that that alkylation,
10:19:30 as you see from the last line, is the alkylation of the
10:19:33 benzindene triol or what is known as referred to here as

10:19:37 BTO. And the level of one or more of those impurities that
10:19:41 is found in the starting batch is lower than the
10:19:43 pharmaceutical composition upon the crystallization -- the
10:19:47 salt formation and crystallization.
10:19:49 Q. Have you prepared a visual representation of what
10:19:52 happens to impurities in Claim 1?
10:19:55 A. Yes, I have. Go the next slide.
10:19:58 So, basically, the starting material, which is
10:20:02 the benzindene triol or BTO that material -- that batch of
10:20:04 material comes with its associated impurities, which are
10:20:07 shown as the -- as the blue square here. And then as that
10:20:12 material is alkylated, that's the alkylation product, and
10:20:15 that would then generate a number of impurities through that
10:20:18 step. And then the hydrolysis step would produce
10:20:22 Treprostinil or the hydrolysis product. That's the starting
10:20:26 batch of Treprostinil as defined in the Claim 1. And then
10:20:32 from there, that material is formed into a salt. And
10:20:36 crystallized, and at that point, the impurities that were
10:20:39 generated in the prior alkylation and hydrolysis steps are
10:20:43 reduced in the final product to provide a more pure product.
10:20:47 Q. Can you take us you through Liquidia's process for
10:20:51 producing its Treprostinil drug product.
10:20:53 A. Sure. If you go to the next slide, at a very high
10:20:57 level, this is the -- at a very high level, this is the
10:21:00 procedure. The API, the Treprostinil sodium, is synthesized

10:21:06 in Korea by a company known as Yonsung, and that material is
10:21:11 sent either to LGM Pharma and then to Liquidia or directly
10:21:15 to Liquidia in some cases, and then from there, to finish
10:21:18 the print process to produce the final drug product, that
10:21:21 material is shipped to Lonza or Xcelience in Florida.
10:21:25 Q. Please take a look at PTX 201. Do you recognize this
10:21:30 document?
10:21:31 A. Yes, I do.
10:21:50 Q. What is it?
10:21:51 A. That's the drug master file from Yonsung.
10:21:56 Q. Did you review this document in forming your
10:21:58 opinions?
10:21:59 A. Yes, I did.
10:22:01 Q. Why did you review this document?
10:22:02 A. This document contains information about how the
10:22:07 material is synthesized and also about the impurities that
10:22:12 were generated during the steps and in the reaction
10:22:16 sequence.
10:22:16 Q. Did you review Yonsung's entire reaction sequence?
10:22:19 A. If you go to the next slide, I can explain that. So
10:22:32 Yonsung's process is actually a 12-step process, but the
10:22:36 only steps that are important are the -- given the context
10:22:39 of this trial, are the last three where the benzindene
10:22:42 triol, the BTO, is reacted with the alkylating agent to
10:22:46 produce what is known as the alkylation product or TN01, as

it will be called through out the trial. Then the hydrolysis of TN01 with base produces TN02, which is the starting batch of Treprostinil. And then that material is treated with a base to form the salt of Treprostinil that is then collected as a solid.

Q. Does Yonsung describe these steps elsewhere in its DMF?

A. Yes. If you go to the next slide, this is the steps 10, 11, and 12 that I was just referring to on the previous slide showing the chemical structures.

So Step 10 shown in the upper left is the structure of BTO. That material is alkylated to produce TN01. Then TN01 in Step 11 is the starting material. That material is then hydrolyzed to form the -- to form Treprostinil, or the starting batch of Treprostinil. And then that material is then formed into the salt in the last step, Step 12, with the -- by the addition of a base, in this case sodium hydroxide to make Treprostinil sodium.

Q. Where did you find this information?

A. That's in PTX 201 at Page 518 to 519.

Q. Now, are these reaction materials pure?

A. So, if you go to the next slide, there's some animation on this that will highlight that. No material is a hundred percent pure. So the BTO, the batch of BTO that you start with comes with its associated impurities. The

10:24:25 next -- and upon alkylation, you'll generate a number of
10:24:28 impurities. Then upon hydrolysis, again, you'll generate
10:24:32 impurities and so on. So, no, the material is -- no
10:24:36 material is a hundred percent pure.
10:24:38 Q. Did you evaluate the impurities in Yonsung's process
10:24:41 for making Treprostinil sodium?
10:24:42 A. Yes, I did.
10:24:45 Q. Can you explain your analyses.
10:24:48 A. If you go to the next slide. Is -- there were --
10:24:53 well, there were three different analyses that I did for
10:24:57 analyzing for impurities. One of those had to do with
10:25:00 looking at the data that was in the DMF that is derived from
10:25:03 the certificate of analyses that Yonsung produced in their
10:25:08 DMF or their drug master file. The second analysis had to
10:25:12 do not with percent of impurities but the total number of
10:25:17 impurities, and then the third eight analysis had to do with
10:25:19 the -- that third analysis had to do with a specific
10:25:23 impurity, which is what's known as an epimer, and that's an
10:25:27 impurity that results with one of the carbon atoms within
10:25:30 the molecular structure having an inverted configuration.
10:25:34 It's referred to as epi such-and-such for each of the
10:25:37 intermediates in the steps.
10:25:40 Q. So, let's first talk about your first analysis, the
10:25:44 percent total impurities. Can you walk us through that.
10:25:46 A. Sure. So this shows excerpts of data -- excerpts of

10:25:51 data from the DMF that were, ultimately, I think, derived
10:25:55 from the certificate of analyses that Yonsung produced. And
10:25:59 they analyze related substance impurities or total related
10:26:04 substance impurities, and those are the highlighted lines
10:26:09 here in yellow. For each of the steps, they have the total
10:26:10 related substance impurities for BTO, they have the total
10:26:14 related substance impurities for TN01 and for TN02, which is
10:26:19 the starting batch of Treprostinil, and ultimately the same
10:26:21 thing for the final salt that is crystallized and collected
10:26:25 as a solid.
10:26:27 Q. I see that there are three -- well, four white boxes.
10:26:34 Each one has three batch numbers. What is the significance
10:26:38 of these batches?
10:26:39 A. Those are the validation batches that they used in
10:26:41 their DMF to report to the FDA. So those would be very
10:26:44 important batches because you're representing that these are
10:26:47 representative batches that are of their -- that represent
10:26:50 their process.
10:26:52 Q. I also see that in each of the columns, there's
10:26:55 different numbers for BTO batch numbers, for TN01 batch
10:27:00 numbers, for TN02 batch numbers, and for TN batch numbers.
10:27:03 How did you correlate these batches to understand the flow
10:27:07 of impurities through the process?
10:27:08 A. At some point during the -- during this process of
10:27:15 preparing reports and such like that, there was a document

that was produced from Liquidia's counsel that correlated all of the batch numbers for the different intermediates so you could track the starting material for one and the products for another, so you could correlate one to the next.

Q. Can you like take a look at PTX 326.

A. Sorry, you said PTX 326?

Q. Yes, I did.

A. Oh, there it is. I see it. Yeah. I'm sorry. Yeah, I'm here.

Q. Do you recognize this document? It's also on the screen.

A. That's not the -- what's on the screen is not the same as -- oh, I'm sorry. Yes, this is the document. I'm sorry. Yes, this is the document that correlates all the batch number, yes.

Q. Now, what does Yonsung's data show regarding total percent total impurities?

A. So, if you go to the next slide, I've tabulated that data here for the three validation batches. And what it shows, this is showing in tabular form what was seen -- what was taken from the COAs. What you see is there's a level of impurities of BTO. Upon alkylation, the impurities goes up. They go up. And then upon hydrolysis, you still have a higher level of impurities in the -- in the Treprostinil --

10:29:10 in the starting batch of Treprostinil or TN02, and then it's
10:29:16 drastically reduced on the salt formation, as required by
10:29:18 the patent.
10:29:19 Q. How do you know that the lowered amounts of total
10:29:23 impurities in Yonsung's Treprostinil sodium are impurities
10:29:27 from the alkylation and hydrolysis steps?
10:29:30 A. Well, because those were the steps that were run
10:29:33 here. So the alkylation step is the first one, so any
10:29:36 impurities above and beyond the value that you see for BTO
10:29:40 would be impurities that result from the alkylation step.
10:29:43 And again, any impurities that you see in the TN02 above and
10:29:48 beyond the impurities that were in the starting material
10:29:51 would be impurities that would -- at least result from the
10:29:54 alkylation and hydrolysis steps. And then, ultimately, the
10:29:57 levels are reduced drastically in the formation of
10:30:02 Treprostinil. So the impurities that were generated in the
10:30:06 alkylation and hydrolysis steps were reduced in the final
10:30:07 crystallization step.
10:30:08 Q. Let's move on to your second analysis, the number --
10:30:11 THE COURT: All right. So, Ms. Wu, why don't we
10:30:14 do this. Why don't we take a morning break for 15 minutes.
10:30:17 Okay.
10:30:18 All right. We'll be in recess.
10:30:21 DEPUTY CLERK: All rise.
10:30:22 (Recess was taken.)

10:33:35 DEPUTY CLERK: All rise.

10:46:22 THE COURT: All right. Please be seated and let's continue.

10:46:28 BY MS. WU:

10:46:33 Q. Dr. Nuckolls, we left off at your second analysis, the number of impurities. Can you explain what you did there.

10:46:35 A. Yes. So if you go to the next slide, I need to first explain a little bit of background. So to analyze the number of impurities rather than the percent impurities, we have -- I had to look at the underlying HPLC or high-performance liquid chromatography data, and just to give you a background on how HPLC works, as a very short primer, in the beige rectangle there, that's a solid phase. The teal sample is loaded onto that, and that sample is -- has two different hypothetical materials in it, a purple band and a green band. You load it onto the solid phase.

10:47:25 You apply a mobile phase, which is a solvent, and as it goes through this column, the two materials that were in this one band now separate into two. It allows you to collect these and analyze these, which is what Yonsung does when they analyze their material with -- or look for impurities, would identify to identify impurities.

10:47:48 So if you go to the next slide, this shows the actual underlying HPLC chromatograms. This is the data as

10:47:55 1 comes off the instrument shown here for BTO, TN01, TN02, and
10:48:01 2 then, ultimately, for Treprostinil sodium. We're not
10:48:05 3 looking at percent. We're looking at number of impurities
10:48:07 4 because, as the -- as the claims says, it says one or more
10:48:12 5 impurities must be reduced. So in the starting batch of
10:48:15 6 BTO, there was one related substance impurity that was
10:48:20 7 identified. In the alkylation product, TN01, for this
10:48:24 8 batch, there were five related substance impurities
10:48:27 9 identified. For TN02, there were three related substance
10:48:32 10 impurities that were identified, and then that three -- the
10:48:34 11 three related substance impurities that resulted from the
10:48:37 12 alkylation and hydrolysis steps were, ultimately, removed in
10:48:39 13 the salt formation -- in the salt formation and
10:48:44 14 crystallization step to form Treprostinil sodium, resulting
10:48:46 15 in only one impurity identified in that material.
10:48:51 16 Q. Who identified these impurities. So these material
10:48:57 17 were identified -- these materials were identified in the in
10:49:01 18 the DMF by Yonsung.
10:49:03 19 And can you explain why the rows highlighted and
10:49:08 20 why some are not highlighted?
10:49:10 21 A. Well, in some cases, you can see that they -- they
10:49:13 22 were either the material of interest, for example BTO, and
10:49:16 23 so that's not highlighted as an impurity. And there were
10:49:20 24 other things that were known impurities that they were
10:49:22 25 looking for, for example, that may have been either not

10:49:25 detected or missing, so those are labeled as missing or not
10:49:30 detected, so I highlighted all the related -- all the
10:49:32 related the substance impurities that they found in each of
10:49:36 these sets -- in each of these sets of data.
10:49:39 Q. Did you prepare a summary of your number of
10:49:42 impurities analysis?
10:49:43 A. Yes. If you go to the next slide, again, for the
10:49:47 validation batches, all -- we only have the underlying data
10:49:50 for two out of the three validation batches, but you see
10:49:53 this is now the data you saw in the previous slide now in
10:49:56 tabular form. You see starting with BTO, the starting
10:50:00 material you have in this batch TN117I010, the benzidine
10:50:11 triol or BTO had one related substance impurity. It goes to
10:50:15 five upon alkylation, and then upon formation of the
10:50:20 hydrolyzed product, you now have three related substance
10:50:24 impurities, and that is, again, reduced to one related
10:50:25 substance impurity.
10:50:27 And you can see the same thing for the other
10:50:29 validation batches that we have the underlying data,
10:50:33 TN117K010. This data can be found in PTX 1410, PTX 1411,
10:50:39 and PTX 1157 and PTX 1543.
10:50:46 Q. Dr. Nuckolls, I neglected to ask you for the prior
10:50:49 underlying data in the prior slide, where you got that
10:50:53 information from. Can we go back one slide, please.
10:50:55 A. Oh, yeah. That was found in the -- in Yonsung's --

10:50:59 in the. Sorry. That was found in the batch production
10:51:04 records and the Q C test sheets that were -- that underlie
10:51:08 the data that's in the DMF.
10:51:11 Q. And where specifically did you find them?
10:51:12 A. They were in the -- they were -- those materials were
10:51:19 contained in the Q C test sheets and the batch production
10:51:23 records that were -- we have all -- many of those types of
10:51:27 documents that I would analyze.
10:51:29 Q. Are those captured in PTX 1536?
10:51:33 A. Oh, yeah. I'm sorry. Those are captured in PTX 1536
10:51:37 at Page 243 and PTX 1542 at 231 to 232 and PTX 1540 at
10:51:43 Page 5 to 6 and PTX 1539 at 166. You can see that on the
10:51:48 lower left of the slide.
10:51:50 Q. Then did you conduct your number of impurities
10:51:54 analysis on all three validation batches?
10:51:56 A. No, if you'll -- there were -- only the underlying
10:52:01 HPLC data -- we were only provided with two of them. The
10:52:04 third one was missing for the validation batch, so I
10:52:06 couldn't perform that analysis on that third batch.
10:52:09 Q. Did you evaluate any batches with regards to a
10:52:15 specific impurity?
10:52:16 A. Yes, I looked at the -- I looked at all of the
10:52:20 batches that I had access to and tracked the epimer, which I
10:52:24 referred to earlier, which is a -- a -- a impurity that
10:52:28 results in one of the -- one of the carbon atoms has an

10:52:32 inverted configuration, and it's referred to as epi
10:52:35 throughout series, so you'll have epi BTO, epi TN01, epi
10:52:40 TN02, and epi Treprostinil, so I tracked that impurity for
10:52:44 all the batches I had access to.
10:52:45 Q. So if you could take a look at your reply expert
10:52:48 report so we can identify the batches that is you tracked.
10:52:55 And if I could direct your attention to Page 14.
10:52:58 A. Yeah, do you know which number that is in the binder?
10:53:02 Q. It's also up on the screen if that's helpful.
10:53:05 A. Yeah, that's helpful, sure. I'm sorry. Can you
10:53:09 repeat your question.
10:53:09 Q. Sure. I wanted to you identify for me the batches
10:53:12 for which you tracked the epi-impurity through the Yonsung
10:53:16 process.
10:53:16 A. Right. So they're highlighted in yellow here. So
10:53:19 TN118E010, TN118F010, TN118H010, TN118K0010, TN119C010,
10:53:31 TN119D010, TN119E010, TN119J010, TN119L010.
10:53:44 Q. Any more?
10:53:47 A. And there were a few more. TN120C010, TN120G010,
10:53:58 TN120I101, TN118F010, and TN119C010.
10:54:04 Q. And what did you find when you tracked the
10:54:07 epi-impurity through the Yonsung process?
10:54:09 A. If you go to the next slide --
10:54:12 MR. SUKDUANG: Your Honor.
10:54:13 THE WITNESS: I have --

10:54:14 THE COURT: Yes.

10:54:15 MR. SUKDUANG: This is the objectionable part. All of those paragraphs discuss a specific process called epimerization. He did not draw the conclusion in his expert reports that he tracks these to determine whether something goes up and down. It's to explain why you don't see something and then it appears back again. And that's -- if you look at the report, really at the very last Paragraph 29, these findings also keep in touch with the findings regarding epimerization. That's the new -- what he's going to offer now is the new opinion based on this data used for a different machine.

10:54:52 THE COURT: Ms. Wu.

10:54:54 MS. WU: Yes, Your Honor if I could have Page 16, please. You can see in his expert report, he talks about in the middle of the page, for example, in batch TN118 at 010 there were no impurities reported to BTO. .58 percent total impurities reported in TN01. .02 percent 15-epi-Treprostinil in TN02, and .076 total impurities in TN02 and no impurities detected in the Treprostinil sodium, and he goes through another example. That's the data we want to present.

10:55:34 MR. SUKDUANG: That's not the data they did present, Your Honor.

10:55:36 THE COURT: Well --

10:55:37 MR. SUKDUANG: These this --

10:55:37 THE COURT: So, let's do this. Let Ms. Wu ask a question. Why don't you keep that slide on the screen. I'll listen to the answer, and if you want to move to strike it afterwards, you can go ahead.

BY MS. WU:

Q. Dr. Nuckolls --

THE COURT: Charge that time to the defendant. Go ahead.

BY MS. WU:

Q. Dr. Nuckolls, did you look at all of the underlying data for the batches that you identified earlier to inspect the epi-impurity amounts in each of BTO, TN01, TN02 and TN?

A. Yes, I did.

Q. And have you prepared a summary setting forth the amounts of the epi-impurity in each of BTO, TN01, TN02, and TN?

THE COURT: So, Ms. Wu, I'm look at that. It only has the word "epi" for TN02. So why would he be offering opinion about -- well, no impurities, I guess that stands -- speaks for itself, but why would he be offering opinions about things that are not broken down here?

MS. WU: He's -- in the prior pages, which we can go back to, he lays out all those numbers, and that's what the summary chart presents.

10:56:54 THE COURT: All right. Well, go ahead then.
10:56:57 BY MS. WU:
10:56:58 Q. So if we go to summary slide 16, can you explain what
10:57:01 this chart is?
10:57:02 A. It's a little bit of --
10:57:02 MR. SUKDUANG: Objection, Your Honor. This
10:57:03 is -- this was a demonstrative that was excluded. And this
10:57:07 is -- this shows exactly the point. In paragraph 28, he
10:57:12 lists a bunch of lots that deal with epimerization in
10:57:17 paragraph 29. That sentence that Ms. Wu pointed to only
10:57:19 talks about two lines. He's now taking that red box and
10:57:23 talking about a whole bunch of different lots. Many of
10:57:26 these in this demonstrative are not even in paragraphs 28 or
10:57:29 29. And this was also excluded.
10:57:32 MS. WU: Your Honor --
10:57:33 MR. SUKDUANG: This is a different opinion.
10:57:34 MS. WU: During the break, we met and conferred,
10:57:36 and I took out the three batches that they contend were not
10:57:41 listed in the paragraphs that we've been looking at that
10:57:44 they contend were not in paragraphs 28 and 29.
10:57:48 THE COURT: All right. So I'm going to overrule
10:57:49 the objection. Go ahead.
10:57:51 BY MS. WU:
10:57:52 Q. Dr. Nuckolls, can you explain your analysis with
10:57:53 regard to the epi-impurity?

10:57:55 A. Sure. So this is a little bit of a busy slide, but
10:58:00 what's shown here is the level of the epi-impurity of BTO
10:58:04 for a batch, and the batches are color-coordinated, and then
10:58:08 for each of the batches that we analyzed or that I analyze,
10:58:12 as you go from the -- as you from go from BTO to TN01, the
10:58:17 amount of epi-TN01 in each case goes down to nondetected in
10:58:22 the -- in the Yonsung data.
10:58:24 And as you go from the 15 epi-TN01 to the 15
10:58:30 epi-TN02, you see that the now the amount of epimer has
10:58:33 increased in that hydrolysis step. The amount of epimers
10:58:36 increased in almost all of the cases and that, ultimately,
10:58:40 upon recrystallization, you see that those values go down.
10:58:43 Because it goes to zero here, to make the graph
10:58:46 a little bit easier to see, I'm just going to blow up the
10:58:49 part that's highlighted in the red rectangle. And
10:58:53 basically, what you see except for the dashed line here
10:58:56 where the amounts -- where the amounts go up, all the other
10:58:59 batches, as you go from the amount of epi-TN02 is reduced in
10:59:05 each of those, so a specific impurity is being reduced in
10:59:09 the -- in that final crystallization step that was absent
10:59:14 after the alkylation step or reduced after the alkylation
10:59:18 step down to not detected.
10:59:21 MS. WU: Your Honor, I am going to show the next
10:59:23 slide which has also has been objected to, but I would like
10:59:25 some guidance, if we could go to the next slide.

10:59:32 Dr. Nuckolls looked at all this underlying data. Should he read that into the record, or should we try and confer and prepare an appropriate list?

THE COURT: Well, we don't really have time to list. If you're going have him read into the record, why don't you just have him read something from his report into the record and you don't need a slide.

MS. WU: We can do that, Your Honor. But in his report, the citation is the Bates number and not trial exhibit numbers. So I endeavored to put those here.

THE COURT: All right. I'm going to allow you to do it.

MR. SUKDUANG: Just -- we just want to reserve because we conferred already. We're not even sure which ones they've taken out or went in. It's the demonstratives.

THE COURT: All right.

MS. WU: Oh, actually, I think my colleague has already removed the objected to ones so --

THE COURT: You may proceed. Yes.

BY MS. WU:

Q. Dr. Nuckolls, can you tell us what underlying information you looked at to evaluate the epi-impurity?

A. So, it's shown on this slide, but it's contained in PDX 2.12.17. Do you -- would you like for me to read each of these?

11:00:43 MS. WU: Your Honor, should he go ahead and do
11:00:45 that or can we admit it?
11:00:47 THE COURT: It's up to you. You know, for my
11:00:50 purposes, if he says I looked at ten of them and talks about
11:00:54 them and they all the show the same thing, it's this, he
11:00:56 doesn't have to be better, but it's your case.
11:00:58 BY MS. WU:
11:00:59 Q. I think for just for the record, Dr. Nuckolls, if you
11:01:01 could read in the PTX so we have them in the record.
11:01:04 A. Okay. So you want me to read the batch number and
11:01:09 the associated PTX numbers?
11:01:10 Q. Yes, if you could.
11:01:11 A. Okay. So TN118F010, PTX 1175 at 537, PTX 1172 at
11:01:23 686, PTX 1170 at 770, PTX 1169 at 819.
11:01:30 For TN118H010, PTX 1546 at 288, PTX 1548 at 638,
11:01:39 PTX 1550 at 279, PTX 1544 at 136.
11:01:45 TN118K010, PTX 1185 27, PTX 1187 at 479, PTX
11:01:57 1189 at 562, PTX 1191 at 178.
11:02:02 TN119C010, PTX 988 and PTX 989, PTX 997, PTX
11:02:13 999, PTX 991, PTX 119D010, PTX990, PTX 989, PTX 998, PTX
11:02:26 1,001, PTX 1228 at 704.
11:02:29 TN119E010, PTX 990, PTX 789, PTX 805, PTX 814,
11:02:38 PTX 795.
11:02:40 TN109J 010, PTX 789, PTX 790, PTX 806, PTX 815,
11:02:49 PTX 796.

11:02:50 TN120C010, PTX 1177, PTX 1202, PTX 1179 at
11:03:00 612 -- oh, I think I missed. Sorry back up.
11:03:03 PTX 1177 at 995, PTX 1202 at 806, PTX 1179 at
11:03:09 612, PTX 1181 at 721, PTX 1183 at 812, PTX 1202 at 806, PTX
11:03:19 730 at 161, PTX 1205 at 346, PTX 1207 at 435, PTX 1209 at
11:03:27 416, PTX 730 at 161, PTX 1197 at 808, PTX 1199 at 33, PTX
11:03:37 766 at 125, and PTX 11 especial 92 at 924.
11:03:44 Q. Thank you so much. I wanted to avoid the situation,
11:03:46 but I, unfortunately, failed. Thank you, Dr. Nuckolls.
11:03:49 If we could move onto Claim 1. Can you explain
11:03:58 whether or not Liquidia infringes the impurities
11:04:01 limitations?
11:04:02 A. Yes, I can. And the way the claim is written, we're
11:04:06 going to start at the bottom, so it says where alkylation is
11:04:09 alkylation of the benzindene triol shown in the red
11:04:12 rectangle. That's Step 10 of the Yonsung process where BTO
11:04:18 or the benzindene triol is alkylated to form TN01.
11:04:23 And then from there, it says providing a
11:04:25 starting batch of Treprostinil having one or more impurities
11:04:28 resulting from prior alkylation and hydrolysis. This is the
11:04:32 starting batch in our percent impurities analysis showing
11:04:36 that those are reduced and also in a number of impurities
11:04:40 analysis and also in the -- in the epimer -- in the epimer
11:04:45 analysis that I just went through showing that the level of
11:04:47 one or more impurities found in the starting batch of

11:04:50 Treprostinil, which is the TN02, is lower in the
11:04:55 pharmaceutical composition.
11:04:59 Q. Does Liquidia's pharmaceutical composition meet the
11:05:02 limitations referencing Treprostinil salt?
11:05:05 A. Yes, it does. If you go to the next -- the next
11:05:10 slide, so the starting batch of Treprostinil shown in the
11:05:15 red rectangle here, highlighted and corresponding to the red
11:05:20 rectangle in the claim limitation, is treated with a base in
11:05:22 the purple rectangle. Sodium hydroxide to form Treprostinil
11:05:26 sodium. And that isolate -- that material is isolated, and
11:05:30 you can see that from the DMF and the steps D, E, F in the
11:05:35 yellow -- yellow or orange rectangle.
11:05:38 Q. Where did you find the information about the
11:05:40 isolation steps?
11:05:40 A. So, this is in PTX 201 at Page 519 and 548.
11:05:46 Q. Does Liquidia's pharmaceutical composition meet the
11:05:48 limitations referencing a pharmaceutical composition?
11:05:50 A. Yes, it does. If you go to the next slide, this
11:05:56 shows the -- this shows material from Liquidia's NDA
11:06:03 Section 2.3.P which shows that Liquidia 861, which is the
11:06:10 bulk inhalation powder, is one of the ingredients listed in
11:06:13 the composition of the drug product.
11:06:19 Q. Let's move on to -- actually, where did you find the
11:06:22 information about the drug product composition?
11:06:24 A. That's in PTX 20 at 588.

11:06:28 Q. Let's move on to Claim 2. What does that claim require?

11:06:30 A. So, that requires that the material is isolated in crystalline form and in Yonsung's material safety data sheet shown in the red rectangle, they describe it as a crystalline solid, and multiple times throughout Yonsung's DMF they refer to recrystallization, which would imply that the product is crystalline.

11:06:50 Q. Where did you find Yonsung's material safety data sheets?

11:06:53 A. That's PTX 104 at Page 177.

11:06:57 Q. What does Claim 3 -- I'm sorry. What does Claim 3 require?

11:07:01 A. Go up to the next slide. It requires that you select a base from the group that's listed, and one of those in that group in the -- is -- your purple rectangle is sodium, and they use sodium hydroxide to treat the starting batch of Treprostinil to make Treprostinil sodium. So they -- and you can see this also in their DMF, so you can see that they use -- they use sodium -- they make the sodium salt of Treprostinil.

11:07:25 Q. Let's move on to Claim 6. What does that claim require?

11:07:29 A. So Claim 6 requires that you can store the isolated salt at ambient temperature.

11:07:36 Q. Have you prepared a demonstrative of how that works?
11:07:40 A. Yes, I have. So, if you go to the next slide.
11:07:45 So, when the -- at Yonsung, when they -- when
11:07:51 they make the material, they isolate the -- they isolate the
11:07:55 API, the Treprostinil sodium, and then that material
11:07:59 throughout various time points is stored. And then up until
11:08:03 they make the stock solution of at Liquidia to begin the
11:08:07 PRINT process, there are various time points at which the
11:08:09 isolated salt is stored at ambient temperature.
11:08:12 Q. Do you -- do you understand that the Court has
11:08:13 construed the term "ambient temperature"?
11:08:15 A. Yes, I do.
11:08:16 Q. What is your understanding of that construction?
11:08:18 A. Of 15 to 30 degrees Celsius.
11:08:21 Q. Did you apply that construction in your analysis?
11:08:23 A. Yes, I did.
11:08:26 Q. Is Yonsung's Treprostinil sodium stable at ambient
11:08:30 temperature?
11:08:31 A. Yes, it is. If you go to the next slide, what you
11:08:35 see here is stability studies that were -- that are
11:08:38 performed in Yonsung's DMF. And what you see is that at
11:08:43 25 degrees Celsius, the material is stable for at least
11:08:47 6 months with no sign of any degradation at 25 degrees C.
11:08:51 Moreover, it was stable for at least three weeks when they
11:08:56 did a higher temperature study at 75 degrees C, and you can

11:08:59 see that in the highlighted sections of the DMF and
11:09:02 summarized in the tables on the left. This can be found at
11:09:05 PTX 112 pages 526, 530 and 532.
11:09:10 Q. Is isolated Treprostinil salt stored at ambient
11:09:14 temperature?
11:09:14 A. There's several points in the process where the
11:09:18 isolated Treprostinil salt is stored in ambient temperature,
11:09:21 yes.
11:09:22 Q. Can you walk us through those.
11:09:23 A. Sure. If you go to the next slide, there are three
11:09:28 places where there's significance storage of the material at
11:09:32 ambient temperature. One of them has to do with
11:09:34 Treprostinil sodium when it's -- after it's -- after it's
11:09:38 finished in the synthesis lab and is awaiting approval into
11:09:42 the warehouse. Another is when the material is stored at
11:09:46 ambient temperature during shipping from the Yonsung to
11:09:50 either LGM or Liquidia. And then the final time at which
11:09:53 the material is stored at ambient temperature is when the
11:09:57 Treprostinil sodium is placed in the dry box awaiting the
11:10:00 first step of the print process at Liquidia.
11:10:03 Q. So let's take each in turn. Can you describe in
11:10:06 further detail the first example.
11:10:07 A. Yes, if you go to the next slide, it will show the
11:10:10 first example, and this shows the procedure from the batch
11:10:15 production record that was followed. And when the

material -- when they -- when they finish making the material and they place it into a -- what's referred to as a storage container, that material awaits acceptance into the warehouse. And that period of time was, you know, was a considerable amount of time that that material would have been held at what appears to be at ambient temperature, which is about 43 days, between it being produced and then placed into the getting acceptance into the warehouse.

Q. How do you --

MR. SUKDUANG: Your Honor, we just recognized in this demonstrative there's a mistranslation. There's missing something in Step 5 that should be in parens.

MS. WU: I don't think this is an incorrect translation. I think we've checked this.

BY MS. WU:

Q. How do you know that the isolated salt is stored at ambient temperature?

A. Well, there's nothing that says it's not stored in -- at ambient temperature, and a POSA would understand if you don't indicate a particular temperature, then it would be stored at ambient temperature.

Q. Where did you find the information about these steps in Yonsung's process?

A. That's PTX 1409 at pages 407, 408, and 428.

Q. Can you walk us through your next example of storage.

11:11:31 A. Yes. So if you go to the next slide, that's storage
11:11:35 during shipping, and what I'm showing you here is a data log
11:11:39 that was placed in with the -- in with the material when it
11:11:42 was shipped, and there were three batches that were included
11:11:44 in the shipment: TN120C010, TN0120G010, and TN120I010.
11:11:55 Those were all three placed in the shame shipper in the same
11:11:58 Box, and they included a data logger in this box and -- and
11:12:03 it shows that the materials was at -- in the zone, which is
11:12:09 this blue rectangle, at ambient temperature for -- for about
11:12:13 nine days while it was being shipped.
11:12:16 Q. Where did you gets this information about the
11:12:18 temperature logger?
11:12:19 A. That's PTX 19 at Page 158 and 162.
11:12:24 Q. Are there any instances of storage at ambient
11:12:27 temperature during shipment?
11:12:28 A. Yes, there are. If you go to the next slide, these
11:12:31 three batches, TN116J010 and TN117K010 and TN 117I010, you
11:12:39 can see that this material at the start of the shipping
11:12:43 process, when the data logger was put in there, and for the
11:12:46 last part of it, it was clearly still at ambient
11:12:50 temperature. It was only briefly, actually, at 2 to 8 for
11:12:54 any period of the shipment.
11:12:55 Q. Where did you fine the information on -- of these
11:12:58 temperatures?
11:12:58 A. That's at PTX -- that's at PTX 117, Page 862 and 863,

and PTX 20 at Page 672.

Q. What is the significance, if any, of these batches?

A. Well, so for the three batches I just described, those were used for Phase III clinical trials and for primary stability studies. So it's significant that if you couldn't store -- if the material was not stable and able to be stored at ambient temperature, you would never use these batches for Phase III clinical trials or for primary stability studies.

THE COURT: Excuse me. Doctor, for the third thing there that you have up on the slide, how long a time period is it that is in the ambient temperature range?

THE WITNESS: At the end of the shipping, that's -- the particular marks at the bottom are in days. So that's about one day.

THE COURT: Okay. Thank you.

BY MS. WU:

Q. What other shipment records, if any, did you review?

A. If you go to the next slide --

MS. WU: Your Honor, I withdraw the question.

BY MS. WU:

Q. Does Liquidia store isolated Treprostinil salt at ambient temperature?

A. If you go to the next slide, please. So at the -- at Liquidia, when they -- they take the material and they put

it into the dry box, that's stored there for about three hours before it begins the first step of the print process, which is adding it to the stock bottle, so that's on the order of about three hours that it's stored at ambient temperature.

Q. Where did you find this information?

A. That's at PTX 70 at Page 51 to 57.

Q. Does Liquidia's pharmaceutical composition meet the storage at ambient temperature limitation of the isolated salts of Claim 6?

A. Yes. If you go to the next slide, so at those three time points, when it's awaiting acceptance into the warehouse, during shipment, during shipping, and also during -- awaiting the first step of the PRINT process in the dry box, the material is kept at ambient temperature.

Q. Let's go on to Claim 8. Can you describe the differences, if any, between what's required by Claim 6 as opposed to Claim 8?

A. So, Claim 8 refers to a pharmaceutical product, and so that would be the finished product. And it requires that the -- that the Treprostinil salt does not necessarily have to be the isolated Treprostinil salt, but it can be stored at ambient temperature as well, so this would include all of the storage that I just described to you, but it would also include storage when this material is mixed with other

11:15:50 excipients and other ingredients in the final drug product,
11:15:54 the LIQ 861 that is, ultimately, prepared in the last two
11:15:57 steps at Lonza and Xcelience.
11:16:01 Q. I also see -- I also see that the claim requires a
11:16:05 process for preparing a pharmaceutical product. Can you
11:16:08 explain what that means to a POSA.
11:16:11 A. Yes, so that's -- the claim requires that you
11:16:16 alkylate -- you alkylate a triol in a medium of that formula
11:16:20 and hydrolyze that compound to form Treprostinil, and we
11:16:23 went through that earlier today. That's Yonsung's process.
11:16:27 Q. What do you consider to be the pharmaceutical product
11:16:30 in this case?
11:16:30 A. So, the pharmaceutical product, I think, would be the
11:16:34 LIQ 861, the drug product after it's been packaged and
11:16:38 prepared and ready to be sold.
11:16:40 Q. Does Liquidia storage Treprostinil salt at ambient
11:16:44 temperature?
11:16:44 A. Yes, they do, if you go to the next slide. So, at
11:16:51 three points during -- in Liquidia' NDA, they mention that
11:16:57 the material is kept between 18 degrees and 24 degrees. And
11:17:04 the procedure is outlined in there in their NDA between
11:17:10 steps -- between print Step 1 and print Step 2, that
11:17:14 material is held at ambient temperature for no more than
11:17:18 71 hours. Between print Step 2 and print Step 3, that
11:17:21 material is held at ambient temperature for no more than

18 hours. And then between print Step 3 and print Step 4, that material is held for no more than 88 hours. So those are times at which the material is being stored. At ambient temperature.

Q. Where did you find this information?

A. That's at PTX 74 at Page 550 to a 553.

Q. Can you explain how Liquidia and Yonsung practice the process of Claim 8?

A. Yeah, so if you go to the next slide, so, there -- they are -- they're alkylating and hydrolyzing in Step 10 and 11 at Yonsung, so alkylating and hydrolyzing BTO or the benzindene triol, so that satisfies the first two claim limitations.

If you go to the next slide, the material -- they form a stable salt of it at ambient temperature, and you see that because in their stability studies, they show that the material is stable at 25 degrees for at least six months.

If you go to the next slide, they show that the material can be stored at ambient temperature at all of the points I described for the isolated salt, but also for the Treprostinil salt when it's being mixed with the other ingredients involved with the print process.

And if you go to the next slide, you can see from the ingredient list that the pharmaceutical product in

the red rectangle, steps 5 and 6 of the print process, refer to that as the drug product, which is equivalent to the pharmaceutical product. And that pharmaceutical product comprises Treprostinil, and you can see the Treprostinil sodium is an ingredient in the -- in the ingredient list for the drug product.

Q. Where did you find the information about the manufacturing process steps?

A. That's at PTX 74 at Page 550 and PTX 230 at Page 588.

Q. Let's move on to the last asserted claim. Does Liquidia satisfy this claim?

A. This is -- requires that a pharmaceutical product prepared by the process of Claim 8. And clearly, they're making a drug product or pharmaceutical product because that's the final material that's finished at Lonza or Xcelience in Florida for -- to finish the print process.

MS. WU: I pass the witness.

THE COURT: Okay. Thank you, Ms. Wu.

MR. SUKDUANG: I'm just going to get some binders, Your Honor.

THE COURT: Sure.

MR. SUKDUANG: May I approach?

THE COURT: Sure.

CROSS-EXAMINATION

BY MR. SUKDUANG:

11:21:09 Q. Hello, Dr. Nuckolls. How are you?
11:21:10 A. I'm doing all right.
11:21:11 Q. My name is Sanya Sukduang. Nice to meet you.
11:21:14 A. Nice to meet you, too.
11:21:14 Q. Did my co-counsel bring a binder up to you?
11:21:16 A. I have it here, yes.
11:21:17 Q. Dr. Nuckolls, can you go to JTX 2, which is the '066 patent in the claims, and it will come up on the screen for you.
11:21:24 A. I'm there.
11:22:05 (Discussion held off the record.)
11:22:05 BY MR. SUKDUANG:
11:22:20 Q. Well, I can ask these questions while this is coming up. Can you can turn to Claim 1 at the end, Dr. Nuckolls, of JTX 2. Let me know when you are there.
11:22:34 Are you there?
11:22:35 A. Yes, I'm' there.
11:22:36 Q. Now, Claim 1 requires a pharmaceutical composition comprising Treprostinil or Treprostinil salt; is that correct?
11:22:43 A. Yes, that's correct.
11:22:45 Q. And so, Claim 1, the pharmaceutical composition can just be Treprostinil for that; is that right?
11:22:49 A. It could be Treprostinil or the pharmaceutically acceptable excuse me salt there.
11:22:53
11:22:57

11:22:59 Q. Correct. And one of them could just be Treprostinil;
11:23:02 correct, not the pharmaceutically acceptable salt?
11:23:06 A. What the language says is that the pharmaceutical
11:23:09 composition can comprise Treprostinil or a pharmaceutically
11:23:12 acceptable salt thereof.
11:23:13 Q. And that "or" you understand to be optional; correct?
11:23:17 A. It could be either Treprostinil or pharmaceutically
11:23:19 acceptable salt thereof.
11:23:20 Q. So the pharmaceutical composition could just be
11:23:22 Treprostinil; correct?
11:23:23 A. In my -- in my opinion, the pharmaceutical
11:23:27 composition is either the isolated Treprostinil salt or the
11:23:34 LIQ 861 powder that's prepared at Liquidia.
11:23:37 Q. So in your opinion, the pharmaceutical composition of
11:23:39 Claim 1 cannot be Treprostinil free acid?
11:23:42 A. I'm referring to the -- to the Liquidia process, but
11:23:47 the claim language requires -- says that it could be either
11:23:50 Treprostinil or a pharmaceutically acceptable salt thereof.
11:23:52 Q. Claim 1 doesn't require any specific purity profile,
11:23:55 does it?
11:23:56 A. Well, it requires that you have one or more
11:24:00 impurities that result from the prior alkylation and
11:24:06 hydrolysis steps that are reduced in the final salt
11:24:10 formation.
11:24:10 Q. But the final product, the pharmaceutical composition

that can be Treprostinil, or a pharmaceutically acceptable salt of Treprostinil, that doesn't require any specific level of purity; correct?

A. As long as impurities that were generated in the alkylation and hydrolysis steps were reduced. That's what the claim requires.

Q. And the claim doesn't require the -- doesn't tell you how much the reduction between the starting batch and the pharmaceutical composition needs to be; correct?

A. It specifies that one or more of the impurities that resulted from the prior alkylation and hydrolysis steps were reduced in the final -- in the final product.

Q. That statement does not identify the amount of reduction, does it; correct?

A. I guess it identifies a number of reduction in the sense that it says one or more impurities from those prior steps were reduced in the prior product.

Q. Does it have to be reduced by 50 percent?

A. Just one or more impurities need to be reduced. There's no percentage mentioned in Claim 1.

Q. So Claim 1, with respect to the reduction, you agree that there's no specific percentage of reduction identified in Claim 1?

A. It just requires that one or more impurities are reduced.

11:25:27 Q. In your opinion, does any amount of reduction meet
11:25:31 Claim 1?
11:25:32 A. So, I think a POSA would understand that as -- when
11:25:38 you're looking at your impurity profile in a particular
11:25:41 reaction, if you've built up impurities from the alkylation
11:25:45 and hydrolysis steps, those impurities would then be reduced
11:25:48 in the final salt formation. That would satisfy this claim.
11:25:52 Q. So let me ask you more specifically. Does your --
11:25:54 does Claim 1, in your opinion, require any -- let me
11:25:59 rephrase.
11:25:59 In your opinion, Claim 1 would permit any
11:26:02 reduction in impurities from the starting material, the
11:26:06 starting batch, to the pharmaceutical composition?
11:26:12 A. In -- it's difficult to say. In an actual example,
11:26:22 which are the ones that I looked at in the batch production
11:26:25 records, you could see significant either numbers or
11:26:28 percents of impurities that were increased in the alkylation
11:26:31 and hydrolysis steps and then, ultimately, these -- those
11:26:33 were reduced in the salt formation.
11:26:34 Q. My question is: With respect to Claim 1, your
11:26:39 opinion is that any amount of reduction between the
11:26:44 impurities from alkylation and hydrolysis in the starting
11:26:46 batch compared in the pharmaceutical composition would carry
11:26:51 at any level, no matter how small?
11:26:53 A. As long as that starting batch of Treprostinil has

11:26:56 one or more impurities that result from the alkylation or
11:26:59 hydrolysis steps that are reduced, that would satisfy
11:27:01 Claim 1.
11:27:03 Q. Does your opinion require an actual reduction in
11:27:09 impurities or just a numerical reduction in impurities?
11:27:13 A. Well, what I saw through the data was that there was
11:27:17 a percent reduction. There was a number reduction. And
11:27:20 there was a specific impurity reduction. And those
11:27:24 satisfied the claims.
11:27:27 Q. So, again, I'm asking you: With respect to the
11:27:29 claims, does this claim require an actual reduction in
11:27:34 impurities or just a numerical -- something that looks
11:27:39 numerically?
11:27:39 A. You have to reduce the -- you have to reduce the
11:27:42 impurities to satisfy the claim.
11:27:44 Q. So an actual reduction, not just a numerical
11:27:47 reduction?
11:27:47 A. I'm not entirely sure if I understand what you mean
11:27:49 by "a numerical reduction."
11:27:51 Q. Can you look at -- well, you understand that you
11:27:55 discussed HPLC; correct?
11:27:57 A. Yes, I did.
11:27:57 Q. And you understand HPLC is an analytical method
11:28:00 conducted by humans; correct?
11:28:02 A. Yes, it is.

11:28:03 Q. And you understand that a human, when conducting HPLC
11:28:08 can run HPLC on the same batch of material and get slightly
11:28:13 different numbers; correct?
11:28:14 A. Yes, and that's why, in our analysis, what I would do
11:28:20 is take a self-consistent batch that had HPLC data run on
11:28:25 the same instrument or run in the same procedure at the same
11:28:28 place and not look at data that was from multiple labs at
11:28:31 different time points.
11:28:32 Q. So then my question, going back to Claim 1, with the
11:28:34 understanding that there's natural variation and error in an
11:28:39 HPLC analysis, in your opinion, does Claim 1 require actual
11:28:43 reduction in impurities or just a numerical reduction based
11:28:46 on an HPLC?
11:28:48 A. Well, there were three different analyses that we
11:28:53 did.
11:28:53 Q. I understand. My question is not the analysis you
11:28:55 did. My question is: When you looked at this claim, you
11:28:59 had to understand what this claim meant in order to apply it
11:29:02 to the opinions you're offering, so my question to you is
11:29:05 specifically to the claim. Do you understand that?
11:29:06 A. Yes, I do.
11:29:08 Q. So my question with respect to the claim,
11:29:12 understanding the nature of HPLC and the error involved,
11:29:16 does Claim 1 require an actual reduction in impurities or
11:29:21 just something that looks numerically different on HPLC?

11:29:25 A. It requires an actual reduction in impurities.
11:29:34 Q. When you looked at total impurities, you did not
11:29:37 determine which specific impurities fell within the umbrella
11:29:41 of total impurities, did you?
11:29:43 A. I'm not entirely sure. Can you ask your question
11:29:48 again. I don't think I understand that question.
11:29:50 Q. Sure. You can have impurities that you can actually
11:29:53 characterize and identify what they are by name; correct?
11:29:55 A. For example, like the epimer that we identified.
11:30:00 Yes.
11:30:00 Q. Sure.
11:30:01 With respect to total impurities, you do not
11:30:03 identify any specific impurity by characterization or name,
11:30:08 did you?
11:30:08 A. So, within the total impurities profile, the epimer
11:30:12 would be included in that.
11:30:14 Q. Okay. And we'll get to that, but other than the
11:30:16 epimer, the 15 epimer, that you talked about, other than
11:30:20 that impurity, there was other total impurities that you
11:30:23 showed in your charts. You didn't identify or you could not
11:30:27 tell what those impurities were by characterization or name,
11:30:30 could you?
11:30:30 A. Well, the -- it's a little bit difficult. So the
11:30:35 POSA would understand that those impurities that were
11:30:37 present in those samples were the result of the alkylation

11:30:41 and hydrolysis steps because they were generated in those
11:30:44 steps. It's actually unusual for a practitioner to know the
11:30:49 identity of the impurities in an organic reaction. It's
11:30:53 more unusual.
11:30:54 The actual way in which a typical practitioner
11:30:57 would work is that they would they would see that they have
11:31:00 impurities that were generated in a particular step. They
11:31:04 may not necessarily know the identities of them, but they
11:31:06 know they were generated in that step, and then they would
11:31:09 find a method to reduce those impurities.
11:31:12 Q. Can you go to your demonstrative PDX 2.9.
11:31:18 A. I'm sorry. I didn't hear. PD?
11:31:20 Q. It will come up on the screen. It will be your
11:31:23 demonstrative PDX 2.9. So you relied on this demonstrative;
11:31:27 is that correct, Dr. Nuckolls?
11:31:29 A. Yes.
11:31:29 Q. And this is your explanation of Yonsung's synthesis
11:31:32 from Step 10 to Step 12 from TN01 all the way to salt
11:31:36 formation; correct?
11:31:37 A. Yes, that's correct.
11:31:38 Q. Now, you added material to what Yonsung actually put
11:31:44 in their DMF; correct? You added words that do not appear
11:31:47 in Yonsung's DMF?
11:31:49 A. Yes.
11:31:49 Q. Particularly the BTO plus impurities, you added that;

11:31:52 correct?
11:31:52 A. Right. I -- and I think I said that in my -- in my
11:31:56 direct testimony, that the plus impurities was added to show
11:32:00 that no material is actually a hundred percent pure and
11:32:02 there would be impurities that would be, for example, in the
11:32:05 starting batch that would be -- that would be -- there would
11:32:08 be impurities that would be generated in the alkylation.
11:32:11 There would be impurities that would be generated in the
11:32:14 hydrolysis step, and there would also be impurities in the
11:32:16 starting material for that which, would be the TN01 and so
11:32:20 and so forth.
11:32:22 Q. So there are compounds within BTO that are not BTO;
11:32:24 correct?
11:32:27 Let me be more precise. 15-epi-BTO, which is
11:32:31 something you spoke about in your direct testimony; correct?
11:32:33 A. Yes.
11:32:34 Q. 15-epi-BTO, your opinion is, can be found as an
11:32:38 impurity in BTO; correct?
11:32:40 A. I don't recall if that was universally true, but in
11:32:46 many, many samples of BTO, if not all of them, there was --
11:32:51 there was 15-epi-BTO in those samples.
11:32:52 Q. And 15-epi-BTO is different from BTO, isn't it?
11:32:57 A. Well, it's -- it's a little bit of a -- you have to
11:33:04 think about it in a way that a POSA would think about it.
11:33:06 BTO here is referring to probably a batch of BTO. And that

batch of BTO would have its associated impurities, which would be 15 epi. But the actual molecule BTO, which is shown in a chemical structure here, is different in the configuration of those -- of one of those carbon atoms within that structure.

Q. So within the batch of BTO, you would agree that there are lots of molecules of BTO and lots of molecules of a different compound, 15-epi-BTO?

A. The batch would -- the batch would comprise BTO plus 15-epi-BTO in most if not all of the cases.

Q. Right. And so, the batch -- with respect to your term impurities, this batch of BTO would include molecules of BTO plus molecules of a different compound, 15-epi-BTO, and molecules of completely -- other types of impurities that you haven't specifically addressed with respect to the batch of BTO; correct?

A. So, the batch of BTO could contain a number of impurities, and that would be contained in that number of impurities analysis that I did. You would see -- if you looked at the BTO samples, you would see how many impurities were in BTO, for example, and one of those impurities in the batch of BTO that the practitioner would know would be included in BTO would be the 15-epi-BTO.

Q. So with respect to the batch of BTO, you've got a bunch of different compounds that undergo alkylation;

11:34:33 correct?
11:34:34 A. So, the alkylation step is the reaction of the batch
11:34:40 of BTO with the alkylating agent, which in this case is the
11:34:45 alpha bromo methyl acetate.
11:34:47 Q. It's not just the batch of BTO. It's the batch of
11:34:49 BTO with BTO molecules plus a whole bunch of different
11:34:52 molecule compounds within that batch?
11:34:54 A. Not entirely comfortable with the "whole bunch of
11:34:57 other molecules" statement. But the BTO plus its -- plus
11:35:02 the associated impurities that they would -- the related
11:35:08 substance impurities, those would then go into the
11:35:10 alkylation step to produce the alkylated product, which is
11:35:15 TN01.
11:35:16 Q. So in Step 10 under your analysis, BTO undergoes
11:35:20 alkylation; correct?
11:35:21 A. The batch of BTO undergoes the alkylation.
11:35:25 Q. And the different compound 15-epi-BTO would also
11:35:28 undergo alkylation; correct?
11:35:30 A. Well, that was in the batch of BTO that I referred to
11:35:32 in the previous answer.
11:35:33 Q. So is that yes, that the different compound 15 BTO
11:35:36 would undergo alkylation?
11:35:38 A. So yes, 15 epi -- 15-epi-BTO would also be alkylated
11:35:43 in that. In that because it's with -- assuming it's within
11:35:46 the batch of BTO.

11:35:47 Q. And these other impurities that you have under your
11:35:50 red here but don't specifically identify, those other
11:35:53 impurities, those other compounds also undergo alkylation in
11:35:58 Step 10; is that correct?
11:35:59 A. They would be -- they would be part of the -- they
11:36:03 would be part of the impurity profile within that alkylation
11:36:06 step.
11:36:08 Q. My question is very specific. The impurities that
11:36:12 are in the batch of BTO that you identified without name,
11:36:18 they undergo alkylation in Step 10 as well?
11:36:22 A. It would -- it would depend on the natures of those
11:36:26 impurities whether or not they would undergo alkylation or
11:36:28 not.
11:36:29 Q. Some of them would?
11:36:30 A. It's possible that they could.
11:36:34 Q. And if -- if 15-epi-BTO and some of these impurities
11:36:38 that could undergo alkylation in Step 10 actually undergo
11:36:43 alkylation, that could result in additional impurities which
11:36:46 you've identified next to TN01 plus impurities; correct?
11:36:51 A. So, those would be -- so the materials that result
11:36:56 after that step when that material is -- after it has been
11:37:00 isolated, there would be an impurity profile, and that
11:37:04 impurity profile would be the profile of the impurities
11:37:08 generated in the alkylation step.
11:37:10 Q. The impurities generated by alkylating 15-epi-BTO and

these other impurities that are not BTO.

A. They would -- they're referred to as related substance impurities, so the related substance impurities that are included in the batch of BTO would also be there as a product of the -- of the alkylation step or some other pathways, they would end up as impurities in the -- in the TN01.

Q. Now, you also understand that within the Step 10 of Yonsung's process, Yonsung performs column chromatography?

A. Yes. So that's at the end of the -- after the reactions -- after they've concluded -- after they've concluded that the reaction is finished, that it's gone to what they consider completion, they'll take that material, and they will then -- once they've concluded it's finished, they will then run -- they will then do column chromatography on that material and isolate on that material along with some associated impurities.

Q. And that column chromatography, it is a purification step; correct?

A. It is, yes.

Q. And so between alkylation and hydrolysis, Yonsung performs a purification step that is not purification by salt formation; isn't that correct?

A. The claim language is a comprising claim. There's nothing that says you can't include a column chromatography

11:38:40 step.
11:38:41 Q. I understand your opinion. My question relates now
11:38:44 to what I said, the process. Yonsung's process includes a
11:38:50 column chromatography purification step between 10 and 11
11:38:55 that is not purification by salt formation?
11:38:59 A. It's not exactly between Step 10 and 11. It's the
11:39:02 last part of Step 10. They run a column chromatography to
11:39:07 generate the batch of TN01 and its associated impurities.
11:39:12 Q. And that -- thank you for that clarification. So at
11:39:16 the end of Step 10, Yonsung performs a column chromatography
11:39:21 step that purifies TN01, and that column chromatography
11:39:26 purification is different from purification by salt
11:39:30 formation?
11:39:30 A. Column chromatography is different than salt
11:39:35 formation, and they perform that step -- they perform that
11:39:40 operation at the end of Step 10.
11:39:44 Q. Now, you analyzed three validation batches for
11:39:50 Yonsung with respect to your total impurities analysis.
11:39:54 Isn't that right?
11:39:55 A. For the percentage impurities analysis, I analyzed
11:40:00 the three validation batches that were in their DMF.
11:40:03 Q. And I believe you testified that you look at those
11:40:05 validation batches because they were submitted in the DMF to
11:40:07 the FDA; is that right?
11:40:08 A. Yeah, those would seem like they're representative

batches that are very important because you can stand behind those numbers reporting to the FDA. That would seem like very important data to look at, so that's why I focused on those.

Q. And so very important data that they -- data that they submitted to the FDA that formed part of your analysis and I think it shows up on PDX 2.10. Okay.

Now, you testified just a moment ago that 15-epi-Treprostinil would be included in the total impurities correct?

A. Yes.

Q. Your demonstrative focuses on the total impurities. Do you see that?

A. In this demonstrative, I was focusing on the total impurities.

Q. So I'd like to look at a different demonstrative. Can you bring up your PDX?

So this is your demonstrative. And we looked at these very important validation batches that you pointed out, and you might be able to see better on your smaller screen. But with respect to 15-epi-BTO, which is a compound that you've testified is an impurity within BTO but different from it, it's detected in each of those three validation batches, isn't it?

A. So in the batch of BTO, each of those three

validation batches contain 15-epi-BTO, yes.

Q. And these are three separate batches of BTO; correct?

A. They're -- the batch numbers are above. So, yes those are three separate batches.

Q. Okay. Now, and each batch has 0.07 percent of 15-epi-BTO; correct?

A. That's what they reported, yes.

Q. And that's a pretty small amount, isn't it? It's less than .1 percent?

A. That number is less than .1 percent.

Q. Can we look at TN01? So if you look at TN01, which forms, in your opinion, after alkylation of the BTO in and all the compounds within BTO, you get this three batches that Yonsung identifies in its DMF; correct?

A. Yes, so for these three validation batches and for other ones I looked at, basically at the TN01 stage, the 15-epi-TN01 was not detected, I believe, in all of the batches I looked at.

Q. Right. So all three validation batches which represent, in your testimony, Yonsung's compound that they're going to make, epi -- 15-epi-TN01, which is the result of alkylation of 15-epi-BTO is not present, not detected?

A. Is was -- it was -- it was not detected. Still could be present in very small amounts.

11:42:58 Q. So it disappears?
11:42:59 A. No, it's just below their limit to be able to detect
11:43:03 it.
11:43:04 Q. So this limit of detection in HPLC that you talked
11:43:07 about; correct?
11:43:08 A. That -- this presumably is below their detection
11:43:12 limit because it says not detected.
11:43:15 Q. Can you go to TN02? Now, TN02 is formed when you
11:43:19 take TN01 and conduct hydrolysis of it to form TN02; is that
11:43:24 right?
11:43:24 A. So, you take the batch of TN01 and you hydrolyze that
11:43:29 to make what's known as the starting batch of Treprostinil
11:43:32 or TN02, yes.
11:43:34 Q. And that TN02 is the starting batch, as you've
11:43:40 interpreted Yonsung's process, overlaid with Claim 1;
11:43:45 correct?
11:43:45 A. So, the TN02 is the starting batch of Treprostinil,
11:43:50 yes.
11:43:51 Q. All right. And when you go to TN02, when you
11:43:56 hydrolyze BTO, you get -- excuse me. When you hydrolyze the
11:44:03 nitrile from TN01, you get Treprostinil, but if you take the
11:44:07 15-epi-TN01 and you perform hydrolysis on it, you're
11:44:11 supposed to obtain 15-epi-Treprostinil; correct?
11:44:15 A. I'm' sorry. I'm not following.
11:44:16 Q. 15-epi-Treprostinil is formed by hydrolyzing -- and

11:44:26 1 if we bring up TN02, TN01 -- 15-epi-Treprostinil is formed
11:44:33 2 by hydrolyzing 15-epi-TN01; is that right?
11:44:41 3 That's the process, the chemical process?
11:44:42 4 A. So the step to go from the alkylated material, TN01,
11:44:47 5 to TN02 is the hydrolysis step. I believe that answers your
11:44:52 6 question.
11:44:52 7 Q. And then with respect to 15-epi-TN01, so I'm focusing
11:44:55 8 on focusing on 15-epi-TN01, when you conduct hydrolysis, it
11:45:01 9 should form 15-epi-Treprostinil?
11:45:04 10 A. So, these were the three batches that I believe were
11:45:09 11 removed from my demonstrative because of the objection. But
11:45:12 12 the other batches that I -- the other batches that I showed,
11:45:16 13 all of those showed an increase in the 15-epi-Treprostinil.
11:45:19 14 Q. I --
11:45:19 15 A. -- in this case.
11:45:20 16 Q. I'm sorry.
11:45:20 17 A. They're not detected.
11:45:22 18 Q. I actually think these are the three batches that you
11:45:24 19 were actually permitted to testify about because you
11:45:26 20 testified about these.
11:45:27 21 A. Oh, okay.
11:45:27 22 Q. But it's not detected, correct, the
11:45:30 23 15-epi-Treprostinil in TN02?
11:45:31 24 A. In these three samples it's not, no.
11:45:33 25 Q. And 15-epi-TN01 is a compound that is different from

11:45:38 TN01, isn't it?
11:45:39 A. It would be part of the batch of TN01. It would be
11:45:44 considered as one of the impurities that would come along
11:45:46 with TN01.
11:45:47 Q. It's a different compound than TN01; correct?
11:45:51 A. One of the carbon centers has an inverted
11:45:53 configuration relative to TN01.
11:45:55 Q. Are you unable to say whether TN01 is a different
11:45:58 compound than 15-epi-TN01? Are you unable to say that?
11:46:02 A. I think I did just say that. I was just clarifying
11:46:05 that it's different in the sense that it has one of the
11:46:08 carbon atoms is inverted in the configuration, but it's part
11:46:11 of the batch of TN01.
11:46:13 Q. Now, can we bring those down and can we bring up the
11:46:16 final TN, Treprostinil sodium?
11:46:20 Now, this is the pharmaceutical composition
11:46:23 that -- from Yonsung's process that you've overlaid onto
11:46:28 Claim 1; correct?
11:46:29 A. Yes, you can refer to the isolated salt of
11:46:34 Treprostinil as a pharmaceutical composition or the bulk
11:46:40 powder LIQ 861 before it's been packaged as the
11:46:43 pharmaceutical composition. I think there's two different
11:46:45 ways to look at it, but yes.
11:46:50 Q. Did you look at impurities in the pharmaceutical
11:46:53 composition of LIQ 861 in your analysis?

11:46:55 A. No.
11:46:58 Q. So, now, again, with Treprostinil sodium, you wanted
11:47:02 to focus in on total impurities. But if you look at
11:47:05 15-epi-Treprostinil, it now is detected, isn't it?
11:47:10 A. So, in these three batches, these three batches, the
11:47:16 15-epi-Treprostinil, yes, it was increased. The level of
11:47:21 that was increased in the -- in the final one.
11:47:24 Q. And so when you look at the total process and
11:47:28 specifically with 15-epi-Treprostinil invalidation batches
11:47:32 which you testified represent Yonsung's product, the
11:47:36 15-epi-BTO shows up in the batch of BTO, but the
11:47:43 intermediate steps -- and you can bring that down -- the
11:47:45 intermediate steps have no 15 epi-impurity, no 15
11:47:52 epi-impurity, and then all of a sudden it shows up again in
11:47:55 the Treprostinil sodium; correct?
11:47:57 A. I mean, I'm not trying to quibble at -- they're not
11:48:01 detected in the intermediate, the TN01 and TN02. But also,
11:48:07 if you look at -- what I said was these were -- this was
11:48:11 data that Yonsung was representing to the FDA as
11:48:15 representative. But in nine other batches that I showed in
11:48:19 my demonstrative, there was another profile that occurred
11:48:23 where the epimer would be not detected in TN01, would
11:48:28 increase in TN02, and then be reduced in Treprostinil
11:48:33 sodium. So, these are three batches, and there were nine
11:48:37 others that show a different -- a different impurity profile

11:48:42 with respect to the epimer.
11:48:44 Q. And those other batches are not validation batches,
11:48:46 are they? These are the three validation batches that you
11:48:49 said were so important representing Yonsung's product?
11:48:52 A. These are the batches that Yonsung reported, but I
11:48:55 looked at -- all the batches I could get the data for, I
11:48:58 looked at. These are batches that they used in their -- in
11:49:01 their DMF.
11:49:03 Q. Can we go to your next demonstrative, PDX 2.11,
11:49:07 please? Just to repeat, PDX 2.11. No, P as in Peter.
11:49:42 Now, you relied on this demonstrative for,
11:49:45 again, the validation batches, the important batches in
11:49:48 Yonsung's DMF, for your analysis of total impurities; is
11:49:51 that correct?
11:49:52 A. So, these are the total percent impurities that were
11:49:56 in those three validation batches, yes.
11:49:59 Q. And with respect to the impurities in TN01 and TN02,
11:50:06 across all three batches, you have not identified where --
11:50:12 whether those impurities were generated from alkylation of
11:50:16 BTO or alkylation of a compound other than BTO, did you?
11:50:20 A. Well, a POSA would understand that the -- would
11:50:25 understand that the material -- that BTO is not an isolated
11:50:30 molecule of BTO. It's a batch of BTO. And so what would
11:50:34 happen is in the alkylation step, you would have a
11:50:36 particular impurity profile that would be generated in TN01

11:50:40 from the alkylation step, and you'd have a particular
11:50:44 alkylated -- you'd have a particular impurity profile that
11:50:46 would be generated in the hydrolysis step following on the
11:50:49 alkylation step. And then would you have an impurity
11:50:52 profile that would result from that final salt formation.
11:50:56 And the important point is what you see is that those
11:50:58 impurities, they go up and then they go down when you reach
11:51:01 the Treprostinil sodium salt formation.
11:51:04 Q. And my question was more specific. The total
11:51:08 impurities that you identify in TN01 and TN02 across all
11:51:12 three validation batches, you do not identify whether those
11:51:16 impurities come from alkylation of BTO itself or alkylation
11:51:21 of a compound other than BTO within the batch?
11:51:25 A. Yeah, I just don't. I don't think that's the way
11:51:28 that a POSA would think about this. Right. I think they
11:51:31 would think about it as this is the impurity profile
11:51:34 generated through alkylation and hydrolysis, but they might
11:51:37 not necessarily know the absolute structure of those. But
11:51:42 if that was germane, if we had the samples, we could have
11:51:46 analyzed it and sorted out what those impurities were, but
11:51:49 we weren't provided with the samples.
11:51:50 Q. I understand that. When you look at the validation
11:51:54 batches for TN, and these are total impurities; is that
11:51:58 correct?
11:51:58 A. Those are the total percent impurities of related

substances.
Q. For each of those batches of TN, that's all just 15-epi-Treprostinil; isn't that right?
A. I believe that's the case. Yes.
Q. And that 15-epi-Treprostinil is derived from alkylating from the starting batch, starting material 15-epi-BTO?
A. I don't -- I can't -- I can't say that definitively because if you look at the other nine batches, what happened was -- is the -- at the TN01 stage, the amount of the epimer in TN01 went down to not detected. And then it increased in the next hydrolysis step. So what that tells me is that something in the hydrolysis step was causing this epimerization, at least in those other nine batches. I can't say in this case, but given the overwhelming evidence of those other batches, I would say that it may not only come from the starting epimer.
Q. Now, with respect to this epimer you talked about, you just mentioned the word epimerization; is that correct?
A. Yes.
Q. Epimerization is not alkylation, is it?
A. I don't think a POSA would think that epimerization is alkylation.
Q. And epimerization is not hydrolysis, is it?
A. It could be -- it would a POSA would understand that

that potentially could be an impurity that could be generated in those types of reactions, but it would not be considered a hydrolysis reaction.

Q. So epimerization is not a hydrolysis reaction; correct?

A. I think that's fair to say.

Q. Right. Now, you discussed epimerization in your expert report, didn't you?

A. Yes.

Q. And you didn't cite any paper, published literature, that evidences epimerization of the type of compound that Treprostinil is; isn't that right?

A. Yeah, I was relying on Yonsung's data. And what I could show there was that they had not detected in many examples after the alkylation step, and then the material -- the epimer would re appear.

Q. But you're not aware of any paper in the published literature describing epimerization that could result in this flip of orientation we've talked about with the type of compound that Treprostinil is?

A. I didn't -- I didn't need such a paper for my analysis, so, no, I didn't -- I didn't look for it.

Q. And you relied on the Yonsung's data to support your epimerization theory; correct?

A. Well, that -- ultimately, we weren't provided the

samples. There was nothing left that we could do other than rely on the data that Yonsung produced.

Q. Now you had access to Yonsung's complete open and closed DMF; correct?

A. I'm not entirely sure if I understand what the term "open and closed DMF" means.

Q. Sure. I appreciate that. You had access to Yonsung's complete DMF; correct?

A. As far as I know, it was the complete DMF.

Q. And Yonsung conducted characterization studies of several of the impurities that are identified in their certificates of analysis; correct?

A. My understanding is that they had various impurities that they listed in their DMF, and they -- and I guess in some cases they looked for those, yes.

Q. And one of them was 15-epi-Treprostinil; correct? The -- one of the impurities you looked into?

A. Yes, in the final -- in the final Treprostinil sodium, they would look for the 15-epi-Treprostinil.

Q. And of all the data that you have from Yonsung and all the papers and their characterization, you didn't see anything where Yonsung concluded, as you've done, that epimerization was actual because of formation of 15-epi-Treprostinil in the final product when it's absent all the way through the process?

11:55:51 A. So, the -- the data in particular for those nine
11:55:55 batches I showed in my demonstrative, in those, it seems
11:55:59 like the only source of that that you could -- the only
11:56:02 conclusion you can draw is that if the epimer is absent in
11:56:07 the alkylated product, TN01, and then it -- it appears in
11:56:11 TN02 and then it's reduced in TN, it seems like the
11:56:14 alkylation -- the hydrolysis step was where the
11:56:17 epimerization occurred.
11:56:19 Q. Now, you testified that "not detected" doesn't mean
11:56:21 it's really not detected, that it really could be there?
11:56:25 A. Well, actually what I -- what I -- if I remember
11:56:28 right, what I said was you said that it was nothing, and I
11:56:31 said not detected doesn't mean nothing. It just means it
11:56:34 could be are a very low amount.
11:56:35 Q. Right so there could be 15-epi-BTO or
11:56:40 15-epi-Treprostinil or 15-epi-TN01 that could be throughout
11:56:41 this process, but the level of detection is too low -- the
11:56:45 amount is so small that it couldn't be detected; isn't that
11:56:47 right?
11:56:48 A. That's why I think -- that's why I think those other
11:56:51 nine batches are important; right? Because what they show
11:56:54 you is that it goes to low level of not detected in TN01.
11:56:57 And then you find that upon hydrolysis, you see that this
11:57:00 epimer appears or it's formed in that step. And then that
11:57:05 it's reduced in the final step.

11:57:07 Q. And so, another possibility of the formation of
11:57:11 15-epi-Treprostinil in the last batch when it doesn't appear
11:57:16 to be here through the process is not epimerization, but
11:57:21 just the level of detection and natural error in HPLC as you
11:57:27 conduct the studies?
11:57:28 A. I took Yonsung's data that they're reporting to the
11:57:31 FDA at face value because I think -- I think they would
11:57:34 probably want to stay up -- stand behind their data and say
11:57:37 that they believe in their data that they're reporting to
11:57:39 the FDA.
11:57:40 Q. Now, you took Yonsung's data at face value. Did you
11:57:42 not assess limit of detection or limit of quantification for
11:57:46 HPLC assays, did you, with respect to Yonsung?
11:57:48 A. I didn't necessarily need to. They were -- they were
11:57:51 identifying peaks in their -- in their HPLC chromatographs
11:57:55 that were above the detection limit, and so they -- so,
11:57:59 those piece peaks that they picked were peaks that they
11:58:03 identified.
11:58:05 Q. But again, just on so the record is clear, you didn't
11:58:07 find it necessary to consider level of detection or level
11:58:10 ever quantification for HPLC assays conducted by Yonsung?
11:58:14 A. It wasn't necessary for my analysis, no.
11:58:16 Q. Can you go to PDX 2.16. And this is another -- oh,
11:58:22 wrong graph.
11:58:23 This is another demonstrative you testified

11:58:24 about?
11:58:24 A. Yes.
11:58:28 Q. And I notice here that your title is
11:58:31 15-epi-Treprostinil Formed During Hydrolysis Step. But you
11:58:35 start not with BTO. You start with a different compound,
11:58:40 15-epi-BTO; isn't that right?
11:58:43 A. No. This is -- I think.
11:58:44 Q. Well, let me -- you start here with 15-epi-BTO in the
11:58:50 chart you testified about; correct?
11:58:52 A. I'm adjust going to try to explain what that is.
11:58:56 Q. You can explain after you answer my question. You
11:58:59 started here looking at 15-epi-BTO; correct?
11:59:04 A. That's the amount of 15-epi-BTO that Yonsung detected
11:59:10 in the BTO batch.
11:59:12 Q. Your chart, your demonstrative, then talks about what
11:59:15 happens when you alkylate 15-epi-BTO to get 15-epi-TN01;
11:59:22 correct?
11:59:22 A. No, that's not what the chart represents.
11:59:24 Q. Your chart doesn't mention that you're alkylating BTO
11:59:28 here. It's 15-epi-BTO that you're starting with.
11:59:31 A. No, that's the measured amount of 15-epi-BTO in BTO.
11:59:36 That's why the BTO is parens, and then when you do the
11:59:40 alkylation step, and after the isolation of TN01, you then
11:59:45 go in and look and see how much 15-epi-TN01 is in TN01, and
11:59:50 that's what the chart is representing.

11:59:51 And then for the next step, when you hydrolyze, that's the amount of 15-epi-Treprostinil that's in the TN02, and you see that it goes from zero up. And then if you track that particular impurity in that material, you see that, again, for all the batches that are on here except for three, that then goes down.

Q. But you don't have a chart that tracks 15-epi-Treprostinil where you discusses alkylation of BTO, hydrolysis of TN01 salt form to form TN02 and then salt formation to get TN. Your chart focuses on 15-epi-BTO.

A. Well, this was one specific impurity that -- it's one specific impurity that -- that Yonsung tracked. And so I'm -- these were read off of their -- off of their COAs, so this is one impurity that is found in those particular batches.

Q. Now, you said this is zero. But you identified it as not detected; correct?

A. I --

Q. And not detected doesn't mean zero; correct?

A. I misspoke when I said zero. It should have been not detected.

Q. And you said zero in your direct testimony, too, didn't you? Did you misstate there?

A. If I said zero, I meant to say not detected.

Q. Can you go to PDX 2.20.

12:01:39 And I want to focus in on the limitation of --
12:01:45 that you pointed to, pharmaceutical composition. You are
12:01:47 not pointing to Yonsung's Treprostinil sodium to support
12:01:53 this limitation, are you? You're pointing to Liquidia's
12:01:56 finished product?
12:01:56 A. I think in my report, I said that, you know, there's
12:02:01 two possibilities. You could either have the isolated
12:02:04 Treprostinil salt that Yonsung prepared and then when they
12:02:08 place it into a bottle and prepare it to send to Liquidia,
12:02:11 that could be the pharmaceutical composition. Or this could
12:02:14 be the pharmaceutical composition, which is everything up
12:02:16 until the -- everything up until they are ready to put it
12:02:21 into the stock bottle in Step 1 of the print process.
12:02:23 Q. And your analysis did not include a comparison of
12:02:28 impurities found in the pharmaceutical composition from
12:02:33 Liquidia that you point to compared to the starting batch of
12:02:39 Treprostinil sodium made -- excuse me. Treprostinil free
12:02:42 acid made by Yonsung, did you?
12:02:44 A. I missed that with the --
12:02:46 Q. Sure.
12:02:47 A. Can you just repeat it.
12:02:48 Q. Sure. Your analysis did not compare the starting
12:02:52 batch of Treprostinil made by Yonsung to the pharmaceutical
12:02:57 composition made by Liquidia in your opinion?
12:03:00 A. Well, when they make the pharmaceutical composition,

they mixed it with a number of excipients and other ingredients. So -- and without samples, it would be very hard to even do that analysis.

Q. You understand that UTC was provided samples of the drug product, weren't you?

A. I don't know if they were or not.

Q. They didn't tell you that?

A. No.

Q. If I don't have the -- if you didn't compare the purity profile of the pharmaceutical composition from Liquidia, how can you meet the limitation that the impurities found in the starting batch of Treprostinil is lower in the pharmaceutical composition?

A. Because that's the -- that's the bulk powder; right? And that material was the same bulk powder that was prepared at Yonsung. The same -- sorry. The same -- sorry. The same the isolated salt that's prepared at Yonsung.

Q. But you're not comparing isolated salt in Liquidia's. You're looking at the drug product. The drug product, you understand, is the formulated composition; correct?

A. So, the drug product is the material that was packaged and prepared in steps 5 and 6 of the print process. And the pharmaceutical composition is the -- is the -- can either be the isolated Treprostinil salt or it can be the mixture of the -- or it can be the mixture, the bulk powder

12:04:29 LIQ 861.
12:04:30 Q. And my question is simple. You didn't compare the
12:04:34 purity profile of the bulk powder to the starting batch of
12:04:37 Treprostinil, did you, the impurity profile?
12:04:42 The answer is either yes, I did, or no, I
12:04:44 didn't.
12:04:44 A. Ask your question one more time.
12:04:47 Q. You did not compare the impurity profile of the final
12:04:50 pharmaceutical composition from Liquidia to the starting
12:04:54 batch of Treprostinil from Yonsung?
12:04:57 A. I think a POSA would understand that it would be the
12:04:59 same as -- the impurity profile of that would be the same as
12:05:02 the isolated -- isolated salt that was prepared by Yonsung,
12:05:07 but I did not do that analysis.
12:05:08 Q. I'd like to move on to storage. Can we go to JTX 2,
12:05:12 which is, again, the '066 patent and Claim 6. Actually,
12:05:18 Claim 6 and Claim 8.
12:05:20 Now, you understand Claim 6 and Claim 8 are not
12:05:38 -- require actual storage of the Treprostinil before making
12:05:46 a pharmaceutical composition?
12:05:46 A. So, claim -- let's take them one at a time. Claim 6
12:05:52 requires that the isolated salt can be stored at ambient
12:05:56 temperature.
12:05:57 Q. And that is before it is made into the pharmaceutical
12:05:59 composition; correct?

12:06:00 A. Yes. There are -- yes.
12:06:04 Q. And Claim 8 also requires that the Treprostinil salt
12:06:11 is stored at ambient temperature before you make the
12:06:15 pharmaceutical product; correct?
12:06:16 A. So, all of the storage that occurred with the
12:06:22 isolated salt would be included in there and then up until
12:06:25 they've made the -- up until they've made the pharmaceutical
12:06:30 product. So that would include the bulk LIQ 861 bulk powder
12:06:35 before it's packaged and ready to go as the bulk product.
12:06:38 Q. So just --
12:06:39 A. As the pharmaceutical product. Excuse me.
12:06:40 Q. Didn't you just previously testify that the bulk
12:06:43 powder was a pharmaceutical composition? And now are you
12:06:45 saying that the finished capsules are the pharmaceutical
12:06:48 composition?
12:06:48 A. No, this is -- oh, that's not -- if I said that,
12:06:51 that's not what I meant to say. What I said was that the
12:06:54 pharmaceutical composition was the -- was the -- was the
12:07:00 bulk API with its excipients before it was sent to Lonza or
12:07:05 Xcelience for Step 5 or 6 where it was made -- or that
12:07:09 pharmaceutical composition was then made into the
12:07:11 pharmaceutical product.
12:07:13 Q. Regardless of Claim 6 and Claim 8, actual storage is
12:07:17 required at ambient temperature; correct? Actual storage?
12:07:21 A. It's -- the claim requires that the material has to

12:07:23 be -- has to be stored at ambient temperature.
12:07:26 Q. Not capable of being stored; correct?
12:07:28 A. It requires storage.
12:07:33 Q. Not capable of being stored; correct?
12:07:35 A. It requires actual storage.
12:07:40 Q. So, you defined storage. You understand the Court
12:07:47 defined -- construed storage to mean plain and ordinary
12:07:50 meaning?
12:07:50 A. Yes, I do.
12:07:52 Q. And your definition of "storage" is storage is
12:07:54 storage?
12:07:55 A. That's a little bit of a -- a little bit of a
12:08:00 misrepresentation. What I said was that a POSA would
12:08:03 understand there what storage is because it's very common.
12:08:06 And what I took -- what I said was that Dr. Winkler's
12:08:10 definition of "storage" is not a particularly bad definition
12:08:17 of storage if you take into account that it can also include
12:08:20 transportation. So I don't think storage has to necessarily
12:08:23 be a static thing.
12:08:27 Q. Can you go to -- so, in your -- are you saying your
12:08:30 definition is no longer storage means storage?
12:08:33 A. I think to a POSA, a POSA would understand what
12:08:35 storage is because this is something that's done almost
12:08:38 every day in a chemistry lab, where you put something into a
12:08:42 bottle and you store it, for example.

12:08:45 Q. In your opinion -- I'm sorry. I didn't mean to interrupt.

12:08:47 A. That's all right. You can also imagine that you can have -- you could also imagine that during shipping, you would have material that would be stored during that time.

12:08:55 Q. So, you disagree with Dr. Winkler's definition of storage?

12:08:58 A. What I said was that the part that it excluded transportation, to me, didn't seem correct because there's a lot of times where I think material is stored during transportation.

12:09:10 Q. In your opinion, storage as used in these claims, does it require actual storage of at least three months?

12:09:20 A. I don't see a limitation in here that requires storage over some time period.

12:09:26 Q. In your opinion, is there any minimal amount of time that storage needs to take place in order to meet this limitation?

12:09:34 A. Well, I think there are -- there are compounds that you can make as a chemist that if they if they were -- if they underwent a particular temperature excursion, they would, you know, they would no longer be good. They would have decomposed.

12:09:58 That is not the case for Treprostinil sodium. Based on their stability studies, even at 75 degrees C and

at ambient temperature, this material is -- is stable at ambient temperature for at least six months; right? So, the material itself is stable at those temperatures. You can -- if you want, you can store it outside of that, but you can see at various points in the process they -- material was at temperatures outside of 2 to 8 degrees C.

Q. I appreciate your response. My question is: In your opinion, for Claim 6 and 8, is there any minimum amount of time that you consider is necessary to meet that storage limitation?

A. I don't have a -- I don't have a -- I don't have a good answer to that other than to say that I consider the points at which I discussed storage where -- were things where it seemed like it was storage that was not for a very, very small amount of time. These were on the order of hours and days. And so I don't have an answer as to what the minimum amount of time would be. It could -- in principle it could be very short.

Q. A few seconds?

A. It's just hard to say.

Q. I take a bottle of milk out of the refrigerator. Pour it into my cereal. Place it on the counter while my child behind me tugs on my leg. I give him the bowl of cereal, bring the milk back. The amount of time that that milk is sitting on the counter, is that storage?

12:11:36 A. I mean, I guess you could consider that storage.
12:11:51 Q. So, placing it down for a moment while I was using it
12:11:54 in order to answer my child, your opinion is that
12:11:59 constitutes the minimum requirement or at least within the
12:12:02 scope of storage?
12:12:03 A. It's just hard within that hypothetical to graft it
12:12:06 onto this claim language because it's a completely different
12:12:09 thing. So, it's -- in your -- it sounded as though you
12:12:13 could have been storing your milk on the table. But what a
12:12:16 POSA would understand is that there are times in which the
12:12:18 material is stored, such as when they put it into a storage
12:12:21 bottle, such as when they put it onto an airplane and let it
12:12:25 store for, you know, a number of days and such. When they
12:12:27 put it into a dry box and let it -- and when they're waiting
12:12:30 to use it, you know, that, I think, is are examples of
12:12:34 storage.
12:12:34 Q. I take Treprostinil sodium out of the Liquidia
12:12:38 refrigerator at 2 to 8 degrees. Put it on the counter
12:12:40 because I was going to use it. My colleague says, hey, I've
12:12:43 got I've -- got to have a question for you. Can you answer
12:12:45 it for me. I pick the Treprostinil back up, put it back
12:12:49 into the refrigerator, for the amount of time of that
12:12:51 interaction, where I put it down, turn around to respond,
12:12:55 and put it back into the refrigerator, is that Treprostinil
12:12:58 sodium sitting on the bench, in your opinion, storage of

12:13:02 Treprostinil sodium?
12:13:03 A. Well, there's almost an equivalent exact example of
12:13:06 what you said that's not a hypothetical. So there was --
12:13:09 they actually take the material and put it into a dry box
12:13:11 for three hours before they use it. And at that point, I
12:13:14 think the material is being stored.
12:13:17 Q. While it's awaiting use? Is that your opinion?
12:13:19 A. They put it into the dry box and they wait for three
12:13:23 hours before they use it.
12:13:24 Q. On that note, can you go to the dry box issue. Can
12:13:30 you go to PDX 2.30.
12:14:36 And I believe you looked at the dry box, which
12:14:38 is the second or the third, the 2-3 in your demonstrative;
12:14:43 correct?
12:14:43 A. Yes, I did.
12:14:48 Q. No temperature is identified there, is there?
12:14:50 A. A POSA would understand if you don't mention the
12:14:55 temperature in particular with a dry box, which it's rather
12:14:58 unusual to have a low temperature capability of that, the
12:15:01 POSA would understand that that's at room temperature.
12:15:03 Q. But you have no evidence that that dry box is not in
12:15:07 a cold room or refrigerator as opposed to being out in a
12:15:10 counter in the office space?
12:15:12 A. I assume, just based -- based on the document if it
12:15:18 was at a different temperature, it would states that in

there in their NDA.

Q. So you assume that; correct?

A. I just think it would be -- in their -- in their filings they would want to have -- in their procedures that they list here, they would want to have the actual procedure, and if it was something like keeping it at 2 to 8 degrees C, they would have said that.

Q. Now, you also talk about storage at Yonsung's facility by the time they make the Treprostinil sodium and then put it in a warehouse; correct?

A. That's correct. Yes.

Q. And your opinion is that by -- from the time period they make the Treprostinil sodium to the time they put it in the warehouse, that is stored at ambient temperature?

A. So, again, in the documents that I relied on for those validation batches, they referred to -- they referred to that material being stored awaiting acceptance into the warehouse. And that was, you know, on the order of -- I can't remember the number of days, but it was on the order of -- I think it was 30 or 40 days that it was awaiting acceptance into the warehouse. And in the documents I reviewed, there was no indication that it was outside of ambient temperature, which the POSA would understand would mean that it's stored at ambient temperature.

Q. So you understand Yonsung's DMF requires storage at 2

12:16:34 to 8 degrees; correct? That's what the DMF says?
12:16:37 A. It -- so, my reading of the DMF, it says for
12:16:42 long-term storage, it should be stored at 2 to 8 degrees.
12:16:45 It could be stored at 2 to 8 degrees Celsius, which looks
12:16:50 like a recommendation rather than a requirement,
12:16:53 particularly given the large number of samples that had
12:16:57 excursions outside of that range of 2 to 8 degrees Celsius.
12:17:02 So I think that coupled with the stability data for the
12:17:06 material at ambient temperature showing that it was stable
12:17:09 for at least six months at ambient temperature and also at
12:17:13 75 degrees C for three weeks, means that that material is
12:17:16 stable at ambient temperature.
12:17:18 Q. Can we bring up DTX 43, please. And DTX 43 is dated
12:17:27 on the top right-hand corner November 30th, 2017; correct?
12:17:31 A. I see that dates up there. Yes.
12:17:35 Q. And it's -- this is a Yonsung document. You can see
12:17:38 that on the bottom right. Yonsung Fine Chemicals, and it's
12:17:41 a list of finished intermediate -- list of finished
12:17:45 intermediate products; correct? The very title?
12:17:50 A. I'm just trying to familiarize myself with this
12:17:55 document. I don't recognize it. Can you just give me two
12:17:58 seconds. The title says List of Finished and Intermediate
12:18:06 Products.
12:18:07 Q. And can you go to Page 6, please. And you see that
12:18:12 Treprostinil sodium is identified there as acronym TN?

12:18:17 A. Yes, I see that.
12:18:20 Q. And the storage conditions is refrigerated; correct?
12:18:24 A. That's what it says.
12:18:25 Q. And refrigerated is not ambient temperature; correct?
12:18:28 A. Presumably not.
12:18:32 Q. Can you go to DTX 154, please. And this is a
12:18:41 Certificate of Analysis from Yonsung fine chemicals;
12:18:45 correct?
12:18:45 A. Yes, it appears to be yes.
12:18:47 Q. And you see the date of -- manufacturing date is
12:18:50 April 5, 2015?
12:18:57 A. I see -- oh, sorry, yes. April 5, 2015, yes.
12:19:00 Q. And that's a few years before the '066 patent
12:19:04 actually issued, isn't that correct, in 2017?
12:19:05 A. I don't remember the date, but I assume that what
12:19:09 you're saying is correct.
12:19:10 Q. And if you could go down to the bottom of the
12:19:13 Certificate of Analysis in the italicized information, it
12:19:19 says "storage conditions should be kept in a tight container
12:19:24 protected from moisture and light and stored at 2 to
12:19:27 8 degrees C long-term storage"?
12:19:30 A. So what it says is it should be kept in a container,
12:19:34 not must be kept. And it also says long-term storage.
12:19:37 Q. So, you think this is an optional requirement by
12:19:41 Yonsung?

12:19:41 A. Apparently, it was, if the number of shipping documents I saw that had excursions outside of that and the number of places in the processing where the material was outside of that range, given the fact that the material, by their own study, is stable at ambient temperature for six months, and it's at 75 degrees for three weeks, I think it's clear that the material could be stored at ambient -- isolated salt could be stored at ambient temperature for at least six months.

Q. Could be stored; correct?

A. Well, their stability data showed that it can be stored at that temperature. It's stable at those temperatures.

MR. SUKDUANG: Your Honor, I'd like to enter into evidence DTX 154 and DTX 43.

MS. WU: No objection.

THE COURT: Admitted without objection.

(DTX Exhibit No. 43 and DTX Exhibit No. 154 were admitted into evidence.)

BY MR. SUKDUANG:

Q. You've -- you have reviewed Liquidia's raw materials specifications, have you not?

A. You mean the batch production records and the Q C test sheets?

Q. The raw material specifications.

12:20:49 A. I believe I have. I've reviewed a lot of documents
12:20:52 in this, but I -- I believe that I have, yes.
12:21:03 Q. Can you go to DTX 0009, please.
12:21:07 And this is Liquidia's raw materials
12:21:16 specification; is that right?
12:21:19 A. That's what it -- that's what it says, yes.
12:21:22 Q. And you see under the store -- this is for
12:21:24 Treprostinil sodium; correct?
12:21:25 A. Yes, it is.
12:21:28 Q. And it says storage conditions 2 to 8 degrees C
12:21:31 protected from light and moisture?
12:21:33 A. I see where it says that, yes.
12:21:35 Q. And that's the Liquidia storage conditions for the
12:21:37 Treprostinil sodium it receives from Yonsung, isn't it?
12:21:42 A. So, those are the storage conditions that are listed
12:21:44 here. But it's difficult to reconcile that with the fact
12:21:48 that in the print process at various points, the material is
12:21:51 stored for a number of hours at ambient temperature. Yes, I
12:21:55 see what it says here.
12:21:56 Q. Let's talk about the print process. You've
12:21:59 identified the print process as having six steps; correct?
12:22:02 A. Yes.
12:22:03 Q. And you understand that once Treprostinil sodium is
12:22:06 put into the print process, it's added to a solution with
12:22:10 other excipients, isn't it?

12:22:11 A. So, partway through --
12:22:16 Q. Step 1.
12:22:16 A. Partway through Step 1, the material is put into the
12:22:21 dry box, and then that -- then once it's added to the stock
12:22:25 bottle, that begins the process.
12:22:25 Q. And the stock bottle is water plus other excipients;
12:22:29 correct?
12:22:30 A. That's my recollection, yes.
12:22:31 Q. And so at that point, Treprostinil sodium is no
12:22:33 longer isolated, is it? It's not by itself?
12:22:36 A. That's where you're starting to make the
12:22:38 pharmaceutical composition, that bulk powder of LIQ 861
12:22:42 before it's been packaged into the pharmaceutical product.
12:22:44 Q. And so I'm in the process now of making the
12:22:46 pharmaceutical product; correct?
12:22:49 I'm in the print process once I put it into
12:22:51 solution and start that process?
12:22:53 A. Correct. And during.
12:22:54 Q. And I'm processing Treprostinil sodium to make the
12:22:57 bulk powder; correct?
12:22:58 A. The API has been added to the -- with the other
12:23:04 excipients, and then at various points between the steps,
12:23:08 it's allowed, within the requirements, for its material to
12:23:11 be held at room temperature or stored at those temperatures.
12:23:14 Q. But it's no longer isolated, and it's during the

12:23:17 print process; correct?
12:23:18 A. It's been mixed with other ingredients and
12:23:21 excipients.
12:23:22 Q. And it's during the print process?
12:23:24 A. It's in between the various steps where it can be
12:23:28 held at those at ambient temperature.
12:23:29 Q. And those hold times you're pointing to, that could
12:23:31 be time periods where the material is drying or other steps
12:23:35 in that process. It's not just sitting there. Something is
12:23:38 happening to that material; correct?
12:23:39 A. So, this is where, you know, if you think about it in
12:23:44 as the analogy of when you store your towel after you get
12:23:47 out of the shower when it's wet on the towel rack, that
12:23:50 towel is being stored, and it's also -- the towel is drying
12:23:52 in the ambient.
12:23:53 Q. So, although the chemical Treprostinil and the other
12:23:56 components are undergoing some change, you consider that to
12:24:01 be storage even though a change is happen together that
12:24:04 product?
12:24:04 A. Well, they've completed the step and they're holding
12:24:06 it there before they begin the next step.
12:24:08 Q. But they're not holding it. They're drying it.
12:24:11 A. It would depend on each of the particular steps. But
12:24:15 to me, those intermediate steps appear to be storage, and
12:24:18 it's held at ambient temperature during that time period.

12:24:20 So if the material was not stable at those temperatures, you
12:24:24 would never have the process set up to have the material at
12:24:27 room temperature for those long number of hours where it's
12:24:29 held there.
12:24:30 Q. So your opinion is that the process of drying
12:24:34 includes -- storage includes the process of drying?
12:24:35 A. It could, just like the example I gave you with the
12:24:39 towel.
12:24:39 Q. Can we go to PTX 0 -- PTX 0074?
12:24:48 And you can go to -- this is the Liquidia
12:24:54 document that you relied on describing the six steps for
12:24:59 Liquidia's print process; correct?
12:25:00 A. Yes, I believe it is.
12:25:06 Q. Can we about to Page 6 of 14; please?
12:25:09 And this is after -- after the bulk powder is
12:25:14 made and before it's put into the capsule; correct?
12:25:17 A. This is Step 4, where they've made the bulk powder,
12:25:22 yes, before it's shipped to Lonza or Xcelience in Florida.
12:25:26 Q. Now, you used a different demonstrative that didn't
12:25:29 have this hold time, six months at 2 to 8 degrees C, did
12:25:32 you?
12:25:32 A. I didn't use this demonstrative, no.
12:25:35 Q. But it says that after you make the bulk powder, you
12:25:37 put it into a bulk pouch, you add desiccant, and you hold it
12:25:42 for not more than six months at 2 to 8 degrees; correct?

12:25:44 A. That's what it says here. I didn't point to this as
12:25:49 being ambient temperature storage, though.
12:25:52 Q. But this is the step before you make the capsules
12:25:55 that you said is the final pharmaceutical product.
12:25:58 A. Right. And I didn't say -- what I said was here are
12:26:03 three time points in the print process where the material is
12:26:05 held at ambient temperature.
12:26:07 Q. This is not being held at ambient temperature, is it?
12:26:09 A. This was not one of three that I identified.
12:26:11 Q. Of course. That makes sense. Okay. You don't want
12:26:14 to identify what the actual process says. That says you
12:26:18 store the bulk powder at 2 to 8 degrees before you make it
12:26:22 into capsules.
12:26:23 A. There were time points during the print process where
12:26:27 the material is held at ambient temperature. This is not
12:26:31 one of them.
12:26:32 Q. Can you go to PTX 117, please. And this is one of
12:26:43 the demonstratives -- excuse me -- exhibits you used.
12:26:46 MR. SUKDUANG: I'm sorry, Your Honor. Can I put
12:26:47 into evidence DTX -- P as in Paul TX 0074?
12:26:56 MS. WU: No objection.
12:26:56 THE COURT: Admitted without objection.
12:26:57 (PTX Exhibit No. 74 was admitted into evidence.)
12:26:58 BY MR. SUKDUANG:
12:26:58 Q. This is one of the exhibits that you relied on

12:27:00 regarding the temperature data logger; is that correct?
12:27:04 A. Yeah, I believe so. I'm having a little bit of
12:27:06 trouble.
12:27:06 Q. Sure. Let's blow up -- well, you were able to see it
12:27:10 pretty clearly on your direct, but let's blow it up. You
12:27:13 can see that the material is Treprostinil; correct?
12:27:15 A. I assume by that they mean Treprostinil sodium, but
12:27:20 yes.
12:27:20 Q. Can you see the date received at Liquidia is
12:27:23 December 11, 2017?
12:27:25 A. Yes, I do.
12:27:27 Q. Can you blow it back out. Can you go to the page
12:27:35 ending in production Number 863. It should be four pages.
12:27:39 Keep going. Right. Right here.
12:27:48 Now, you pointed to this graph, which is the
12:27:53 data from the temperature logger; correct?
12:27:55 A. Yes, that is the data from the temperature logger.
12:27:58 Q. Okay. And the temperature logger is a device that's
12:28:03 separate from Treprostinil sodium. It's a little puck or
12:28:07 something like that that goes into boxes; correct?
12:28:09 A. So just so we're clear, my understanding is that the
12:28:15 temperature logger will be put in there to monitor the
12:28:18 temperature of the thing that you're shipping, which would
12:28:20 be the Treprostinil sodium.
12:28:21 Q. Right.

12:28:22 A. So you would have the temperature logger there with
12:28:24 the material to, you know, to ensure that if the material
12:28:29 actually had to be stored at 2 to 8 degrees C, that it would
12:28:32 be at 2 to 8 degrees C. And actually, for this material,
12:28:35 you can see that there were temperature excursions all the
12:28:38 way down to minus 50 degrees, almost minus 50 degrees
12:28:43 Celsius all the way up to room temperatures.
12:28:46 Q. Let's look at the December 7, 2017, the top part.
12:29:00 Now, December 7, 2017, at 8:15, you see that the
12:29:06 temperature logger goes above nine degrees and then down to
12:29:11 47ish, minus 47 C; correct?
12:29:14 A. Yeah, I guess maybe another way to say it is it looks
12:29:18 like it goes from ambient temperature down to about minus
12:29:21 50, so there's about a 60-degree temperature swing for this
12:29:25 sample.
12:29:25 Q. Do you have any evidence that Treprostinil sodium was
12:29:27 actually in the box at that time?
12:29:29 A. Well, the point of the logger is to --
12:29:32 Q. Let me ask you: Do you have any evidence that
12:29:36 Treprostinil sodium is in that box during the time period
12:29:40 the temperature logger is going down to temperature?
12:29:43 A. I can only assume that if you put a temperature
12:29:47 logger in a box with material, you're using it to monitor
12:29:50 the temperature of the material in the box. So, I think
12:29:53 that they have -- they would -- the material would be in

there, and it would be monitoring the temperature of the Treprostinil sodium in the box.

Q. Right. So you are assuming that?

A. I have no other way other than the temperature log. I don't have any other data.

Q. Now, you look at the top there. There's a box that says stop time, December 13, 2017. Do you see that?

A. Yes, I see that.

Q. And do you understand what stop time means?

A. I assume that's when they're -- when the material is would be shipped and received, but I don't know what it means.

Q. Isn't the stop time the time period where the temperature logger data was stopped and you can go download the data onto the computer?

A. So, that's probably the time at which they pulled the material out of the box, I guess.

Q. Well, let's go down and let's look at the bottom graph, the very bottom graph. Do you see you pointed to this spike in temperature there, and you see the date December 11th, 2017. Do you see that date?

A. I see the -- the December 11th date, yes.

Q. And December 11th, 2017 is three days before the stop time of the temperature logger that we saw December 13th, 2017, isn't it?

12:31:15 A. Yeah, so I assume that the material from 12/11 to
12:31:21 12/13 is at the temperature that the data logger is
12:31:24 presenting.
12:31:24 Q. But you're making that assumption. You don't know
12:31:28 from that time period where the spike is all the way three
12:31:32 days later that Treprostinil sodium is actually with the
12:31:36 temperature logger, do you?
12:31:37 A. All I can tell you is this was the temperature logger
12:31:40 that was put in the box with the Treprostinil sodium. And
12:31:43 if they -- if they wanted to stop it when they took -- if
12:31:46 you're saying they took it out of the box on 12/11 and
12:31:50 stopped it, then you know, I don't have any way of knowing
12:31:53 that. All I know is what the temperature logger data shows
12:31:56 me, and the temperature logger data shows that it -- it went
12:32:00 up to ambient temperature for some amount of time.
12:32:03 Q. Have you ever received material under cold packaging
12:32:06 and cold shipping with a temperature logger associated with
12:32:10 it?
12:32:10 A. Oh, I'm sure we have.
12:32:12 Q. Okay. So when you open the box up and that material
12:32:15 is cold, do you just let it sit there, or do you put it into
12:32:18 the refrigerator?
12:32:19 A. I guess if you -- I guess if you knew --
12:32:22 Q. What do you do?
12:32:22 A. If the POSA knew -- if the POSA knew that the

12:32:27 material was stable at ambient temperature, you would store
12:32:30 it at ambient. It wouldn't matter.
12:32:31 Q. So it gets shipped all the way, all that expense,
12:32:35 under cold conditions only to when you receive it, I'm going
12:32:38 to open it up and be willy-nilly with it?
12:32:40 A. I don't think that's a fair representation.
12:32:43 Q. That's what you're describing here; correct?
12:32:44 A. No, what I'm actually saying is if the requirement
12:32:48 was to keep the material at 2 to 8 degrees Celsius, you
12:32:52 wouldn't have a 60-degree temperature swing in that material
12:32:55 when it's in the box.
12:32:56 Q. You don't know that this time period is actually
12:33:01 Treprostinil sodium with the logger or just the logger that
12:33:04 hasn't been stopped, do you?
12:33:05 A. All I can tell you is this is the data logger that
12:33:08 was put in with the material, and I accept the data at face
12:33:12 value, that it was -- the material was there until they
12:33:14 turned off the data logger.
12:33:16 MR. SUKDUANG: Thank you, Dr. Nuckolls, I
12:33:17 appreciate your time.
12:33:52 REDIRECT EXAMINATION
12:33:52 BY MS. WU:
12:33:58 Q. Dr. Nuckolls, let's start by looking back at the
12:34:03 demonstrative you had with your percent total impurities
12:34:08 analysis. I believe you were asked some questions about the

12:34:15 epi-impurity with the slide. Do you recall being asked
12:34:19 those questions?
12:34:21 A. Yes, I do.
12:34:30 Q. Thank you.
12:34:30 Now, can you walk us through what the total
12:34:35 percent of impurities are in BTO?
12:34:36 A. So, the total impurities in BTO for each of these
12:34:44 three batches?
12:34:44 Q. Yes.
12:34:45 A. Is that what you're asking? Yes. So, the values are
12:34:49 .07 percent. Sorry, it just disappeared. .07 percent for
12:34:56 BTO. Thank you so much. BTO 117I010. And it was .08 for
12:35:03 BTO117J010. And it was .38 percent for BTO 117K010 for each
12:35:13 of the three batches.
12:35:14 Q. And what are the total percent impurities in TN01?
12:35:19 A. So, the total impurities for TN01117I010 are .59,
12:35:30 0.59 percent. And for TN01117J010, it was .77,
12:35:38 0.77 percent. And for TNO1117K010, it was 0.52 percent.
12:35:44 Q. What are the total impurities in TN02?
12:35:48 A. The total impurities in TN02 for TN02117I010 is .2
12:36:00 percent. For TN02117J010 it's 0.2 percent. And
12:36:06 TN02117K010, it was 0.21 percent.
12:36:16 Q. So the percent total impurity numbers, which are
12:36:19 greater in TN02, from what steps did they result?
12:36:24 A. They resulted from the alkylation and hydrolysis

12:36:27 steps.
12:36:27 Q. And looking at the total impurities for TN, can you
12:36:32 walk us through that?
12:36:33 A. Sure. You can see that they are -- the total
12:36:38 impurities are now reduced because they're .03, .01 percent,
12:36:43 and .01 percent, so they're drastically reduced.
12:36:49 Q. You were asked whether you analyzed impurities after
12:36:53 Liquidia began processing the Treprostinil sodium. Do you
12:36:58 remember that?
12:36:58 A. Yes, I do.
12:37:00 Q. Now, who performs the steps of alkylation and
12:37:04 hydrolysis that you analyzed?
12:37:05 A. Those are done by Yonsung in Korea.
12:37:09 Q. Would Liquidia's processing of that Treprostinil
12:37:13 sodium impact the impurities from alkylation and hydrolysis?
12:37:17 A. I wouldn't expect so, or they wouldn't have made that
12:37:20 into their process.
12:37:24 Q. I'd like to take a look at a demonstrative that
12:37:31 Defendants put up with you, and it was PDX 2.16.
12:37:56 (Discussion held off the record.)
12:38:05 MS. WU: Can you bring up the version that you
12:38:06 used with Dr. Nuckolls.
12:38:07 MR. SUKDUANG: I didn't show. That's the one we
12:38:10 used.
12:38:12 (Discussion held off the record.)

12:38:15 MS. WU: Thank you.

12:38:16 BY MS. WU:

12:38:17 Q. Dr. Nuckolls, earlier, we looked at this chart during your direct. Do you recall that?

12:38:22 A. Yes, I do.

12:38:25 Q. And you looked at a similar chart during cross-examination with Liquidia's counsel. Do you recall that?

12:38:33 A. Yes, I did.

12:38:35 Q. Now, would -- are there any differences between the chart that we looked at during the direct and what was shown during your cross-examination?

12:38:44 A. There were some that were moved -- that were removed during my direct compared to the cross-examination, if I remember right.

12:38:52 MR. SUKDUANG: Your Honor, can I make a -- they never gave us the new demonstrative. So she's trying to establish getting other batches in. They never electronically sent us the new demonstrative that they changed literally five minutes in the courthouse. So if her point is trying to move into evidence additional stuff, that's because they never did what they were supposed to do and send us the demonstrative electronically so we could use it. We had to use what they sent to us the night before, and she changed it while their witness was on the stand.

12:39:20 MS. WU: I changed it to address your objections. You can ask us to put it up, and instead you put up the objected to exhibit.

MR. SUKDUANG: Your Honor.

THE COURT: All right. Well, I'm not going to let the objected to exhibit in because, obviously, we're doing things on the fly here. So, go ahead with whatever your question is.

BY MS. WU:

Q. So, with respect to the -- are there three batches TN116J010, TN117I010 and TN117K010, that you did not discuss earlier during the direct testimony?

A. With respect to this demonstrative, no, I did not. Those are the ones with the dashed lines here.

Q. Okay. I'd like to turn to some questions about the storage.

THE COURT: Actually, before you do that, can we go back to the first demonstrative that you put up, the one that has the four -- the four -- the three batches and at the various stages. Could you blow up one of the two middle boxes, like the TN01.

So, Dr. Nuckolls, one thing that I was curious about when I was looking or watching this was there are highlighted in yellow as total impurities. And above that is any other impurity. Above that is 15-epi-TN01.

12:41:24 And so, the any other impurity is, in the first
12:41:29 batch is .46 percent less than or equal 4.6 percent, and
12:41:34 then total impurities is .59 percent.
12:41:41 Do you have an explanation as to why those two
12:41:44 numbers are different?
12:41:45 THE WITNESS: So, the any other impurities is
12:41:48 referring to one of them. And then the total impurities is
12:41:51 the sum of all of them that they picked up in the HPLC.
12:41:55 That's why if you look at the number of impurities analysis,
12:41:58 you would see that there would be several peaks that would
12:42:00 be included, I believe, in that total impurities analysis.
12:42:06 THE COURT: Well, so, I guess, what I'm
12:42:07 wondering is, maybe you just told me, but I didn't
12:42:10 understand it --
12:42:11 THE WITNESS: That's okay.
12:42:11 THE COURT: -- was that the implication is the
12:42:15 thing that's not detected, the 15-epi-TN01, it seemed to me
12:42:21 that unless there's some other -- are you saying there's
12:42:28 other impurities that are not part of the related
12:42:30 substances?
12:42:30 THE WITNESS: No, they're -- the related
12:42:33 substance to any other impurities is just referring to one
12:42:35 of those with the greatest amount. And then the total
12:42:38 impurities is the sum of all of those.
12:42:40 THE COURT: Oh, okay. I get it.

12:42:41 THE WITNESS: And the epi didn't factor into
12:42:43 that sum because in this sample, it was not detected.
12:42:47 THE COURT: All right.
12:42:47 THE WITNESS: But there were other things that
12:42:49 were identified. If you go to the slide that had the number
12:42:52 of impurities, you could see that there were a number of
12:42:54 them, I believe, in the sample that were summed up to give
12:42:57 that value.
12:42:57 THE COURT: But I think I understand now is when
12:43:00 it says any other impurity, you're talking about just one
12:43:04 impurity or three impurities that was -- the other two would
12:43:08 be smaller. The math would work.
12:43:11 THE WITNESS: That's how I would sum it up.
12:43:12 That's my recollection, yes.
12:43:14 THE COURT: Okay. Sorry. You know, I have to
12:43:16 write an opinion later on. And sometimes it's things that I
12:43:23 need to review later on.
12:43:23 THE WITNESS: I totally understand. That's
12:43:25 understandable.
12:43:28 BY MS. WU:
12:43:29 Q. All right. If we could put up DTX 009, which is
12:43:34 Liquidia's raw materials specification.
12:43:42 Dr. Nuckolls, does this document impact what
12:43:45 happens at Yonsung?
12:43:46 A. No, because this is after the material has already

12:43:51 been received by Liquidia.
12:43:53 Q. And so, does it control the shipment of material from
12:43:58 Yonsung to Liquidia?
12:43:59 A. This would be after the material has arrived at
12:44:05 Liquidia.
12:44:11 Q. Now, you were asked some questions about storage and
12:44:15 how short storage could be. Do you recall those?
12:44:18 A. Yes.
12:44:20 Q. Now, when you look at the storage of isolated
12:44:25 Treprostinil salt and just Treprostinil salt, on what order
12:44:30 was the time frame of those storage examples?
12:44:34 A. So, with the ones that occurred at the warehouse at
12:44:38 Yonsung, I believe that was on the order of 30 or 40 days,
12:44:42 if my recollection is correct. During the shipping, it was
12:44:46 on the order of maybe five to seven days, but don't hold me
12:44:52 to the exact number, but on the order of some number of
12:44:55 days. And then in the -- when it was placed in the dry box
12:44:58 before it was used, it was on the order of three hours.
12:45:02 Q. Let me show you PTX 74. This is a description of the
12:45:12 print process.
12:45:12 Do you agree?
12:45:13 A. Yes, it is.
12:45:15 Q. Okay. Can you take a look at the second page of this
12:45:22 exhibit?
12:45:25 Does this document explain under what

12:45:29 conditions, with respect to temperature, the print process
12:45:33 is conducted under?
12:45:34 A. Yes. So, if you go to the paragraph under Step 6, it
12:45:40 says that it's -- yeah, there you go. The bulk LIQ861
12:45:46 inhalation powder, it says that it's stored at 18 to
12:45:50 24 degrees C.
12:45:52 Oh, and then even below that, sorry, there's an
12:45:57 18 to 24. And I believe there's another -- yeah, 18 to 25
12:46:02 is for the powder encapsulation packaging.
12:46:07 Q. So, can you explain -- you've talked about six steps
12:46:10 of the print process. So, which steps are associated with
12:46:15 which temperatures?
12:46:16 A. So, Steps 1 through 4 would be with the 18 to 24 and
12:46:22 Steps 5 and 6 that were done at Lonza and Xcelience would be
12:46:26 at 18 to 25.
12:46:27 Q. You were asked some questions about, you know, the
12:46:29 temperature of the dry box in Step 1. What would the
12:46:33 temperature of the dry box have been at?
12:46:35 A. I think a POSA would understand, based on this
12:46:39 document, that it was at ambient temperature 18 to 24.
12:46:44 Q. Okay. And I think you were also asked some questions
12:46:47 about storage versus processing. If we could take a look at
12:46:51 the next page.
12:46:52 What is this?
12:46:53 A. This is Step 1, the preparation of this aqueous stock

12:47:04 solution.
12:47:05 Q. What's the last step of this process?
12:47:07 A. That there's a hold time of not more than 71 hours.
12:47:15 Q. Okay. And what is the -- are there any other
12:47:22 manufacturing steps happening between the end of Step 1 here
12:47:26 and the start of Step 2 during the hold time?
12:47:29 A. I don't believe so. No.
12:47:32 Q. Let's go to the next page. What is this?
12:47:34 A. This is Step 2 of the print process.
12:47:42 Q. What's the last step, the last manufacturing step of
12:47:46 Step 2?
12:47:46 A. It's a hold time for not more than 18 hours.
12:47:51 Q. So, let me -- what is the box next to the hold time
12:47:55 box?
12:47:56 A. Oh, that's where they put -- put it in -- within a
12:48:00 bag and a desiccant. The PET substrate roll will contain
12:48:05 the adhered particles as packaged. And then it's held -- it
12:48:08 can be held for not more than 18 hours.
12:48:10 Q. And so, during this hold time, is there any
12:48:12 processing happening, processing to the PET substrate roll?
12:48:17 A. It doesn't appear -- so it just looks like they put
12:48:19 it into the bag when it was packaged.
12:48:22 Q. Let's go to the next page. What is this?
12:48:26 A. This is Step 3 of the print process.
12:48:30 Q. And can you describe the last manufacturing

12:48:33 processing step?
12:48:35 A. It says hold time not more than 88 hours in a
12:48:38 desiccator at not more than 15 degrees relative -- percent
12:48:43 relative humidity.
12:48:44 Q. Can you explain the two boxes to the left of that?
12:48:46 A. So, those are the -- where they put the bag and the
12:48:50 desiccants, and then they add the bulk LIQ861 inhalation
12:48:54 powder to that.
12:48:56 Q. So, you know, while the bulk LIQ861 inhalation powder
12:49:00 is in the bag, is there any processing happening to the
12:49:05 material during the no more than 88 hours hold time?
12:49:08 A. It doesn't appear so, no.
12:49:10 Q. Okay. And for each of these three hold times, so do
12:49:15 you know whether these are being held at ambient
12:49:18 temperature?
12:49:18 A. Based on the first document you showed me, it looked
12:49:22 like they would be held at ambient temperature, yes.
12:49:27 MS. WU: I have no further questions, but I'd
12:49:29 like to move in a long list of exhibits which were used
12:49:32 during Dr. Nuckolls' direct testimony.
12:49:36 MR. SUKDUANG: Your Honor, can we just correlate
12:49:37 to make sure none of those exhibits --
12:49:39 THE COURT: All right. Why don't we do this.
12:49:41 Do you have any redirect or you're done; right?
12:49:43 MR. SUKDUANG: No.

12:49:43 THE COURT: All right. So, why don't we take
12:49:44 our lunch break. You all can figure out the long list of
12:49:47 exhibits. We'll start up again at about quarter of 2:00.
12:49:51 So, we'll be in recess.
12:49:53 Dr. Nuckolls, I can't remember. Are you
12:49:55 testifying about invalidity, too?
12:49:56 THE WITNESS: No, I'm not.
12:49:57 THE COURT: All right. Well, then you're
12:49:59 excused and watch your step.
12:50:00 THE WITNESS: Thank you so much.
12:50:02 DEPUTY CLERK: All rise.
12:50:04 THE COURT: We'll be in recess.
12:51:01 (Luncheon recess was taken.)
01:44:16 DEPUTY CLERK: All rise.
01:44:25 THE COURT: All right. Let's be seated. And I
01:44:27 guess, Plaintiff, keep going.
01:44:30 MS. WU: Your Honor, one housekeeping matter.
01:44:32 The list of exhibits.
01:44:34 THE COURT: Yes.
01:44:35 MS. WU: We've agreed to with Defendants -- I'm
01:44:42 sorry -- PTX 19, PTX 20, PTX 112, 1117, 201, 326, 510, 730,
01:45:02 766, 709, 790, 795, 796, 805, 806, 814, 815, 988
01:45:19 through 991, 997 through 999, 1001, 1157, 1169, 1170. 1172,
01:45:35 1175, 1177, 1179, 1181, 1183, 1185, 1187, 1189, 1191, 1192,
01:45:55 1197, 1199, 1202, 1205, 1207, 1209, 1228, also PTX 1409

01:46:11 through 1411, 1536, 1539, 1540, 1542 through 44, 1546, 1548,
01:46:28 1550.
01:46:30 Defendants also wanted me to move in two of the
01:46:33 exhibits they used. I have no objection to them. It's DTX
01:46:37 009, PTX 117.
01:46:41 THE COURT: Okay. So admitted without
01:46:43 objection.
01:46:43 (PTX Exhibit Nos. 19, 20, 112, 1117, 201 326,
510, 730, 766, 709, 790, 795, 805, 806, 814, 815, 988
through 991, 997 through 999, 1001, 1157, 1169, 1170, 1172,
1175, 1177, 1179, 1181, 1183, 1185, 1187, 1189, 1191, 1192,
1197, 1199, 1202, 1205, 1207, 1209, 1228, 1409 through 1411,
1536, 1539, 1540, 1542 through 44, 1546, 1548, 1550, and 117
were admitted into evidence.)
(DTX Exhibit No. 009 was admitted into
01:46:43 evidence.)
01:46:43 MS. WU: Thank you, Your Honor.
01:46:46 MR. CARSTEN: Light reading for Your Honor.
01:46:49 United Therapeutics calls its next witness,
01:46:51 Professor Dean Toste, and conducting the examination, I'll
01:46:55 introduce my colleague Kathy Pappas.
01:47:13 DEPUTY CLERK: Please state and spell your full
01:47:16 name for the record.
01:47:17 THE WITNESS: F. Dean Toste. Dean is D-E-A-N
01:47:17 and Toste is T-O-S-T-E.

01:47:24 DEPUTY CLERK: Do you affirm that the testimony
01:47:25 are you about to give to the Court in the case now pending
01:47:28 will be the truth, the whole truth, and nothing but the
01:47:30 truth, do you so affirm?
01:47:31 THE WITNESS: I do.
01:47:31 F. DEAN TOSTE, the witness herein, after having
01:47:31 been duly sworn under oath, was examined and testified as
01:47:33 follows:
01:47:33 DEPUTY CLERK: Thank you. The microphone is
01:47:34 right there, so make sure you speak right into it.
01:47:37 THE WITNESS: Awesome. Thank you.
01:47:44 DIRECT EXAMINATION
01:47:44 THE COURT: Go ahead. Was it Ms. Pappas?
01:47:46 MS. PAPPAS: Yes.
01:47:47 THE COURT: Okay. Go ahead.
01:47:48 BY MS. PAPPAS:
01:47:49 Q. Good afternoon, Dr. Toste.
01:47:51 A. Good afternoon.
01:47:52 Q. Please introduce yourself.
01:47:53 A. I'm professor F. Dean Toste. Dean is D-E-A-N and
01:47:59 Toste is T-O-S-T-E. I'm the Gerald E. K. Branch
01:48:02 Distinguished Professor of the University of California
01:48:05 Berkeley. I also hold an appointment at the Lawrence
01:48:08 Berkeley National Laboratory. I'm a fellow of the National
01:48:14 Academy of Sciences of the United States and of the American

Academy of Arts and Sciences.

Q. How are you involved in this case?

A. I was retained by -- by UTC to opine on the infringement of their '066 patent.

Q. Briefly, what is your educational background?

A. I have a undergraduate degrees from the University of Toronto in chemistry and biochemistry. I have a Ph.D. in chemistry from Stanford university, and I was a post-doctoral fellow in the lab of a Nobel Laureate at California Institute of Technology.

Q. Let's pull up PTX 423.

A. And which of these binders do you think that would be in?

Q. It's up on the screen?

A. Oh, okay.

Q. Dr. Toste, what is this document?

A. That's a copy of my CV.

Q. Does it appear to be an accurate copy of your CV?

A. Certainly looking at this page, it's accurate.

MS. PAPPAS: Plaintiff moves to admit PTX 423, CV of Dr. Toste.

MR. SUKDUANG: No objection.

THE COURT: Admitted without objection.

(PTX Exhibit No. 423 was admitted into evidence.)

01:49:21 BY MS. PAPPAS:
01:49:22 Q. Dr. Toste, do you have an area of expertise?
01:49:24 A. My research -- my background is in chemistry and
01:49:29 organic chemistry. My research group focuses on multiple
01:49:33 aspects of organic chemistry, ranging from what we call
01:49:35 physical organic chemistry, which is understanding of the
01:49:39 properties and reactivity of organic molecules all the way
01:49:43 to applications of those organic molecules and those
01:49:47 reactions to problems in material science, energy, biology,
01:49:52 chemical biology. When we perform that type of research, we
01:49:56 use tools in chemical synthesis, purification, HPLC
01:50:01 analysis. For example, when we do enantioselective
01:50:04 synthesis we analyze particular mixtures of compounds, we
01:50:09 purify them. All of that is part of my research program.
01:50:15 MS. PAPPAS: Plaintiff tenders Dr. Dr. Toste as
01:50:17 an expert in organic chemistry, chemistry, chemical
01:50:20 synthesis and purification, and enantioselective synthesis,
01:50:25 biochemistry, process chemistry, pharmaceutical chemistry,
01:50:30 analytical techniques such as HPLC identification and
01:50:35 quantification of impurities.
01:50:37 MR. SUKDUANG: No objection.
01:50:37 THE COURT: All right. You may proceed.
01:50:40 BY MS. PAPPAS:
01:50:40 Q. Did you prepare slides for today?
01:50:42 A. I did.

01:50:46 Q. If we can pull those up. What is a person of
01:50:50 ordinary skill in the art or POSA?
01:50:50 A. In the context of this case, or this patent case, a
01:50:56 POSA would have an advanced degree in chemistry in one of
01:50:59 the outlying fields like physical chemistry or
01:51:01 pharmaceutical chemistry and then, you know, some years of
01:51:05 experience working in preparing pharmaceutical product --
01:51:10 products, either directly preparing those or as part of a
01:51:13 team or collaboration that prepares those. I also believe
01:51:17 that a person would still be a POSA if they had a lesser
01:51:19 degree but they had more experience in those aspects that I
01:51:23 just mentioned.
01:51:24 Q. Did you apply that framework when considering and
01:51:27 issuing your opinion this is this case?
01:51:28 A. I sure did.
01:51:31 Q. What claims did you opine on in your infringement
01:51:34 analyses?
01:51:35 A. My analysis focused on Claim 1, which is the one
01:51:39 that's on the slide now. And to the extext that they were
01:51:43 dependent, subclaims 2, 3 and 4 but only to the extent that
01:51:48 they depended on Claim 1.
01:51:50 Q. I'm sorry. For the record, which were those
01:51:52 dependent claims?
01:51:53 A. I'm sorry. 2, 3 and 6 in the context that they were
01:51:56 dependent.

01:51:57 MR. SUKDUANG: Your Honor, I'll just note
01:51:59 Dr. Toste's expert report and depositions only focused on
01:52:03 Claim 1.
01:52:03 THE COURT: I interpreted what he said there was
01:52:06 he doesn't really have anything to add to 2, 3 and 6 but
01:52:09 it's buried within 1.
01:52:10 Is that what you said?
01:52:11 THE WITNESS: That's correct, yeah.
01:52:13 BY MS. PAPPAS:
01:52:15 Q. Briefly, based on your analysis, how would Liquidia's
01:52:19 proposed product infringe Claim 1 of the '066 patent?
01:52:21 A. So, can we get the next slide, please? So, if you
01:52:26 look at the language in the patent, the first clause of the
01:52:29 patent is pharmaceutical composition comprising Treprostinil
01:52:32 or a pharmaceutically acceptable salt. This is what's
01:52:35 prepared in Step 12 of Yonsung's DMF. It's what's described
01:52:39 to be used in -- in Liquidia's NDA, so we can put a
01:52:44 checkmark next to that.
01:52:46 There we go. Thank you.
01:52:47 And then it goes on to describe a starting batch
01:52:50 of Treprostinil with one or more impurities --
01:52:50 THE REPORTER: Could you please slow down.
01:52:55 THE WITNESS: Thank you. I have a tendency to
01:52:57 do that even when I'm teaching.
01:53:04 So it's -- it says starting batch of

Treprostinil with one or more impurities resulting from prior alkylation and hydrolysis steps and -- and there is this -- definitely a bit of Treprostinil that has impurities that result from the alkylation and hydrolysis steps. These are steps 10 and 11 specifically in Yongsung's DMF. It goes on to say a formation of a salt of Treprostinil by combining that with a base and then isolating that salt and using that to prepare a pharmaceutical composition. This is, essentially, a summary of Step 12 in Yonsung's DMF.

And then continuing, it says, a level of one or more impurities in the starting batch of Treprostinil is lower in the pharmaceutical composition that is in transforming Treprostinil to pharmaceutical composition the impurities must be lowered, and that's, again, what happens as a result of Step 12 in Yonsung's DMF.

It refer -- referring back to the alkylation that we mentioned a couple of steps earlier, it says that the alkylation is of benzidine triol. And indeed, alkylation of benzidine triol is Step 10. It's exactly Step 10 of what Yonsung's DMF is.

Q. How does this relate to the dependent claims?

A. Can I get the -- so, the dependent claims mention a pharmaceutical composition, and this pharmaceutical composition is one that we've been describing and discussing so far as prepared in Claim 1.

01:54:34 Q. How did you remember perform the analysis that you
01:54:37 just described for Claim 1?
01:54:38 A. So, can I get the next slide. Yeah, thank you.
01:54:43 So as I started just by looking at Claim 1, the
01:54:46 beginning of Claim 1, says it's a starting batch of
01:54:48 Treprostinil having one or more impurities. So to a process
01:54:52 chemist, to a POSA, you would take your batch, and you would
01:54:54 simply ask the question is one more impurities in that
01:54:58 batch?
01:54:58 So that's, you know, in cartoon form. It's
01:55:00 represented here; right? So if you imagine your
01:55:02 Treprostinil as these red squares, you would simply ask is
01:55:06 there something in there that's not red squares? That would
01:55:08 be an impurity. For example, are there red rectangles in
01:55:12 this thing? So these red rectangles would be impurities in
01:55:16 that starting batch of Treprostinil. By definition, a
01:55:20 process chemist would call these process impurities, which
01:55:22 is like a textbook definition.
01:55:24 And then it says it results from prior
01:55:27 alkylation and hydrolysis steps. Again, it's pretty ease
01:55:30 easy to understand if it is resulting from prior alkylation
01:55:33 and hydrolysis steps, you simply look to see if there are
01:55:36 red rectangles that existed prior to those alkylation and
01:55:40 hydrolysis steps. There are no red rectangles prior to the
01:55:43 alkylation hydrolysis steps, there's only one place they

could have come from, is those alkylation hydrolysis process steps because, again, by definition how a person practicing chemical synthesis would view this. These are process impurities resulting from these process steps. No red rectangles, red rectangles. Red rectangles resulted from these process steps.

Can I get the next slide.

The claim goes on to read where one -- whereby a level of one or more impurities found in the starting batch of Treprostinil is lower in the pharmaceutical composition. Again, very simple analysis. Start with your starting batch of Treprostinil as described in the patent. Look for your impurity, red rectangles, and just see if when you isolate your Treprostinil salt, are there fewer red rectangles. That is, do your process impurities that are red rectangles decrease as a result of the salt formation? Do the impurities decrease as a result of Yonsung Step 12 in their DMF? Very simple analysis.

Q. What documents did you review to perform this analysis?

A. So in order to perform this analysis, of course, you have to identify impurities, and in order to identify those impurities, I looked at the certificate analysis and, to the extent I had it, the underlying data provided by Yonsung and Liquidia.

01:57:05 Q. And what was the methodology employed in the
01:57:09 underlying data that you reviewed?
01:57:10 A. Yonsung and Liquidia used a process called HPLC. I
01:57:18 believe Dr. Nuckolls described that, so I won't waste the
01:57:21 Court's time reiterating that. Just to say HPLC separates
01:57:24 impurities by running them down a column as Dr. Nuckolls
01:57:27 articulated, and these impurities are separated by how much
01:57:30 they interact with the column. So the stickier you are in
01:57:34 the column, the slower you run down that column. If you
01:57:37 stick a lot, you stay up. If you you're not sticky, you run
01:57:40 down. And that relies on sort of interactions
01:57:43 intermolecular reactions between the compounds and the
01:57:45 column. So you have want to imagine if the compounds are
01:57:47 really similar, they would have a -- about the same
01:57:51 stickiness and they would have about the same retention time
01:57:54 because they're very similar. And if they're very
01:57:56 different, then they would run very differently in -- on
01:58:00 HPLC.
01:58:01 Q. How often is HPLC used to measure impurities in your
01:58:06 field?
01:58:06 A. It's -- we use it all the time in my lab. I think we
01:58:10 have several HPLCs in my lab. It is the method of choice
01:58:13 for analyzing mixtures of non-volatile organic compounds.
01:58:17 Q. So, what one or more impurities did you analyze for
01:58:22 your infringement opinion?

01:58:23 A. So, I focused on one specific impurity, so the
01:58:29 equivalent of my red rectangles is an impurity called
01:58:31 epi-Treprostinil if I can get its next slide.
01:58:34 Epi-Treprostinil is shown here compared to
01:58:38 Treprostinil, and it's already come up quite a lot on --
01:58:40 in -- on the trial today. So I won't say too much about it
01:58:44 except to say as Dr. Nuckolls articulated, it's -- it
01:58:48 differs from Treprostinil in the stereochemistry of one
01:58:51 carbon atom. So stereochemistry is a property of, in this
01:58:54 case, a carbon atom that one can relate to handedness. So
01:58:57 if your hands are -- enantiomers. In the case of this case,
01:59:03 they're epimers. They're epimeric to each other. And
01:59:06 that's represented on this slide as a cartoon of two hands
01:59:10 holding a molecule. One has hydrogen pointing to the right
01:59:13 and one has hydrogen pointing to the left. And
01:59:16 epi-Treprostinil and Treprostinil, rather than left and
01:59:18 right, they're represented as up and down using the standard
01:59:22 nomenclature which is a wedge for up and a dash for down.
01:59:27 We've also heard these words epimerization, and
01:59:29 a epimerization is simply the process of flipping the up to
01:59:32 the down. So you can imagine if you had a right-handed
01:59:35 glove and you flip that glove inside out now, you'd have a
01:59:39 left-handed glove. You would have epimerized that glove.
01:59:44 Q. Why does that difference between the
01:59:50 15-epi-Treprostinil and Treprostinil matter?

01:59:52 A. It's -- it's generally believed to be important, the
01:59:55 stereochemistry of molecules. Our bodies -- if I'm going
01:59:58 too fast, please tell me.
01:59:59 Our bodies are also composed of molecules that
02:00:02 have this property of stereochemistry, our proteins and
02:00:05 nucleic acids all have this property of handedness. So you
02:00:08 can imagine if you put a molecule into your body, its
02:00:10 property of handedness will interact differently with the
02:00:13 handedness of molecules in your body just like it's easier
02:00:16 to shake a right hand than it is to shake a left hand with
02:00:18 your right hand. And this is really critical and it's been
02:00:21 known for you know for a long time. And sort of the classic
02:00:24 and very sad case of this is a molecule in a drug called
02:00:28 Thalidomide where one-handedness of the molecule was
02:00:32 administered -- it was -- Thalidomide was administered to
02:00:35 pregnant women in the '60s. And one handedness of that
02:00:38 molecule cured morning sickness. That's why it was being
02:00:42 used. And it turned out the other handedness of that
02:00:46 molecule caused deaths in about 2,000 children and severe
02:00:47 birth defects, sadly, in about 10,000 kids. So it's been
02:00:50 known for, you know, multiple decades now that's it's
02:00:53 important to control even small amounts of the
02:00:56 wrong-handedness of molecules.
02:00:58 Q. So, what did you find when you analyzed the HPLC data
02:01:03 from the Yonsung's starting batch of Treprostinil?

02:01:05 A. So, here's a couple of representative examples I
02:01:09 think we're going to look at. The one on the left shows a
02:01:14 really large peak for Treprostinil. A much smaller but
02:01:18 clearly resolved -- resolved meaning the HPLC has succeeded
02:01:21 in separating these two molecules based on their
02:01:24 interactions, to the point that one could look at this data
02:01:28 and say, I'm pretty confident in saying there's 0.065 or
02:01:33 0.07 percent of epi-Treprostinil in this sample because I
02:01:38 have nice resolution. And if I had access to the underlying
02:01:41 data, I could be comfortable with that number.
02:01:44 On the right-hand side is a very different
02:01:46 looking chromatogram where there's this large of peak of
02:01:50 TN02 and then that sort of trails into what looks like a
02:01:54 shoulder on that TN02. A POSA would conclude that that
02:01:58 shoulder is, more likely than not, unresolved
02:02:03 epi-Treprostinil that just hasn't -- the HPLC just hasn't
02:02:08 worked to the extent that -- where it can separate it to --
02:02:10 to see the differences. When I saw data like this -- so,
02:02:15 Yonsung would report this as not detected; right? Because
02:02:19 the HPLC machine was unable to separate the Treprostinil
02:02:24 from the epi-Treprostinil. I look at it and I think a POSA
02:02:26 would look at it and say, you know, more likely than not
02:02:29 that shoulder is the epi-Treprostinil that's bled into the
02:02:31 Treprostinil. And therefore, when I saw data like this, I
02:02:37 wouldn't include it in my analysis because it was relatively

02:02:41 inconclusive for my purposes.

02:02:45 MS. PAPPAS: May I approach to hand the witness
02:02:47 a pointer to --

02:02:49 THE COURT: Sure.

02:02:50 MS. PAPPAS: Thank you.

02:02:53 THE WITNESS: There is a pointer here, Kathy.

02:02:55 BY MS. PAPPAS:

02:02:55 Q. Oh, wow.

02:03:00 A. I want to try this one.

02:03:04 Right. So there's the -- just to reiterate,
02:03:06 that's the resolved peak there. And see how close it is to
02:03:09 the -- to the Treprostinil? The epi is very close but
02:03:12 clearly resolved, and here it's just as close but somehow
02:03:16 they haven't resolved -- the HPLC can't detect that, so
02:03:21 Yonsung says it's not determined. I would think this is
02:03:23 inconclusive for the purposes of my analysis, and, in
02:03:26 general, not use that data.

02:03:30 Q. For the record, what was the reading on the one on
02:03:35 the right?

02:03:35 A. I'm sorry. Not detected. I know I said not
02:03:38 determined but not detected.

02:03:40 Q. Thank you. So was there 15-epi-Treprostinil in the
02:03:44 BTO?

02:03:45 A. In any of the data I saw, looking at BTO, there was
02:03:49 no epi-Treprostinil in there. There were no -- again, to

02:03:53 use my analogy, there were no red triangles -- red
02:03:57 rectangles in the BTO. The only time I saw red rectangles
02:04:02 was in HPLC that looked like this.
02:04:07 Q. What did you find when you analyzed the HPLC data to
02:04:11 compare levels of 15-epi-Treprostinil between the starting
02:04:15 batch of Treprostinil and after the salt formation step?
02:04:17 A. Okay. Next slide.
02:04:19 So I did a very similar analysis to the one we
02:04:22 just described, so I won't again show all the, you know,
02:04:25 show more than one HPLC data just to say this is a
02:04:27 representative HPLC data. We're going to see Treprostinil
02:04:31 and the epi-Treprostinil here. And when I had data like
02:04:33 this from Yonsung -- so Yonsung provided underlying HPLC
02:04:36 data. Liquidia, I didn't get any underlying HPLC data.
02:04:39 When I had the data like this, especially if the
02:04:42 Yonsung data was validated, was validated by the Liquidia
02:04:46 data, so they were consistent, even though I didn't have
02:04:49 underlying data from Liquidia, I had only HPLC from Yonsung,
02:04:53 when the Liquidia numbers were consistent with the Yonsung
02:04:57 numbers, I used that data to create a chart that looks like
02:05:01 this. And so the yellow bars being the epi-Treprostinil in
02:05:05 the TL 2 and the blue bars being the epi-Treprostinil in the
02:05:11 TN after Step 12 of the Yonsung DMF. We can see that in
02:05:16 these cases, the amount of epi-Treprostinil -- the process
02:05:20 impurity in the TN02 batch is decreased in the Treprostinil

as a result of the step 12.

Q. Which underlying documents did you rely on in making that figure on the left?

A. I used the Yonsung Certificate of Analysis and their underlying data, their quality control test sheets.

Q. Are those documents listed?

A. Yeah, they're listed at the bottom of the slide, starting with PTX 54 on and going on and ending at PTX 538.

MS. PAPPAS: Plaintiff offers PTX 548 into evidence, along with the underlying HPLCs, which are PTX 344, 166, 641, 1164, 204, 205, 426, 1170, 686, 1169, 702, 1550, 705, 1544, 1000, 1240, 1227, 1002, 1242, 993, 1228, 1244, 995, 1229, 1246, 1230, 816, 797, 723, 1181, 725, 1183, 734, 1207, 736, 1209, 766, 768, and 1192. And to correct I had said before 166, but I meant 1166.

MR. SUKDUANG: No objection.

THE COURT: All right. Admitted without objection.

(PTX Exhibit Nos. 548, 344, 1166, 641, 1164, 204, 205, 426, 1170, 686, 1169, 702, 1550, 705, 1544, 1000, 1240, 1227, 1002, 1242, 993, 1228, 1244, 995, 1229, 1246, 1230, 816, 797, 723, 1181, 725, 1183, 734, 1207, 736, 1209, 766, 768, 1192 were admitted into evidence.)

BY MS. PAPPAS:

Q. Dr. Toste, did you find any instances where the

15-epi-Treprostinil actually went up?

A. There were some data from Yonsung and some data from Liquidia where the amount of epi-Treprostinil went up from -- as a result of Step 12. That is the -- there were more red rectangles in the product than there were in the TN TN01.

But there was no instance where both the Yonsung data and the Liquidia data for a single batch, for the same batch, both suggested it went up. That is to say, there was no corroborating data from both sources in a single example that went up. So, while one could cherry pick a batch and say, hey, this one looks like it went up, for the sake of accuracy, I only used batches where there were corroborating data. In the absence of that, I didn't include them. I think if I did include them, it wouldn't have changed my analysis. You know, a single batch where it goes up doesn't -- it doesn't refute my view of this as a strong trend where the amount of epi-Treprostinil goes down. In science, we look for trends, and when you have a trend that it says it goes down that's overwhelming, you have to conclude that it goes down.

Q. So, what causes the 15-epi-Treprostinil to go down?

A. So if I could just get to the next slide just so we could look at my cartoon again.

All right. So the process of crystal

02:09:08 crystallization is cartoony shown here. So a crystal is a
02:09:12 packed form of a molecule. So in crystallization, you're
02:09:15 inducing the molecule that was once in solution to now pack.
02:09:19 And this packing is controlled by thermodynamics of
02:09:23 intramolecular forces. That is to say how sticky molecules
02:09:25 are with each other. And molecules that are the same tend
02:09:27 to be stickier with each other. Molecules that are similar
02:09:30 tend to be stickier with each other. So in this case, it's
02:09:33 actually kind of surprising -- again, rectangles are pretty
02:09:37 similar to squares, epi-treprostinil is pretty similar to
02:09:39 Treprostinil -- that the crystallization would be able to
02:09:40 distinguish between those two. There could be similar
02:09:43 stickiness. But it does happen that in this case, the
02:09:46 epi-Treprostinil is excluded as the Treprostinil molecules
02:09:52 come together to form a crystal leaving behind
02:09:57 epi-Treprostinil that hasn't stuck to that crystal, it's
02:09:59 left in what we would call the mother liquor from -- the
02:10:02 mother liquor in the sense that it's formed when the crystal
02:10:05 was born. So a process chemist would say the impurities are
02:10:09 rejected into the mother liquor leading to the purification
02:10:12 of your final molecule.
02:10:18 Q. Let's please take a look at PTX 2039.
02:10:25 What is this document?
02:10:26 A. It's a scientific article published by Aaron Cote et
02:10:35 al. in the journal of crystal growths and design where he

was published, you know, just last year sort of talking about the process of crystallization and because it's so important in the pharmaceutical industry, the challenges with doing that. And so what it basically says, even as late as last year or as early as last year, it's still very difficult to predict conditions for crystallization. Even using, sort of, modern computational power tools like machine learning and AI which chemists are starting to use a lot now. It's really hard to predict crystallization and what the conditions are in order to -- to achieve a crystallization a priori without sort of inventing something to do it without doing experimentation to do it. So basically, of the ability to rationally design, scale, crystallization process to achieve the recognized process, et cetera, et cetera, it remains an often elusive ambition. So it's an AI design of crystallization. It's elusive even using our modern approaches. That's what this document basically says.

MS. PAPPAS: Plaintiff offers PTX 2039 into evidence.

MR. SUKDUANG: No objection.

THE COURT: Admitted without objection.

(PTX Exhibit No. 2039 was admitted into evidence.)

BY MS. PAPPAS:

02:11:57 Q. So, Dr. Toste, what do these data tell a POSA?
02:12:01 A. So again, returning to my earlier analysis, and I
02:12:05 hate to keep using the rectangles things, but it's just
02:12:08 easier for me to talk about. If you look at a batch of
02:12:11 Treprostinil, it has a process impurity called
02:12:15 epi-Treprostinil in it. And if you ask if the
02:12:18 epi-Treprostinil existed before the alkylation and
02:12:21 hydrolysis steps, there's no evidence that epi-Treprostinil
02:12:23 existed in the Yonsung BTO. Therefore, it's logical to
02:12:28 conclude, and it's a textbook example of a process impurity
02:12:33 being generated as a result of steps 11 and 12.
02:12:37 Then you look at the product after step --
02:12:42 sorry. It's logical to conclude that it results after steps
02:12:45 10 and 11. And you look at the product after Step 12, the
02:12:50 salt formation and crystallization, that has less
02:12:53 epi-Treprostinil in it than it did in the batch of
02:12:56 Treprostinil prior to that Step 12. Therefore, that was --
02:13:02 impurities were decreased. The end result of that is
02:13:04 exactly what the patent calls for, and that, in my opinion,
02:13:09 Liquidia infringes on UTC's '066 patent.
02:13:16 MS. PAPPAS: Plaintiff also moves to admit PTX
02:13:21 532, 536, and 538.
02:13:38 MR. SUKDUANG: No objection.
02:13:38 THE COURT: Admitted without objection.
02:13:40 (PTX Exhibit No. 532, PTX Exhibit No. 536, and

PTX Exhibit No. 538 were admitted into evidence.)

MS. PAPPAS: No further questions at this time.

THE COURT: All right. Cross-examination.

MR. SUKDUANG: Your Honor, may I approach.

THE COURT: Yes.

CROSS-EXAMINATION

BY MR. SUKDUANG:

Q. I don't know if I can see you --

A. I know.

Q. -- under there.

A. There's a lot of binders. Oh, you're going to add more.

Q. No.

MR. SUKDUANG: No. No.

MR. CARSTEN: Should we remove our binders?

THE WITNESS: I can put them down.

MR. SUKDUANG: We'll probably use the screen if you need to move to a document.

THE WITNESS: Sure.

MR. SUKDUANG: May I proceed Your Honor.

THE COURT: Yes.

BY MR. SUKDUANG:

Q. Hello. Nice to see you again.

A. Nice to see you, too.

Q. I'd like you to turn to the patent, JTX 2, for me,

please. And take a look at Example 2 for me.

No, before we get to Example 2, in order to conduct your infringement analysis, you had to rely on actual data comparing impurities from the starting batch -- and in Yonsung nomenclature that's TN02 -- to the pharmaceutical composition -- and in Yonsung's nomenclature that's TN; correct?

A. That's correct.

Q. Can you go to Example 2, please of the '066 patent. JTX 2. And Example 2, please. It's Column 10 and 11. Now, it spans two pages.

Dr. Toste, this Example 2 is the hydrolysis step that results in Treprostinil; correct?

A. Are we starting?

Q. We're starting.

A. Okay. Yeah. That that's what's depicted in that structure. Yes.

Q. And so the hydrolysis of the benzidine nitrile in Example 2 of the patent leads to Treprostinil free acid; correct?

A. Well, this is -- for clarification, this is starting the nitrile. I believe we were talking about hydrolysis of the -- of an ester.

Q. Yes, I'm asking about the patent here.

A. Oh, in the patent.

02:16:54 Q. So with respect to the patent, it's benzidine nitrile
02:16:57 that gets hydrolyzed to a Treprostinil free acid; correct?
02:17:01 A. In the context of the patent, yes, that's correct,
02:17:03 sir.
02:17:04 Q. And can you go to the patent 11, please. And
02:17:09 column 11 the -- no, I'm sorry. That's Column 12, Derrick.
02:17:13 So column 11, keep going.
02:17:22 Doesn't provide any purity data for the
02:17:27 resulting Treprostinil free acid created after hydrolysis;
02:17:35 isn't that correct?
02:17:36 A. Give me just a second if that's --
02:17:41 Q. Sure.
02:17:43 A. I -- I don't see any mention of purity data here.
02:17:53 Q. And Example 2 is the starting batch of Claim 1; isn't
02:17:58 that correct?
02:17:59 A. Example 2 is the -- is the starting batch of
02:18:07 Treprostinil.
02:18:10 Q. Can you go to Example 4 for me, please? Which is
02:18:14 column 13.
02:18:30 Now, Example 4 is a slurry of Treprostinil and
02:18:36 diethanolamine salt; isn't that right?
02:18:37 A. I think that's the -- that's the title. And it's --
02:18:47 it used to be what they're forming.
02:18:49 Q. And the Treprostinil diethanolamine salt can be the
02:18:53 pharmaceutical composition -- please keep that up -- the

pharmaceutical composition of Claim 1; correct?

A. To the extent that a diethanolamine salt is an acceptable pharmaceutical salt, yes.

Q. Okay. If you take a look at the bottom part of Example 4, there's analytical data there. Do you see that?

A. I do.

Q. Can you blow that up. The whole chart at the bottom there, Derrick.

And in that data, there is HPLC data; correct?

A. Yes.

Q. And HPLC data that you testified to provides purity -- a standard purity -- excuse me -- a standard analysis technique to determine purity?

A. Right. In general, HPLC data is a technique used to assess purity.

Q. And do you see one of the batches of the Treprostinil diethanolamine salt has a purity of 104 -- 100.4 percent? Do you see that?

A. I see that number, yes.

Q. And you know that a compound cannot be 100.4 percent pure; isn't that right?

A. That's correct.

Q. And so this value that was generated by HPLC shows an HPLC error, at least in this example of at least 0.4 percent when conducted according to the inventors; is that right?

02:20:11 A. Right. So my take of this is in line of what you
02:20:14 just said. Out of a hundred percent, there is .4 percent
02:20:18 error. There might be a hundred -- a .4 percent error. I
02:20:23 don't know. I haven't seen this HPLC data. I don't know
02:20:25 how it was analyzed. It could have -- there's multiple
02:20:27 reasons that could happen, but you're right. The take-home
02:20:31 message is it's .4 higher than 100 percent. So there's a .4
02:20:35 discrepancy out of 100.
02:20:38 Q. Correct.
02:20:38 A. .4 discrepancy.
02:20:40 Q. Sure. You mentioned there could be a variety of
02:20:43 reasons. One of those reasons that could cause this error
02:20:46 is just HPLC error; correct? Just error in terms of running
02:20:50 the analysis?
02:20:50 A. Yeah, I believe that error would have been assessed
02:20:54 before running this analysis.
02:20:58 Q. Now, you focused your testimony on a particular
02:21:03 impurity called 15-epi-Treprostinil; is that right?
02:21:06 A. That's correct.
02:21:07 Q. And in your expert report, you provided a schematic
02:21:10 of how 15-epi-Treprostinil can be formed; correct?
02:21:18 Well, let me show you. I don't want you to
02:21:20 guess.
02:21:20 A. Yeah.
02:21:20 Q. Can we go to PTX 419, please? And Page 14?

02:21:26 This is your opening expert report; isn't that
02:21:29 correct, Dr. Toste?
02:21:30 A. I believe so, yes.
02:21:33 Q. And if you go to Page 14 and you take a look at the
02:21:35 top diagram, this is a schematic that you put into your
02:21:45 report that explains how the process of alkylation and
02:21:49 hydrolysis can result in either TN02, which is Treprostinil
02:21:54 free acid, or epi-TN02, which is epi-Treprostinil free acid;
02:22:00 correct?
02:22:00 A. That's correct.
02:22:01 Q. And on the top, you depict the process of alkylating
02:22:07 the BTO compound, and when you alkylate and conduct
02:22:12 hydrolysis of the BTO compound, you end up with the result
02:22:15 of Treprostinil free acid TN02; correct?
02:22:18 A. If I -- I'm sorry. You're asking me if in -- if I
02:22:23 just look at the structure of BTO, just that structure, not
02:22:27 the compounds the BTO that Yonsung has or?
02:22:30 Q. I'm asking you what you depict here in your example
02:22:34 is that you alkylate BTO, you conduct hydrolysis, and you
02:22:38 form Treprostinil free acid TN02; correct?
02:22:41 A. Yeah, that's the simplified version as one would
02:22:46 teach in sort of a sophomore organic chemistry. That's
02:22:49 correct.
02:22:49 Q. Great. And if you look at the bottom structure, you
02:22:51 talk about epi-BTO; is that right?

02:22:53 A. Yes, sir.
02:22:54 Q. And you know epi-BTO is a different compound than
02:22:58 BTO; correct?
02:22:58 A. Sure.
02:23:00 Q. And when you alkylate and conduct hydrolysis on
02:23:04 epi-BTO, you end up with epi-TN02; correct?
02:23:07 A. That specific reaction is correct.
02:23:10 Q. So the alkylation and hydrolysis of the compound BTO
02:23:14 doesn't result in the compound epi-TN02, does it?
02:23:18 A. In the sophomore organic definition of that question,
02:23:22 that's correct.
02:23:29 Q. Now, you mentioned the batches. I think you
02:23:31 mentioned the batches of BTO that Yonsung uses. You heard
02:23:38 Dr. Nuckolls' testimony this morning; correct?
02:23:39 A. I did.
02:23:39 Q. And we talked about batches of BTO that have the BTO
02:23:43 in it but then it has epi-BTO and a bunch of other
02:23:47 impurities; correct?
02:23:48 A. Yes, sir.
02:23:49 Q. And when you take that batch of BTO, the total batch,
02:23:56 some of it is going to be alkylation hydrolysis of BTO and
02:23:58 some of it is going to be alkylation and hydrolysis of
02:24:01 compounds that is are not BTO; correct?
02:24:02 A. Can you -- I'm sorry.
02:24:08 Q. Sure. Absolutely. When we have that batch of BTO,

02:24:11 from Yonsung that you described --
02:24:13 A. Yeah.
02:24:13 Q. -- there's going to be BTO in that batch as well as
02:24:16 other compounds that are not BTO within that batch?
02:24:21 A. Yeah, that's the batch of BTO as you described.
02:24:23 Q. Right. And when you alkylate that batch of BTO,
02:24:26 you're going to get alkylation of BTO in some instances, and
02:24:30 then you're going to get alkylation of compounds that are
02:24:33 not BTO in other instances?
02:24:36 A. So if I take that batch and I conduct those two
02:24:40 process steps, the result of that will be a batch of TN02
02:24:45 containing processed impurities.
02:24:48 Q. And those --
02:24:49 A. I'm sorry, I -- that's how a POSA would see it.
02:24:53 Q. So there's process impurities?
02:24:55 A. Yes.
02:24:55 Q. TN02 is not a process impurity; correct?
02:24:57 A. TN02 is not a process impurity.
02:25:00 Q. Okay. When you get those process impurities after
02:25:07 alkylation, those are process impurities that result from
02:25:11 alkylation of compounds within the batch that are not BTO?
02:25:16 A. To a POSA, those processes of impurities would be
02:25:19 from the alkylation hydrolysis process steps of the batch of
02:25:23 BTO.
02:25:24 Q. And I understand, but just for clarity sake, that

batch of BTO includes compounds that is -- are not BTO that get alkylated?

A. That is one of the potential sources for impurities.

Q. Okay. Now, you mentioned the process of epimerization during your direct testimony; correct?

A. Yes, sir.

Q. And you had some -- you were sitting with Dr. Nuckolls' testimony and you talked about epimerization there as well; correct?

A. Yes, sir.

Q. And in your expert report, you actually discuss epimerization, don't you?

A. I do.

Q. Can we go to PTX 419, which I think we're in at paragraph 42. And can you bring up the footnote that spans the bottom of Page 13 and the bottom of Page 14? Now, in this footnote, you reference a paper called Merritt; correct?

A. I do.

Q. And that's a 1980 paper?

A. Yes.

Q. And that Merritt paper addresses a compound that is not Treprostinil; correct?

A. It's a relative. It's a prostaglandin. It's a relative of Treprostinil but it's not Treprostinil.

02:26:58 Q. And the compound that is depicted in the Merritt
02:27:01 paper is considered to be a tertiary allylic alcohol;
02:27:05 correct?
02:27:06 A. That is correct.
02:27:07 Q. And Treprostinil is not a tertiary allylic alcohol,
02:27:11 is it?
02:27:12 A. It does not contain a tertiary allylic.
02:27:16 Q. And it's considered, actually, a secondary
02:27:19 non-allylic alcohol; correct?
02:27:21 A. Yes, sir.
02:27:23 Q. And in your footnote, if we pull out the whole thing
02:27:29 -- oh, that's the whole thing I apologize.
02:27:30 You state that because of the lack of an allylic
02:27:33 tertiary C-15 alcohol in Treprostinil makes it less likely
02:27:37 to be occurring in the hydrolysis alkylation reactions. And
02:27:41 then you say this process cannot be excluded as an
02:27:44 additional source of epi-Treprostinil; correct?
02:27:48 A. That's what I said, yes.
02:27:49 Q. So you believe that because Treprostinil is not a an
02:27:52 allylic tertiary C-15 alcohol, epimerization is less likely
02:27:58 a reason as to why you might see no epi-BTO -- excuse me --
02:28:04 epi-Treprostinil in one batch, but then the very next batch
02:28:07 that you make, it increases?
02:28:09 A. Less likely relative to the prostaglandin, yes.
02:28:14 Q. Now, can we go to that Merritt paper, which I believe

02:28:18 is 5 -- D as in David DTX 577.

02:28:37 This is the Merritt paper that you relied on in your expert report, Dr. Toste?

02:28:43 A. I -- I believe so.

02:28:45 MR. SUKDUANG: I'd like to enter DTX 577 into evidence.

02:28:47 MS. PAPPAS: No objection.

02:28:50 THE COURT: Admitted without objection.

02:28:52 (DTX Exhibit No. 577 was admitted into evidence.)

02:28:53 BY MR. SUKDUANG:

02:28:54 Q. Now, the structures of the compounds depicted in Merritt that underwent epimerization are identified in the left corner; is that right?

02:28:55 A. Yeah, it's the ones that you were -- that you have on the screen right now.

02:29:00 Q. And you agree that you cannot draw a conclusion based on that epimerization of Treprostinil occurred based on the tertiary allylic alcohol compounds in Merritt; isn't that right?

02:29:05 A. All I can say is that there's been an observation of epimerization of prostaglandin synthesis that raises the possibility, but I don't have any firm conclusions. I couldn't run experiments myself to validate that in the Treprostinil sample.

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02:29:38 Q. Now, you understand UT makes Treprostinil; correct?
02:29:40 A. I do.
02:29:43 Q. And you didn't ask UT for samples of their
02:29:46 intermediate Treprostinil to conduct experiments; is that
02:29:50 correct?
02:29:50 A. I didn't have an opportunity to conduct those
02:29:54 experiments.
02:29:54 Q. And you testified during your deposition that even if
02:29:56 you had those samples, you wouldn't be able to conduct
02:29:59 testing in your laboratory because it's -- it belongs to the
02:30:02 university; isn't that right?
02:30:04 A. What I meant by that is I couldn't conduct in my own
02:30:08 laboratory. We would have had to -- I would have had to
02:30:10 outsource those experiments because I can't use government
02:30:13 resources to conduct experiments. I'm certainly -- my group
02:30:18 would have had the expertise to conduct those. I certainly
02:30:21 know how to do mechanistic experiments. It's one of my
02:30:26 expertises, but I wouldn't have been able to use state
02:30:30 resources and federal funds to conduct experiments.
02:30:33 Q. Now, you also don't provide any -- other than this
02:30:36 paper, don't provide any example in the literature of the
02:30:40 epimerization of a secondary non-allylic alcohol like
02:30:47 Treprostinil, do you?
02:30:48 A. Certainly, I'm certain that there are examples of the
02:30:56 epimerization of secondary alcohols. If you add the clause

like Treprostinil, I don't believe I have an example of that.

Q. You gave deposition testimony that if you had any evidence, any evidence at all in the literature of epimerization of a secondary non-allylic alcohol like Treprostinil, you would have put it in your report?

A. I don't -- I don't recall exactly what I said, but I'm certain if I had examples that was related to Treprostinil, I would have included it in my report.

Q. Now, you testified that you reviewed Yonsung's certificate of analysis and other underlying data to evaluate the increase and decrease of 15-epi-Treprostinil within TN02 and TN; is that correct?

A. That's correct.

Q. And you made a chart, which I think we saw as PDX 30.10 or it's in Page 34 of your report, PTX 419.

That's the chart that you provided?

A. Yes, it is.

Q. And that's the chart that you provided to the Court today?

A. I believe it is.

Q. And this chart provides instances where the 15-epi-Treprostinil and TN02 decreased when compared to the pharmaceutical composition of TN?

A. This chart provides the examples, as I described,

of -- from my analysis of Yonsung's data where I had underlying HPLC data and -- or it was corroborated by Liquidia's Certificate of Analysis.

Q. Okay. Now, this data that you presented on the left-hand side, there are values there; correct?

A. Yes, sir.

Q. And those are percentages, percent values; correct?

A. Yes.

Q. Not actual numerical amounts of any particular batch of epi TN02 or epi-Treprostinil; correct?

A. Those are percent values as represented in the certificates of analysis.

Q. And to make this diagram in your report, you included an appendix in your report that identified the batch records, all of the batch records that you considered to form this table; is that right?

A. Yeah, that's correct.

Q. Can we go to the appendix. It should be Appendix 1.

And this appendix spans, I think five pages. Do you recall that?

A. I -- I don't recall how many pages there are, but there was a lot of data, so I could believe it could be five pages.

Q. Sure. And it looks like up to five pages of charts that you provided; correct?

02:34:27 A. Yeah, I don't recall. The five sounds about right.
02:34:33 Q. And some of the batches that you analyzed, as you
02:34:35 discussed, included -- include instances where the
02:34:39 15-epi-TN02 is lower than the 15-epi-Treprostinil in the
02:34:48 pharmaceutical batch; correct?
02:34:50 The analysis goes opposite than what you
02:34:53 presented on this chart?
02:34:53 A. Yeah, what I said is you could find some batches that
02:34:58 it did go as you described, that it did go up in the TN
02:35:02 versus the TN02. But I -- I don't recall, and I believe
02:35:07 that none of those batches had corroborating data from both
02:35:11 Yonsung and Liquidia.
02:35:12 Q. Are you sure all of these batches that you put in
02:35:14 here have corroborating data from both Yonsung and Liquidia?
02:35:17 A. Either that or I could look at the HPLCs and feel
02:35:21 really comfortable that, as I showed, that the resolution
02:35:26 was good.
02:35:26 Q. There are some batches in your chart that do not have
02:35:28 corroborating data from both Liquidia and Yonsung; correct?
02:35:31 A. I -- I think that's right. They -- but they would
02:35:36 have the underlying data from Yonsung, the HPLC, so I could
02:35:39 look at them and see, yeah, this is good resolution. I can
02:35:43 trust this number.
02:35:45 Q. Now, I'd like to take a look at the data that you did
02:35:47 not put in this chart. Can we bring up DDX 12.1.

02:35:52 And, Dr. Toste, we pulled this data from your
02:36:12 appendix PTX 149.
02:36:14 A. Mm-hmm.
02:36:15 Q. And we used the same color coding for Yonsung yellow,
02:36:20 Yonsung blue, and then we added Liquidia in green. Do you
02:36:23 see that?
02:36:23 A. I do.
02:36:25 Q. And these are instances where either Yonsung or
02:36:31 Liquidia observed more 15-epi-Treprostinil in the final
02:36:35 batch than they do in the yellow starting batch; correct?
02:36:40 A. That's correct.
02:36:41 Q. And if you take a look at TN11J010 --
02:36:47 A. Mm-hmm.
02:36:47 Q. -- which is the one in the middle here, there's
02:36:50 actually one, two, three, four, five different analyses
02:36:54 conducted on the same batch -- excuse me. Four analyses
02:36:58 conducted on the same batch of the final composition TN;
02:37:02 correct?
02:37:02 A. Yes, sir.
02:37:03 Q. And there's variability in the results, even within
02:37:08 Liquidia; correct?
02:37:09 A. Yeah, so it's my recollection about this batch -- I'd
02:37:13 feel more comfortable if we could actually pull up, let's
02:37:16 say, the cover sheet for the certificate of analysis for
02:37:19 that large green -- is that possible -- for that large

green --

Q. We can in a moment, but for your analysis you didn't go to a specific COAs to conduct your analysis for the Court, did you?

A. I certainly did.

Q. You didn't show up the COAs?

A. I'm sorry?

Q. Did you show display the COAs?

A. Did I -- oh, to the Court?

Q. No.

A. No, but I used them in my analysis.

Q. And this is from your analysis; correct? All these -- let me do -- we'll fine the COA for you. Okay. It will take a second. But let me ask my question.

(Discussion held off the record.)

BY MR. SUKDUANG:

Q. We talked about error in HPLC; correct?

A. Yes, sir.

Q. And you didn't assess when you were doing your analysis the error associated with HPLC that might be observed within Yonsung or Liquidia, did you?

A. I looked at in Yonsung's DMF. They have an error analysis which I certainly looked at. I don't remember doing that for Liquidia's.

Q. But you didn't apply that error analysis in your

02:38:19 analysis for the your expert report, did you?
02:38:21 A. I applied -- so Yonsung's lowest detection limit that
02:38:25 they report was 0.011. That's what they reported. And
02:38:32 that's what I took as the lower limit for detection.
02:38:35 Q. Well, let's take a look at some that have validation
02:38:37 data. Can we go to PTX 427, please? And this is Yonsung's
02:38:52 DMF that you considered; correct?
02:38:56 A. Yes, sir.
02:38:56 Q. And can we turn to page ending in 364.
02:39:01 And do you see here that within Yonsung's DMF,
02:39:13 they conducted an analysis of 15-epi-Treprostinil using
02:39:18 various concentrations of 15-epi-Treprostinil?
02:39:21 A. I do.
02:39:23 Q. And the concentrations on the top box are 60 percent,
02:39:28 80 percent, and 120 percent of 15-epi-Treprostinil?
02:39:32 A. I'm -- I was actually more interested in the number
02:39:34 in micrograms per milliliter.
02:39:36 Q. We'll get there in a minute. But you looked at --
02:39:39 this is some data in Yonsung's DMF where they actually tried
02:39:44 to detect 15-epi in various concentrations within the
02:39:48 samples; correct?
02:39:49 A. Right. In the concentrations of those depicted and
02:39:52 sort of in the middle that have in micrograms per mL, yes,
02:39:55 sir.
02:39:55 Q. And the concentration of the solutions tested, 60,

02:39:59 80, and 120 percent, those concentrations of 15-epi are much
02:40:04 higher than the amounts of 15-epi that you can actually see,
02:40:07 that you actually looked at percentage-wise in the data you
02:40:11 analyzed for the Court?
02:40:12 A. I -- I don't think so because if you look at the
02:40:15 concentration, that's what's relevant. The percentage is
02:40:18 irrelevant to -- because when you're integrating is -- is
02:40:22 concentration. You're integrating micrograms per
02:40:25 milliliter. The percentage is irrelevant.
02:40:27 Q. So, but you used percentage in your analysis, didn't
02:40:30 you? Not micrograms per milliliter?
02:40:32 A. Percentage relative to the entire batch, not
02:40:35 percentage relative to some testing data.
02:40:38 Q. If you take a look at the recovery, you can see for
02:40:40 the 60 percent, values of 106, 98, and 106. Do you see
02:40:46 that?
02:40:46 A. Yeah.
02:40:48 Q. And you provided testimony that that value, those
02:40:52 values, indicate from a 4 to 6 percent error rate in the
02:40:58 assay; correct?
02:40:59 A. Well, the -- the relative standard deviation says,
02:41:02 you know, four percent in that specific assay. So if you go
02:41:08 down to concentrations of less than a microgram per
02:41:11 milliliter, you get a four percent deviation on that
02:41:15 microgram per milliliter concentration. That's how you

would read that.

Q. And you talked about seeing trends, I think, on your direct testimony. You want to see trends in HPLC assays; right?

A. Yes.

Q. And the trend here is that as you decrease the concentration of 15-epi-Treprostinil in a sample, the error rate increases?

A. Well, you have to be careful in doing that right because the error is relative to the amount you put in. So four percent of .976 is -- it's bigger but not that much bigger than the .49 percent or 1 percent of 1.22, right. So, you're right. It does. But those numbers, the percent RSD, sort of exaggerates that when you're looking at it relative to concentrations.

Q. So you're saying 4.18 percent is not much different than 0.49 percent?

A. When you're talking about concentrations because you have to multiply the number of the percent error by the concentration number. Remember, HPLC is assessing concentration. We are reporting that as a percent error, but what it's really looking at is the amount, and the amount is relative. It's a microgram in a milliliter. It's not -- the HPLC doesn't know your percentage. It only knows the amount that's in there. It says it's microgram per

02:42:30 milliliter then we calculate the percentage afterward.
02:42:33 Q. And your analysis just looked at percentages, not
02:42:36 micrograms per milliliter within the Yonsung samples?
02:42:40 A. Percent related to the micrograms per milliliter.
02:42:42 Q. Correct. But your analysis is not the specific
02:42:45 micrograms per milliliter you point to here. Your analysis
02:42:47 is to the percentage?
02:42:49 A. But they're directly proportional.
02:42:56 Q. Now, you understand that Yonsung had to validates its
02:42:59 HPLC assay; correct?
02:43:00 A. Yes, sir.
02:43:00 Q. And you understand that even with validated HPLC
02:43:03 assays, there's normal error in measurements?
02:43:06 A. Yes, sir. I mean, that's what it says in here.
02:43:10 Q. And as the amount of impurities decrease, the
02:43:14 likelihood of having some error would increase; correct?
02:43:17 A. I can't conclude that. I mean, it's -- if you look
02:43:19 at the bottom one, on --
02:43:21 Q. The bottom Treprostinil ethyl ester?
02:43:25 A. Yeah. Again, if you look at that trends, it goes up
02:43:27 and then down. So.
02:43:28 Q. But you didn't point to Treprostinil ethyl ester in
02:43:31 your report. You're focusing on 15-epi-Treprostinil, and
02:43:33 that shows a trend, doesn't it?
02:43:35 A. But your question was with regard to HPLC in general,

wasn't it?

Q. With respect to HPLC, you'll see error; correct?

A. Yes, sir.

Q. And with respect to 15-epi-Treprostinil, the trend is the lower the concentration the higher the error?

A. But again, you're taking a trend from a single trend and then if I just extend that HPLC technique to the bottom one, that trend no longer holds. I would want to see reproduction of that trend before I reached that strong of a conclusion. I can certainly agree with you that this data suggests that this is a single data point. That, to me, is not a trends.

Q. But this data point is in Yonsung's DMF that they submitted to the FDA validating their HPLC assay?

A. Yes, sir.

Q. And you relied on that type of data to conduct your analysis of infringement of the '066 patent; correct?

A. That's correct. Because even if you took the maximum error here, 4 percent. 4 percent, and if you want to stick with percentages because it seems that's maybe easier to think about because that's what I used, four percent error on .02 percent. So, if you multiply four percent to .02, that is a small number that's way outside the range of the error that I used in my analysis.

Q. But that's based on a 60 percent concentration.

02:44:51 We're talking much less in the samples that you're looking
02:44:53 at.
02:44:54 A. No, that's based upon .976 milligrams per microliter.
02:45:02 Q. Do you recall submitting a declaration recently in
02:45:05 this case regarding the ability to analyze infringement
02:45:10 based on the data that you had?
02:45:13 A. I do.
02:45:13 Q. And do you recall saying in your declaration that you
02:45:15 were unable to meaningfully explore possible explanations
02:45:18 for deviations or discrepancies in the impurity profiles?
02:45:22 A. Yeah, I do.
02:45:26 Q. And so because you're unable to meaningfully explore
02:45:30 possible explanations for deviations and discrepancies, you
02:45:32 can't rule out that the changes you see in your analysis in
02:45:36 your report that you presented to the Court are due to just
02:45:38 error or deviations in the -- in the HPLC assays?
02:45:42 A. Well, there's, A, there's a clear trends. B, there's
02:45:46 data from both Yonsung and Liquidia that were provided by
02:45:49 them, and I could look at the underlying HPLC and get pretty
02:45:53 comfortable with that. So in the face of underlying HPLC
02:45:55 data, corroborating evidence from Yonsung and Liquidia, and
02:45:58 a clear trend, I'm very, very comfortable in reaching that
02:46:01 conclusion.
02:46:02 Q. Now, talked about a clear trend, but we saw batches
02:46:05 where you had where it went up and we saw batches where it

02:46:07 went down. So what is the clear trend? If you're only
02:46:10 looking at the evidence that you want to point to, there's a
02:46:13 trend, but if you look at the totality of the evidence that
02:46:15 you analyzed, there isn't a clear trend, is there?
02:46:18 A. Well, I'm happy to go through the batches that I
02:46:21 excluded with you and tell you the reasons why I excluded
02:46:23 them, but even if I include, you know, one or two of those
02:46:27 batches, the preponderance of the evidence leads me to
02:46:29 conclude that more likely than not Yonsung is going to
02:46:32 infringe.
02:46:32 Q. Then why did you tell the Court you're unable to
02:46:36 meaningfully explore possible explanations of deviations
02:46:37 discrepancies?
02:46:37 A. Because I didn't have samples.
02:46:39 Q. One additional question I skipped, and I apologize.
02:47:09 Can you go back to JTX 2, which is the patent.
02:47:12 And can you -- with respect to your analysis for
02:47:23 infringement, you compared the batch of TN02 that was made
02:47:30 to use the batch of -- was used to make the batch of TN;
02:47:34 correct?
02:47:34 A. Yeah, I think so.
02:47:38 Q. Can we go to Example 6?
02:47:39 Now, Example 6 spans two pages, columns 15 to
02:48:03 17. And at the end of column 17 and the chart -- up in the
02:48:11 chart, Derrick -- there's a purity identified there;

02:48:14 correct?
02:48:14 A. Yeah, that's -- yes, sir.
02:48:16 Q. And one of the purities is for the former process and
02:48:19 another purity is for the process according to the present
02:48:22 invention?
02:48:25 A. Yeah, I believe that's correct.
02:48:26 Q. Now, for your infringement analysis, we're looking at
02:48:29 the patent Claim 1, you can't compare the batch from the
02:48:33 former process against the batch of the process according to
02:48:38 the invention in order to conclude infringement, can you?
02:48:41 A. I don't understand.
02:48:44 Q. Sure. The batch of the former process at bottom,
02:48:47 that's not the starting batch that was used to make the
02:48:50 batch in the right hand column; correct?
02:48:52 A. In this specific example?
02:48:58 Q. Correct.
02:48:58 A. I believe that's correct.
02:49:04 Q. And because the batch on the left wasn't used to make
02:49:08 the Treprostinil that's shown on the right, you are -- can't
02:49:11 compare 99.0 to 99.9, in terms of an infringement analysis;
02:49:16 correct?
02:49:16 A. I mean, by saying I can't compare is I don't have the
02:49:22 knowledge to know if that batch is the one that was made to
02:49:25 that, so I can't reach that conclusion.
02:49:28 MR. SUKDUANG: I don't think I have anymore

02:49:31 questions. Thank you, Dr. Toste.

02:49:49 THE COURT: Go ahead.

02:49:50 REDIRECT EXAMINATION

02:49:50 BY MS. PAPPAS:

02:49:53 Q. Dr. Toste, in terms of what data you relied on and
02:49:57 included in your analysis, could you explain the distinction
02:50:02 between the certificate of analysis and the underlying data
02:50:06 that you referred to.

02:50:07 A. Right. So I don't know if we can pull up -- maybe
02:50:11 the one that counsel brought up would be a nice one to look
02:50:14 at for a Liquidia Certificate of Analysis. The counsel
02:50:22 brought one up and you said --

02:50:23 Q. The batch TN116J010 or the --

02:50:28 A. The one with the two green bars and he said look at
02:50:31 this green bar and I said, yeah, I would like to look at the
02:50:34 Certificate of Analysis.

02:51:04 Q. Can we please pull up PTX 343. Let me navigate down
02:51:30 to --

02:51:31 Dr. Toste, could you direct us to when we should
02:51:33 stop.

02:51:33 A. Yeah, keep going. I think here. Right. This would
02:51:40 be -- can we blow up sort of in the middle there? Yeah.
02:51:44 Perfect. Thank you so much.

02:51:45 So this is the typical certificate of analysis
02:51:49 provided by Liquidia. And you can see, just like

02:51:53 Dr. Nuckolls shows, with the -- the typical impurities,
02:51:57 epi-Treprostinil and some other related impurities, and, you
02:52:00 know, total impurity analysis here. And so when I look at
02:52:04 this, there's things written in here, things scratched out.
02:52:10 And I have no HPLC data provided by Liquidia. I just have
02:52:15 this.
02:52:17 And when you compare this to the HPLC data I
02:52:20 showed in my direct testimony, where I showed that the big
02:52:23 peak and the small peak next to it, you can really look at
02:52:26 that, and you can judge. Did the machine do a good of
02:52:29 separating these? Did the machine do a good job of
02:52:32 integrating it? When you see this type of data, then you --
02:52:34 you feel uncomfortable using it. I certainly think I can't
02:52:37 use this data. Don't know why this was scratched out.
02:52:41 There are instances like this, where I didn't use this data
02:52:44 because I don't know what this data means, especially in
02:52:48 comparison to when I have underlying data. By underlying
02:52:52 data, I mean just the HPLC trace I mentioned in my
02:52:55 testimony. So I would exclude this as corroborating data
02:52:58 because I don't know where this data comes from. I don't
02:53:01 have HPLC data. I just have this with stuff scratched out
02:53:05 on it.
02:53:05 As an example of a Certificate of Analysis, you
02:53:08 just see these numbers. You don't know why where they come
02:53:11 from. If they corroborate data where they have an HPLC, so

I have an HPLC and this data and the Certificate of Analysis corroborates it, two pieces of data corroborated, clean data, good to use. When you see data like this, you can't use it. I couldn't. I don't know who wrote that. I don't know where that data comes from.

Q. Could we also pull up DTX 222.

And again, Dr. Toste, please direct us to wherein this document to stop.

A. Keep scrolling. Right here. So, again, you know, this says not detected, not detected, not detected, not detected for epi-Treprostinil.

And this Liquidia data, I couldn't go to the HPLC to see if not detected was a result of bad integration, bad separation, operator did not manually integrate. I don't know what this ND comes from, so I can't feel comfortable using that unless I could look at the Yonsung data and it also said not detected. If I could look at HPLC, see that it was not detected there, Yonsung's data looks guide, Liquidia's data corroborates it, I could use it. In the absence of that, you can't use this data.

Q. And then if we could also pull up the last one, I believe, that was on that chart, PTX 641.

A. Oh, that was already on the first page. Maybe not. Yeah, again, it's the same thing. I think despite being in Korea, I think we can understand what epi-Treprostinil is

and what and ND is. It's the same issue. When there's no underlying data, we can't -- we can't look at this and make any conclusions in the absence of corroborating, underlying data from a different source like Yonsung.

Q. So, which document does this appear to be from?

A. Yeah, this -- it's in Korean, so I'm certain this is a Yonsung one, so I think if think if we keep scrolling down, we'll eventually see the HPLC data.

Q. And then do you recall there was a -- on that chart, there was another green bar from the Liquidia's COAs. Do you recall reviewing that COA as well?

A. This is the 116J batch?

Q. Yes.

A. I do. So if this is J batch, it might not have HPLC data, and I guess it doesn't have HPLC data in this specific batch. There was some earlier batches that were provided by Yonsung where they didn't provide HPLC data. And in those cases when there was ND, it was the same problem. I couldn't look at the HPLC data, so I couldn't assess it.

Q. So, how did your ability to review the underlying data affect your conclusions in the COAs compared to the underlying records that you just described?

A. Oh, yeah. As I think I described, they're much more confident. A POSA is much more confident. Not just in the context of this case. In my lab, if a student tells me I

have this compound that I made with, you know, 95 percent purity, I will ask them, before we submit the paper, I will say, provide me the HPLC data because we're going to need that HPLC data to submit it. And then I will feel confident and the reviewers will feel confident in that result. So when you have HPLC, not just in the context of this case, but in the context of my everyday life as a professor who practices in organic chemistry and stereochemical synthesis, I need that HPLC data to be confident now. The reviewers of my papers need that HPLC data to be confident. And the in the absence of that, it's just a number. And you might feel confident if the number comes from two different sources so you know it's validated internally and externally. But beyond that, you really want that underlying HPLC data.

Q. It sounds like you did review a large amount of data. Let me just ask you. How strong is your opinion that Liquidia's proposed product will infringe based on the data that you saw?

A. Well, there's no epi-Treprostinil in BTO. You undergo these process steps. You generate textbook example of a process impurity, epi-Treprostinil in TN02. The salt crystallization, all the evidence suggests that that -- there's a preponderance of the evidence that suggests more likely than not Yonsung process will decrease the amount of epi-Treprostinil in Step 12. And I think my conclusion that

it -- Yonsung or Liquidia will infringe on UTC's patents is absolute. I'm highly confident in that.

Q. And you were asked a bit about in the specification of the '066 patent, there was a figure in column 13 or at -- and by figure, I mean the assay percent value that was there. Did you -- did you review underlying data or the analysis for that in particular?

A. You mean the table from the patent that counsel put up during my cross?

Q. Yes.

A. The only thing I saw was that data in the patent.

Q. So, is epi-BTO the same as epi-Treprostinil?

A. They're entirely different compounds. If you gave me a sample of epi-BTO, I could inject it on an HPLC, I could run other characterization techniques like NMR, and I would also always concludes epi-BTO is not epi-Treprostinil. Therefore, epi-Treprostinil could not exist in Yonsung's BTO.

Q. In the materials you reviewed from Yonsung's process, in what instance did the 15-epi-Treprostinil first appear?

A. It first appears in Yonsung's batches of TN02.

Q. And when is that relative to the alkylation and hydrolysis steps?

A. It appears after -- after steps 10 and 11, you know. So the alkylation and hydrolysis process steps in Yonsung's

DMF.

MS. PAPPAS: Thank you. No further questions.

MR. SUKDUANG: I'm sorry. Go ahead, Your Honor.

THE COURT: I was going to say, so we're done; right?

MR. SUKDUANG: Yeah, we're done.

Yeah, I just needed to enter some exhibits. That's all.

THE COURT: Well, so, Doctor, you're done. You can step down. Watch your step.

THE WITNESS: Thank you.

THE COURT: Go ahead, Mr. Sukduang.

MR. SUKDUANG: It was the exhibits that we put in from Dr. Dr. Toste's appendix, and I'm going to read them. They come from PTX had 419, which is we're not entering them, just to say it's the appendix from, that report.

The documents we're submitting to enter are PTX 809, PTX 330, PTX 810, PTX 330, D as in David TX 220, P as in Peter TX 344, PTX 341, PTX 343, PTX 641, D as in David TX, P as in Peter TX 656, PTX 658, DTX 223, DTX 127, DTX 181, DTX 225, PTX 607, DTX 210, P as in Peter TX 814, PTX 795, D as in David TX 227, P as in Peter TX 712, P as in Peter TX 71, and P as in Peter TX 1916.

MS. PAPPAS: We object. This is a new chart not

previously disclosed, and it inaccurately represents. As you may recall, counsel said that that is a chart based on data from Dr. Toste's opening report.

THE COURT: Dr. Who?

MS. PAPPAS: I am sorry.

THE COURT: I'm sorry. Speak up a little.

MS. PAPPAS: As you may recall, counsel represented that that is a chart based on data from Dr. Toste's opening report and stated that it comes from the appendix of that report and the data reported therein, which spans five pages.

Dr. Toste released a supplemental opening report after Liquidia produced further documents underlying the HPLC documents and data after Dr. Toste's opening report was served. And in the updated report from Dr. Toste, the supplemental report, there were further batches, more data that was presented in the chart on Page 10 of his supplemental opening report. That is actually the chart that we displayed on direct examination and the supplemental appendix to that spans onto the sixth page. So this is an inaccurate representation and --

MR. SUKDUANG: I'm not bringing in the other batches.

THE COURT: I'm sorry. Which of the 25 different exhibits that were mentioned there are you talking

about?

MR. SUKDUANG: These are all in his supplemental appendix; correct? It's just additional exhibits that are missing, if I understand you correctly.

MS. PAPPAS: To the extent that you contend that this is a further supplementation or completion of Dr. Toste's data, we believe it's an inaccurate representation, and we were not able to consider this chart before now.

MR. SUKDUANG: Sure. We're not asking to submit the demonstrative. We're submitting the underlying exhibits. If they're saying this just comes with his opening report, fine. We'll just submit these with the opening report. If they want the other ones in, we can put those in too, but I don't think this chart --

THE COURT: So, didn't you run through -- or somebody. Didn't you go through a lot more exhibits than you actually used with him?

MR. SUKDUANG: No, I didn't. I only put in -- I used a paper and I put the paper into evidence. And then we used this chart and then the other thing was his expert report, which doesn't come into evidence.

THE COURT: Right. But so we're talking -- I stopped writing down as you read along the -- there was something that was admitted that went away as you went

along. The things you're trying to get in, I have no idea what they are.

MR. SUKDUANG: They are the underlying data. The same thing that they used with Dr. Toste in his chart. It's its underlying data from his appendix. This is his data that he relied on. What Ms. Pappas is saying is that there might be additional data that's not in his chart. Okay. We're just seeking to enter into evidence what's on this chart. If they believe more evidence should come in, then we have no objection --

THE COURT: But what is the point of all this underlying data?

MR. SUKDUANG: That's what Dr. Toste said. We need to look at all the underlying data. The patent doesn't have the underlying data. These are verified HPLC assays --

THE COURT: But how is all of this stuff relevant? Why are we even arguing about it? What am I going do with this? You know, both sides are just admitting exhibits for no particular reason so far as I can see. And now you're arguing over it.

You know, it's one thing if you're just going to admit a thousand exhibits for no reason and not argue about it, but if you're going to argue about it, then tell me why I should let any of them in the first place.

MR. SUKDUANG: Well, I think it goes to the

totality. These are -- these are evidence that they rely on to establish infringement. They believe it's relevant. We don't think it is because it's a different -- it's a different impurity. Nonetheless, they're relying on this evidence.

THE COURT: Well, so --

MR. SUKDUANG: The evidence we presented --

THE COURT: Is your expert going to say something about each of these pieces of evidence?

MR. SUKDUANG: He's going to talk about what that evidence shows.

THE COURT: Okay. Well, when we get there and he or she does something with them, let's deal with them then. But right now, I have no context. I have no idea why you're doing any of this, and since I don't have any idea, as far as I'm concerned, it's irrelevant.

MR. SUKDUANG: Well, their exhibits are the same, Your Honor.

THE COURT: Yeah. Yeah, well they're irrelevant, too.

MR. SUKDUANG: Thank you, Your Honor.

THE COURT: And to try to avoid this in the future, from now on, if there's some exhibit you want to get in, move it in at the time. Because I can't deal with just reading off, you know 30 exhibits and having someone object

to them. I mean, that's impossible.

MR. SUKDUANG: Understood, Your Honor.

MR. CARSTEN: Understood, Your Honor.

THE COURT: So what, Mr. Carsten, are you going to tell me you're resting?

MR. CARSTEN: Unfortunately, Your Honor, no. We've got some video clips to play. The next witness is by video, Kelli Collin.

THE COURT: Okay. Go ahead.

MR. CARSTEN: Thank you.

(Video playing.)

Q. And can you please states your full name for the record.

A. Kelli Reynolds Collin.

Q. And you mentioned out-of-specification event. Can you explain what those are.

A. An out-of-specification event falls under two categories. One category is an instrument that is out of calibration, so it is not operating correctly. And the other event is an analytical result that may be out of the specification.

Q. When you say an analytical result that might be out of a specification, can you explain to me what that means.

A. So, for example, if you have a defined range of Ph that is part of your process, and this is hypothetical

because I do not remember the ranges for Liquidia. Say your range is 5 to 7 and you take a test result for pH and that result is 7.5, you have to investigate why that would occur and what the impact of that have. That would be done under an out-of-specification event.

Q. Is there a common approach on how to deal with out-of-specification events in the field?

A. There's a regulatory guidance document for dealing with out-of-specification events that is provided by the FDA.

Q. Is that entitled Receipt, Handling, and Control of Materials?

THE WITNESS: Yes. To the best of my knowledge.

Q. If Liquidia changes the standard of procedure for receipt, handling, and control of materials, does it have to inform the FDA?

THE WITNESS: No.

Q. This document has Bates number LIQ 02798133. Let me know when you can see it.

And this is a receiving inspection report for Treprostinil sodium API; correct?

A. Yes.

Q. If you go down two or three -- I guess three rows, there is a row that says verified transport condition. Temperature, if applicable.

Do you see that?

A. Yes.

Q. That's also checked as the requirements met; correct?

A. That is correct, on this form.

Q. And how would that answer be verified?

THE WITNESS: That depends on the material, whether or not there was a temperature device. Like, so it says temperature if applicable, or if it's -- if there are packaging configurations and the materials like specification, then they would verify that.

Q. How would you determine what happened to Liquidia lot number LIQ 00572?

A. By looking at this documentation as it stands, I would go into GMP storage and look for the document or for the material and see if it is -- what the label is.

Q. Does that room contain just documentation, or does it contain the lots as well?

THE WITNESS: It contains the material itself.

Q. Is the GMP room temperature controlled?

A. The GMP room itself is not temperature controlled. There are chambers for temperature control in the room, and those are monitored.

Q. What monitors the temperature in the chambers in the GMP room?

A. There are sensors in the chambers.

03:11:41 Q. Are there reports on the sensors in the chambers?
03:11:47 A. There are trends -- uh-huh -- and alarms.
03:11:51 Q. You will see that there is a declaration letter from
03:11:54 Yonsung.
03:11:55 Do you see that?
03:11:55 A. I do.
03:11:56 Q. Great. In the second sentence, it says, "If the
03:12:02 material is exposed to the excursion at freezing conditions,
03:12:04 which is lower than our recommended storage range of plus 2
03:12:07 degrees Celsius to about 8 degrees Celsius, we are also able
03:12:11 to guarantee that the quality of Treprostinil sodium at the
03:12:14 temperature at freezing condition would have no issue";
03:12:17 correct?
03:12:17 A. That's correct.
03:12:19 Q. During your time at Liquidia, are you aware of
03:12:22 receiving shipments that had excursions?
03:12:26 THE WITNESS: Sure.
03:12:29 Q. And what is an excursion?
03:12:33 A. Anything that is outside of the storage range.
03:12:39 Q. Does Liquidia have a policy concerning excursions?
03:12:42 THE WITNESS: We have a material specification
03:12:45 for the storage, and it includes requirements for the
03:12:50 storage of the material.
03:12:51 So, if it's outside of that, then we would
03:12:54 review that.

Q. I guess I'm asking after you review it, is there -- does Liquidia have a protocol concerning what to do if a lot has been subjected to an excursion?

A. I would have to read the SOP to determine, but there are multiple possibilities. And so the answer is that it depends.

Q. Would requirements for data loggers be outlined in an SOP?

A. I don't recall an SOP specific to data loggers.

Q. And so, is it your understanding that the Treprostinil sodium that is being referenced here is stable at 25 degrees Celsius for up to six months under accelerated conditions?

THE WITNESS: It is my understanding that there was no degradation detected by HPLC for the three batches in question under this report.

Q. So again, my question is confirming that the section of the NDA, of Liquidia's NDA that cross-references stability in Yonsung's DMF that confirms that Treprostinil sodium is stable when stored at 25 degrees Celsius, correct?

THE WITNESS: It showed that there was no degradation in a six-month stability study at 25, correct.

Q. Correct. Okay.

A. Correct.

(Conclusion of video.

MR. CARSTEN: And, Your Honor, you'll be relieved to know that the only document that was use in that was PTX 19, which is already in evidence.

Next, we would call by video Marisa Law. This video runs about six minutes, Your Honor. After that, we'll have a live witness.

THE COURT: Okay.

(Video playing.)

Q. You --

MR. CARSTEN: Actually, Your Honor, you waived off the binders on the last witness. We have them when the Court --

THE COURT: Yeah, I just give them to the court reporter. I don't think the rest of us need them.

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

(Video playing.)

Q. -- are you currently employed by Liquidia; is that right?

A. Yes.

Q. What's your current position?

A. Director regulatory and PV operations.

Q. What does that mean?

A. Regulatory and pharmacovigilance operations.

Q. Regulatory and what?

A. Pharmacovigilance.

Q. What's pharmacovigilance?
A. It's drug safety.
Q. What are your responsibilities with respect to Liquidia's NDA product?
A. To handle the submission filings.
Q. When you say "handle the submission filings," what do you mean by that?
A. I collect the prepared documents and work with our publisher for submissions.
Q. Since starting with Liquidia, what types of filings have you submitted?
A. I've submitted safety adverse event reports, annual periodic reports, and NDA updates.
Q. Who else at Liquidia is involved with Liquidia's regulatory submissions relating to Liquidia's LIQ861 pharmaceutical product?
A. Just me.
Q. In what ways has it been updated or modified since that original submission?
A. We have updated sections of the NDA and provided additional documents per the FDA's request.
Q. When you say "most current filing," what do you mean?
A. Our electronic viewer allows us either to review by sequence number or the NDA in its entirety with the most current versions.

Q. So, if you make a submission, do you always update every section?

A. No.

Q. Who determines what sections are updated?

A. It's a collaboration between the CMC group, the clinical, and the non-clinical group.

Q. So who -- you mentioned the CMC group, the clinical group, and the non-clinical group. That -- they -- it would be all of them as a team; right?

A. Yes.

Q. At that time before you had filed, when Liquidia was deciding what to file, who would have been on the team?

A. My main contact for the CMC would have been Kristy White, and then my main contacts for clinical would have been Tobi Bonham and Rob Roscigno, and my main contact for non-clinical would have been Stephanie Anderson.

MS. PAPPAS: We're going to pull up another document marked as Tab 5, with Bates stamp LIQ 02797556, which is marked as Exhibit 9.

Do you recognize this document?

THE WITNESS: I do not.

Q. Do you recognize this type of document?

A. I do not.

Q. Do you agree that it appears to be a receiving inspection report?

A. Yes, in viewing the document, it is.
Q. Do you recognize Liquidia's headers on this document?
A. Yes, I do recognize the headers.
Q. Do you have any reason to question that this document is what it appears to be?
A. In reviewing it, no.
Q. Are these receiving inspection reports submitted to the FDA?
A. I do not know.
Q. Who would you ask to find that out?
A. I would probably ask a member of the CMC group if they could direct me to the person that would be knowledgeable on this.
Q. This references at the top a standard operating procedure and D.O.C. number SOP LIQ 01609. Are you familiar with Liquidia's standard operating procedures?
A. I am not familiar with this procedure that is referenced.
Q. Are standard operating procedures submitted to the FDA?
A. They are not.
Q. If Liquidia changed their standard operating procedures, would Liquidia have to notify the FDA of that change?
A. They would not.

Q. If Liquidia changes an SOP for, for example, the receipt, handling, and control of materials, does Liquidia destroy all batches if the parameters change?

A. I do not know.

(Conclusion of video.)

MR. CARSTEN: Your Honor, United Therapeutics would call as its next witness Cesar Matto.

THE COURT: All right.

MR. CARSTEN: My colleague, Adam Burrowbridge, will be conducting the examination.

THE COURT: Okay.

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

THE WITNESS: Cesar Matto, C-E-S-A-R M-A-T-T-O.

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

THE WITNESS: Yes, I do.

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

MR. JACKSON: Your Honor, may I approach with a binder?

THE COURT: Yes.

MR. JACKSON: And if it's okay, Your Honor, we'll pull those other binders away.

MR. BURROWBRIDGE: May I start, Your Honor?

THE COURT: Yeah, sure.

DIRECT EXAMINATION

BY MR. BURROWBRIDGE:

Q. Good afternoon, Mr. Matto.

A. Good afternoon, sir.

Q. What is your professional background?

A. I -- my professional background covers the area of quality assurance, compliance, and compliance regulatory and compliance with the CRF 10 through 11 regulatory compliance that is complex in application. I've been with the industry 30 years. And last ten years, I've been with FDA in the office of compliance as a senior policy analyst. My responsibilities while in the industry include a number of activities within quality assurance. That is receiving of materials, reviewing materials, testing of those material, the results, analyzing the results, and I also, in the quality assurance area of finished goods, stability data for release those reports, and within the FDA, I was also responsible for reviewing multiple inspection reports, making decisions on facilities that would impact the application that is a regulation of a firm to produce its parent product safety applications.

Q. Can we please review PTX 508. It should be in your binder, Mr. Matto.

A. Okay. Yeah, I recognize that document. That is my CV. Could you run down, please. Mm-hmm.

Q. This looks like an accurate representation of your CV?

A. Yes. Yes.

MR. BURROWBRIDGE: I move to admit PTX 508.

MR. PIVOVAR: No objection, Your Honor.

THE COURT: Admitted without objection.

(PTX Exhibit No. 508 was admitted into evidence.)

MR. BURROWBRIDGE: Your Honor, United Therapeutics offers Mr. Matto as an expert in the field of pharmaceutical manufacturing and regulatory oversight, including the application of the code of federal regulations to current good manufacturing practices, quality assurance, material receipt, storage, and release, vendor qualifications, regulatory compliance, and enforcement of development, clinical supply, and commercial manufacturing including GMP requirements, protocols, and systems, U.S. and foreign regulatory audits, FDA inspection, and compliance.

MR. PIVOVAR: Your Honor.

THE COURT: Okay. Go ahead.

MR. PIVOVAR: Yeah, it's hard for us to discern

from that definition exactly what he's being proffered for.

THE COURT: You've read his report. That's what he's being proffered for.

MR. PIVOVAR: So we're objecting to the scope of that because we don't know anything that is included in that. It's going beyond what the actual expertise. During his deposition, I asked him are you claiming to be an expert in the chemical stability of Treprostinil sodium? He said no, I'm not a chemist, so if there are any issues where he wants to opine as a chemist, that's wrong. Excuse me.

And he said -- and I asked him what are you an expert in? He said I'm an expert in regulatory compliance issues associated with this case. As long as we agree that that's the scope of what his testimony will be, then we are --

THE COURT: That seems to be basically it. So charge them five minutes un and let's go on ahead.

MR. BURROWBRIDGE: Thank you, Your Honor.

BY MR. BURROWBRIDGE:

Q. Mr. Matto, have you prepared slide for the Court?

A. Sure, could you repeat that.

Q. Have you prepared slides for the Court?

A. Yes, I have prepared. Yeah.

Q. Who regulates API manufacturing of drug substance for the United States?

A. Food and Drug Administration.
Q. And what's the API drug substance at issue in this case?
A. Treprostinil sodium.
Q. Who is the manufacturer of the drug substance at issue in this case?
A. That would be Yonsung Fine Chemicals.
Q. Can you pronounce that again for the record.
A. Yeah. Yonsung Fine Chemicals.
Q. Thank you.

And what did Liquidia submit to the FDA to seek authorization to sell its drug product?

A. Liquidia submitted the DMF from Yonsung.
Q. Have you reviewed Liquidia's NDA?
A. I have reviewed certain sections. Those are more well into the CMC section, specifically for when I'm being retained by counsel, which is having to do with materials exposure to temperatures that had -- were outside generally.
Q. What does Liquidia incorporate in its NDA to authorize use of Yonsung's drug substance?
A. I'm sorry. Could you repeat the question again.
Q. Yes.

What does Liquidia incorporate in its NDA to authorize use of Yonsung's drug substance?

A. Yonsung's DMF, which incorporates information

concerning the stability of the drug material, the drug substance material, which is the case in point in this case.

Q. And does the NDA incorporate Yonsung's DMF?

A. Yes, it does by reference. In the drug substance section.

Q. What in the DMF ensures the quality criteria of the drug substance is met?

A. The document that ensures that this material is fit for use refers to a Certificate of Analysis that's produced by Yonsung, which is based on the specifications for this material that were created by Yonsung.

Q. And so does the Yonsung DMF incorporate or include a specific Yonsung specification for its drug substance?

A. Yes, it does.

Q. And does Yonsung's specification include temperature criteria?

A. No, it doesn't, and there's no reason why it should. In all my years of pharma sector and working in FDA, we've never considered temperature source conditions as far as Certificate of Analysis. The reason why is because specifications are tested. So it lists the tests that describes the quality criteria that must be met within each limit and it includes a test method. Anything outside that is not part of the certificate of analysis and it shouldn't be part of it, of the specification, like storage

conditions, for example.

Q. What definition of ambient temperature did you apply in this case?

A. According to this Court's claim construction this is between 15 and 30.

Q. And I believe you already mentioned this, but are stability studies part of the DMF?

A. Yes, stability studies are part of the DMF as they rightfully should. Those stability studies -- I'm sorry.

And the stability studies include accelerated stability studies, which is in accordance with the product label which says refrigerate. If you go to ICHQ 1A, it -- in that guidance document, you basically know how you should test for it. So materials that are labeled as refrigerated have to be tested on accelerated conditions. That's 25 plus or minus two, which would be ambient temperature conditions that are defined by this Court, and it also tests long-term conditions, which is basically 2 to 8. In addition to that, we do stress testing, which is thermal stress testing, which basically means that at 75 degrees C for 21 days, which is very harsh. I should add the point of saying the accelerated conditions are run for six months, which also is the way to demonstrate that when this material is exposed to those conditions, it will still remain fit for use.

DEPUTY CLERK: Mr. Matto, do you mind just

slowing down a little bit if you can.

THE WITNESS: I'm sorry.

DEPUTY CLERK: Just slow down.

THE WITNESS: Sorry.

DEPUTY CLERK: Thank you. It's okay.

BY MR. BURROWBRIDGE:

Q. So let's unpack some of that. So it sound -- so have you reviewed the accelerated stability studies at issue in this case within the DMF?

A. Yes, I have reviewed. I have reviewed accelerated studies, yes.

Q. And have you reviewed those stability studies for specific lots at issue in this case?

A. I have reviewed accelerated stability studies for two of the lots that were received in the month of December, I believe. And those, we have an inspection report, but for those two lots, I did review the accelerated studies because that information was included in the documentation that was essential to Liquidia. And the reason why that information was submitted to the Liquidia because those two batches were exposed to conditions outside the 2 to 8. So, LGM received those materials and released this material to Liquidia, and there's an email trail from LGM to Liquidia where it's stated that, yes, this material was exposed to up to 16 degrees outside the recommended temperature of 2 to 8.

However, because we have stability data at 25 plus or minus two that says the material is perfectly stable, there are no problems with degradation. The assay doesn't change, and the physical nature of the material resembles that of a freshly made batch. This material is fine. So they released it to Liquidia.

Now it was released to Liquidia. Liquidia accepted this material, issued a lot number on those materials, and this was a package of three lots, by the way.

Q. Mr. Matto, if you could just slow down a little bit for the court reporter, that would be helpful.

A. Yeah, sure.

Q. And so, Mr. Matto, let me just follow up on some of that. So you reviewed the accelerated stability studies for some of the lots that we've discussed earlier today; correct?

A. Correct.

Q. Did you review those stability studies for the lot TN 1170I010?

THE WITNESS: I have.

MR. PIVOVAR: Your Honor, we have an objection. These are exhibits that we handled this morning that were out that he never considered in his report.

MR. BURROWBRIDGE: So, Your Honor, he's considered these lots in a few different ways. They're

cited in the DMF that he's reviewed. He also reviewed Kindig's deposition where Kindig discusses different representative lots at issue.

THE COURT: I take it the opinions he's about to give are ones he gave before. The thing is he's now citing the specific lot number, and he didn't cite that before?

All right. Well, I'm going to overrule the objection.

BY MR. BURROWBRIDGE:

Q. And I believe you also -- did you also mention that you reviewed the thermal degradation of stress test stability studies?

A. Yes, I did.

Q. And so you've reviewed all the relevant stability studies in the DMF; is that correct?

A. I surely did.

Q. What did the FDA conclude based upon all stability studies?

A. Well, what Yonsung concluded and what FDA would also conclude is that, materials exposed at 25 plus or minus two, or materials that were exposed to 2 to 8 degrees, those materials behave in exactly the same way. It wouldn't --

Q. You have --

A. It wouldn't have a problem accepting either materials for fit-for-use as a test.

03:34:48 Q. And how long were the materials exposed to ambient
03:34:51 temperature?
03:34:51 A. The ambient temperature of those materials, I believe
03:34:57 they were exposed to up to 16 degrees for, if I recall
03:34:59 correctly, for about nine days.
03:35:01 Q. And are you aware -- okay. Do you have -- can you go
03:35:06 to slide five, please? Slide five, please.
03:35:20 Was lot TN 117I010 exposed to ambient
03:35:25 temperatures?
03:35:26 A. Yes, it has.
03:35:28 Q. Can you explain the graph to the Court, please?
03:35:31 A. Sure. If I put on my FDA hat and look at this entire
03:35:34 chart that was presented to me, I would look at the chart
03:35:37 and I would say that, first of all, the temperature exposure
03:35:41 was initially way below the two degrees. And then it creeps
03:35:44 up again and reaches a point where it crosses into ambient
03:35:47 temperature for a brief period of time, very brief, and then
03:35:51 goes into ambient temperature where it remains until the end
03:35:55 of the shift.
03:35:57 Q. And where does the temperature -- where does the data
03:35:59 logger start?
03:36:00 A. Well, I don't see the start time. Usually, the data
03:36:06 logger is when you print out, gives you the start and the
03:36:09 end.
03:36:09 Q. I'm sorry. Let me ask a better question. At what --

03:36:11 does the data logger show that the temperature started above
03:36:16 15 degrees?
03:36:16 A. Yes, that's right. That's the starting point. Yeah,
03:36:20 from this graph.
03:36:22 Q. And do you know if any of these lots from were
03:36:24 provided to patients?
03:36:25 A. Yes, of course. Those lots were provided -- were
03:36:30 provided to patients for clinical studies. So, material
03:36:34 that was exposed to temperatures outside of the 2 to 8
03:36:38 recommended temperatures went to use in humans.
03:36:42 Q. Why does the FDA permit lots that have been exposed
03:36:45 to ambient temperature to be used in clinical studies with
03:36:48 humans?
03:36:48 A. Sure. Again, I put my FDA hat on, and looking at
03:36:53 this, I would look at the stability studies from Yonsung.
03:36:57 The stability study from Yonsung gives you the confidence
03:37:01 that those materials are fit for use. They can be used for
03:37:04 humans.
03:37:05 Q. For FDA inspectors examining the NDA, other than
03:37:09 looking at the stability studies, what else would they
03:37:11 reference?
03:37:13 A. They would reference the DMF.
03:37:14 Q. And which portion of the DMF?
03:37:15 A. The DMF portions that referred to stability studies
03:37:19 and the testing them that was done on those materials, which

is the issue on the Certificate of Analysis.

Q. Would they also review the DMF specification?

A. Oh, certainly. The specification that Yonsung attached as well to a supply agreement that was signed in 2020 between LGM and Liquidia and Yonsung and that's -- it's a supply agreement that includes the Yonsung specification. Just to be clear, Yonsung specification doesn't have temperatures conditions. That's right. That's the way it should be. Now -- I'm sorry.

Q. Just to try to keep us on track. Was lot TN 120I010 exposed to ambient temperatures?

A. Yes.

Q. And can you explain this graph to the Court.

A. Yeah, this is the graph temperature of the two receiving reports that I reviewed. So, this happened January -- I'm sorry, February -- December of 2021. Maybe wrong on the date, but I've reviewed those. And basically what it shows is that this material, when shipment was below the two degrees, again, and it creeped up, it crossed again to the 2 to 8 for very brief period of time, a few days, but then for the majority of the trip, it went out of -- it became, basically, exposed to temperatures above the eight degrees, which are ambient conditions.

Q. And did you review the receiving inspection reports for this lot?

A. Yeah, I received -- I reviewed the receiving reports for this batch. Correct.

Q. Let's take a look at the -- excuse me. Let's take a look at the receiving inspection reports.

A. Sure.

Q. I believe it's PTX 19. Thank you.

Who received this batch?

A. This batch was received by materials person. Her name is Dana Paris. Liquidia materials person. Yeah, Dana Paris.

Q. And did Ms. Paris verify transport and applicable temperature conditions?

A. Well, she did because along with this certificate of analysis -- or I'm sorry -- receiving report, it had a email address from LGM to Liquidia. In it, it was reporting to Liquidia that the temperature that this material had been exposed to -- and they had this graph, by the way -- had been outside the 2 to 8. It went up to 16 degrees for nine days.

However, because Liquidia -- I'm sorry -- LGM had requested several substantial studies in conjunction, they also tested batches, and they said because these temperature are within what was accepted by FDA in terms of -- in terms of accelerated studies, 25 to plus or minus two, this test shows that this material is fit-for-use, and

there's no problem, so good. Release it. They advised Liquidia of this, and they -- and then it was sent to Liquidia. Liquidia accepted this inspection report that you just shown the Court has accepted. Yes.

Q. You may have mentioned this, but what's attached to this email?

A. Oh, it's -- what's attached to the email is basically the -- the -- these reference the accelerated stability study for the three batches. That's right.

Q. Did Ms. Paris verify temperature conditions against this certificate of analysis as well?

A. She verified those conditions on the -- on the basis of the email trail that was sent that provided her the information that she needed to feel confidence that, even though it was outside the recommendation, it would not be relevant to the FDA. It wouldn't be a concern to the FDA at this point.

Q. And so, if we look at the third line on the receiving inspection report, do you see where it says "Verified Temperature Conditions against COA"?

A. Yes. Mm-hmm.

Q. What COA is that referring to?

A. That COA is probably referring to the Yonsung COA that was also submitted with this batch.

Q. Let's take a look at the Yonsung COA.

03:41:42 A. Okay.

03:41:55 Q. And so I think we've seen this COA before. If we can
03:41:58 highlight -- well, let's explain what the document is first.
03:42:01 A. Sure. This is a Certificate of Analysis that's
03:42:05 issued by Yonsung for the material. And I'd like to call to
03:42:11 your attention, Your Honor, that the Certificate of Analysis
03:42:13 in this case has all the quality, criteria, and tests. And
03:42:18 the first column says what they're testing for, the
03:42:21 specification that they're testing it against, and the
03:42:24 limits, the results. That's a perfectly fine document.

03:42:30 Can you please scroll down? Yeah. Second page.
03:42:35 Mm-hmm.

03:42:37 Can you blow that up? Thank you.

03:42:39 So, the Certificate of Analysis is relatively
03:42:47 speaking to when it gets to the point where you've completed
03:42:49 the line of the testing that's for, the next thing is this
03:42:55 the administration. But when this says below, it's not part
03:42:59 of the spec.

03:42:59 Q. Now --

03:43:00 A. So, particularly, you can say that on Yonsung's
03:43:03 Certificate of Analysis, it says, "The above product is in
03:43:07 conformity with the in-house specification." And that's a
03:43:10 correct statement because the in-house specification from
03:43:12 Yonsung does not include storage conditions. That's the way
03:43:17 we look at it, and that's the way FDA would look at it.

03:43:20 Q. So, just to be clear --
03:43:21 A. Now --
03:43:21 Q. So, would the FDA view the recommended storage
03:43:24 conditions as part of the specification?
03:43:25 A. No, it wouldn't for the simple reason that you cannot
03:43:33 test temperature. It's not testable. It's not repeatable.
03:43:36 You can only test on those quality criteria that I've just
03:43:41 referred to in the first column test for.
03:43:43 Q. If instead of recommended -- or instead of saying it
03:43:46 should be kept at a certain temperature, if the COA just
03:43:51 said 2 to 8 degrees Celsius, would the FDA consider that
03:43:55 part of the specification?
03:43:56 A. No, it wouldn't. That wouldn't change my opinion on
03:43:59 that.
03:44:01 Q. If we can go back to the top of the Receiving
03:44:05 Inspection Report, what else did the Receiving Inspection
03:44:18 Report identify?
03:44:18 A. It identifies the Liquidia lot number which is below,
03:44:25 Liquidia lot number. It also shows RMS specification, and
03:44:31 that's pretty much on the first page. Sorry.
03:44:34 Q. What does it mean to the FDA that this document or
03:44:37 that this lot received a Liquidia lot number?
03:44:39 A. Well, once you receive a lot of material into your
03:44:44 system, now you have an SOP in your system that drives the
03:44:49 rest of the process. And let's just -- I want to be clear

about that. If you receive a material, regardless of what the material is, and your receiving person checks it's a purchase order, checks the specification, and confirms that something is not right. It could be received from a different vendor. The purchasing specification doesn't match as the spec.

And in the documents sent from Yonsung, any of those conditions, or the material is damaged. That's a known fact. Especially check for drum damage, if it's properly labeled, properly named, a lot those things, lot number. If any of those things fail, you reject; right? There, you actually don't receive it into your system, so it's not even rejecting. It's not received into the system, and it's sent back to the truck, to the supplier in this case.

Q. Mr. Matto, was this lot -- did this lot receive a quarantine labeling?

A. Yes, that material was labeled quarantine. Mm-hmm.

Q. And where --

A. It says --

Q. Where would drug substance materials from NDA lots have been quarantined?

A. It would have a quarantine page.

Q. Would they be quarantined in the same place that that lot would be quarantined?

03:46:00 A. Of course.
03:46:01 Q. And Liquidia -- in Liquidia's system or in Liquidia's
03:46:04 process flow, are all batches that are received quarantined?
03:46:09 A. Yes.
03:46:13 Q. Why would drug substance be used in an NDA batch
03:46:16 without temperature tracker data?
03:46:18 A. I'm sorry. Could you repeat that question?
03:46:21 Q. Why would a drug substance be used in an NDA batch
03:46:28 without temperature tracker data?
03:46:30 A. That, as I explained before, there's information
03:46:35 concerning multiple batches that have been received that
03:46:40 have, like loggers, been monitoring the temperature.
03:46:46 There's information from Yonsung regarding the stability of
03:46:50 materials. If you are referring to no data loggers, the
03:46:53 only information you have is historical information, which
03:46:59 shows that the batches, when they're shipped from Yonsung to
03:47:03 Liquidia through LGM had temperature exposures that are
03:47:08 consistent, historically, and have not reached above 30.
03:47:12 The ones that I've seen haven't even reached 30 degrees.
03:47:14 Q. Mr. Matto, is storage at ambient temperature an
03:47:19 out-of-specification result?
03:47:19 A. No, it's not.
03:47:23 THE COURT: I'm sorry, Mr. Burrowbridge. We
03:47:24 need to take an afternoon break here. So, we'll finish up
03:47:28 at four o'clock. All right?

03:47:30 MR. BURROWBRIDGE: Understood. Thank you, Your Honor.

03:47:32 DEPUTY CLERK: All rise.

03:47:33 THE COURT: We'll be in recess.

03:51:16 (Recess was taken.)

04:00:35 DEPUTY CLERK: All rise.

04:00:42 THE COURT: All right. Let's sit down and continue.

04:00:49 MR. BURROWBRIDGE: Bill, can you pull up Slide five?

04:01:04 BY MR. BURROWBRIDGE:

04:01:12 Q. Mr. Matto, were you in the courtroom earlier today when opposing counsel asked Dr. Nuckolls about this graph?

04:01:15 A. Yes, I did.

04:01:20 Q. And do you remember when opposing counsel asked -- opposing counsel asked, essentially, how someone would know whether or not the drug substance was in the shipment the whole time? Do you remember that back and forth?

04:01:22 A. I remember that back and forth.

04:01:28 Q. And so if -- if a drug supplier told an FDA inspector that the drug substance was removed from the shipment with the data logger, what would an FDA inspector think about that?

04:01:36 A. If it's removed after it's been received?

04:01:38 Q. Well, if this data logger was -- the data logger that

the company had --

A. Right.

Q. -- and the company told the FDA inspector that the drug substance was moved -- removed from the shipment at some point in time earlier than when the data logger was turned off, what would the FDA inspector think about that statement?

A. Well, that statement is -- it's the kind of statement that an FDA inspector investigator would be looking for if you want to cite the company for something that's been done. In my experience, 30 years in the industry, putting data loggers in the shipments, the practice is always been and it's always an SOP regarding this. I believe I've heard that some one of the witnesses describe that there's no SOP in the orders from Liquidia. But in my experience, the SOP says you remove the data logger when it's received into the system. That's when you remove it, and then you download it in your computer so you have a chart because that becomes a permanent record of that shipment. The entirety of the shipment.

Q. Would the FDA permit Yonsung to continue to store its drug substance at ambient temperatures?

A. Yes, of course. We have the stability data that shows the material, when it is stored at ambient conditions, it's perfectly fine. No conditions that affect the

04:03:27 usability of this material.
04:03:29 Q. And would the FDA also rely on the Yonsung DMF
04:03:33 specification to make that determination?
04:03:35 A. Yes, the FDA would look at the specification in the
04:03:39 DMF.
04:03:41 Q. Will the FDA permit Liquidia to continue using
04:03:45 Yonsung's drug substance stored at ambient temperature in
04:03:48 humans?
04:03:48 A. If it's maintained within the 25 degrees plus or
04:03:54 minus 2 degrees at ambient conditions, yes, it would permit.
04:03:56 Definitely.
04:03:57 MR. BURROWBRIDGE: Thank you, Mr. Matto. I pass
04:04:05 the witness.
04:04:06 THE COURT: All right. Cross-examination.
04:04:22 MR. PIVOVAR: May I approach, Your Honor?
04:04:24 THE COURT: Sure.
04:04:26 MR. PIVOVAR: May I approach the witness stand
04:04:28 with this binder, Your Honor?
04:04:29 THE COURT: Yes. Yes.
04:04:31 THE WITNESS: Thank you.
04:04:32 CROSS-EXAMINATION
04:04:32 BY MR. PIVOVAR:
04:04:36 Q. Good afternoon, Mr. Matto. How are you?
04:04:38 A. Good afternoon, sir.
04:04:40 Q. All right. You are not an expert in the chemical

stability of Treprostinil sodium, are you?

A. No, I'm not. I am a microbiologist by training.

Q. Thank you.

And you would agree that between you and the manufacturer Yonsung, that Yonsung actually has the expertise to assess the stability of Treprostinil sodium; right?

A. Yonsung does.

Q. Right. And when -- what Yonsung says in its DMF is it recommends storage between 2 and 8 degrees Celsius; right?

A. I've read that in the COA.

Q. Right. And Yonsung is also aware of the stability data that you've been testifying about; right?

A. That is correct.

Q. And I believe you said that -- and I'm going to quote you here -- you said it was perfectly stable at ambient temperatures between up to 25 degrees.

A. Yonsung's stability studies that have stated very clearly that materials exposed to ambient conditions behave no differently than materials stored at 2 to 8 degrees.

Q. Okay. So I'm trying to figure out if Yonsung knows about your stability data, and it's perfectly stable at ambient conditions, why are they recommending storage between 2 degrees and 8 degrees Celsius?

A. Well --
Q. Do you know the answer to that?
A. I can tell you it would make because it makes sense. So they run -- Yonsung runs stability studies at 2 to 8 degrees. They run for 36 months. Accelerated stability studies was already run for six months. If I'm the firm trying to get the most bang for my buck, I would choose the temperature that gives me the most shelf life, in this case the 2 to 8. But in regards to the FDA's concerns as far as safety and efficacy the drug product, they're looking at the stability studies that were run. And those stability studies concluded that in neither of those conditions the material was affected. It was fit for use.
Q. So, again, you don't know why, if there is no stability concerns, why Yonsung doesn't just recommend storage at ambient temperatures? You don't know why?
A. It's proposed, sir. If you read the conclusion on Yonsung's stability records, and I've read it multiple times, it uses the term "proposal." Propose or recommendation, Your Honor, means, Your Honor probably knows better than I do, it means that you should consider it. Consider it. If you look at the definition of "recommendation," consider it. But it doesn't categorically state that you have to keep it at that temperature.
Q. But you understand that Liquidia's raw material

specification for Treprostinil storage or Treprostinil sodium storage adopts as 2- to 8-degree Celsius range based on the DMF from Yonsung; right?

You understand that?

A. You're referring to Liquidia?

Q. Yes.

A. Okay. If I'm an FDA inspector, I will go into the DMF, which has the specification from Yonsung. If you look carefully at that specification from Yonsung, it doesn't have storage conditions.

Q. Mr. Matto, my question was a little different than that. I said you understand that Liquidia's raw materials specification for Treprostinil sodium set a storage temperature of 2 to 8 degrees Celsius based on Liquidia following the recommendation in the DMF from Yonsung. You understand that; right?

A. I've read it. If you want to -- if you want to let me express I've read that, but that has no place in the specification.

Q. Can you --

A. You chose to do it, but it has no place there.

Q. Can we bring up Mr. Matto's deposition testimony Page 15, line 4 through 10.

And, Mr. Matto, you were deposed in this case; right?

04:08:31 A. Yes, sir.
04:08:32 Q. And that was in January; right?
04:08:34 A. Yeah.
04:08:36 Q. And you took an oath to tell the truth before you
04:08:40 were questioned at your deposition; right?
04:08:42 A. Absolutely.
04:08:47 Q. It was on Page 15, lines 4-10.
04:09:22 So there in your deposition, I'm going to read
04:09:25 this to you. I asked the question: Question: "So your
04:09:29 understanding is that Liquidia's raw material specification
04:09:33 setting a storage temperature of 2 to 8 degrees Celsius is
04:09:37 based on Liquidia following the recommendation of the
04:09:39 manufacturer, Yonsung; correct?
04:09:42 And you answered, "That is my understanding."
04:09:44 Right? That was the question and your answer
04:09:47 during your deposition; right, Mr. Matto?"
04:09:49 A. Yeah, that's what I said.
04:09:58 Q. Now, if you could turn to your direct binder. I'm
04:10:02 going to go to PTX 19, please. And PTX 19 is a Receiving
04:10:16 Inspection Report for the three lots that you've testified
04:10:18 about here today; right, Mr. Matto?
04:10:20 A. Yes, that's correct.
04:10:23 Q. All right. Can you please turn all the way to the
04:10:25 back page of that exhibit. This is the last three Bates
04:10:29 162.

04:10:32 Can we zoom in on that, please?
04:10:34 A. Hold on. Which page?
04:10:36 Q. We're on the very last page.
04:10:37 A. Oh, very last one.
04:10:38 Q. Right. You can follow along on your screen or on the
04:10:42 projector.
04:10:44 Right. You see where in the middle there's a
04:10:47 column that says batch number?
04:10:48 A. Yeah.
04:10:49 Q. Right. And those are the three of the batches that
04:10:51 you were talking about earlier today; right?
04:10:54 A. Yes, they are.
04:10:56 Q. Right. And you talked in particular about the bottom
04:10:59 two batches that were received in and put into quarantine;
04:11:03 right?
04:11:04 A. I believe it was.
04:11:06 Q. Okay. Do you see that top one in line 1 it says
04:11:10 TN120C010?
04:11:14 A. Mm-hmm.
04:11:14 Q. Right. You didn't discuss that today, did you?
04:11:17 A. Well, I didn't discuss that because the two
04:11:21 inspection reports that were given to me were only TN120G010
04:11:25 and TN120I010.
04:11:28 Q. Right. So you don't know what the disposition is of
04:11:30 batch number TN120C010; right?

04:11:33 A. Well, the packaging slip that came with the batches
04:11:39 listed all three of them. And what we -- I read Mr.
04:11:45 Kindig's deposition, and in Mr. Kindig's deposition, he
04:11:48 lists all those batches. And Mr. Kindig stated, basically,
04:11:52 that those batches would be -- were in quarantine. He
04:11:57 also -- and Mr. Battistoni, also, I believe. I reviewed
04:12:02 that very lightly, but I believe that it did say that those
04:12:05 batches were being -- would not be used for GMP manufacture.
04:12:09 Q. Right. So you understand that Liquidia's witnesses,
04:12:11 the corporate witnesses, said we are never going to use
04:12:14 these batches that experienced a temperature excursion above
04:12:18 8 degrees and in GMP manufacturing of a finished drug
04:12:18 product. You understand that; right?
04:12:23 A. I understand that's a statement, but the FDA doesn't
04:12:27 accept statements.
04:12:28 Q. Understood. Now, did you hear Mr. Battistoni's
04:12:35 testimony here today? It was played on the video.
04:12:37 A. Unfortunately, I didn't hear that testimony.
04:12:40 Q. Okay. So you didn't hear the reason why Liquidia is
04:12:44 not going to use these lots that were part of your testimony
04:12:50 for a GMP manufacturing?
04:12:53 A. I recall reading the deposition, hard copy, but if
04:12:56 you can bring that deposition, that would be very helpful.
04:13:00 Q. So I'll remind you. Here's what Mr. Battistoni said.
04:13:03 He said being outside of the temperature range represents a

quality risk we are not willing to take. That's what he said. Okay?

A. Is there any way you can put that up because it's --

Q. That's fine. We can get that out later, but the bottom line is I thought you said that an FDA inspector could ding a company if they saw the temperature data. What did you mean by that?

A. For example, when you're reviewing the documentation, if this comes up, they would just basically base on the fact that your SOP is not clear what to do with it. Not the fact -- and I'm just going to -- I'm just going to go with what you've stated from Mr. Battistoni's deposition. There's no safety issue with this material. FDA would be able to look at the stability data, and if you were to claim that's how -- use Mr. Battistoni's sort of reason why you placed under quarantine and in GMP -- I am sorry -- remain in quarantine because you've got GMP concerns, I would just basically look at you bewildered because I would say, what are the safety concerns? Here's the -- the stability data from Yonsung.

Q. Because you know more about the stability data and the storage conditions of Treprostinil sodium than Yonsung; right?

A. No, that's not what I said. Don't put words in my mouth.

04:14:23 Q. Can you bring up PTX 149, please.
04:14:25 A. That is not what I said.
04:14:27 Q. In your black binder is a document that is PTX 149, Mr. Matto. And that is a copy of your opening expert report in this case. Do you see that?
04:14:39 A. This one here?
04:14:40 Q. Yeah. And then if we can go to the last page -- or page, I believe, 13.
04:14:45 A. Excuse me.
04:14:51 Q. Do you see on Page 13 -- do you see your signature there, Mr. Matto?
04:14:56 A. Okay. Page 13. Hold on a second. Yeah, I see my signature. Right my signature.
04:15:06 Q. And you signed it on October 15th, 2021; right?
04:15:09 A. This is December the 10th, 2021.
04:15:14 Oh, October 15, 2021. Which one is it?
04:15:17 Q. No problem. And do you see where you said I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct? Do you see that?
04:15:24 A. Yeah, I see that.
04:15:26 Q. Okay. Let's go to paragraph 46, please. It's on Page 12.
04:15:30 A. Which PTX is it?
04:15:32 Q. Oh, I'm sorry. This is PTX 149 in that black binder.

04:15:37 A. 149. Okay. Got it. Got it. Now I have it. Okay.
04:15:40 Q. And if we can blow up paragraph 46, that would be
04:15:42 great.
04:15:44 Now, Mr. Matto, do you see in the middle of this
04:15:46 paragraph there are three lot numbers that are written out
04:15:48 there? It's TN120C010, TN120G010 and TN120I010. Do you see
04:15:59 those.
04:15:59 A. Yeah, I see those.
04:15:59 Q. Those numbers are the same as what we just reviewed
04:16:02 in the inspection report in, I believe it was, PTX 19;
04:16:05 right?
04:16:05 A. Mm-hmm.
04:16:06 Q. Okay?
04:16:07 A. Yeah.
04:16:07 Q. Now, I want to go to the first sentence here. I want
04:16:10 to see what you said in your expert report.
04:16:12 A. True.
04:16:12 Q. Okay. You wrote "In this sort of circumstance, where
04:16:15 there is a shipping temperature excursion, it is up to the
04:16:19 manufacturer to decide whether to use a batch of material
04:16:22 from its supplier."
04:16:25 That's what you wrote; right?
04:16:26 A. Yes.
04:16:26 Q. It says, "It's up to Liquidia to decide whether or
04:16:30 not it's going to use a batch that has experienced a

04:16:32 shipping temperature excursion"; right?
04:16:34 A. It's their business.
04:16:34 Q. Right. And you know from their witnesses they've
04:16:38 testified that they are not going to use any of those lots
04:16:40 in GMP manufacturing; right?
04:16:43 A. But you also stated that because Mr. Battistoni had
04:16:47 GMP concerns, something to that effect. And what I'm
04:16:53 stating here is that if I'm the FDA person and I'm asking
04:16:57 about those batches, I would wonder and I would say what GMP
04:17:01 concern? What safety concerns do have you it about it?
04:17:03 Because if I pull the stability data from Yonsung, it shows
04:17:06 no concerns insofar as they could test, insofar as assay
04:17:10 changes, or characteristic changes.
04:17:14 Q. Okay. Can we please go back to PTX 19. This is -- I
04:17:18 apologize, Mr. Matto. This will be in your white binder.
04:17:21 This is going back to the receiving inspection log.
04:17:23 A. Sure.
04:17:24 Q. And I'd like to go to the last page, Bates Number
04:17:28 162, again.
04:17:29 A. Yeah.
04:17:31 Q. Now, we just read in your expert report where you
04:17:34 referred to a temperature excursion; right?
04:17:39 And we've been hearing a lot about what a
04:17:41 temperature excursion is; right?
04:17:43 A. Mm-hmm.

Q. Right?
A. Yeah.
Q. And according to you, a temperature excursion is a temperature that goes outside of the range of 2 to 8 degrees in Liquidia's raw materials specification; right?
A. I understand it's a deviation from that 2 to 8 range.
Q. Right. So you are using "excursion" as proxy for a temperature that is going outside the 2 to 8 degrees Celsius range; right?
A. Not sure I understand. Using as a proxy for?
Q. Like, when you refer to a temperature excursion, you're meaning a temperature that's either below 2 or above 8?
A. "Excursion" means anything outside the 2 to 8.
Q. Yeah. Thank you.

And what I wanted to make sure that we all understood here is that when these lot were shipped to Liquidia --

A. Mm-hmm.
Q. -- you see where it says storage temperature there?
A. Sorry. Where is it?
Q. It's right -- it's the third one from the right.

You can highlight that, too, Mr. Cole, where it says refrigerated.

Refrigerator, refrigerator, refrigerator.

Sorry. Right?

A. It says refrigerator.

Q. Right. So the storage temperature that was intended for these the shipment of these lots was to be at a refrigerated temperature; right?

A. To me, that refers to something that you have to tell me specifically what temperature you're referring to. And the reason why I'm saying this, sir, because in science, and especially regulatory science, we have to be very accurate, very precise. So to me, refrigerator could mean many things. It's like you tell me I want to store this in my refrigerator, and how do I know what temperature it is?

Q. Okay. But you agree on this page, on this shipping label, the storage temperature, the intention is for it to be stored in a refrigerator. You at least agree with that; right?

A. I only agree that I'm reading it. I don't necessarily agree with the content of it.

Q. Can we go to Bates last three digits 160 and it's two pages earlier.

And if we look where it says alarm summary, if you can blow up the left-hand side of that and pull out the third box. Keep going down. That's good.

Okay. Do you see it has an alarm summary there?

A. Yeah.

04:19:53 Q. And do you see it says ideal range greater than 2
04:19:56 degrees C and less than or equal to 8 degrees C?
04:19:59 A. I do.
04:19:59 Q. Do you see that?
04:20:00 A. Yeah, I see that.
04:20:01 Q. Right. And then it has an alarm that goes over 8 --
04:20:04 A. Mm-hmm.
04:20:05 Q. -- and alarm that goes under 2.
04:20:06 A. Mm-hmm.
04:20:07 Q. Doesn't that tend to tell you that the shipping that
04:20:10 was desired for this specific shipment of lots was supposed
04:20:15 to be between 2 and 8 degrees Celsius, just like in the raw
04:20:18 materials specification that Liquidia has for Treprostinil
04:20:21 sodium?
04:20:21 A. I have to, basically, reaffirm what I said before.
04:20:29 That's a recommended. Recommended storage condition.
04:20:35 Recommended meaning that if I have doubt about it, I go back
04:20:39 to the NDA, go back to the DMF, and pull the DMF and
04:20:44 stability studies from Yonsung, and that will give me my
04:20:47 answer. Which means that that temperature is not within --
04:20:50 it's not outside the limits that have been studied by
04:20:54 Yonsung to demonstrate that the product is exposed to
04:20:58 ambient conditions perfectly fine for use.
04:21:00 Q. So, Mr. Matto, I appreciate all that, but that's not
04:21:03 responsive to the question I asked you. I asked you doesn't

the fact that the shipment of these lots had a range of 2 to 8 degrees Celsius and alarms if it was going to go out of that range --

A. Mm-hmm.

Q. -- show you that they were shipping it cold and that they were trying to target 2 to 8 degrees Celsius, exactly as in the raw material specification that Liquidia has for Treprostinil sodium?

Do you agree with that?

A. I don't understand that. What are you trying me to agree to?

Q. I'm trying to understand if you understand what's on this page.

A. Well, I understand. I'm reading it.

Q. Right.

A. I understand doesn't mean I agree with it.

Q. And it's setting a range between 2 and 8 degrees Celsius; right?

A. It says ideal range. Ideal range. If you define to me what is ideal.

Q. Well, I think we can go off this. The point I wanted to make is if it's outside of 2 to 8, then it's an excursion; right?

A. Like many excursions or shipments, sir. In my 30 years of private sector, I have come across many

04:22:06 instances where shipments have come with excursions. Does
04:22:09 it mean that the firm is going to throw the batch away? I
04:22:11 don't think so.
04:22:12 Q. But you would agree here that they're not trying to
04:22:15 ship this ambient. This is not meant to be shipped ambient.
04:22:18 They're shipping it -- it says refrigerator, and they're
04:22:22 showing you the ideal range for the temperature that is not
04:22:25 ambient. You would agree with that; right?
04:22:26 A. I understand what you're saying, but here let me
04:22:28 explain you something. I may have a label that says 2 to 8.
04:22:32 Perfectly fine. That's what you're trying to -- that's what
04:22:35 you're trying to achieve when you ship it. But what I have
04:22:39 to rely on is what I -- the DMF states and the stability
04:22:43 studies states, and if it comes to a decision time, because
04:22:45 I think that's what you're trying to arrive at, I'm not
04:22:48 sure, if it comes to decision time whether I can or cannot
04:22:50 use this batch, I have to rely back on the stability
04:22:53 studies. This means nothing to me other than, other than it
04:22:57 tells me that my batch has been exposed to temperatures
04:23:00 outside of the 2 to 8.
04:23:11 Q. Okay. So just so I'm clear, you see this information
04:23:15 that's on the screen right now that shows the shipping
04:23:18 conditions for the three lots that you're relying on for
04:23:21 your opinions here?
04:23:22 A. Mm-hmm.

04:23:22 Q. And you can't say that they were actually shipping -- that they're intending to ship that cold?
04:23:25
04:23:27 A. That's not what I said.
04:23:28 Q. Okay. So you can?
04:23:29 A. I'm sorry?
04:23:30 Q. You can then?
04:23:32 A. No.
04:23:32 Q. You can?
04:23:33 A. You've got to be clear. Ask me the question again.
04:23:35 Q. Sure. The shipment of the three lots that are depicted here in PTX 019, that you relied on in formulating your opinions --
04:23:39
04:23:44
04:23:45 A. Mm-hmm.
04:23:46 Q. -- those were actually shipped --
04:23:47 A. Mm-hmm.
04:23:48 Q. -- cold, not at ambient temperatures; right?
04:23:51 A. You show me the graph, I can confirm that to you.
04:23:55 Q. Right. But like when it started, this is the shipping condition; right?
04:23:57
04:23:59 A. Yeah. They said the ideal range. It's an ideal range; right?
04:24:03
04:24:03 Q. So the point being is that an excursion is a departure from when what they were trying to target; right? It was a deviation from the temperature range --
04:24:07
04:24:09
04:24:12 A. It's a deviation of the excursion like that, yeah.

04:24:18 But, again, you know, I think --
04:24:19 Q. Can we go back to PTX 159 please?
04:24:22 THE COURT: Wait for a question.
04:24:24 MR. PIVOVAR: Sorry, Your Honor.
04:24:25 THE COURT: No, I'm sorry. You go ahead.
04:24:28 BY MR. PIVOVAR:
04:24:30 Q. Can we go to Page 8, paragraph 34. And I would
04:24:37 like -- I can tell you what page. Okay. And we can blow up
04:24:50 the header for -- in 34, that would be great.
04:24:54 Right. We already went over that you've signed
04:24:56 this under penalty of perjury; right? So I want to look at
04:24:59 what you said here in your expert report.
04:25:01 Now, before we do that, though, these are your
04:25:04 words; right?
04:25:05 A. That's correct.
04:25:05 Q. You typed these in?
04:25:06 A. Yeah.
04:25:08 Q. You were thoughtful about the words you were using
04:25:10 when you wrote your report?
04:25:10 A. Yes, sir.
04:25:11 Q. You wanted to be precise?
04:25:12 A. Very much.
04:25:13 Q. Right. Okay. So in the title or in the Section 4
04:25:19 title it says -- and you wrote this; right?
04:25:22 A. Mm-hmm.

04:25:22 Q. "A drug substance may be used in the commercial
04:25:25 manufacture of a drug product despite exposure to
04:25:29 out-of-specification temperature storage conditions."
04:25:32 Right?
04:25:32 A. Yes.
04:25:33 Q. That's what you wrote?
04:25:34 A. That's what I wrote.
04:25:35 Q. By the way, when you're talking about exposure to
04:25:37 out-of-specification temperatures storage conditions, you're
04:25:40 talking about a temperature excursion; right?
04:25:42 A. Is this from my first report, sir?
04:25:44 Q. I'm asking you a different question, but the answer
04:25:46 is, yes, this is from your first report, and I'm asking you
04:25:49 exposure to out-of-specification temperature storage
04:25:52 conditions. That's a temperature excursion; right?
04:25:55 A. When I refer to out-of-specifications there, I
04:25:59 corrected myself on the second report, on my rebuttal. In
04:26:03 my second report, I established that I had been using
04:26:06 interchangeably "out of spec," "the deviations," and
04:26:09 "excursion." So my second report, if you have read it, it
04:26:12 will state that I was using the interchangeable; however,
04:26:15 I'm remain -- I retain only the use of excursions or
04:26:19 deviations. I corrected myself.
04:26:21 Q. Sir, if you look down to beginning on the third line,
04:26:24 it says drug product even though. Do you see that?

04:26:28 Then it says the batch has been exposed to
04:26:30 storage temperatures outside of that specified in the DMF or
04:26:35 NDA; right?
04:26:35 A. I read that.
04:26:36 Q. Right. So you're referring to a temperature outside
04:26:39 that specified in the DMF or the NDA, and that's a
04:26:42 temperature excursion; right?
04:26:43 A. That's what I read there.
04:27:33 Q. Mr. Matto, is it your opinion that stability testing
04:27:38 alone is sufficient for a drug manufacturer to use an API
04:27:43 that has experienced a temperature excursion outside of the
04:27:47 specification?
04:27:47 A. I've said that in my -- one of my reports, but I also
04:27:53 added something else, that stability studies alone along
04:27:57 with an investigation of that temperature excursion would be
04:28:00 necessary, sir.
04:28:02 So what's happening here is that some terms or
04:28:05 some sentences are pulled out of context, but you have to
04:28:08 frame it within the full report, and in various parts that
04:28:11 have report also stated that your report have to have a full
04:28:14 investigation. As a matter of fact, it states in the
04:28:16 report, if I may be right, that the Q A -- the Q A
04:28:20 department of that firm would have to take all that evidence
04:28:23 in consideration before releasing the batch.
04:28:25 Q. All right. Mr. Matto, we're going to go back to your

04:28:27 deposition.

04:28:28 And can we bring up Page 113, lines 2 through 9,

04:28:33 please.

04:28:34 Sir, remember we were talking about whether

04:29:08 stability data alone is sufficient to justify the use of an

04:29:14 API --

04:29:15 A. Mm-hmm.

04:29:15 Q. -- out-of-specification temperature excursion; right?

04:29:18 A. Yeah, we talked about that.

04:29:21 Q. Right. And during your deposition I asked you this

04:29:23 question: "QUESTION: And -- and -- and just so I can

04:29:26 understand this right, is it your opinion that stability

04:29:28 testing alone is sufficient for a drug manufacturer to use

04:29:32 an API that it had experienced a temperature excursion

04:29:36 outside of specification?"

04:29:38 Your answer: "Not alone. No. No. No, sir.

04:29:42 Definitely."

04:29:43 Did I read that question and answer correctly?

04:29:45 A. Yeah.

04:29:46 Q. Right. And that was the testimony that you gave

04:29:48 during deposition; right?

04:29:49 A. That's -- that's correct.

04:29:52 Q. And do you stand behind your deposition testimony

04:29:54 here today unequivocally?

04:29:56 A. Absolutely. When I said that alone, means that it

04:29:59 1 required other information, meaning stability data and
04:30:03 2 investigation, which is also stated in my deposition -- in
04:30:06 3 my -- not deposition, but in my reports.
04:30:15 4 Q. Okay. One final question, Mr. Matto. If 25 degrees
04:30:23 5 Celsius is fine to ship Treprostinil sodium, why do you call
04:30:29 6 it an out-of-temperature excursion?
04:30:34 7 A. It's only an excursion from the sense of the label.
04:30:39 8 The product, when it ships, has a label that says 2 to 8.
04:30:42 9 And it's within that context that you refer to an excursion.
04:30:47 10 Now, if the label had said 25, plus or minus two, I wouldn't
04:30:50 11 call it an excursion. The fact is that Liquidia chose to
04:30:56 12 recommend the temperature that was in Yonsung report just a
04:31:00 13 recommendation. Not an obligation.
04:31:04 14 MR. PIVOVAR: Thank you, Mr. Matto. Appreciate
04:31:05 15 your time.
04:31:06 16 No further questions, Your Honor.
04:31:07 17 THE COURT: All right. Anything further,
04:31:09 18 Mr. Burrowbridge?
04:31:09 19 MR. BURROWBRIDGE: Nothing from Plaintiffs.
04:31:11 20 Thank you, Mr. Matto.
04:31:12 21 THE COURT: All right. Mr. Matto. You're done.
04:31:15 22 You may step down. Watch your step.
04:31:16 23 THE WITNESS: Thank you.
04:31:21 24 MR. JACKSON: Your Honor, Plaintiffs have a
04:31:23 25 couple of additional video depositions to play. And I think

that we'll end today.

So, first, we call Benjamin Maynor. I think it's about six minutes, Your Honor.

MR. JACKSON: May I approach?

THE COURT: Yeah. Yeah. Sure.

(Video playing.)

And to get started, can you state your full name, please.

THE WITNESS: Yes. Benjamin Waltz Maynor.

Q. Do you understand, Dr. Maynor, that you're providing testimony today both in your personal capacity and then also on behalf of Liquidia for certain topics?

A. I do.

Q. Sure. When you were evaluating potential active ingredients for development of a therapy, what would -- what would you look for in terms of chemical stability for an -- for an active ingredient to be a promising avenue for development?

THE WITNESS: Normally, we just empirically determined, using our standard manufacturing parameters, could the active -- was the active well-behaved or not.

Q. In other words, you didn't search the world for stability data, you just made a formulation and tried it?

A. Basically, yes.

Q. What size do you consider the particles for LIQ861?

04:33:31 THE WITNESS: I would say they are nominally one
04:33:35 micron in -- in -- in physical size.
04:33:40 Q. I'll ask you to you pull up, please -- this will be
04:33:44 Exhibit 9 -- LIQ 00943263.
04:33:51 Great. Dr. Maynor, do you recognize Exhibit 9?
04:33:56 THE WITNESS: I recognize the content of
04:33:59 Exhibit 9. But I don't know if I've ever seen the exact
04:34:08 presentation. I may have.
04:34:09 Q. Thank you.
04:34:09 And so the -- the -- I'm just looking across the
04:34:15 row, 20 out of 25, 40 out of 50, up to 120 out of 150. It
04:34:21 looks like about 80 percent -- that the emitted dose is
04:34:26 80 percent, approximately, of the capsule fill weight; is
04:34:29 that about right?
04:34:33 THE WITNESS: It does appear like that is -- is
04:34:37 a fair statement.
04:34:38 Q. With your experience developing PRINT and working on
04:34:44 LIQ861, does that 80 percent emitted dose sound correct?
04:34:51 THE WITNESS: It -- it's correct for this data
04:34:55 as presented, yes.
04:34:57 Q. What do you personally believe about a human patient
04:35:05 taking a dose of LIQ861 in terms of the percentage that the
04:35:11 emitted dose is of the entire capsule fill weight?
04:35:17 THE WITNESS: It -- it is -- it is variable in
04:35:22 patients depending on technique and -- and breathing pattern

and -- and patient anatomy and use of the device.

Q. Yeah. Just -- what -- what do you think that emitted dose percentage is for a real patient taking LIQ861?

THE WITNESS: I would say 60 to 100 percent would be my guess.

Q. Okay. And this is Exhibit 10 LIQ 00623136. If you could -- well, first, let me ask you. Do you recognize this email thread, Dr. Maynor?

A. I do.

Q. Next, I wanted to go up to -- it recites most accurately "54 micrograms is an approximate emitted dose from nine breaths of TYVASO."

And then in the third line of the paragraph, it mentions, "We have established a PK bridge between 75 micrograms of LIQ861 and 9 breaths Of TYVASO most accurately."

Do you see that?

A. Yes.

Q. And so I just wanted to ask is -- is the reason you are comparing 54 micrograms of TYVASO to 75 micrograms of LIQ861 because of that emitted dose fraction we were talking about earlier where some of the Treprostinil stays inside the capsule or the dry-powder inhaler with LIQ861?

THE WITNESS: In our regulatory interactions with the FDA, they requested that we establish a relative

bioavailability between some dose of LIQ861 and some dose of TYVASO.

And this email describes thinking around establishing the pharmacokinetic bridge as established by relative bioavailability between a 75-microgram capsule dose of LIQ861 and nine breaths of TYVASO.

Q. Do you think that the emitted dose was the main factor in the close relative bioavailability of the 75-microgram of 861 to the nine breaths of TYVASO?

THE WITNESS: It was a factor, but the dry-powder is so different from a nebulized solution that there's a number of factors in addition to that.

Q. Liquidia -- excuse me. Liquidia selected a particle size for LIQ861 that is less than five microns; correct?

A. Correct.

Q. Setting aside the specific Phase 1 study involving 57 healthy volunteers, the purpose of LIQ861 is to treat patients with pulmonary hypertension; correct?

THE WITNESS: That is my understanding.

(Conclusion of video.)

MR. JACKSON: Your Honor, plaintiffs move into evidence PTX 160 and 161, which were used in that deposition.

MR. PIVOVAR: No objection, Your Honor.

THE COURT: Admitted without objection.

(PTX Exhibit No. 160 and PTX Exhibit No. 161 were admitted into evidence.)

MR. JACKSON: Now Plaintiffs call Dr. Robert Roscigno, which is another deposition video. It's -- I believe it's literally about a minute, Your Honor.

(Video playing.)

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

A. My name is Robert Frank Roscigno.

Q. And is Exhibit 36 a copy of the clinical research protocol for the LTI-201 study?

A. I believe it is, yes.

Q. And on the second page, is that your signature dated 26 September of 2018?

A. Yes.

Q. And so is it true that Liquidia's LTI-201 study involved measure of -- measurement of the hemodynamic measures identified on Page 5?

A. Yes.

Q. Have you ever seen any results from the LTI-201 study?

A. My recollection -- from my recollection, this study was in progress when I left the company.

Q. So have you ever seen any results related to the LTI-201 study?

A. I don't recall.

(Conclusion of video.)

MR. JACKSON: Your Honor, Plaintiffs move into evidence PTX 1843, which was used in that deposition video.

MR. PIVOVAR: No objection.

THE COURT: Admitted without objection.

(PTX Exhibit No. 1843 was admitted into evidence.)

MR. JACKSON: And now, Your Honor, plaintiffs call Dr. Werner Seeger by deposition video as well. And just so Your Honor is aware, I know that where the time is on the day, Doctor Seeger's video, you'll recall, he's the individual who was in Germany, and there was debate about whether or not there was -- certain documents were by another. There was a motion in limine on him. So we're using his deposition to bring that in. It's about 33 minutes is why I ask.

THE COURT: Okay. Go ahead.

MR. JACKSON: Thank you, Your Honor.

(Video playing.)

MR. JACKSON: I'm --

Q. Good morning, Dr. Seeger. Can you state your full name, please.

THE WITNESS: Werner Seeger.

Q. Dr. Seeger, you have just been handed what will be Exhibit 4, a document stating at the top, United States

Patent and Trademark Office. Towards the middle of the page, it states Declaration of Dr. Werner Seeger.

Do you have a copy of it?

A. Yes.

Q. Feel free to look at Exhibit 4 as needed, Dr. Seeger, but do you recognize this as a copy of a declaration that you prepared in connection with IPR 2021-00406?

THE WITNESS: Without being able to read every word, remember everything, I am able to say that, yes, this is a copy of a declaration I made.

BY MR. DYKHUIS:

Q. If I refer to you that article identified in paragraph 3 as the Ghofrani article, will you understand that I'm referring to the article identified in paragraph 3?

THE WITNESS: Yes.

Q. Did you participate in writing the Ghofrani article?

A. Yes.

Q. Were you involved in writing the Voswinckel 2006 article identified in paragraph 18 of your declaration?

THE WITNESS: Yes.

BY MR. DYKHUIS:

Q. Can you describe, please, your collaboration with the other inventors of the '793 patent.

THE WITNESS: The first meeting was in the fall of 2003. In addition to me, we had the Giessen team. The

Giessen team consists of the employees of the university: Olschewski, Schmehl, and Voswinckel in addition to me.

So, the other participants, Mr. Rubin. Voswinckel, Roscigno, Karl Sterritt from UTC worked on a strategy and planning of the development of the program for inhalation therapy for pulmonary hypertension.

THE WITNESS: Monica, forgive me. It's Karl Sterritt and Roberts Roscigno from UT and Lew Rubin -- not from UT -- but another U.S.-based, well-known scientist in the field of pulmonary hypertension.

Q. Did your collaboration with Drs. Rubin, Voswinckel, Olschewski, Schmehl, Roscigno and Sterritt lead to any patents?

A. Yes.

Q. Did your collaboration lead to the '793, '240, and '507 patents, among others?

THE WITNESS: Yes.

Q. Can you turn, please, to paragraph 28 of your declaration, Dr. Seeger, on Page 15.

A. Yes.

Q. It states: "I hereby declare that all statements made herein of my knowledge are true and that all statements it made on information and belief are believed to be true." And it goes on.

Do you see that?

THE WITNESS: Yes.

Q. Whose signature is this on the right-hand side of Page 15 of your declaration?

THE WITNESS: On Page 15 of my declaration, it is my signature.

BY MR. DYKHUIS:

Q. When did you sign this declaration?

THE WITNESS: The date is indicated on the same page, 10th of May, 2021.

BY MR. DYKHUIS:

Q. Was everything you said in this declaration true on May 10, 2021?

THE WITNESS: Yes.

BY MR. DYKHUIS:

Q. Is everything in this declaration true today?

THE WITNESS: Yes.

Q. What is Exhibit 5, Services Agreement?

A. In this document, we jointly developed the program for inhaled Treprostinil as therapy for pulmonary hypertension.

Q. Exhibit Number 6, the title is Executive Committee, Actions from NY Meeting October 22nd, 2003.

Dr. Seeger, do you recognize Exhibit 6?

A. Yes.

Q. What is it?

A. This is, apparently, the agenda of the meeting mentioned in New York, in the fall of 2003.

Q. Is this the agenda that is referenced in paragraph 23 of your declaration?

THE WITNESS: Yes.

BY MR. DYKHUIS:

Q. Is -- is the work following the 2003 meeting with the inventors of the '793 patent the work that eventually led to clinical studies that became the basis of the application leading to the '793 patent?

A. Yes.

Q. Dr. Seeger, you have just been handed a copy of a document with a German title. It bears production number in the bottom right corner Liquidia's Exhibit 1010. It also says LIQ 02800749. Then approximately on Page 8 of the English translation, then it appears it says -- and then it appears to contain the title of New Therapies in the Treatment of Pulmonary Hypertension.

Do you have a copy of Exhibit 7 in front of you, Doctor Seeger?

A. Yes.

Q. What is Exhibit 7?

A. It's an overview work. It does not present original data. It addresses German public pneumologists and cardiologists in order to explain to them in an overview the

current status of the treatment of pulmonary hypertension. It was also connected with the presentation of a few development opportunities.

Q. Is this Exhibit 7 the Ghofrani article that's referenced in your declaration?

THE WITNESS: Yes.

BY MR. DYKHUIS:

Q. Are you one of the authors of the Ghofrani paper, Dr. Seeger?

A. Yes.

Q. Who directed and managed the writing of this Ghofrani paper?

A. I did as a director of this area, and this is expressed in my role as a senior author.

Q. Is Dr. Ghofrani identified as author on this paper because he wrote the section on the introduction phosphodiesteric inhibitors, vasoactive therapy, and inhaled Iloprost?

THE WITNESS: Yes.

BY MR. DYKHUIS:

Q. Who wrote the section of the Ghofrani paper on "inhaled Treprostinil describing initial trials in Giessen?

A. Robert Voswinckel and myself.

Q. Dr. Ghofrani did not write that section?

A. That is correct. Dr. Ghofrani did not write this

section.

Q. Did Dr. Ghofrani participate in the design of the clinical studies referred to in the Ghofrani paper involving inhaled Treprostinil?

THE WITNESS: No.

BY MR. DYKHUIS:

Q. Did Dr. Ghofrani select the dosing regimen used in the clinical studies referenced in the Ghofrani paper on the inhaled Treprostinil?

THE WITNESS: No.

BY MR. DYKHUIS:

Q. Did Dr. Ghofrani conduct analysis of patient results from the clinical trials described in the Ghofrani paper relating to inhaled Treprostinil?

THE WITNESS: No.

Q. Who wrote the section of the Ghofrani paper on "Selective Endothelin A Receptor Antagonists"?

A. Friedrich Grimminger and Frank Reichenberger.

Q. Did Dr. Reichenberger and Dr. Grimminger write the section on initial clinical trials in Giessen relating to inhaled Treprostinil?

THE WITNESS: No.

Q. Did Dr. Reichenberger and Dr. Grimminger participate in the design of the inhaled Treprostinil clinical trial in the Ghofrani paper?

04:55:35 THE WITNESS: No.
04:55:35 BY MR. DYKHUIS:
04:55:39 Q. Did Dr. Reichenberger and Dr. Grimminger select the
04:55:43 dosing regimen that was used in the inhaled Treprostinil
04:55:46 clinical trial?
04:55:47 THE WITNESS: No.
04:55:50 BY MR. DYKHUIS:
04:55:50 Q. Did Dr. Reichenberger and Dr. Grimminger conduct
04:55:56 analysis of patient results from the inhaled Treprostinil
04:56:00 clinical trial?
04:56:00 A. No.
04:56:05 Q. Is the reason that Dr. Reichenberger and Grimminger
04:56:09 are identified as authors of the Ghofrani paper because they
04:56:13 wrote the section on "Endothelin A Receptor Antagonists"?
04:56:19 A. Yes.
04:56:20 BY MR. DYKHUIS:
04:56:21 Q. Were Dr. Olschewski, Roscigno, Rubin, Schmehl,
04:56:27 Sterritt involved, along with you and Dr. Voswinckel, in the
04:56:34 clinical trials described -- described in the "Inhaled
04:56:38 Treprostinil" section of the Ghofrani paper?
04:56:42 A. Yes.
04:56:44 BY MR. DYKHUIS:
04:56:45 Q. I'll ask it again, Dr. Seeger. I apologize,
04:56:49 Dr. Seeger. Did Dr. Ghofrani, Dr. Reichenberger, or
04:56:55 Dr. Grimminger come up with the idea to perform the work

described in the "Inhaled Treprostinil" section of the Ghofrani article?

A. It is correct that they -- it's correct, yes. They didn't have the idea, no.

Q. Thank you.

Who decided who would be listed as authors on the Ghofrani paper?

A. I did.

Q. And then, Dr. Seeger, you've been handed a copy of what will be marked as Exhibit 8. Exhibit 8 is a -- states at the top, "Annals of Internal Medicine." At the bottom right corner, it states "Liquidia's Exhibit 1009."

And on Page 5, Dr. Seeger, there is a heading that says "Clinical Observations." On Page 5, under the heading "Clinical Observations Inhaled Treprostinil for Treatment of Chronic Pulmonary Arterial Hypertension." And that section continues on to Page 6.

Do you see those two pages, Dr. Seeger?

A. Yes.

Q. And on Page 6 of the document on the right-hand column, it identifies you and Dr. Voswinckel, Dr. Ghofrani, and Dr. Olschewski as authors?

A. Yes, the authors are Voswinckel, Ghofrani, Olschewski, Grimminger and myself.

BY MR. DYKHUIS:

04:58:42 Q. So, just to be clear, Dr. Seeger, is Exhibit 8 the
04:58:49 Voswinckel 2006 article referenced in this declaration?
04:58:54 A. Yes.
04:58:57 BY MR. DYKHUIS:
04:58:57 Q. Does Voswinckel 2006 Exhibit 8 describe a clinical
04:59:00 study?
04:59:01 A. No. A clinical study, of course, always comprises
04:59:13 many more patients. Under the heading "Clinical
04:59:21 Observations," there is a short report about three patients.
04:59:33 Those are more or less single case reports.
04:59:43 Q. Are the three patients described in Voswinckel 2006
04:59:55 part of the work you did in collaboration with the other
05:00:00 inventors of this '793 patent?
05:00:04 THE WITNESS: Yes.
05:00:06 BY MR. DYKHUIS:
05:00:08 Q. Did you and the other inventors identify the dosage
05:00:11 amount that was given to patients in Voswinckel 2006?
05:00:14 A. Yes, me and the inventors of -- this is '793 patent.
05:00:27 Is that what you mean?
05:00:36 Q. Dr. Ghofrani is listed as an author. Did he design
05:00:41 the trial that's described in Voswinckel 2006?
05:00:45 THE WITNESS: No.
05:00:48 BY MR. DYKHUIS:
05:00:49 Q. Dr. Grimminger is listed as an author. Did he design
05:00:52 the trial that's described in Voswinckel 2006?

05:00:55 THE WITNESS: No.

05:00:59 BY MR. DYKHUIS:

05:00:59 Q. We talked earlier about routine management and
05:01:03 administrative work relating to clinical trial. Were
05:01:07 Dr. Ghofrani and Dr. Grimminger listed as authors on this
05:01:11 paper, the Voswinckel 2006, because of their participation
05:01:15 only in routine management in administrative work?

05:01:19 THE WITNESS: It is not just routine management.
05:01:36 I have described in detail what is required for clinical
05:01:41 studies to be possible. To repeat briefly, the guidance of
05:02:04 the patients, the selection of the patients, and the
05:02:07 management of the study in general.

05:02:13 The management of all who takes care surrounding
05:02:18 the clinical trial. And the care after the study, in this
05:02:35 case in particular, two patients who were monitored or
05:02:40 observed long term.

05:02:41 BY MR. DYKHUIS:

05:02:42 Q. If I understand correctly, Dr. Ghofrani and
05:02:46 Dr. Grimminger participated in management or application of
05:02:50 the study, but they did not design the clinical trial; is
05:02:57 that correct?

05:02:58 THE WITNESS: Yes.

05:03:02 BY MR. DYKHUIS:

05:03:02 Q. Did Dr. Roscigno, Dr. Rubin, Dr. Schmehl, or
05:03:08 Dr. Sterritt participate in writing the Voswinckel 2006

article?

THE WITNESS: No.

BY MR. DYKHUIS:

Q. Is that why they weren't listed as authors on Voswinckel 2006?

A. Yeah.

BY MR. DYKHUIS:

Q. Who directed and oversaw the preparation of the "Voswinckel 2006" article?

A. In this case, Mr. Olschewski and I.

BY MR. DYKHUIS:

Q. Even though not all the inventors on this '793 patent are identified as authors, did Voswinckel 2006 describe work that you did in collaboration with the other '793 patent inventors?

A. Yes, there are patient findings that are from the development program prepared with the other inventors.

BY MR. DYKHUIS:

Q. Dr. Seeger, I am handing you a copy of what will be marked as Exhibit 9. It states "United States Patent and Trademark Office," and it's entitled "Declaration of Dr. Werner Seeger."

The cover also identifies "Inter partes review Number 2017-01621." And above that it states the patent number, Number 9,358,240. Do you have -- do you have

Exhibit 9, Dr. Seeger?

THE WITNESS: Yeah.

Q. On the last -- can you turn to the last page, please?

A. Yes.

Q. Do you have the last page, Dr. Seeger? Whose signature is on the last page?

THE WITNESS: It is my signature.

Q. Dr. Seeger, I'm handing you a copy of Exhibit 10. It is entitled, "United States Patent and Trademark Office, Second Declaration of Dr. Werner Seeger." And it identifies an IPR relating to Patent 9,358,240 and also Patent 9,339,507.

Do you see that on the first page, Dr. Seeger?

A. Yes.

BY MR. DYKHUIS:

Q. Can you turn to the last page, Dr. Seeger, and then my question is: Whose signature is shown on the last page of Exhibit 10?

THE WITNESS: My signature.

BY MR. SUKDUANG:

Q. Did you keep any of the communications that you had with Dr. Ghofrani regarding the drafting of the Ghofrani 2005 article?

THE WITNESS: (In English.) The same as I answered a minute ago. No, I think we did not take -- keep

drafts of this or any written background of this.

BY MR. SUKDUANG:

Q. Did you keep any communications with Dr. Reichenberger regarding drafting the Ghofrani 2005 article?

THE WITNESS: (In English.) No, at least I'm not aware that we kept any communication of this. It was -- it would not be our routine as to this -- this type of article, as I said.

BY MR. SUKDUANG:

Q. Did you keep any communications with Dr. Grimminger regarding the drafting of the Ghofrani 2005 article?

A. (In English.) Same answer. No, I'm not aware that we kept any communication concerning this article in 2005 because this is not our routine to keep these communications on such type of article.

Q. Did you keep any drafts of the portions of the Ghofrani 2005 article that you wrote?

A. (In English.) Same answer again. I'm not aware that we kept any drafts on article of this type, which is not our routine.

Q. Did you keep any communications between yourself and Dr. Voswinckel, Ghofrani, Grimminger, or Olschewski regarding the clinical observations letter, Exhibit 8?

THE WITNESS: (In English.) I cannot answer for

sure. This is now already far, far more than ten years ago. The routine where we keep files concerning our publication, I cannot exclude that I would spend a lot of energy going to files around those years to find something, but I would not necessarily expect to have kept these files. I cannot answer whether or not I might find some communication concerning the preparation of this article.

Q. Can you take out Exhibit 4, which is the declaration of Dr. Werner Seeger, for the '793 patent. Paragraph 2 says you're a paid consultant for United Therapeutics. Was that true when you signed the declaration in May of 2021?

THE WITNESS: Yes, I assume it was true for sure; otherwise, I would not have signed it.

BY MR. SUKDUANG:

Q. Are you a paid consultant for United Therapeutics currently?

A. (In English.) Yes, I am.

Q. Are you being paid to appear today?

A. (In English.) Yes, I would be paid on an hour basis for my contribution to this deposition, I think it's called.

Q. And what is your, if you recall, your hourly compensation rate?

A. (In English.) My standard -- my current standard hourly compensation rate is 500 USD per hour, and I'm pretty sure I know this -- I'm pretty sure, I think, it's the same

rate. So, I ordered my secretary taking care of this to use as my standard consultancy rate on all bases.

Q. Will you send an invoice to United Therapeutics for your deposition today?

THE WITNESS: (In English.) Yes, my secretary will do.

BY MR. SUKDUANG:

Q. There are other lawyers in the room with you, Mr. Facey and a Mr. Bepler; that correct?

A. (In English.) Yes, this is correct.

Q. Are you paying Mr. Facey and Mr. Bepler, or is United Therapeutics paying Mr. Facey and Mr. Bepler?

THE WITNESS: (In English.) I pay Mr. Facey, but this is recompensed from United Therapeutics and also the work Dr. Bepler does as an attorney is compensated from United Therapeutics. In essence, the work of both Mr. Facey and Dr. Bepler is compensated from United Therapeutics.

BY MR. SUKDUANG:

Q. Will United Therapeutics compensate Mr. Facey and Mr. Bepler for their presence here today?

THE WITNESS: (In English.) Concerning Mr. Bepler, this goes directly to United Therapeutics; and concerning Mr. Facey, he bills me, and I'm recompensated. And, yes, for the contribution today, they are compensated.

Mr. Facey's compensation goes when my office

organization, but is also re -- also compensated or recompensated by UT. Hopefully, that is pretty clear now.

BY MR. SUKDUANG:

Q. Yes. How long did you meet with Mr. Dykhuis yesterday to prepare for your deposition?

THE WITNESS: (In English.) Six hours.

Q. During your six hours of preparation with Mr. Dykhuis yesterday, counsel for UTC, did you review documents that helped you remember activities that occurred in relation to your work with inhaled Treprostinil for United Therapeutics?

THE WITNESS: (In English.) I looked at the patents. I looked at the publications, which were on the table to be discussed, and I looked at the declaration.

BY MR. SUKDUANG:

Q. Dr. Seeger, when you were working with United Therapeutics on inhaled Treprostinil, did you ever use a powdered formulation of Treprostinil for inhalation?

A. (In English.) No.

Q. When you were working with United Therapeutics on inhaled Treprostinil, did you ever use a dry-powder inhaler?

THE WITNESS: (In English.) No.

BY MR. SUKDUANG:

Q. Did United Therapeutics ever approach you to test a dry-powder formulation of inhaled Treprostinil?

THE WITNESS: (In English.) No.

BY MR. SUKDUANG:

Q. Did you ever discuss with the other inventors on this '793 patent trying dry-powder form of Treprostinil for inhalation?

A. (In English.) I was just thinking, not yet talking. I do not -- I do not recollect. Probably, yes, because we discussed all types of procedures and also alternatives, strategies, but I cannot really answer your question.

BY MR. SUKDUANG:

Q. Dr. Seeger, why didn't you try powdered formulation of Treprostinil with UTC?

THE WITNESS: (In English.) So, in a nutshell, our experience is primarily based on inhaled solutions, so that's what we did with iloprost, and we have where we have also aerosol, technology-wise a lot of expertise, and we simply followed this route of expertise to use inhaled solutions.

In addition, I could start now, but I won't, for the sake of time, a longer discussion, that bringing something down as a powder may or may not be simply identical to bringing something down with the fluid solution. It may impact local pharmacokinetics, to some extent. But the general answer is we followed our expertise and then this brought solution, and we were happy to find a solution to use this solution-based, nebulization-based

technology.

Q. For the record, I'd like to mark as Exhibit Number 11 a document from the New England Journal of Medicine titled "Inhaled Iloprost For Severe Pulmonary Hypertension." It starts at Bates number LIQ02803911.

Dr. Seeger, is this your paper on the pivotal studies on inhaled iloprost for severe pulmonary hypertension?

THE WITNESS: (In English.) Yes, it's the final trial, the pivotal Phase III trial I've just mentioned. It was published in the New England Journal and then paved the way to having inhaled iloprost to prove in Europe and in the United States, yes.

BY MR. SUKDUANG:

Q. And if you look at the list of authors, on the second line Dr. Lewis J. Rubin is an author on this paper; is that correct?

A. (In English.) Yes.

BY MR. SUKDUANG:

Q. And this was published, your work on inhaled iloprost for pulmonary hypertension was published before your New York meeting with United Therapeutics on Treprostinil; is that correct?

A. (In English.) Yes.

Q. And United Therapeutics consulted with you on inhaled

Treprostinil because you have expertise on inhaled iloprost for pulmonary hypertension; is that correct?

THE WITNESS: (In English.) I assume, yes. So, I'm not the brain of United Therapeutics, but it's very probable -- obvious, really -- that this is the reason why they contacted me, yes.

(Conclusion of video.)

MR. JACKSON: Your Honor, Plaintiffs move into evidence Exhibits 267, 836, 1722, 2035, 1935, and 1940 as well as -- sorry -- and 1726.

MR. PIVOVAR: No objection.

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

Okay. So, we're done for today.

MR. JACKSON: Your Honor, may I just indulge? We have one last video, and then we're done. I believe we can provisionally rest. It's a minute and 40 seconds.

THE COURT: Okay.

MR. JACKSON: I'm just trying to make sure -- we're trying to make sure we're done with evidence as quickly as possible. I figure a minute and 40 seconds.

THE COURT: Yeah. The amount of time we're talking about it, we could have done it. So, why don't we do it.

MR. JACKSON: Thank you. We call Tushar Shah,

please, Your Honor.

THE COURT: All right.

(Video playing.)

Q. Good morning, Dr. Shah. Can you please state your full name for the record.

A. Yes. My name is Tushar Shah.

Q. And where do you work now, sir?

A. I work at Liquidia Corporation.

Q. What is your title at Liquidia?

A. I'm the chief medical officer and the head of R & D.

Q. So, you understand that you're providing testimony at this deposition today in a corporate capacity on behalf of Liquidia; correct?

A. Yes.

Q. Other than the instructions for use that we reviewed earlier, does LIQ -- - does Liquidia intend to provide any additional training to patients or doctors on the use of LIQ861?

THE WITNESS: I would anticipate we would provide training information to physicians and patients on how to use the product properly. As I explained earlier, technique and use of inhaled devices is really a challenge for patients, and providing sources of information that are more easily understood and -- and like a video, things of that type, that helps individuals understand how to use a

product, is very commonly done for these types of complex devices. And I -- though, I'm not aware yet if any decision has been taken about the plans to do these things, I would anticipate this would be done to ensure the patients understand how to use this product properly to get the benefit.

(Conclusion of video.)

MR. JACKSON: Thank you, Your Honor.

THE COURT: All right. So, we're done for today. I guess we'll start tomorrow at 8:30, and I guess we'll start with the Defendants' case.

Anything else before we -- before I leave the courtroom?

MR. JACKSON: I have one quick thing. We have one other infringement witness, but he's a doctor. He was treating patients. We've agreed with Defendants to schedule him on Wednesday. So, we are provisionally resting subject to being able to call him when he's available.

THE COURT: Okay.

MR. JACKSON: Thank you, Your Honor.

THE COURT: That's fine. All right. Well, then we're done for the day.

DEPUTY CLERK: All rise.

(Court was recessed at 5:21 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