IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF NEW JERSEY

JANSSEN PRODUCTS, L.P., et al.,	:	Civil No. 10-cv-5954(WHW)
Plaintiffs,	:	
v.	:	TRANSCRIPT OF TRIAL PROCEEDINGS
LUPIN LIMITED, et al.,	:	VOLUME 2
Defendants.	:	

Newark, New Jersey
March 19, 2014

BEFORE:

THE HON. WILLIAM H. WALLS, U.S.D.J.

Reported by:
CHARLES P. McGUIRE, C.C.R.
Official Court Reporter

Pursuant to Section 753, Title 28, United States Code, the following transcript is certified to be an accurate record as taken stenographically in the above entitled proceedings.

s/CHARLES P. McGUIRE, C.C.R.

CHARLES P. McGUIRE, C.C.R.

which we couldn't use. And then every day, everybody was trying and trying, and then after a number of weeks, finally one gay said, Piet, I think I have it, and one of the experiments succeeded. And typically, the first time is the most difficult one. Later, you can use some of the powder as seeds for the next experiment and then you don't need to do the scratching any more. But for the first time, with 20 people, we were scratching for -- for over an hour in the morning, over an hour in the afternoon, and finding the right way to convert the oil to a powder.

Q. Okay. I'm going to break that down a little bit in a second, but --

A. Yes.

Q. -- before we do that, you were referring to scratching tubes and illustrating them, and maybe we can give a physical demonstrative.

MS. ROYZMAN: May I approach, Your Honor?

THE COURT: Yes.

Throughout the trial, all of you have the right to approach the various witnesses.

But may I ask why you need to break it down?

MS. ROYZMAN: I think I need to explain what techniques were being used. That's important to the case.

THE COURT: What? You need to explain what?

MS. ROYZMAN: Explain what techniques

Dr. Wigerinck was using, because that's important to the case.

THE COURT: What techniques he was using?

MS. ROYZMAN: Yes. I have a couple --

THE COURT: He's already explained what he was doing. He said he had 20 chemists scratching oil in vials. We don't know how long, but it took some time. How much more do I need to know?

MS. ROYZMAN: Just a tiny bit in terms of solvents and conditions that they were using.

THE COURT: Go ahead, but I doubt that it will be that important in the long run. But go ahead.

MS. ROYZMAN: Okay.

Q. You said you were using a contractor to try to help you get a powder; right?

A. Yes.

Q. And the contractor failed; is that right?

A. That was ChemShop.

Q. And was ChemShop using crystallization techniques to try to get your powder, TMC 114?

A. Yes.

Q. And did they succeed in crystallizing TMC 114 in any solvent whatsoever?

A. No.

Q. And what was your reaction to ChemShop's failure to

crystallize TMC 114?

A. Set up the whole effort I mapped out a couple of minutes ago.

THE COURT: You're involved in a recapitulation, almost. We've heard this.

MS. ROYZMAN: I'm just trying to get at what the crystallization efforts were, just --

THE COURT: Well, they were futile.

MS. ROYZMAN: Yes.

THE COURT: So we know that.

MS. ROYZMAN: Okay.

Q. And were you using different solvents to try to crystallize TMC 114 initially?

A. Yes, and as part of that exercise, I was -- I went back into the lab myself. Normally I did not work in the lab any more, but I went back into the lab and instructed the people every day, checked with them to come to a solution.

Q. Did you and ChemShop try to crystallize TMC 114 straight from ethanol?

A. We tried many times.

THE COURT: When did you start scratching, before or after crystallization?

THE WITNESS: You scratch to obtain the first crystal.

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Plaintiffs, :

v. : TRANSCRIPT OF TRIAL PROCEEDINGS

LUPIN LIMITED, et al., : VOLUME 3

Defendants. :

Newark, New Jersey
March 21, 2014

BEFORE:

THE HON. WILLIAM H. WALLS, U.S.D.J.

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cause it to crystallize, and what we want to do is reduce the solubility of the material that we're looking for.

So the oldest crystallization process is, in fact, salt, because people made salt from seawater going back to ancient times, and what they did is they let the seawater into a -- to a -- basically a container that had a lot of surface area, and they'd let the sun evaporate the water, and because when you evaporate water you increase the concentration, eventually, the concentration exceeds that which is the solubility of salt in the seawater and you get crystalline sodium chloride. So that's the simplest example of a crystallization process.

The other ways you can crystallize things is, you can use the fact that most things' solubility is a function of temperature, so hot fluids dissolve more than cold fluids. So if you heat something up and you dissolve all you can from the material in it and then you cool it back down then you can cause crystals to form.

The third method we've heard something about in the trial so far is called antisolvent crystallization, or changing solvent composition. So if you have something dissolve in a particular solvent, and you add another solvent where the material is not soluble, that mixed solvent system now reduces the solubility, and eventually, you should get a crystal.

Now, this all assumes that the material easily crystallizes. There are many things where you do -- you attempt to do this, then you get something called an amorphous solid or an oil. That can happen for a variety of reasons: Impurities, rate, or the complexity of the molecule.

Q. Okay. So are all drug products, solid pills or tablets that we take, are they all crystalline forms?

A. No. There are drug products in which the active ingredient are amorphous, meaning they're solids but not crystalline, and there are also drug products where the active ingredient is actually dissolved inside a fluid that's inside the tablet or capsule, like Liquigel, for example.

Q. Now, can a single drug molecule, a drug like darunavir or aspirin or any other drug, can it crystallize in more than one way or more than one form?

A. Yes. That's a phenomena known as polymorphism.

Q. Okay, and we have an example not relating to drugs, but to carbon. Can you explain this concept of polymorphism a little bit more?

A. Yes. Those of us who work in the field like to use this as an example. Polymorph means compounds that can crystallize in more than one structure. When they're applied to elements, they're called allotropes, but same

basic concept. So if we look at graphite and we look at diamond, they're both crystalline forms of carbon. The only difference is the way the atoms are bonded together in their three-dimensional lattice structure. And we all know that they have very different properties: We put graphite in pencils, and we put diamonds on women's fingers.

Q. Now, crystal is a three-dimensional structure as you've described. Is it sometimes also appropriate to describe polymorphism in a two-dimensional format just for simplicity?

A. For simplicity, we can demonstrate in a two-dimensional way, which is what we have in this demonstrative.

Q. So what's the difference between Polymorph 1 and Polymorph 2 in this exhibit?

A. The regular structure, the way the molecules are arranged are different from each other, and that difference would propagate in all directions as we expand it.

Q. Okay. Now, we've been talking so far about what I think you referred to earlier as a single component crystal. Can you explain a little bit more what you mean by that?

A. Sure. So when we talk about polymorphs, we're talking about crystals of a given molecule, okay, with no other species present in the crystal except possibly a little bit of an impurity, but generally we just mean that the single

component we're interested in is forming the crystal.
Q. Okay. So if we go back to the diamond and graphite example, is it just one kind of molecule carbon that is arranged in a particular three-dimensional order?
A. Yes. In this case, an element, but yes, that's correct.
Q. Okay. Are there also crystals that have more than one component?
A. That's correct.
Q. Okay. So can you explain, then, how -- what a solvate is and how that compares to a single component crystal?
A. Yes. So a solvate is a crystalline solvent in which solvent is part of the crystalline structure. And we have an example here of a solvate just showing solvent molecules in a regular position with respect to the API or the solute molecules.
Q. Okay. So that's slide seven of the demonstratives, the solvate.

And what is the relationship between the green solvent molecules and the orange blocks, the underlying molecule; how are they connected to one another, if they are at all?
A. Well, in this type of solvate, they would be bonded in the structure. Just like the molecules of the drug or the API, if we're talking about a drug, would be bonded

together, the molecules of the solvent would also be bonded to the drug in the crystalline structure.

Q. Okay. Now, we've also heard some talk in the trial so far about a channel solvate. Can you explain using this Demonstrative 8 what that is?

A. Yes. A channel solvate is a special kind of solvate. In a channel solvate, we have channels running through the three-dimensional crystal structure, and the solvent is all inside the channel, so the solvent fills up the channels and stabilizes, normally stabilizes the structure by being in those channels, and typically, the solvent is weakly bonded to the API within the channel.

Q. Okay. So if we look at these side by side, can you just quickly explain the difference again between non-channel and channel solvates?

A. Sure. In a non-channel solvate, we have the solvent molecules in regular -- in positions within the crystalline lattice where they're individually bonded to the solute or the API molecules.

In the channel solvate --

THE COURT: What is API again?

THE WITNESS: I'm sorry, I'm using that as active pharmaceutical ingredient, but I can --

THE COURT: No, I just want to make sure that --

THE WITNESS: Okay. Sure.

THE COURT: Go ahead.

A. And in the channel solvate, we would have the solvent only in these channels that are between layers, for example, of solute or API molecules, and they're weakly bonded, typically, to the solute molecules or the API molecules within the channel and typically stabilizing the structure that way.

THE COURT: What causes the channel?

THE WITNESS: The channel -- the only --

THE COURT: How do they come about?

THE WITNESS: Oh. So when you're crystallizing something, it turns out that the only way that you can form a stable three-dimensional structure is by forming these channels with the solvent inside. Typically things --

THE COURT: So that's the creation of a chemist.

THE WITNESS: It's --

THE COURT: Isn't it? Go ahead.

THE WITNESS: Yes, it's something you discover when you're looking for solid forms. Often things that are channel solvates won't form any other crystals because you need the solvent to stabilize the structure, but they tend to be unique structures and not as common as non-channel solvates.

THE COURT: All right. Go ahead.

BY MR. ZALESIN:

Q. And what kind of solvate does darunavir form?
A. Darunavir is a channel solvate.
Q. All right, and we've seen this picture, I think, on Mr. Diskant's opening, but can you explain what we're looking at here in slide 10?
A. Yes. This is actually the crystal structure of darunavir shown in -- with these lines, they show the darunavir molecules and how they're oriented to each other in three dimensions, and we've made these -- these yellow circles to demonstrate where the channels are. So those yellow circles, if you go in them, that would be the direction the channels would be.
Q. Okay. Now, let's just get some terminology straight before we move forward.

You were talking about solvent that can go inside these channels. Are there different solvents that can appear inside a channel solvate like darunavir?
A. Yes. Typically what determines what can go inside the channels is basically the size of the channels, right? So any molecule -- any solvent molecule that's not too big can often fit inside the channel and stabilize the structure.
Q. All right, and we've heard the term "ethanolate" used during the course of the trial. Can you explain what an ethanolate is in this context?
A. Yes. An ethanolate is a solvate which the solvent is

ethanol.

Q. All right, and we've also heard, for example, isopropanolate. I imagine that's a solvate in which the solvent is isopropanol?

A. That's correct.

Q. All right, and then hydrate; what kind of solvate is that?

A. That's a solvate where the solvent in water.

Q. All right. Now, a little bit more, then, on channel solvates. How do the properties of these channel solvates typically compare to the single component -- or, excuse me, the other kind of nonchannel solvate that you describe? Are there any differences between channel solvates and non-channel solvates in terms of how they behave?

A. Well, typically, channel solvates will give up their solvent when put in -- can give up their solvent or actually gain additional solvent when put in an environment where you have vapor of that solvent present.

Q. Okay. And we have -- first of all, before we do that, the patent defines solvate in a particular way. Can you just review that? And this was part of the claim construction proceeding -- and Your Honor ruled on this -- but can you just explain what is meant here and the definition of solvate in the patent, this stoichiometric versus non-stoichiometric business?

A. Sure. Well, as the term "solvate" is defined, it's a crystal form that contains either stoichiometric or non-stoichiometric amounts of solvent.

Now, stoichiometric solvates are much more common. Those would be like the first type of solvate we were looking at, meaning that there's always a fixed number of solvent molecules per API molecule, so it could be one-to-one or two to one or three to one or half to one. And that also can be the case in channel solvates, but channel solvates can also be non-stoichiometric if they're exposed to certain conditions that causes more solvent to pack in the channel or less solvent to come out of the channel, you can start having odd numbers, "odd" meaning non-integer numbers.

Q. Can you remind us non-math majors what that means?

A. That means numbers -- in fact, to even be more specific, numbers that are not one, two, three, four or five, or a half or one and a half or two and a half - numbers more like .37, something like that.

Q. Okay. All right. Now, you were talking about this tendency of channel solvates to either lose their solvent or gain a different solvent.

We have an animation here. Maybe you can just talk us through this, explain what we're looking at.

A. Sure. If we're looking at a channel solvate, and this

is an ethanolate, which has the molecule and has ethanol in the channel, and if we take that and we put it in an environment where there's a lot of water vapor, then the water vapor is going to go in and push out the ethanol, and now you're going to have a hydrate.

Q. Now, when that happens, will that have any effect on the structure of the crystal lattice?

A. Well, what we're looking at here are what we call isostructural channel solvates, meaning that the structure doesn't really change when we change the solvent molecule. The only thing that actually happens is the lattice can flex a little bit if the size of the molecules are bigger or smaller, so it just kind of pushes up the channel a little bit or the channel contracts a little bit. But basically the structure remains essentially the same.

Q. Now, you also mentioned that channel solvates can lose their solvent in certain conditions. Is there a term that refers to that?

A. Yes. The process of removing solvent from a solvate is called desolvation, and desolvation normally results in a very high percentage of cases in the structure collapsing and you getting what we call an amorphous solid.

Q. All right. So if we look at this channel solvate, and what happens when the solvent leaves, we saw they collapse. Is that what you mean by amorphous?

A. Yes. An amorphous solid is a solid that does not have long-range order; it's not crystalline, but it's still solid. Typically, the example most people like to use with an amorphous solid is window glass, which is a solid, and it's amorphous, but it's not crystalline.

Q. So you've been talking about these quirks or properties of channel solvates, their ability to exchange solvent or sometimes even lose their solvent and collapse into amorphous.

Do those characteristics have any implications for the use of channel solvates in drug products?

A. Yes.

Q. What are they?

A. Well, generally, you don't like to use solvates in drug products as a general rule, for -- the first reason is, most solvents have some toxicity, right? Other than water, and to a lesser degree ethanol, you don't want to ingest solvents, right? You don't want to have methanol or isopropanol or isotone in your drug. So that's one reason that you don't like to have solvates in drugs.

The second reason is processing. So when you -- after you isolate your active ingredient, let's say there's a solvate, you then have to go into what we call secondary manufacturing, which is manufacturing when you're making a tablet, for example, and that typically involves taking the

active pharmaceutical ingredient, blending it with excipients in something that looks a lot like a blender, and then if it's a simple formulation, then you would take that and put it in a tablet press, where you actually put lots of pressure on the solid and make your tablet, and then typically you might coat it. You put a coating on it, which involves putting some kind of polymeric material or sugar with some moisture and then you have to dry it.

Now, each of those operations can result in desolvation, right? When you are putting a lot of pressure on something, you're mixing something up with a blender or you're heating something up, those can result in desolvation, which is a problem. You don't want that to happen.

So generally the pharmaceutical industry always prefers to use non-solvated forms where possible. Of course, sometimes, it's not possible, and they'll attempt to develop a solvate form.

Q. Okay. And with that background, Dr. Myerson, why don't we now take a closer look at the '645 patent, which, again, is Exhibit 1, PTX1, the first tab in your binder.

And the first thing I'd like to go to is the summary of the invention, which is at column 2, beginning at line 46, and can you just describe for us in general terms what this patent teaches and what the invention is about?

A. Well, the invention is about pseudopolymorphic forms, which you've already defined, which can be used in pharmaceutical formulations, and in the summary, it says pharmaceutical and formulation in improved stability and bioavailability and can be manufactured in sufficient high purity to be acceptable for pharmaceutical use.

Q. Okay. So let's understand a little bit about those three terms you used, stability, bioavailability, and purity.

Stability I think you talked about in terms of manufacturing and their ability to withstand external pressures. Is that what you mean?

A. Well, there are two types of stability that we need to talk about which have already been talked about in the trial. One is chemical stability; that is, is the compound going to decompose or not under certain conditions?

The other type of stability when we're talking about the solid forms is solid-form stability; that is, there's a solid form going to maintain the same solid form during processing, or is it going to become amorphous or change to another solid form.

Q. All right. And what about bioavailability; what is the role of a pseudopolymorph or solvate in bioavailability of a drug?

A. Okay. Well, bioavailability of the drug, if it's the

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Plaintiffs,	:	
v.	:	TRANSCRIPT OF TRIAL PROCEEDINGS
LUPIN LIMITED, et al.,	:	VOLUME 9
Defendants.	:	

Newark, New Jersey
April 1, 2014

BEFORE:

THE HON. WILLIAM H. WALLS, U.S.D.J.

Reported by:
CHARLES P. McGUIRE, C.C.R.
Official Court Reporter

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rule or not.

THE COURT: He did. He's already answered that question. You can pursue it. He already said he wasn't aware of it. He told us that.

Neither one of you listen to what the witnesses say.

So you want to move on?

MR. ZALESIN: I'm going to move on.

THE COURT: We'll move on. I'm still going to see if I can find a case. All right?

MR. ZALESIN: It's noteworthy, Your Honor, while we're waiting for the witness, that the Defendants want to put in a lot of deposition testimony of the inventors of this '645 patent, so I'm not really sure what their position ultimately is going to be, but I think we've had the witness' testimony, and we can move on to another subject.

THE COURT: You do any and everything to win within the rules.

MR. ZALESIN: Okay.

THE COURT: When you stretch the rules, you do that, too, if you have a gullible court. All right?

THE WITNESS: Come on up, sir, and we're moving on.

(The witness resumed the stand.)

BY MR. ZALESIN:

Q. Okay. Dr. Zaworotko, let's talk about your opinion that darunavir was a compound of interest in this time frame leading up to May 10th, 2002, the priority date for the '645 patent.

First of all, we can agree that that is an essential premise of your opinion: If the person of skill wouldn't have had any motivation to work on darunavir, then they certainly wouldn't have found any new crystal forms of it; correct?

A. Yes, that was step one of my pathway.

Q. Okay. And that's true even if it would have turned out to be a routine exercise to do the experiments on darunavir, there was no motivation if it wasn't a compound of interest, then they would have never gotten to the invention; correct?

A. If darunavir was not known, and if darunavir was not known to be a very potent molecule in terms of its activity against HIV protease inhibitors, there would have been no motivation to conduct a crystallization screen.

Q. Right. Now, it was well known by May of 2002 that crystalline forms of a drug substance could profoundly affect dissolution and bioavailability as well as properties such as stability and -- stability to humidity and temperature; correct?

A. In order to answer that question, I would need to know

the context.
Q. Well, how about the context of your declaration in this case? On December 23rd, 2013, at paragraph 141, you told the Court: "...it was well-known by May 16, 2002, that the crystalline form of a drug substance could 'profoundly affect dissolution and bioavailability' as well as other properties such as stability to humidity and temperature." Correct?
A. Correct.
Q. Okay. And you've also told us that the chemical structure and the potency, at least in a test tube, of darunavir was known no later than Dr. Ghosh's 1998 paper; correct?
A. I can't remember if the '775 patent was available before the Ghosh 1998, but it would have been around 1998.
Q. The '775 patent was June of 2001, okay? So at least -- at least as of 1998 in your testimony by Ghosh's publication, darunavir and its potency were known; right?
A. I'm relying on other witnesses as part of my opinion in this matter, in particular the testimony of Drs. Marshall and Zingman, and I also relied on Ghosh 1998 and the '775 patent.
Q. Okay. From the publication of Ghosh 1998 up until the '645 patent, we can agree that no one had published a recipe for how to make a solid crystalline form of darunavir;

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Plaintiffs, :

v. : TRANSCRIPT OF TRIAL PROCEEDINGS

LUPIN LIMITED, et al., : VOLUME 10

Defendants. :

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Newark, New Jersey
April 2, 2014

BEFORE:

THE HON. WILLIAM H. WALLS, U.S.D.J.

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crystallization process, he testified to that.

THE COURT: He's got that in his report?

MR. ZALESIAN: Certainly he discusses the three-step crystallization process.

THE COURT: I haven't read the report, so I have to go on what has occurred.

MS. MAZZOCHI: Your Honor, I can assure you that the word "seed" does not appear anywhere in Dr. Myerson's expert report. Nor does he ever offer the opinion that you somehow need to go through some isopropanol crystal before you can get to the ethanol solvate.

THE COURT: I will permit that. As far as the seeds, so be it. I'll take a representation in the absence of your colleague being able to give me something definite.

MR. ZALESIN: Okay.

THE COURT: All right. I sustain the objection.

MR. ZALESIN: Okay.

Q. Let me just ask you this, Dr. Myerson. Have you seen any evidence throughout this trial or on any point in your work in this case that darunavir can be crystallized for the first time directly in ethanol?

MS. MAZZOCHI: Same objection, Your Honor. This is not in his expert report.

THE COURT: I'll permit it.

A. No.

THE COURT: I'll permit it because I don't think you were surprised. All right?

Go ahead.

BY MR. ZALESIN:

Q. All right. Let's move on to the various types of crystals that you might get.

Now, you mentioned a moment ago that there are several kinds of crystals, single-component, hydrate, solvate, et cetera. As you're going through the process of doing these experiments, are you -- do you have any way of knowing or is there any information you're learning that tells you what kind of crystal you might ultimately be able to create?

A. No, not really.

Q. Okay. And again, we've seen a lot of literature on these issues, mostly through the testimony of Dr. Zaworotko.

As an expert in this field, are you aware of any literature that says that you can predict what kind of crystal might form if a crystal forms?

A. No, I am not.

Q. You talked about the properties of these various crystals that might arise. What do you mean by properties? What kinds of properties matter?

A. Well, the property of crystals that are important in the pharmaceutical solid dosage form or API to be used in a

dosage form include such properties as chemical stability and solid state stability, also solubility, dissolution rate, hygroscopicity - that is, whether it absorbs water from the atmosphere or not. Those would be -- and purity, of course. Those would be the main -- some of the main properties that you'd be interested in.

Q. Okay. Let's just understand a couple of those.

What's the difference between chemical stability and solid state stability?

A. Chemical stability refers to whether the given drug that you're dealing with will decompose with time and decompose into other chemicals, which is not a good thing if you want to store the drug in your medicine cabinet. So that's chemical stability.

Solid state stability refers to the solid form of the drug, the crystalline form of the drug changing to another crystalline form or an amorphous form. So if you had an amorphous formulation and it became crystalline, that would be a solid form transformation or vice versa, or if you had one crystalline polymorph or solvate that became another one, that could be a transformation.

Q. And you also mentioned solubility and dissolution. Why do they matter to a pharmaceutical product?

A. Well, solubility and dissolution rate contribute greatly to bioavailability. How fast something dissolves in

your body as well as how much can dissolve is very important.

Q. By the way, when you first obtain crystalline material, can you tell just by looking at it what its properties are going to be, whether it's going to be stable or soluble or pure?

A. No, you have to do tests.

Q. Okay, and what kind of tests do you do to find out that information?

A. Well, you could do a number of tests. You would measure the solubility by seeing how much can dissolve in water, for example. There's a standard way to measure dissolution rate, for example. If you were interested in that, you would measure its melting point, you would measure its purity, you would characterize the -- its fingerprint using powder x ray diffraction, a number of other analytical techniques that you could use.

Q. And I think you took us through some of this information in the '645 patent when you were here earlier in the trial --

A. Yes.

Q. -- but is that kind of information reflected in the '645 patent?

A. Yes, it is.

Q. And prior to that publication of that patent, was that

information available to people of skill in the art concerning darunavir?

A. No.

Q. Now, Dr. Zaworotko yesterday spent some time talking about Defendants' Exhibit 983, which was the Byrn article from 1995. Are you familiar with that paper, Dr. Myerson?

A. Oh, yes.

Q. Okay. And in particular, he showed us this chart or flow chart or decision tree on the top of page 949 and suggested that this pretty much tells you everything you need to know about how to run one of these crystallization screens.

Can you take us through this flow chart and what it does and does not teach in terms of how to run a screen and find a new crystal form that hasn't been discovered before?

A. It basically just lists variables. For example, it says hydrates, discovery, question mark, and then you look at -- it says different crystallization solvents, different polarity, vary temperature concentration, agitation, pH water content, pretty much the same kind of variables I was talking about previously, and it talks about doing tests to see what the properties are that you might get. It doesn't actually tell you exactly what experiments to do, how to do them, just lists variables and tests that you can do.

Q. Okay. And then with respect to different physical properties, does it give you any road map or recipe for how to make a crystal that has desirable properties?

A. No. No, it basically says do lots of experiments and see what you get and analyze the results.

Q. Okay. Was this information known in the art before Dr. Byrn published his paper in 1995?

A. Oh, certainly.

Q. Okay. Does this mean that you can now take a recipe and make a crystal from scratch that's never been made before?

A. No.

Q. While we're on this page, let me ask you about another paragraph that appears in this Byrn paper. It begins here, we're on page 949: "With a very few exceptions, the structural solvent contained in marketed crystalline drug products is water."

Is that consistent with your understanding of the use of solvates in marketed products?

A. Yes.

Q. And it goes on to explain a variety of reasons why one might nevertheless find it desirable to characterize other solvated crystalline forms.

And so we're clear, the darunavir ethanolate at issue in this case is another solvated crystalline form?

A. Yes.
Q. Okay. So according to Dr. Byrn in this paper, what are the reasons one would ordinarily even bother to characterize something like an ethanolate?
A. Well, you're interested in these other solid forms. They might be useful in purification. You might take that solvate and desolvate in the final drawing step. And it says "might be used in recovery for subsequent rework." So you can use solvates as intermediates, for example, in purification, or you can desolvate them after you've made them to make a nonsolvated form.
Q. You read Dr. Byrn to be suggesting that solvated crystalline forms might be good for final marketed drug products?
A. No, he's not suggesting that.
Q. Okay. Now, Dr. Zaworotko also talked to us yesterday about an FDA guideline having to do with crystallization screening. Are you familiar with that FDA Guideline?
A. Yes, I am.
Q. DTX1021, from 1987.

I want to direct your attention to page 31, which is where the discussion of solid state drug substance forms in relationship to bioavailability appears, and in particular the paragraph on the bottom of the page, which reads, at least starts out: "By the time of an NDA

raised and discussed before.

MS. MAZZOCHI: Well, Your Honor --

THE COURT: I note your objection.

MS. MAZZOCHI: Thank you, Your Honor.

MR. ZALESIN: Just so the record is clear, in Dr. Myerson's rebuttal report, at paragraph 50, he responds directly to Dr. Zaworotko's hydrogen bonding theory and discusses it for about a page. So...

MS. MAZZOCHI: And he nowhere makes any reference to this article or suggests --

THE COURT: I took your point, but I rejected it.

MS. MAZZOCHI: I understand, Your Honor. Thank you.

THE COURT: All right. Let's continue with this saga.

(Laughter)

THE COURT: This is not going to be renewed for next season.

(Laughter)

THE COURT: Go ahead. Go ahead.

BY MR. ZALESIN:

Q. Do you have any comment on Bernstein, Dr. Myerson?

A. Well, I mean, generally, what Dr. Bernstein is saying, which is not unreasonable and I don't disagree with, that you can use this as a possibility; it seems reasonable.

However, you can't use it to predict or the result of any particular experiment or set of experiments, which is basically exactly what I just said.

Q. Is there any literature anywhere that says you can use hydrogen bonding and chemical structure to predict crystal formation?

A. Well, I mean, there's an earlier article, I think that was mentioned by Desiraju, that talks about that, and pretty much the same argument that Dr. Zaworotko made, Dr. Bernstein doesn't agree with it, there are other papers that don't agree with it, I don't agree with it. So this is, let's say, an area of controversy among us in this field.

Q. Okay. Let me ask this question. Is there any paper you're aware of that proves that the predictability theory based upon hydrogen bonding is correct?

A. No, not that I'm aware of.

Q. All right. Let's talk about the particular crystal form at issue in this case, the ethanolate solvate of darunavir.

Directing your attention to the patent, which is PTX1 or DTX1, if you prefer, and specifically in column 2, --

MR. ZALESIN: Sorry, Your Honor.

THE COURT: I think we will recess now. I forgot:

The Court Reporter's been working.

We'll start again at 20 before the hour. All right?

MR. ZALESIN: Thank you.

THE COURT CLERK: All rise.

(Recess taken)

THE COURT CLERK: All rise.

(The witness resumed the stand.)

THE COURT: Let's resume.

BY MR. ZALESIN:

Q. Professor Myerson, I've put up on the screen claim 4, which of course depends from claim 3 of the '645 patent.

In a nutshell, what do you understand that invention to be?

A. It's the composition comprising an ethanolate solvate of darunavir in a ratio of about one to one and a pharmaceutically acceptable inert carrier.

Q. Okay. Prior to the teachings of the '645 patent, would a person of skill in the art had a reasonable expectation that he could make a one to one ethanolate solvate of darunavir?

A. No.

Q. Prior to the teachings of the '645 patent, would a person of skill in the art had a reasonable expectation as to the conditions under which such an ethanolate solvate

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF NEW JERSEY

JANSSEN PRODUCTS, L.P., et al., : Civil No. 10-cv-5954(WHW)

Plaintiffs, :

v. : TRANSCRIPT OF TRIAL PROCEEDINGS

LUPIN LIMITED, et al., : VOLUME 11

Defendants. :

----------x

Newark, New Jersey
April 3, 2014

BEFORE:

THE HON. WILLIAM H. WALLS, U.S.D.J.

Reported by:
CHARLES P. McGUIRE, C.C.R.
Official Court Reporter

Pursuant to Section 753, Title 28, United States Code, the following transcript is certified to be an accurate record as taken stenographically in the above entitled proceedings.

s/CHARLES P. McGUIRE, C.C.R.

CHARLES P. McGUIRE, C.C.R.

issue about the level of ordinary skill.

Can you briefly describe your disagreement with Dr. Ganem and Laird?

THE COURT: First, no, excuse me, why don't you tell me what you consider the ordinary skill in the art?

THE WITNESS: Someone with a Master's in chemistry with a couple of years of experience in lab.

THE COURT: Why do you say that?

THE WITNESS: I had a group of 160-something chemists -- I had a group of 160-something chemists. We had a rule, I should state an objective that we had a one-to-one ratio of Ph.D.s and non-Ph.D.s, and that's what the group was: It was half and half. So I think it's lower than Ph.D.s because a lot of my best people didn't have Ph.D.s, and they were -- they did just fine.

THE COURT: All right. Go ahead.

Q. But even -- does it make any difference to your analysis if you accept the Ganem-Laird school of thought that you have to have a Ph.D.?

A. No, it makes no difference to the analysis.

Q. And in doing your work, did you review the file wrapper for the '015 and the '411 patents?

A. I did.

Q. Did you review Tibotec documents and testimony?

A. I did.

Q. Did you attend most of the trial, sitting there in the back?

A. I have.

Q. Did you review the prior art?

A. I did.

Q. Overall, and I'll go into detail in a moment, do you have an opinion as to the validity of the '411 and the '015 patent?

A. I do.

Q. And what's that?

A. I believe they're innovative and inventive. They're not obvious.

Q. Okay. Let's first start with the '015 patent, which you told us is about the manufacture of bis-THF; is that right?

A. That's correct.

Q. And is this bis-THF over here on the left?

A. It is.

Q. Is it a complicated molecule?

A. It is, because of the three chiral centers, incredibly complex, and I believe that -- I heard Dr. Wigerinck testify that it's responsible for about 90 percent of the cost of darunavir.

Q. There's been some testimony in the case about Dr. Darun Ghosh. Do you know him?

A. Yes. We worked together in Merck.
Q. And during what years did he work at Merck?
A. He came a few years after I did. I actually don't know the answer to that question. I believe he came in the late 80's or early maybe 1990, and I think he departed by '94, '95.
Q. Okay. And what kind of work did he do at Merck?
MS. MAZZOCHI: Objection, Your Honor; narrative.
THE COURT: What kind of work did he do at Merck is a narrative?
MS. MAZZOCHI: No.
THE COURT: Is that what you said? Is that what you said? It's a narrative?
MS. MAZZOCHI: Yes, he's asking for a narrative. He's asking him what did Arun Ghosh do at Merck?
THE COURT: So? If he knows.
MS. MAZZOCHI: Well, that --
THE COURT: If he knows. What's wrong with that? I mean, every question is some form of narrative, so what do you mean, it's a narrative?
MS. MAZZOCHI: Well, it's such an open-ended question, I have no idea how long and convoluted of a response we're going to get.
THE COURT: Let's find out. Let me do it my own direct way.

Did you know what he did?

THE WITNESS: Yes, he was a medicinal chemist in West Point in our labs in Pennsylvania.

THE COURT: Okay. Let's move on.

Q. Did --

THE COURT: We're moving beyond the cemetery at high noon. Go ahead.

Q. Did the Merck team formulate bis-THF?

THE COURT: I'm sorry, I can't hear you.

Q. Did the Merck team formulate bis-THF?

A. Yes, the group in West Point working on HIV protease inhibitors were the first to apply that chemical structure, the bis-THF moiety in the context of HIV protease inhibitors. Arun was part of that team.

Q. Did Merck decide to commercialize a product using bis-THF?

A. No.

Q. Why not?

A. We decided it was too complex and we passed. We had Crixivan, and we decided not to pursue the pharmacophore.

Q. I'm sorry. We've seen a bunch of Ghosh publications. This is the very first.

Do you know these co-authors?

A. Yes, I know all of them.

Q. Who employed them?

A. That was the West Point or a good part of the West Point protease team for Merck.
Q. Did Ghosh leave and go to academia at some point?
A. He did.
Q. By the time of this article, he gets a footnote, it says his present address is the University of Illinois at Chicago?
A. That's correct.
Q. The rest of the guys stayed behind at Merck?
A. Yes.
Q. Okay. You heard Dr. Ghosh say at his deposition, which was played in court, that no one in his right mind would attempt to synthesize a bis-THF. What's your opinion?
A. I don't know that I would use that phrase, but it was a formidable challenge.
THE COURT: I'm sorry.
MS. MAZZOCHI: I'm sorry, Your Honor.
THE COURT: He didn't say that?
MS. MAZZOCHI: I don't know what he's talking about. We haven't played any sections of Dr. Ghosh's deposition in court as far as I'm aware.
MR. DISKANT: That's not correct. It was played during the cross of Dr. Ganem and read twice.
THE COURT: I saw Dr. Ghosh on that screen.
MR. DISKANT: That's what I'm referring to.

THE COURT: And that was not in a dream, I mean --

(Laughter)

THE COURT: I mean, seriously. Come on now.

MS. MAZZOCHI: I had no idea what he was referring to, Your Honor.

THE COURT: Well, wasn't that reflecting his appearance at a deposition?

MS. MAZZOCHI: Well, Your Honor, my understanding -- I thought he was somehow suggesting that the Plaintiffs had done his deposition testimony as part of the read-ins.

THE COURT: All right.

MS. MAZZOCHI: Like I said, Your Honor, they haven't given me any -- I don't have an exhibit for this.

THE COURT: Let's move on. Thank you so much.

We note that Dr. Ghosh appeared on that screen at a deposition, and we saw and heard him. All right?

Go ahead.

Now, the question was, do you agree or disagree with him characterizing something as not in his right mind, something like that; right?

MR. DISKANT: That's correct.

THE COURT: Put the question again.

Q. Do you agree with -- Dr. Ghosh said in his testimony that no one in his right mind would attempt to make bis-THF. What's your view?

A. I agree with his -- his conclusion. I wouldn't have used the same terms. It's a highly formidable challenge, and -- I agree with Dr. Ghosh.

Q. Does the '015 patent solve the problem?

A. It does.

Q. Does it provide a commercial scale process for making bis-THF?

A. It does.

Q. Okay. Let's look at the prior art.

MR. DISKANT: And there are a couple prior art references that aren't yet in evidence. I'd like to offer them. Those will be Ghosh 95, which is PTX222, the '506 patent, which is PTX 35, and Ghosh '99, which is DTX 790.

MS. MAZZOCHI: No objection, Your Honor.

THE COURT: Thank you.

(Plaintiff's Trial Exhibits 35 and 222 and Defendants' Trial Exhibit 790 marked in evidence)

Q. Does this slide depict the various prior art ways of making bis-THF?

A. It does.

Q. And can you tell what one of ordinary skill as of 2001 would learn from the prior art?

A. They would learn that dihydrofuran, the simple molecule in that top box -- sorry, in the top box that says Starting Compound -- I don't like to do this very often, but