IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

PFIZER INC. and UCB PHARMA GMBH	:	C. A. No. 1:15-cv-000079(GMS)
Plaintiffs,	:	Consolidated
v.	:	
MYLAN PHARMACEUTICALS INC.,	:	
Defendant.	:	

CONFIDENTIAL

Oral deposition of LEONARD J. CHYALL, Ph.D. taken pursuant to notice, held on Tuesday, August 23, 2016, at the office of Kilpatrick Townsend & Stockton, 1114 Avenue of the Americas, New York, New York, commencing at 9:01 a.m. before Jamie I. Moskowitz, RPR, CRR, a Registered Professional Reporter and Notary Public.

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I N D E X

Testimony of: LEONARD J. CHYALL, Ph.D.

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E X H I B I T S

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EXHIBIT NUMBER	DESCRIPTION	PAGE
Exhibit 1	Expert Report of Leonard J. Chyall, Ph.D. Regarding Validity	
Exhibit 1A	Exhibit A	
Exhibit 2	Rebuttal Expert Report of Leonard J. Chyall, Ph.D. Regarding Validity	
Exhibit 2A	Exhibit B	
Exhibit 3	Opening Expert Report of David R. Janero, Ph.D.	
Exhibit 4	United States Patent No.: US 6,858,650 B1	
Exhibit 5	Document entitled Schwarz Pharma AG	
Exhibit 6	E-mail to Arth from Meese dated 8/3/99	
Exhibit 7	Document entitled Analytical Summary SPM 909 (007)	
Exhibit 8	Gould paper	
Exhibit 9	Document entitled Salt selection for basic drugs	

EXHIBIT NUMBER	DESCRIPTION	PAGE
Exhibit 10	Document entitled International Application Published Under the Patent Cooperation Treaty (PCT)	

LEONARD CHYALL, Ph.D., after having been first duly sworn, was examined and testified as follows:

EXAMINATION BY MR. HOLLOWAY:

Q Dr. Chyall, could you please state your name for the record?

A Leonard J. Chyall.

Q And you have been retained as an expert witness in this case; is that correct?

A Yes, I have.

Q Were you retained by White & Case or by UCB Pharma and/or Pfizer?

A I don't remember from the engagement letter.

Q And you provided two reports in this case, correct?

A Yes, sir.

Q And when I say "this case," I'm talking about the case that Pfizer and UCB Pharma have brought against Mylan, as opposed to the case where you previously testified before Judge Sleet concerning fesoterodine; is that fair?

A Yes.

Q If at any point in time before I hand you your reports if you'd like to see them, just let

me know and I will hand them to you, okay?

A Okay.

Q About how many times -- and I don't mean to exclude -- let me just start over.

How many times including times where you have testified have you been retained as an expert in the pharmaceutical field?

A With respect to -- I have to think a little carefully because I just don't know offhand. I personally have worked on about 35 projects in the capacity of an independent consultant. Nearly all of them relate to pharmaceuticals.

Q And these projects, are you talking about everything you do in your profession, or are you limiting it -- are you limiting that to consulting for attorneys or companies in the patent context?

A The 35 would be everything. It would be a smaller number for providing consulting to attorneys. But the bulk of the work that I'm doing now is assisting attorneys understand scientific matters. With respect to expert witnessing, I average about two projects a year, and I probably have the best numbers there because I know from my CV where I'm required to list expert testimony. In

any given moments my CV usually contains eight matters, so it works out to be about two a year.

Q And do -- I'm looking for a proportion of your time spent in a given year. What's the proportion of time spent where you are working with attorneys providing technical consulting as you just explained versus the other work that you're doing in your independent consultancy?

A It's going to vary depending on the year. At present more than half.

Q And about how long has that been the case?

A For the past two or three years, I believe.

Q What kind of work do you do when you're not providing assistance to attorneys on legal matters?

A One example that I worked on involved helping a company troubleshoot an issue with their manufacturing process.

Q And how did you go about helping -- if the details you can't share with me because they're confidential or whatever, I don't necessarily want those, or if they're covered by a privilege that's beyond what your current counsel has with you. I'm

just trying to get a understanding of the nature of the type of work that you would do.

A That's understood. That's fair. There was some product that was not passing their quality specification. And the product had to be -- could not be sold because of that. And I was tasked with trying to understand why that was so from a chemistry perspective.

Q Was this a pharmaceutical product?

A It was a personal care product.

Q Personal care product. So was it something that had to go through any type of FDA clearance in order to be sold or marketed?

A I believe so. I wasn't involved in that aspect of it, but I believe that product would fall under the umbrella of the FDA.

Q Was the product already being sold and then you were helping figure out why it was failing in the market, or were they trying to get the product to market and having difficulties doing that?

A It was a commercial product that could not be released because it had failed an internal test.

Q Okay. And what was the nature of the

science that you worked on in assisting that company?

A Related to organic chemistry. It was an aspect of organic chemistry, which is my area of expertise.

Q And was it part of the manufacturing process, the chemistry, or would it have to do with the specific organic molecules in the product that were degrading?

A I believe that it was due to both.

Q In the cases that you have consulted with -- in the projects where you have consulted with attorneys, how many of those have related to the chemistry involving the salts of a pharmaceutical compound?

A Offhand roughly half a dozen, maybe more.

Q Before you started in your consultancy, did you have any specific experience in salt chemistry or organic salt chemistry?

A Yes.

Q And could you describe the nature of that previous experience?

A From the year 2000 until I founded my own company in 2011, I worked for an expert contract

research lab called SSCI. That lab was in the business of conducting salt screens and salt selection work for the pharmaceutical industry. So in my capacity as an employee of that company, I did a lot of salt screening.

Q And so you were there 11 years?

A I believe so, yes.

Q When you started at -- was it SSCI?

A Yes.

Q When you started at SSCI, what was your job title?

A Research chemist, I believe, something like that.

Q What did you do on a daily basis?

A It definitely varied. Because of the nature of contract research, I had a variety of different responsibilities. Some of those responsibilities included working on protocol projects on behalf of clients. I was also involved in some research and development for the company. So I didn't really have a routine day there.

Q You have talked -- I think you have said twice now that SSCI was in the contract chemistry work. What do you mean by that?

A SSCI would be hired by other companies

to carry out one aspect of the drug development process for that company. SSCI had a great deal of expertise in pharmaceutical solids. So that type of research would be contracted to SSCI to conduct.

Q So -- and part of that work I understand would be helping the company that might have an active pharmaceutical ingredient to find a viable salt so that it could be turned into a formulation; is that correct?

A That was one aspect of our service offerings, yes.

Q In your 11 years there did you have experience in that specific aspect of it?

A Absolutely, yes.

Q So describe the typical case for me where a pharmaceutical company that's not SSCI comes to SSCI and says, We need help.

A The business model of SSCI was not cookie cutter in that we had a typical service offering. So the research protocols were highly tailored towards particular clients, and the particular molecule, and the specific needs that that client needs be addressed.

Q So when a third-party pharmaceutical company first contacts SSCI, it's not, We need help

finding a salt? Is it more specific than that when they first contact you?

A Again, it is going to depend. There could be very specific tasks that the pharmaceutical company might ask us to do, but some projects were extraordinarily general in that -- one example would be we have -- we have a very promising, active moiety. Moiety is a term of the art that means a group, active group. We need to render this active group into a form that's going to be commercializable. And we don't know what it is yet. Can you help us figure that out?

So salt selection might be on the list. Crystal form screening might be on the list. So those projects tend to be more general than, say, a project that was highly focused on one particular thing such as I have an amorphous compound and I need to crystalize it. SSCI, would you please help me crystalize it? That would be another example of a project.

Q You said crystal form analysis. Is that looking for different polymorphs of a crystal?

A No. That project that I -- that hypothetical project I just mentioned would have involved trying to render something that wasn't

crystalline into a crystalline form.

Q So is that the same thing as when you just described having an amorphous compound and wanting it made crystalline?

A Correct. That's one type of research project that I worked on. And you mentioned polymorph screens. That's another type of research project that I'm familiar with.

Q But the polymorph screens, that wasn't what you were referring to when you said, they might want us to do some crystalline form analysis?

A Correct.

Q In your own consultancy that you just started, do you do any salt screen or salt selection work?

A Yes.

Q And about how many of those projects has your firm undertaken in the last five years?

A Two, one or two.

Q One or two, okay. And who are they for?

A I'm not at liberty to say, but in general they are for pharmaceutical companies.

Q Were either one of them for UCB?

MS. MEDINA: Objection.

THE WITNESS: I'm not at liberty to say.

BY MR. HOLLOWAY:

Q So if they were for UCB or Pfizer, I would get to know that?

MR. COUNIHAN: Are you talking about privileged information or are you talking about research?

MR. HOLLOWAY: I will tell you that this is as far as the question goes. I'm not going to ask any details about what it is or anything like that. I would just like to know if either of the salt screening projects he's done at his own company have been for UCB or Pfizer.

MR. COUNIHAN: Yes. So I'll just instruct the witness that he can answer yes or no as long as it doesn't reveal any privileged information.

I also -- just out of an abundance of caution, I'm not sure whether stuff that Dr. Chyall has talked about is confidential, but I do want to mark this transcript confidential at this point, even though there are some automatic provisions in the protective

order you're well aware of regarding confidentiality.

So with that instruction, Dr. Chyall, you can answer yes or no.

BY MR. HOLLOWAY:

Q So I'll go back to it. Do you understand what he's saying you to?

A Yes.

[redacted]

Q So I'm going to leave that, so don't mistakenly think that my questions have to do with that project, okay?

A Okay.

Q So actually I'll make it even easier. Let's go back to SSCI.

A Okay.

Q Did you ever have an experience at SSCI where a pharmaceutical company came in and said, we have an active pharmaceutical ingredient; we'd like you to find a salt for it?

A Yes.

Q And could you describe for me how that process would have worked in your time at SSCI?

A The client would have worked with a director of the company to understand specific issues, in particular the reasons why a salt screen was being requested. And based on our expertise if that basis was reasonable scientifically, then we would design protocol work that was tailored to that particular drug.

Q When you say to determine if there was a basis scientifically for going down the salt screen process, what would be an example of a nonscientifically sound basis for going through salt screening?

A If the client had generated -- as one example, if the client had generated a solid that was amorphous and they felt like they needed the salt because the amorphous solid wasn't crystalline, we -- SSCI would say that perhaps the issue is just that you haven't identified the right conditions to

render this amorphous solid into a crystalline solid. So perhaps it would make sense to make sure that you're not excluding the drug in its present form just based on the fact that you cannot render it crystalline. Perhaps we should try that first.

Q And so assuming that the director at SSCI found that there was a scientifically valid reason for proceeding down salt screening, how would that have played out internally at SSCI going forward?

A We would have asked the company to provide us with as much information as possible concerning the scientific characterization that had been done on that particular drug. We would be interested in a whole variety of properties of the drug substance.

And then based on the structure and some other issues that would have been uncovered and a review of that body of work, directors of the company would have designed a protocol that laid out a proposed research program to identify salt forms. And costs and timing and things like that would have been included in the protocol.

Q What are some of the properties of the pharmaceutical compound that would have been brought

to SSCI, are the properties that you were referencing in the body of work that would need to be reviewed?

A Well, certainly the structure is important.

Q When you say the structure, you mean the chemical structure of the molecule?

A Correct, the manner in which the atoms are bonded together. So the solubility of the drug substance would have been of interest. We would have been interested in the types of functional groups that are present in the molecule. And I guess that's part of the structure. But we would have had an eye toward the properties with respect to acid-based chemistry.

Q By that you mean like PKA or PKB values?

A Yes. And any kind of characterization of the material is the starting point, a liquid or a solid. That would have been important.

Also, any kind of information from the sponsor of this work with respect to pharmacokinetic issues, will this be an oral tablet, will it be administered transdermally, those types of things. If there's any information that those involved in

the pharmacokinetic aspects of the drug could provide to us that would guide us in selecting starting points, then we would do that.

Q In your experience at SSCI, was it more common for a pharmaceutical company to investigate oral dosage forms or transdermal dosage forms?

A We did a lot of work for different delivery mechanisms other than oral. Certainly we did a lot of work for all dosage forms, but a lot of the work we did was indeed directed toward some rather scientifically interesting delivery devices. We did work on pharmaceutical stents, lozenges, as well as transdermal work. So I have seen a lot of different types of drugs.

Q In the salt screens that you worked on at SSCI, what was the proportion of oral dosage forms to the rest?

A Certainly more than half. I'm not sure exactly.

Q You mentioned characterization of the material, is it a liquid or a solid. You're referring there to the starting material that's the active pharmaceutical moiety that the pharmaceutical company would have brought to you?

A Correct.
Q If it was a solid, what would be some of the characteristics that SSCI would be interested in at the beginning of the salt screening phase?
A Certainly the solubility of the solid.
Q Is that it?
A Any kind of stability issues, whether it was light sensitive or not.
Q I'm assuming included in this would be melting point information?
A Yes.
Q What about DSC information?
A The sort of the granular information concerning characterization work, yes, we would have been interested in any kind of characterization related to the starting material.
Q Why is that?
A Because you can be a lot more rational the more information you know from the very beginning.
So we would be interested in reviewing everything, even simple things like an AMAR spectrum of the drug substance would be very useful in determining purity. If you have an impure material, number one, that could be the reason why the solid

is not very stable. So we have our eyes toward all the characterization. Whether it was useful or not, you know, you had to evaluate the data.

Q When you say useful or not, you mean useful in helping you in the salt screening process?

A Correct.

(Whereupon, a discussion was held off the record.)

(Whereupon, Exhibit 1 was marked for Identification.)

(Whereupon, Exhibit 2 was marked for Identification.)

BY MR. HOLLOWAY:

Q Dr. Chyall, I have marked for you as Exhibit Number 1 to your deposition, your Opening Expert Report regarding validity in this case. And we have also marked as Exhibit Number 2 to your deposition your Rebuttal Report concerning validity in this case.

Earlier I asked if you had given two reports. Do you recognize these are the reports that you have given?

A Yes, I do.

Q I'm going to start with your opening report. Based on my reading of your opening report,

it seems to fall into two sections. The first is a section on what the claims, the asserted claims in this case cover. And the second is a discussion of whether a nexus exists between Toviaz and claims covering the hydrogen fumarate salt; is that fair?

A If we look at Section 5, yes, those are the two opinions in Section 5 of my report.

Q So aside -- are you providing opinion as to what you feel a person of ordinary skill in the art would be in Section 4A?

A Yes, I am.

Q So this is -- did you come up with this person of ordinary skill in the art, or are you agreeing that this is the person of ordinary skill in the art?

A This is something that I considered in the previous litigation involving fesoterodine. I believe it's consistent with what I had in my other reports for the first fesoterodine litigation. And I came up with it at that time, and I believe it's reproduced here.

Q Do you disagree with the person of ordinary skill in the art as described by Dr. Janero in his opening report?

A Somewhat, yes.

(Whereupon, Exhibit 3 was marked for Identification.)

BY MR. HOLLOWAY:

Q Dr. Chyall, I have marked as Exhibit 3 the opening report of Dr. Janero in this matter. And Dr. Janero provides his definition of a person of ordinary skill in the art at Paragraphs 25 and 26. What in Dr. Janero's definition do you disagree with?

A I believe it's just a little too narrow because it only covers a hypothetical person that's involved in the drug discovery, drug design, and drug synthesis aspects. It doesn't include others that I believe that the patent would be understood by, the patents and suit would be understood by.

Q So turning to your definition, a person of ordinary skill in the art; which part of your definition do you suggest is broader than Dr. Janero's definition?

A So my opinion is that a person of ordinary skill could have some expertise in the field of pharmacology, pharmacokinetics, and not necessarily understand issues concerning, you know, synthetic chemistry. They would still be able to

follow the chemistry but they wouldn't necessarily work in that field.

So also in my rebuttal report I discussed how understanding of the physiology of the bladder, someone that's involved in the treatment of OAB would be included in that.

Q That's not in your opening report, is it?

A Yes, it is, but kind of in a general way. That's why I clarified it in the second report.

Q How is it generally in your first report?

A "The desired and favorable characteristics of pharmaceutical compounds," that's in Paragraph 26 of my report. So understanding how the pharmaceutical compound could be used to treat OAB.

Q So are you saying a person of ordinary skill in the art has to have that characteristic?

A Not necessarily, but they could.

Q So is it your understanding of Dr. Janero's report that he would be excluding people that have that ability?

A It's not clear that those people are

included. In fact, the way I read it is that they would be excluded because he is focused on those with experience in drug discovery, drug design, and synthesis. So to me that speaks more to a medicinal chemist, an organic chemist, and not to those that are involved in pharmacokinetics or physiology.

Q You both included pharmacology in your definition of a person of ordinary skill in the art, correct?

A Yes, we did.

Q In your previous answer to one of the questions, you pointed to your inclusion of pharmacology as a degree field as encompassing this pharmacokinetics and pharmacodynamics issues that your person of ordinary skill in the art would need to understand?

A Yes.

Q So you're offering an opinion in Section 4A of your opening report. Are you offering an opinion in Section 4B of your report?

MS. MEDINA: Objection, form.

THE WITNESS: Section 4B lays out my understanding of the law as explained to me by counsel.

BY MR. HOLLOWAY:

Q So that's your understanding of the law. You're not going to offer an opinion as to what the law is, correct?

A Of course not. I'm not an attorney.

Q So you are offering an opinion in Section 4A. And my first question was asking if I understood the opinions you're offering in your report. You pointed me to if I was talking about Section 5, that is correct. So let me ask my question.

Within Section 5 of your opinion, it seems to be divided into two sections; the first being what the claims cover and the second being that a nexus exists between Toviaz and the claims covering the hydrogen fumarate salt; is that fair?

A Yes.

Q Let's start talking about the first section.

(Whereupon, Exhibit 4 was marked for Identification.)

BY MR. HOLLOWAY:

Q Dr. Chyall, I have handed you what's been marked as Exhibit Number 4 for your deposition. And it's a copy of the '650 patent. You recognize that, correct?

A Yes, I do.
Q I'm going to ask you some questions about the claims. You would agree that Claim 1 is to a genus of compounds that would include any acid in the salt form, correct?
A No.
Q Why not?
A If I remember the claim correct, there's a limitation to the acid. The acid residue must be physiologically compatible, so that's a limitation to the claim.
Q So Claim 1 is to a genus of any physiologically compatible acid in the salt, correct?
A Correct.
Q In your -- in the nexus section of your opening report, you say that there's a particularly compelling nexus exists as to Claim 5 and 23. Is that correct?
A Can you point me to that particular paragraph?
Q Sure, 100.
A Yes, I did. I did write that.
Q So just so that's clear, in the nexus section of your opening report you say that a

"particularly compelling nexus exists as to Claims 5 and 23," correct?

MS. MEDINA: Objection.

THE WITNESS: You're reciting half of a sentence. The full sentence is, "While it is my view that a nexus exists between all claims covering fesoterodine and any objective indicia of its nonobviousness, e.g., any commercial success of Toviaz, it is also my opinion that a particularly compelling nexus exists as to Claims 5 and 23 of the '650 patent."

BY MR. HOLLOWAY:

Q Are you offing an opinion as to the nexus between any claims and evidence of long-felt but unsatisfied need?

A My opinion is limited to demonstrating that Toviaz is a commercial embodiment of the asserted claim.

Q So you don't provide any opinion as to whether a nexus exists between the claimed subject matter of the asserted claims, and any evidence of a long-felt but unsatisfied need in the industry?

MS. MEDINA: Objection.

THE WITNESS: It's my understanding that other experts will be addressing those

issues. My opinion concerns relating the commercial product to the claims.

BY MR. HOLLOWAY:

Q So are you offering any opinion as to whether there is a nexus between the claimed subject matter of the asserted claims, and any evidence of a long-felt but unsatisfied need in the industry?

MS. MEDINA: Objection.

THE WITNESS: I'm offering the opinion that the commercial product is covered by the claims. And it's my understanding that others will be opining on the long-felt need on the commercial -- that aspect.

BY MR. HOLLOWAY:

Q Are you offering any opinion as to whether there exists a nexus between the asserted claims and any evidence of an unexpected benefit arising from the claim subject matter?

MS. MEDINA: Objection.

THE WITNESS: Yes. I'm demonstrating that Toviaz is covered by these points that are a being asserted.

BY MR. HOLLOWAY:

Q So in your sentence when you read the full sentence, it says commercial success but

neither of the other two, correct?
MS. MEDINA: Objection.
THE WITNESS: As an example of nonobviousness, I'm calling out the commercial success as one example of nonobviousness.
BY MR. HOLLOWAY:
Q You're not going to provide any evidence or testimony that the commercial product is unexpectedly better than prior art products, are you?
A No.
Q And you're not going to provide any testimony or evidence that the commercial product satisfied an unfelt -- long-felt but unsolved need in the industry, are you?
A That's correct.
Q You're not going to do that, right?
MS. MEDINA: Objection.
BY MR. HOLLOWAY:
Q You're providing testimony that you believe the commercial product is covered by the asserted claims, correct?
A Yes.
Q You're not going to provide evidence or testimony of the long-felt but unsatisfied need

that the Toviaz product met, correct?

A I don't plan to, no.

Q Is it your opinion that a nexus exists between any evidence of Toviaz's commercial success and Claim 1 of the '650 patent?

MS. MEDINA: Objection.

THE WITNESS: Toviaz is covered by Claim 1, and as a result there is -- there is a nexus between the product and the claim.

BY MR. HOLLOWAY:

Q So in other words, the reason a nexus exists between Claim 1 and any other evidence of nonobviousness, is that within the genus of Claim 1 is the numeric acid of the specific ester that's active -- sorry. Let me start that question over again.

Your opinion that there's a nexus between Claim 1 and any evidence of nonobviousness, is based on the fact that there's within that genus the fumarate acid of the specific ester active that's marketed as Toviaz?

MS. MEDINA: Objection.

THE WITNESS: The fumarate counterion is certainly physiologically compatible. But also the structure of fesoterodine is covered

by the genus claim.

BY MR. HOLLOWAY:

Q Let's break this down a little bit. There's two genuses in Claim 1. There's the genus of the active compound which includes the molecule that's marketed as fesoterodine, correct?

A Yes. The -- there's a genus of compounds that vary by changing the function of the ester.

Q And there's another genus that is the genus of physiologically compatible inorganic and organic acids, correct?

A Correct.

Q And your evidence of nexus between Claim 1 and any evidence of nonobviousness is based on one species of the active genus paired with one species of the acid genus, correct?

MS. MEDINA: Objection.

THE WITNESS: I didn't really approach it that way. I mean, I looked at the active ingredient in Toviaz, fesoterodine fumarate, and based on its structure, it's covered by Claim 1.

BY MR. HOLLOWAY:

Q Did you look at any other of the

structures of the active part of the genus and determine that because of that product there is a nexus between the evidence of nonobviousness and the subject matter of Claim 1?

MS. MEDINA: Objection.

THE WITNESS: My analysis was limited to comparing the commercial embodiment, Toviaz, to Claim 1.

BY MR. HOLLOWAY:

Q Do you know -- are any of your degrees or graduate degrees in organic chemistry?

A I have a bachelor of arts degree with a major in chemistry from Oberlin College, and my Ph.D. from the University of Minnesota involved a dissertation related to aspects of organic chemistry.

Q So, again, back to our -- there are two genuses within Claim 1. Do you know how big the genus of active molecules is?

A Yes.

Q How big?

A It would be quite large.

Q Do you know how -- can you give me a number?

A It's certainly in the thousands.

Q And how big is the -- now not combining them, don't multiply, but we will come to that question in a second. Don't multiply the genus of the active times the salt yet.

How big is the genus of the physiologically compatible inorganic/organic acids?

A I would image that to be in the thousands as well.

Q So if we were to look at the overall size of the combined acid salt, we would have to look at all the permutations between the genus of the active and the genus of physiologically compatible inorganic or organic acids?

A I think the entire scope of Claim 1 is going to really depend on whether those compounds could exist or not. If we just look at numbers in the hypothetical sense, you could draw -- you could draw a bunch of molecules on a piece of paper. But whether they actually exist or not, I don't know.

Q What do you mean by "whether they actually exist or not"?

A Well, because you can have certain functional groups for the R group, for example, that are just not stable, or just there's no way to make them.

Q Okay. And does the same kind of rule of whether they exist or not apply to physiologically compatible inorganic or organic acids?

A There could be some compatible acids that are just not capable of forming salts.

Q What does that mean?

A See, your question was, well, how many of these acids exist, and I said thousands. But I don't know for certain that every single one of those acids could react with the fesoterodine free form to generate the salt.

Q So going to Claim 2. Now, in Claim 2 the genus of the active doesn't change, correct?

A That's correct.

Q And but we do see a reduction in the size of the genus of the physiologically compatible inorganic or organic acids, correct?

A That's correct.

Q And if I added this correctly, I believe there are 36 acid species in Claim 2. Do you agree with that?

MS. MEDINA: If you need to take the time to read that over, please do.

(Whereupon, a discussion was held off

the record.)

THE WITNESS: I counted 38. I'm not sure if we agree on the exact number, but it's around that.

Q Okay, so you counted 38?

A Don't hold me to that number, because I really haven't considered this claim and those terms. But that's just based on looking at it here.

Q So we can agree it's somewhere in the 30 to 40 range?

A That's fair.

Q Okay. And it includes the hydrochloric acid salt, correct?

A Right. And I don't know if this is material or not, but I view the word ester as a typo. I believe it should be acid residue in Claim 2.

Q But the hydrochloric acid is listed as the acid to the salt of Claim 1, correct?

A Correct.

Q And does that recitation of hydrochloric include the hydrate form?

A Yes, it would.

Q So any time we see an acid listed, specifically in Claim 2, it would include a hydrate

form if a hydrate form could be formed, right?

A Presuming those forms exist, yes. I don't believe there's any limitation to a particular solid form in Claim 2.

Q Other than hydrate forms, would there be other solid forms available within each of these assets? So for example, for hydrochloric acid it would include the hydrochloric hydrate. Are there any other solid form variables that could exist?

A Yes.

Q Such as what?

A You would include also solvate forms, forms where molecules other than water are incorporated into the lattice hypothetically. I'm not sure which solvates would or could exist for these compounds.

Q Okay. So other than hydrate or solvate additions to the lattice, are there any other solid state variables that could occur for the listed acids?

A Offhand I can't think of any.

Q Is it your opinion that a nexus exists between evidence of Toviaz's commercial success and Claim 2?

MS. MEDINA: Objection.

THE WITNESS: Claim 2 covers Toviaz. It covers fesoterodine fumarate.

BY MR. HOLLOWAY:

Q And again, that's the selection of one species of active and the fumarate acid residue of that salt, correct?

MS. MEDINA: Objection.

THE WITNESS: Yes. That's one of the examples that's covered by Claim 2.

BY MR. HOLLOWAY:

Q And your analysis on nexus isn't based on any of the other acid residue forms listed in Claim 2, other than the fumarate acid salt, correct?

A That's correct.

Q Of the claimed acids in Claim 2, do you know how many were tested by the inventors?

A I don't remember exactly, but I know at least two.

Q At least two of the ones listed in Claim 2?

A Yes.

Q Is that the hydrochloric and the fumarate?

A Those are the two that I immediately remember.

Q But as part of your answer when you said you don't know all but you could remember two, the two that you could remember were the hydrochloric and the fumarate?

MS. MEDINA: Objection.

THE WITNESS: The hydrochloride monohydrate and the fumarate, I know they're actually disclosed in the specification of the '650 patent. I know that UCB was engaged in some salt screening work and studied other salts, but I don't remember precisely which ones they were related to what's listed in Claim 2.

(Whereupon, Exhibit 5 was marked for Identification.)

BY MR. HOLLOWAY:

Q Dr. Chyall, I'm going to hand you what's been marked now as Exhibit Number 5, that bears the Bates numbers PFE1826854 through 857. Have you seen this document before?

A It looks familiar, but I have seen a lot of documents so let me just see if I considered it for this matter.

It looks like my reports don't contain the materials considered, so I'm not sure if I

reviewed it for this matter or not.

MR. HOLLOWAY: Could you hand me the marked ones? I am sorry about that. I am going to give you the attachments to your opening report. And we can stick those on if it's okay with Counsel. Or we can just look at it, I don't care.

(Whereupon, a discussion was held off the record.)

MR. HOLLOWAY: I apologize about that, Dr. Chyall.

THE WITNESS: No worries. Unfortunately, it looks like this --

MR. HOLLOWAY: Oh, is it only in Exhibit B? Is it only in your rebuttal report? Which doesn't have it either, I guess.

Let's mark this one as 1B, if that's okay.

(Whereupon, Exhibit 1A was marked for Identification.)

MR. HOLLOWAY: 2B, sorry 2A.

(Whereupon, Exhibit 2A was marked for Identification.)

BY MR. HOLLOWAY:

Q So what we have marked now as 1A are

the attachments to your opening expert report. We've now marked as 2B, as Exhibit B from your rebuttal report. So you should have now the materials you have considered in this case. Apologies for that.

THE WITNESS: Yes, this looks like it was part of Christopher R's deposition as an exhibit. And I can see it's marked as Arth 9. This is something that I vaguely remember, so I probably glanced at it.

BY MR. HOLLOWAY:

Q Okay. So in your experience in salt screening programs, does this document make sense to you? Do you understand what's being reproduced in this document?

A Yes.

Q And in your words, what's being reproduced in this document?

A This looks like a summary of some salt screening work that Schwarz Pharma had conducted on fesoterodine.

Q And so what's described -- so under the heading Salt Formation, correct me if I'm wrong, but we see here are acid residues that were attempted to be paired with the fesoterodine base in

the formation of a salt?

A Yes.

Q And the document is dated August of 1999, correct?

A Correct.

Q So there's A through H that as of that date had been -- had been attempted by the inventors. Do you agree with that?

A I don't know.

Q Someone had attempted to salt A through H as of August of 1999, based on what this document says, correct?

A Yes, assuming that this document is accurate. I don't have any reason to believe it's not. And there's A through H experiments that are laid out here.

Q But that's what you understand as a person of ordinary skill in the art, that's what's being reproduced here and what we have marked as Exhibit 5?

MS. MEDINA: Objection.

THE WITNESS: I'm not a person of ordinary skill in this art form. I'm an expert.

BY MR. HOLLOWAY:

Q As an expert in this field, is that what you understand to be being reproduced in Exhibit 5?

A Exhibit 5 encompasses eight experiments, salt screen experiments.

Q And if you go into this table under Salt Formation, there's the first column has the letters of A through H. Those were the experiments, correct?

A Correct.

Q And then a second column is SPM 8224 in milligrams, correct?

A Yes.

Q That's the amount of fesoterodine molecule; is that correct?

A That's how I understand it, yes.

Q In the next column, what are the numbers in brackets versus not in brackets?

A The bracketed numbers are the molecular weight of the organic acid, and the amount in milligrams are the nonbracketed values.

Q And then if you turn to Page 2 of 2 of this document which ends in Bates 856 -- it's actually the third page of the exhibit. Do you see that? Do you see that Page 2 of 2 is 856?

A Yes.
Q And then if you look there's -- about halfway down the page it says AC-8273.H. Do you see that?
A Yes.
Q And then if you go to the end it's got a description of the organic substitutions, and then it has "FUM" at the end. Do you see that?
A Yes.
Q Does that mean -- this is referring to the fumarate salt of the fesoterodine molecule, correct?
A I think so.
Q And then if you go down under HPLC results, that's a type of analysis that tells you the constituent molecules in a sample, correct?
A Probably not the most precise definition. HPLC can be used to identify purity of compounds primarily as well as chemical identity as long as you have a reference standard.
Q And in this report it seems to be telling you the purity by reporting how much of the fesoterodine compound compared to another compound, that's identified as the plus form of a 2 hydroxide substitution; is that correct?

A I don't know. I would have to spend some more time with this document. That's why I said I wasn't completely certain about whether this AC8273H refers to fesoterodine fumarate. I'm not sure of this plus OH-OH nomenclature. It seems like some shorthand version to define what the compound is.

Q Okay. So you don't know what plus OH/OH is?

MS. MEDINA: Objection.

THE WITNESS: From this document I'm not certain. It could be referring to the substitution. Plus and minus typically refer to chirality. So I believe that the plus in brackets refers to a particular enantiomer. And then the OH-OH, this looks like shorthand to describe a compound.

BY MR. HOLLOWAY:

Q So if you go back up to OH, that line I pointed you to that said AC-8273, you see it has the plus sign for chirality that you identified?

A Yes.

Q And then it's got a first OH and then a slash. Do you see that?

A Yes.

Q And then a capital O, lower case I, capital B, lower case U, lower case T. Do you see that?
A Yes, I do.
Q Do you understand in the context of this case that the plus sign OH/OiBut refers to the fesoterodine base?
A I think that's right.
Q And so if that's the fesoterodine base, when you come down and see the plus form of the two hydroxide form under HPLC Results, does that help your recollection as to what the plus OH/OH refers to?
A I wouldn't say help my recollection because what I'm trying to do here is figure out this document for the first time. As I mentioned before, this is something that I just glanced at.
Q Oh, I understand that. But in the context of the case, you don't know what -- when we're talking about the molecules that are at issue in this case, you don't have an understanding today of what the plus OH/OH molecule is?
MS. MEDINA: Objection.
THE WITNESS: I would really need to spend some more time with the document and

confirm. It appears to be the hydrolysis product, but I don't want to offer an opinion on that until I can confirm it.

BY MR. HOLLOWAY:

Q So I'm not trying to get you to speculate on things, okay? Let me ask my question, maybe the more important part of my question.

Whatever this molecule is, plus OH/OH, whatever that molecule is, it's shown in the first line at a 2.09 percent. Do you see that?

A Yes, I do.

Q That means the HPLC detected proportionally within its sample, 2.09 percent of whatever this plus OH/OH molecule is, correct?

A If the analysis involves a salt form, chemical purity is really related back to the API. And then the percent of the impurity could be related either to the weight of the salts or to the amount of the API.

So it's just not -- it's not possible for me to know without digging into the data how this 2 percent is calculated. There's a couple of very reasonable possibilities here.

Q I think you're really close to answering my question.

As part of your answer you said when you're doing this analysis as part of a salt form analysis, is the -- in this study, is the plus OH/OH molecule in salt form?

A Nothing is in salt form in HPLC analysis because the compound is dissolved in a buffer typically and salt is disassociated. This is a liquid analysis. So you have disassociation and perhaps even conversion to the base form in order to conduct the analysis.

Q So this HPLC study, this is run after I have crystalized my fesoterodine base in the fumarate salt, correct?

A Not necessarily. We don't know whether the solids -- or even if they are solids, whether they're analyzed. So it could be a liquid form, it could amorphous form, or a crystalline form.

Q So let's make sure we're talking about the same section here. So I'm in the section that starts a AC-8273, right? And we agreed that that molecule is the fumarate -- or I'm sorry, the fesoterodine based in an acid salt with fumaric acid, correct?

A I think you misspoke. I think you're

referring to AC-8273.H?

Q Yes.

A I agree that this document indicates that that particular sample code relates to the product obtained from the reaction of fesoterodine with fumaric acid.

Q And then if you go down three entries, you see DSC, correct?

A Yes.

Q Just be careful not to mark on it. Sorry.

And the DSC indicates a melting point of 90 to 91 degrees Celsius, correct?

A That's what's written here, yes.

Q So this H -- this AC-8273.H, that is the crystalline salt form of fesoterodine base with a fumaric acid residue, correct?

A We don't know whether it's crystal or not.

Q So you don't know from looking at this if it's crystalline or not?

A Correct.

Q So even if it's not -- even if you don't know if it's crystalline or not, when you conducted the HPLC part of the analysis, you don't

know if the plus OH/OH molecule was complexed with fumaric acid?

MS. MEDINA: Objection.

BY MR. HOLLOWAY:

Q Or do you know that?

A We don't know one way or the other from this document.

MR. HOLLOWAY: We have been going over an hour. Do you guys want to take a short break?

MS. MEDINA: Sure.

(Whereupon, a short break was taken.)

BY MR. HOLLOWAY:

Q Welcome back, Dr. Chyall.

A Thank you.

MR. HOLLOWAY: We're going to mark that as 6.

(Whereupon, Exhibit 6 was marked for Identification.)

BY MR. HOLLOWAY:

Q Dr. Chyall, we have marked as Exhibit Number 6 a document bearing the Bates numbers PFE1826846 through 847. Have you seen this document before?

A Yes, I believe in the same manner that

I have looked at the exhibit that's marked Arth 9. It was part of Mr. Art's deposition, so it's something that I just probably flipped through very, very quickly.

Q And you would agree with me that the document marked as Exhibit Number 5 discussed the formation of salts or the attempted formation of salts, correct?

A Yes, sir.

Q And then if you go back to Exhibit Number 6, it's talking about things like "shows partly crystalline character in polarized light," Do you see that?

A Can you give me a moment to read through the document so I can answer?

Q Uh-huh.

A There's a statement in this memo that says, "In polarized light the substance shows partly crystalline character."

Q So some of the -- I'm going to ask you questions about what kinds of things are described in here. So one of the things that's described in here is that the substance shows partially crystalline character in polarized light, correct?

A Yes.

Q Something else it talks about is a melting point of 90 to 91 degrees Celsius?
A Yes.
Q It talks about "melting completely and clear and does not decompose." Do you see that?
A Yes.
Q And it talks about "A DSC analysis will be done tomorrow." Do you see that?
A Yes.
Q And then it says "Will have a final determination of the molar ratio of the present salt would be completed tomorrow." Do you see that?
MS. MEDINA: Objection.
MR. HOLLOWAY: Let me rephrase that one.
BY MR. HOLLOWAY:
Q After the DSC analysis and it talks about, there's going to be a determination of the molar ratio of the present salt tomorrow. Do you see that?
A Sure. Here is what's written. "The analysis for chemical purity as well as quantification against external standard for the determination of the molar ratio of the present salt will most likely be completed tomorrow."

Q Okay. And when it talks about the determination of the molar ratio of the present salt, is that talking about the moles of acid moiety to moles of base in the salt?

A That's the way I understand it.

Q And is this the type of information earlier referred to? I'd want to know the body of work to begin salt screening. Is this some of the information that would be of interest to you in beginning a salt screening analysis?

A Well, certainly yes. When SSCI conducted salt screening research if the client -- if SSCI's client had started their own program, we definitely would be interested in what they learned.

Q And included in that would be information such as does it show any crystalline character; what the melting point is, the DSC results, things of that nature?

A In designing the protocols, the directors would ask for pretty much everything that they had, including the things that we mentioned if they existed.

Q Going back to Exhibit Number 5 for me, if you turn to the third page of the exhibit, there's a -- entry H is the fumaric acid. Do you

see that?

A Yes. Fumaric acid is the acid that was used in that salt screen reaction.

Q And when you go to the column -- the column farthest to the right, is this being -- what's being described in this column? What are those three bullet points describing?

A The first bullet point, it's my understanding this describes the solvent that was used to run the reaction, the acid-based reaction between fumaric acid and fesoterodine base.

And then discussion of the result, which is turbid at dropping point. That describes the nature of the solution. And then plus 1 N hexane turbid 0 degrees oil, these are just sort of shorthand notes that the chemist likely made. And if I understand this exhibit directly, this is a translation from the laboratory notebook.

Q And so what you see is in the first bullet point, dissolve in 4 isopropanol plus 2 cyclohexane. And then what follows the comma is your understanding is the description of what the solution looked like or characteristics of the solution at that time?

A Yes.

Q And then the next step would have been add one normal hexane, and then further description of the conditions that were occurring at that time?
A No, you misunderstood the entry.
Q Okay.
A It's add one part of N hexane.
Q Got it.
A N hexane just means hexane that is 6 carbons linked together in a straight chain.
Q Okay.
A And the one part relates to the ratio of isopropanol to cyclohexane.
Q And then after the comma, the turbid 0 degrees Celsius oil concentrate, that's a description of the conditions that existed at that time?
A That's a description of what the chemist, I believe, did to this particular solution. So it looks like the chemist cooled it to 0 degrees and then got -- and then got an oil and then concentrated that solution. So it's a mixture of laboratory manipulations, as well as descriptions of the results of those laboratory manipulations.
Q Okay, thank you. And then we go to the second bullet point. And that's the next step,

or is that a different way of doing it?

A It's what -- I believe it's what the chemist did after the sample was concentrated. The foam that was the result of that concentration procedure was then dissolved in two parts acetone plus 1.1 parts of cyclohexane.

Q And then the end of that is obtaining, again, a concentrate. And then we start the third bullet point of dissolving into an oil, and then again, what's added to the mixture. And then starting at the comma, there's a greater than sign and then crystals, right?

MS. MEDINA: Objection.

THE WITNESS: So, what's generally described here is a chemist's description of how this oil was rendered into a solid. I just caution you to not conclude that the solids were crystals without some independent confirmation of crystallinity, because organic chemists tend to improperly attribute any solid to being a crystal solid.

And it's a little bit more nuanced than that. Solids can be noncrystalline but still be solid.

MR. HOLLOWAY:

Q What I was trying to understand is, does that mean the addition of, say, "C crystals," or is that an observation?

A I'm not sure. I would have to -- based on how this is written, I would -- I would probably believe it to be an observation that this oil was rendered into a solid by treatment with two parts of tubouterine and half a part of cyclohexane.

But I'd probably want to look at the notebook and understand this entry along with what else was done around the timeframe of this entry to be certain.

Q Okay, thank you. Based on your experience of what you did at SSCI, the experiments that we see under salt formation in Exhibit 5 that are A through H, would you classify that as a salt screening for the fesoterodine base?

A I believe the goals of these eight experiments were part of a salt screening program.

MR. HOLLOWAY: We will mark as Exhibit 7. That will be 7.

(Whereupon, a discussion was held off the record.)

(Whereupon, Exhibit 7 was marked for

Identification.)

BY MR. HOLLOWAY:

Q Dr. Chyall, we have marked as Exhibit Number 7 to your deposition a document bearing the Bates numbers PFE1826848 through 850. Do you see that?

A Yes.

Q Have you seen this document before? Was it part of the materials you considered in preparations of your report?

A This is a similar document to the others that we have been discussing. They are from the Arth deposition exhibits, so this would have been something that I just very cursory looked through, and I'm actually not remembering spending any significant time with this document.

Q Part of your opinion, correct me if I'm wrong, is that based on the work that the inventors themselves performed, it's your belief that it wouldn't have been obvious to obtain the salt forms that are claimed because it's an unpredictable art, correct?

MS. MEDINA: Objection.

(Whereupon, an interruption occurred.)

THE WITNESS: I'm sorry with the

interruption.
BY MR. HOLLOWAY:
Q Let me focus it a little bit more. If you go in your rebuttal report to Paragraphs 43 to 45.
A Yes.
Q And in Paragraphs 43 to 45 you're talking about "Dr. Meese's Work On Fesoterodine Exemplifies the Unpredictability of Salt Formation," correct?
A Yes.
Q And so its your intention to give an opinion to the court that, based on the work done by the inventors, a person of ordinary skill in the art wouldn't have found it obvious to use a salt screening technique to obtain the salts claimed in the asserted claims, correct?
MS. MEDINA: Objection.
THE WITNESS: The skilled person wouldn't -- I think that paraphrase is probably not accurate. It's my view that a skilled person would not be able to predict in advance which particular salt forms, if any, could be used for a particular compound.

BY MR. HOLLOWAY:

Q And in part you're basing that on the work -- part of your opinion is based in part on the work performed by the inventors, correct?

A Yes.

Q And what I have shown you in Exhibits 5, 6 and 7, are documents evidencing the work done by the inventors in attempting to find salt forms for the fesoterodine base, correct?

MS. MEDINA: Objection.

THE WITNESS: It's part of the work that they've done, yes. There was much more work, obviously.

BY MR. HOLLOWAY:

Q So as part of your opinion you have looked at the work of the inventors, including Exhibits 5, 6 and 7, as part of your opinion that a person of ordinary skill in the art wouldn't have reasonably predicted -- wouldn't have been able to reasonably predict a viable salt form for the fesoterodine base?

MS. MEDINA: Objection.

THE WITNESS: The invention record is -- it's more than just those three documents. And I'm aware of other work that

UCB put into this problem, and it was extensive. And with respect to the hydrochloride salt, there was quite an unexpected result later on.

It's my opinion that a skilled person cannot look at a salt screen as a routine exercise with the very obvious, predictable outcome of obtaining a commercially viable salt or really even any salt that's stable.

BY MR. HOLLOWAY:

Q In your Paragraphs 43 to 45 of your rebuttal report, do you point to a single document that's not testimony of an inventor?

MS. MEDINA: Objection.

THE WITNESS: Not in -- not in these particular paragraphs, but there are other parts of the report where I point to documents.

BY MR. HOLLOWAY:

Q In other parts of your report you point to documents that discuss the inventors' efforts in trying to salt fesoterodine base?

A No. I believe your question was related to documents in general. So I have talked about the Burgie reference in other parts of my report.

Q Let me rephrase my question then.
In Paragraphs 43 to 45 of your report, do you discuss any documents relating to the inventors' efforts in attempting to solve fesoterodine base?
MS. MEDINA: Objection.
THE WITNESS: These paragraphs discuss his trial testimony, his sworn testimony and the materials considered. I certainly remember looking at the invention records and the internal documents, the notebooks in particular. I remember looking at the notebooks. Not these translations. I'm not sure if I cited those in my materials considered for this litigation, but certainly for the previous litigation I had an opportunity to look at a lot of UCB internal documents.
BY MR. HOLLOWAY:
Q So going back to what I have marked as Exhibit Number 7, would you agree with me that this is a document concerning the inventors' attempts at salting the fesoterodine base?
MS. MEDINA: Objection.
THE WITNESS: This document looks like

a status report on the salt screening program.
BY MR. HOLLOWAY:
Q The salt screening program undertaken by the inventors?
MS. MEDINA: Objection.
THE WITNESS: I know that Dr. Meese was involved in this work. The specific technicians who did the work, I don't believe they would be inventors. They're not listed as inventors. But this report appears to be authored by Dr. Arth.
BY MR. HOLLOWAY:
Q Is Dr. Arth the name on any of the patents in this case?
A No.
Q So if you go to the first paragraph under Analytical Summary, do you see that it says in the parentheses OH/OiBut compound. Do you see that?
A Yes.
Q And that's identified as SPM 8224, R-enantiomer. Do you see that?
A Yes.
Q Do you understand that to be the fesoterodine free base?
A Yes.

Q If you go down to under column -- under heading 2, Analytical Summary of Salt Formation, do you see the first line refers to a dihydroxide compound SPM 7605?

A Yes.

Q It says that that compound was succeeded by crystallization?

A I see the sentence, but I don't understand it.

Q Do you understand that sentence to mean that they had successfully crystalized the dihydroxide compound identified as SPM 7605?

MS. MEDINA: Objection.

THE WITNESS: I don't understand the sentence as written. I don't understand what "succeeded" means in this context.

BY MR. HOLLOWAY:

Q Do you understand that the dihydroxide compound identified as SPM 7605 is the molecule known as 5-HMT?

A Yes.

Q And how do you understand that?

A Because it's my understanding that 5-HMT is compound that does not have the ester functional group at the phenolic position.

Q Did you look back at Exhibit Number 5 and the chemical structure with the substitutions at the top to make that determination?

A I relied on my memory, and then I also just wanted to look at the structure as written --

Q Okay.

A -- for confirmation.

Q Okay. So working from memory was that the dihydroxide compound is the molecule known as 5-HMT?

MS. MEDINA: Objection.

THE WITNESS: I don't really know what goes on my in my brain when I answer these questions. I mean, I consider a bunch of different things. I mean, I have been working on this project for a couple years now. I know 5-HMT. So precisely how I came up with the answer, I don't know. Certainly the document is something I looked at.

But asking me to figure out like what percentage of my brain was related to coming up with the answer, related to the structure, versus my memory, versus the dihydroxide, I don't know.

BY MR. HOLLOWAY:

Q Doctor, I'm just asking if you know from just being involved in this case.

A You asked me why I knew and how I knew, so that's how I answered your question.

Q We have been good so far today on letting me finish my questions and you finishing your answers. It's really hard for her to take it down if you talk over me.

A That's fair.

Q All I'm asking is: From your experience in this case you understand that the dihydroxide compound is 5-HMT?

A Yes.

Q My other question about your document, if you knew it, you knew it. If you figured it out, you figured it out. I just wanted to know which it was.

A That was the question I had trouble with.

Q If you go down to the, what I'll call the third paragraph under part 2, Analytical Summary of Salt Formation, it begins with the sentence, "Second most important improvement during salt formation..." Do you see that?

A Not yet.
Q Okay.
A Would you remind me what paragraph?
Q Yeah. It starts with the words "Second-most important improvement..." Do you see that?
A Yes.
Q If you go ahead and read to the end of that paragraph, I'm going to have a couple of questions about it.
A Okay.
Q There's a part that talks about "selective esterification of phenolic hydroxyl group of DI-OH compound leading to monoester SPM 8224."
I just want to make sure I understand what this is talking about. This is talking about the esterification of the 5-HMT compound leading to monoester SPM 8224, which is the fesoterodine free base, correct?
A Correct.
Q With negligible amount of educt dihydroxide. Is that right, e-d-u-c-t?
A That word is listed. That's what's written here. I'm not really sure what they mean.
Q Okay, so you don't know what they mean

by that?

A I believe it means byproduct, but educt is not a word that I typically use.

Q Okay, that's fair. The next sentence talks about formation of the hydrogen fumarate salt SPM 87 -- I'm sorry, hydrofumarate salt SPM 8272. Do you understand that to be talking about creating the hydrogen fumarate salt of the fesoterodine free base?

A Yes.

Q And Recrystallization, "Final product with chemical purity of 99.3 percent and .11 percent amount of SPM 7605 was available." Do you see that?

A Yes.

Q And, again, the SPM 7605, that's the 5-HMT molecule, correct?

A Yes.

Q This sentence -- that sentence that starts with "After formation..." and ends with "was available," is it saying that there was .11 percent of 5-HMT in the hydrogen fumarate salt of the fesoterodine base?

A I didn't understand your question.

Q Okay. So the sentence that starts with "After formation..." and ends with "was

available," does this sentence mean that there's .11 percent of 5-HMT in this sample of the hydrogen fumarate salt of the fesoterodine base?

A I don't know, because it all relates back to the question concerning how this .11 percent was calculated. If it was done by HPLC, I would have to look at how they did their math. It could be on the basis of fesoterodine active group, or it could be on the basis of a weight of the hydrofumarate salt. There's two different plausible possibilities here.

Q Would you agree that a person of ordinary skill in the art at the time would look at the base molecule, and based on what they know about the intrinsic properties of the base, come up with a set of acids to try?

MS. MEDINA: Objection.

THE WITNESS: I don't think that there's a standard way of screening for salts. A skilled person could use some judgments about what that particular skilled person would do. But depending on the person, you're going to get a different set then that that person would do.

In my experience as an expert in this

field, I see a lot of work that's really based on some naive concepts. And that's where I can come in and help remedy the problems that have been presented by individuals that embark on this endeavor, that just frankly don't know what they're doing.

BY MR. HOLLOWAY:

Q So does the person of ordinary skill in the art, in the world of forming a salt compound for a pharmaceutical base, does that include these people that you're talking about, to use your words, "have no idea what they're doing"?

MS. MEDINA: Objection.

THE WITNESS: A skilled person has a variety of techniques or a variety of knowledge and experience. And when we talked about particular persons, then obviously individuals, particular individuals will have different experiences and different skill sets.

Trying to put that all into one hypothetical person, it's really -- it's tough to do. I understand that's a legal construct.

So in my view, I mean, the skilled person for these inventions understands salt formation. But whether that person actually --

that particular person has the skills to actually do one, I don't know.

BY MR. HOLLOWAY:

Q For the purposes of determining whether a person of ordinary skill in the art would have found obvious the discovery of a specific salt form, my question to you is: Does that person, to use your words, know what they're doing?

MS. MEDINA: Objection.

THE WITNESS: A person of skill could likely design some experiments with some -- with some rational basis in doing a salt screen. But whether they'd be successful or not would depend on their particular experience. And I don't believe -- you know, it's my opinion that a skilled person wouldn't believe necessarily that they would be successful with this endeavor.

BY MR. HOLLOWAY:

Q Where is your lab located?

A I do not have my own testing lab, but I do have relationships with other testing labs that I use, in particular SSCI where I used to work.

Q So if you were going to be using SSCI equipment and facilities to conduct a salt screen,

where would you physically be located?

A In SSCI's laboratory.

Q Which is where?

A West Lafayette, Indiana.

Q Okay. So let's assume for a second I'm a person of ordinary skill in the art, and my lab is in Atlanta, Georgia and yours is in Indiana. So we've got two people that are going to undertake the salt screening analysis for a specific pharmaceutical ingredient.

I think you would agree that you might come up with a rational basis to try a group of acids in your salt screen, and as a different person located in Atlanta, I might try a different set of acids in my attempt to find a viable salt form for a pharmaceutical. Would you agree with that?

MS. MEDINA: Objection.

THE WITNESS: I will say that, first of all, I would not have the eyes of a person of ordinary skill on the problem. I would be using my expertise in this area. And in my view, an expert would consider things that a person of ordinary skill wouldn't do. The fact that the labs are located in different cities, not quite relevant, but I see your point.

Different people will do different things. Persons of ordinary skill that are different would likely do different things, yes. An expert would do different things from those people of ordinary skill.

BY MR. HOLLOWAY:

Q Do you employ anyone to do the type of bench work that we have been talking about this morning?

MS. MEDINA: Objection.

THE WITNESS: When I work in the lab, I do the work myself.

BY MR. HOLLOWAY:

Q So you don't have any employees who do parts of the salt screening process for you?

A As a -- as a consultant, if a client needs lab work, then I would subcontract the lab work to a testing facility and I would either oversee the work or do it myself. I do have the ability to do work at SSCI with my own two hands, but I have also supervised their employees in doing work.

Q So let's take a step back. So we have two people of ordinary skill in the art that are working on the same problem in different places.

Follow me so far?

A Yes. But I want to just caution you that one of those ordinary skilled people cannot be at SSCI because that is an expert lab.

Q Okay. Two people of ordinary skill in the art that are working on the same pharmaceutical product in different places. You with me?

A Uh-huh. Yes. Yes, I'm with you.

Q So we're both working on the same pharmaceutical products, we're both trying to find an acceptable salt form. Would you agree with me that we're not going to start with every known acid out there?

MS. MEDINA: Objection.

THE WITNESS: Likely not, no.

BY MR. HOLLOWAY:

Q Instead we're both going to try some subset of all of the known acids to try to come up with a viable salt product, right?

MS. MEDINA: Objection.

THE WITNESS: If you could help me understand what you mean by "known acids."

BY MR. HOLLOWAY:

Q So there's Claim 1, for example, basically says any pharmaceutically compatible acid,

right?
A No, it doesn't.
Q What's it say?
A I believe you're referring to Claim 1 in the '650 patent?
Q Yes.
A Claim 1 requires an acid residue over a physiologically compatible inorganic or organic acid.
Q The inorganic or organic acid, take the word "physiologically" out of it for a second. But the organic and inorganic acid, that's basically any acid, right?
A Yes.
Q So it's only modified by the word "physiologically compatible," right?
A Yes, sir.
Q And I think you already agreed with me that the world of physiologically compatible inorganic and organic acids is still a pretty big world?
A Yes.
Q So you would agree we me that our two people of ordinary skill in the art, who are working on the same problem but not together, they are both

going to start with some subset of physiologically compatible organic or inorganic acids, right?

MS. MEDINA: Objection.

THE WITNESS: If the salt screen is for a pharmaceutical application, yes. The screen should be limited to materials that are generally regarded as safe.

The FDA has what's called a GRAS list, G-R-A-S, and this is a very large list of all the chemicals, food additives included, that are safe for human consumption.

BY MR. HOLLOWAY:

Q How big is the GRAS list?

A It's quite extensive.

Q Do you have an idea of what the numbers is?

A Thousands.

Q Realistically, the two people working on this problem of finding an acceptable pharmaceutical salt of the same active base, they're not going to start by testing thousands of acids, correct?

A Not thousands, no.

Q Instead our two people of ordinary skill in the art, who are working on the same

problem but in different places, are probably going to choose -- each of them are going to choose an even smaller subset of acids in an attempt to find an acceptable pharmaceutical salt, correct?

MS. MEDINA: Objection.

THE WITNESS: The list of thousands that are conceivable would be whittled down initially to a manageable amount. And what one chemist considers manageable versus another is going to vary.

BY MR. HOLLOWAY:

Q And part of what they consider manageable could in part be dictated by their available resources that that chemist has at their -- at their ready, right?

A Yes.

Q So if I had a team of 15 people working on the problem, and my other hypothetical person not at SSCI only has three available people to work on it, my set might be larger than their set of acids to try, correct?

MS. MEDINA: Objection.

THE WITNESS: I don't know.

BY MR. HOLLOWAY:

Q Would you agree that my set -- even if

we both started with ten acids, I might choose a different set of ten acids than the other person of ordinary skill in the art working on the same problem?

A Yes.

Q And part of the decision-making that the person of ordinary skill in the art would go through in picking their starting set of acids would be to look at the base molecule, and based on what they know about the intrinsic properties of that base, guide them in their initial selection of acids to try?

A You know, you would think that, but in my experience that's not always the case. I have seen some salt screens that involved some compounds that just don't have the right acid-based properties.

Q And do those ultimately lead to the finding of successful pharmaceutical compound?

A You know, there are indeed complexes called cocrystals that involve molecular packing of materials that do not involve proton transfer that are in various stages of development. I think there is even one commercial cocrystal out there. It's not a salt. And as a result, I would view it as a

different molecular complex.

But it shows you that you can have successful products that involve complexation of other molecules that aren't salts.

Q I appreciate your answer, but let's try to answer actually the question I asked. Would a person of ordinary skill in the art in determining their set of acids, to try at the beginning of their salt screen, would they look at the intrinsic properties of the base to come to a decision on what the first round of acids should be that they try?

MS. MEDINA: Objection.

THE WITNESS: I already told you. I said that there's certain -- in my experience there's certain examples where people that embark on these salt screens do not consider PKAs. I said that. That was my answer.

BY MR. HOLLOWAY:

Q That's the first time you said that a person wouldn't consider PKAs. Okay? You agree with that?

MS. MEDINA: Objection.

THE WITNESS: No. It's probably just an issue of the precise words. But in my response I said that selection of acid-based

properties isn't always considered by people that do this work.

BY MR. HOLLOWAY:

Q So in your caveating of your answer when you talk about in your experience, you are answering me saying, what I have seen as an expert in this field is that there are people who have tried to salt screen where they don't care about the acid-based chemistry. Is that a fair paraphrase of your answer?

MS. MEDINA: Objection.

THE WITNESS: It's not that they don't care, it's just that they're not being rationally scientific in designing the screen. And that's just because they don't have the necessary expertise.

BY MR. HOLLOWAY:

Q So in your view, the person of ordinary skill in the art that we should be applying to this case, would also include those people who are irrational and lack scientific experience?

MS. MEDINA: Objection.

THE WITNESS: No, not at all. Not at all. I think the issue is that we, when we talk about someone of ordinary skill, we're

talking about a hypothetical person. And when we start talking about the hypothetical person actually doing the work, now I'm answering it based on my experience as to what those people do.

And we were talking about how different people who have different lists, and then the basis for selecting those lists is going to depend on that particular individual. And I'm just relying on real life examples of what I have seen. So they are individuals that are embarking on salt screens that have different criteria for selecting what they screen against.

BY MR. HOLLOWAY:

Q But we should exclude -- based on what I understand from your answer, we should exclude from the constraints that you're going to put on the hypothetical person's skill in the art, which is what's relevant to this case. We should exclude from that list those people who behave irrationally and without scientific experience.

A I don't necessarily believe it's an irrational thing. Let's just look at my definition of an ordinary skilled person. It takes some

experience in this field to do a salt screen, and my person of ordinary skill doesn't necessarily have to have within their skill set experience in salt screening. They just need to have a degree in a related area, as I have said in Paragraph 26 of my opening report and then qualified in my rebuttal report on Paragraph 17 -- excuse me, Paragraph 16 of my rebuttal report.

Q So I just want to make sure we are clear. So the person of ordinary skill in the art that you're applying to this case, would that include or would it not include people who would embark on the salt screening process using irrational or scientifically baseless tactics?

MS. MEDINA: Objection.

THE WITNESS: It isn't that that person is deliberately doing something that makes no sense to them, to them in their mind. It could be that the salts is a reaction between an acid and the base, but they haven't fully considered whether that reaction would take place.

So the first experiment with my expertise I could say this first experiment didn't really have a much of a chance to make a

salt. They may not have appreciated the acid-based properties of the molecules that they were working with.

BY MR. HOLLOWAY:

Q So back to where we started on this. So you don't agree that a person of ordinary skill in the art, embarking on the process of salt selection would look at the base molecule, and using what they know about the intrinsic properties of that molecule, come up with a set of acids to try?

MS. MEDINA: Objection.

BY MR. HOLLOWAY:

Q They wouldn't look at the base properties of the base before they started?

MS. MEDINA: Objection.

THE WITNESS: You see, that type of information may not even be available to them. If it's a new molecule, you may not have an appreciation of what the basic properties are. So you maybe see a functional group that looks like it's a base, but you don't have an understanding of the PKA because you haven't measured it yet. So your salt screening is not designed with that data because you just don't have it.

BY MR. HOLLOWAY:

Q So again my question is kind of a yes or no question. A person of ordinary skill in the art setting out on a salt screening, would that person, the hypothetical person, would they consider the base properties of the base molecule in determining a set of acids to try?

MS. MEDINA: Objection. I think he's answered the question.

MR. HOLLOWAY: You can just say objection.

THE WITNESS: It's kind of not a yes or no answer, because a person of skill may not be able to consider because they don't have the information necessary to make that consideration. But that doesn't hold them up in doing the work.

BY MR. HOLLOWAY:

Q And why doesn't it hold them up in doing the work?

A The hypothetical person may be entrenched in moving the project forward, and is going to try the empirical approach that's part of this technology.

Q What do you mean by "the empirical

approach that's part of this technology"? What does that mean?

A Salt screening is not the type of scientific endeavor that you can rationally select in advance; things that you know for certain are going to work. You have to try it and see, and see in the inventor's notes here. They had -- it looks like the folks that were working on these salt screens here that are in my Exhibit Number 5, there was quite some difficulty in rendering these oils into a solid form. Things like that.

I mean, you can't predict in advance whether you're going to have a nice crystalline solid at the end. You have to do the work.

Q Let's say the person of ordinary skill in the art has a base that they are trying to make into a pharmaceutical salt. And they decide -- however they get there, they decide there are 10 acids they want to try in the first round. Are you following me?

A Uh-huh. Yes.

Q Is that a reasonable number to try?

A It depends. It really depends on the molecule. It depends on really a lot of things. And there is no -- there is no reasonable starting

point. In my view, just looking at one would be an unreasonably low number. Upper bounds, I don't know, I personally have done salt screens that have involved greater than 50 different possibilities for the counting line.

Q So let's take the example of you're trying to find a salt for a base molecule and you're going to start with 50 acid residues, okay? Okay? You following me so far?

A Yes.

Q So I have got a base. I'm trying to make a pharmaceutical-acceptable salt. I have got 50 acids started. Would the person of ordinary skill in the art know at the beginning that if there is a viable acid-based salt within this group, I have a reasonable likelihood of finding it?

MS. MEDINA: Objection.

THE WITNESS: No.

BY MR. HOLLOWAY:

Q Why not?

A Because of the fact that you cannot predict whether or not a stable salt can be formed from really any of those 50.

Q I think maybe you misunderstood my question. I have got 50 and I'm going to try them

all. You got it so far?
A Yes.
Q Okay. Would a person of ordinary skill in the art know that if one exists, if a viable salt form exists out of these 50 combinations of acid and base, based on the way the chemistry works, can the person say, if it's in this group of 50, I'm going to find it?
MS. MEDINA: Objection.
THE WITNESS: No.
BY MR. HOLLOWAY:
Q Why not?
A Because the skilled person wouldn't know that they were necessarily doing the right type of experiment in order to provide the right conditions that are conducive to forming stable materials. In my experience, working as an expert in an expert lab, we have come to the rescue, so to speak, of many failed salt screens. Their technologies just weren't right, and they were set to give up. But they hired the experts and we were able to help them in identifying the right conditions for the reactions that in their hands failed.
Q So if I have a base and I'm going to

start with 50 acids, do I understand you to say that because the bench work necessary to get any one acid and base to actually form a crystal is so variable, that even if I started with just one and I knew this acid and base would form a sufficiently pharmaceutical salt, you're saying that a person of ordinary skill in the art would not have a reasonable expectation of being able to do it?

MS. MEDINA: Objection.

THE WITNESS: If I understand the hypothetical, there's one active ingredient that's going to be screened against 50 different salt formers. And that skilled person, in my opinion, would not have an expectation that one of those 50 would necessarily work.

BY MR. HOLLOWAY:

Q So again, my question is: If in that population of 50 there was one that works -- I understand you're saying a person couldn't predict which of the 50 would work or even if one of the 50 would work. Let's say that within that group one would work. Would the person of ordinary skill in the art have a reasonable likelihood of finding the one that would work of the 50?

MS. MEDINA: Objection.

THE WITNESS: It's so -- it's so compound dependent; it's really going to depend on the particular compound and the challenges presented with that compound. I have definitely worked on salt screens where the sponsor of the research that was in the contract, the search setting of course. So my involvement has been to look at the work that's done.

And sure, when the drug company starts out, they expect to be able to find something. But that's more aspirational than it is rational. When the work doesn't pan out, then there could be a reason for it that's related to the intrinsic properties of the molecule, or it could be a reason related to the fact they haven't done the right things. So you just really don't know in advance if anything is going to work.

And I should also say that I, myself, as an expert in this field have been confronted with drugs that just will not form salts. And it could be that I as an expert even haven't done the right things or it just could be the

fact that this particular molecule, the nuances of the structure, don't lend itself to salt formation.

BY MR. HOLLOWAY:

Q Do you think in the obviousness analysis that the level of prediction -- let me start over.

Do you think that in the obviousness analysis, a person of ordinary skill in the art has to be able to predict every possible outcome in order for something to be obvious?

A It's my understanding from how the attorneys have explained obviousness to me, that the skilled person has to have a reasonable expectation of success in coming up with the claimed invention.

Q Does that mean they need to be able to predict -- back to my original hypothetical; two people of ordinary skill in the art trying 10 acids for their pharmaceutical base to find a salt -- does that mean that a person of ordinary skill in the art would have to be able to say that Molecule 1 of 10 is going to yield me an acceptable pharmaceutical salt for it to be obvious?

MS. MEDINA: Objection.

THE WITNESS: I think the analysis has

to consider the claims, because it's the claims, right, that are going to be argued that are obvious in light of prior art.

BY MR. HOLLOWAY:

Q So how would you apply that to Claim 1? In Claim 1 would someone have to be able to say with absolute certainly that the specific substitution on the active ingredient, when reacted with this specific acid, will yield me a pharmaceutically acceptable salt?

Is that level of prediction required for an obviousness analysis?

MS. MEDINA: Objection.

THE WITNESS: For Claim 1 in the '650 patent, the skilled person I believe would recognize that salt forms are claimed by the claimant. But the particular salt forms, which ones are stable and which ones are not is going to be a matter of experimentation that they wouldn't necessarily know the outcome of those experiments without the benefit of the teaching of the patent.

BY MR. HOLLOWAY:

Q Okay. So let's take -- I'm trying to figure out in your application of what's obvious or

not, and what's reasonably predictable or not -- which is what I understand you're going to be testifying about at trial -- I'm trying to understand where you're applying certain things.

So when you talk about the unpredictability of the art, my question is: If a person of ordinary skill in the art has a base ingredient that they would like to see made into a pharmaceutically acceptable salt, are you saying that a person of ordinary skill in the art would have to be able to predict whether for any given acid I would obtain or not a pharmaceutically acceptable salt of my base?

MS. MEDINA: Objection.

THE WITNESS: It would depend on the claim, because Claim 5 of the '650 patent concerns two compounds, a hydrochloride salt in the hydrate form and the fumarate salt. So in order for that claim to be obvious, in my view, a person of ordinary skill would have to be able to predict if those salts are stable. And they would not be able to do that without the benefit of the patent.

BY MR. HOLLOWAY:

Q So let me make sure I'm clear on this.

So let's talk about just Claim 5 for a second. You agree with me that both salt forms in Claim 5 are the R-enantiomer of the molecule that's marketed as fesoterodine?

A Yes.

Q The differences between the two compounds in Claim 5 is one is the hydrochloric hydrate and the other is the fumarate acid residue, correct?

A Yes, the hydrogen fumarate, the 1-to-1 ad-ups.

Q So if one were going to demonstrate that Claim 5 was obvious, the person of ordinary skill in the art would have to have been able to say before doing any experimentation, I predict when I take the R-enantiomer of the fesoterodine molecule and a fumarate acid residue, I'm going to obtain a pharmaceutically acceptable salt?

MS. MEDINA: Objection.

THE WITNESS: That's not a limitation of Claim 5 that it be pharmaceutically acceptable. So I don't agree with your statements.

BY MR. HOLLOWAY:

Q So would the person of ordinary skill

in the art -- in order for something to be obvious, would the person of ordinary skill in the art have needed to understand that if I take the R-enantiomer fesoterodine and react it with fumarate I'm going to get a stable salt?

A My view is that in order for the skilled person to view any of the two salts that are listed in Claim 5 as obvious, they would have had to appreciate in advance that those salts could be made and isolated. And they can't do that without the benefit of the patent.

Q So, again, to be clear, for Claim 5 to be obvious, at the time of the invention a person of ordinary skill in the art would have had to have said, if I react the R form of fesoterodine with a fumarate acid residue, I'm going to obtain and be able to isolate a stable salt?

MS. MEDINA: Objection.

BY MR. HOLLOWAY:

Q Is that your opinion?

A With respect to stability, that's not a -- it depends on really what you mean by "stable." Here the compounds are by themselves. They're not in solutions or anything like that. So in my view Claim 5 is directed toward a compound that you can

isolate. Stability depends on context for that word. Stable enough to hold in your hand is different than stable enough to put into pharmaceutical formulation, for example.

Q So Dr. Chyall, what does one of ordinary skill in the art for Claim 5 to be obvious -- and I understand it's your opinion it's not -- Claim 5 to be obvious, what would a person of ordinary skill in the art have to have been able to predict?

A It's my understanding from the lawyers, the legal standard is that they have to have an expectation that trying to make these salts that they would be successful.

Q So I had to sit down -- before I did any of the work, I had to sit down and say, I expect fesoterodine, the R form of fesoterodine to form a salt with fumaric acid?

MS. MEDINA: Objection.

THE WITNESS: No, I don't think that's the way -- it's not the way I would look at it.

BY MR. HOLLOWAY:

Q Okay. Explain how you look at it, what needs to be predictable to a person of ordinary skill in the art for Claim 5 to be obvious?

MS. MEDINA: Objection.

THE WITNESS: They would have had to have know in advance -- first of all that the salts could be made from fesoterodine base. And with respect to Claim 5, they'd have to know that the fumarate salts is going to be one of those salts, and the hydrochloric hydrate salts is going to be one of those salts that can be made. And that's where because of the unpredictability of crystallization and solids formation, they wouldn't know that in advance.

BY MR. HOLLOWAY:

Q So a person of ordinary skill in the art, for Claim 5 to be obvious, would have to be able to predict that the R form of fesoterodine could be made into a salt, and more specifically that the R fesoterodine form could be made into a salt with fumaric acid as the acid residue?

MS. MEDINA: Objection.

THE WITNESS: I believe they'd have to know that the compound could exist, either of those compounds could exist in advance of doing any experiments. So if they would have done the experiments to demonstrate that, those experiments would have -- they would have known

the outcome in advance without having to do the experiments.

BY MR. HOLLOWAY:

Q As between the fumarate salt and the hydrochloric hydrate of Claim 5, have you seen any evidence that the active ester when paired with one of those acids imparts a greater benefit on a patient than when dosed with tolterodine?

MS. MEDINA: Objection.

THE WITNESS: I haven't considered that.

BY MR. HOLLOWAY:

Q As between the fumarate salt and the hydrochloric hydrate of Claim 5 of the '650 patent, have you seen any evidence that the active ester when paired with one of those acids imparts a greater benefit on a patient than when dosed with 5-HMT?

MS. MEDINA: Objection.

THE WITNESS: That's another thing I haven't considered.

BY MR. HOLLOWAY:

Q Have you seen any evidence that the salt form used in Toviaz, as between the hydrochloric hydrate and the fumarate salt, impacts

the amount of active that can be dosed to a patient?

MS. MEDINA: Objection.

THE WITNESS: I haven't considered that issue either.

BY MR. HOLLOWAY:

Q Would you agree with me that a viable pharmaceutical candidate must be highly crystalline?

A No.

Q Would you agree with me that when we're talking about crystalline salts, it's absolutely necessary to have stable salts which are chemically and thermally stable on the shelf?

MS. MEDINA: Objection to form.

THE WITNESS: It depends on what context we're talking about crystalline salts.

BY MR. HOLLOWAY:

Q How does it depend on the context when we're talking about crystalline salts?

A Because precisely what surrounds the issues will determine whether that statement is true or not.

Q Is it safe to say that based on your experience, and view of salt screening, that the identification and selection of an acid residue for a known active base could never be obvious?

MS. MEDINA: Objection.

THE WITNESS: The outcome of that acid-based reaction can't be predicted in advance. The chemistry in solution can be predictable, but whether or not the solid could be isolated as a solid even, one doesn't know that in advance.

MR. HOLLOWAY: We have been going over an hour, so if you want to take a break, let me know.

THE WITNESS: I'm fine.

BY MR. HOLLOWAY:

Q In your rebuttal report, if you will go to Paragraph 32, please.

A Yes.

Q And it references Dr. Janero's report. And the preceding paragraph is talking about the Gould reference in a section that's talking about the Berge reference.

THE WITNESS: If you don't mind, could you withdraw the question? I'd like to take a quick break, and then you can pick up your question later or I can answer the question that you have pending.

MR. HOLLOWAY: I haven't asked the

question yet. I just asked you to turn to a paragraph. We'll take a break. We'll just mark this while we're on.

(Whereupon, Exhibit 8 was marked for Identification.)

(Whereupon, a short break was taken.)

BY MR. HOLLOWAY:

Q Welcome back, Dr. Chyall.

A Thank you.

Q Before the break I marked for you the Gould paper, the Berge reference. You have Dr. Janero's report, and I was pointing you to Paragraph 32 of your rebuttal report.

A Yes.

Q So is what you're saying -- the last sentence of Paragraph 32, take a second and read that, and then I will ask the question.

A Okay.

Q Are you saying that because, if you look the like the Gould paper, for example, because the 42 percent that's attributed to hydrochloric acid is less than 50 percent, what you're saying is that the majority of salts are not HCL?

A That's true.

Q But you would agree if you look at the

relative proportions, hydrochloric is far more than even the next highest proportion of salts?

A Yes.

Q Question on the Berge paper. You would agree that one of the points of the Berge paper was to provide a rational basis for selecting a suitable salt form, correct?

MS. MEDINA: Objection.

BY MR. HOLLOWAY:

Q Just so we're clear, that's not the Berge paper.

A Yes, that's one of the goals of the paper. But with respect to satisfying that goal, I don't believe that they provided a road map that everyone can follow and be successful.

Q But you would agree that one of the points of the Berge reference was to provide a rational basis for selecting a suitable salt form?

A I would agree that that's one of their goals, but as I said, I don't believe that that goal's been satisfied.

Q If you go to the Gould paper, which is Exhibit Number 9, you would agree that one of the things that the Gould paper does is to set out what it calls go or no-go issues in salt selection,

correct?

A In the context of using project management techniques, that's what Gould has tried to apply to doing salt screening.

Q And one of the things under the go/no-go issues is basically whether it has a PKA that suggests you can actually salt the base, correct?

A Yeah, I appreciate what you're asking. I wouldn't refer to it in those terms. I will help you and say that strengths of the acids and bases are considered in a no-go/go issue.

Q And then also under the go/no-go issues are questions related to toxicity of the products, correct?

A Yes.

Q And Table 1 of Gould provides a listing of salts that have been marketed since 1974?

A Yes.

Q And would you agree with me that the list provides about 50 salt anions that make up nearly all of the salts used at the time?

A Based on this list there's about 50, yes.

Q Also in the Gould paper there are

described what the authors call a list of wants. Do you agree with that?

A Yes.

Q And included in that list of wants, you want it to be chemically stable, correct?

A That would be ideal. But before discussion of chemical stability, Gould writes, "It's somewhat difficult to provide a complete overall specification of wants."

Q Right. And what he's saying there, right, is that ideally it would be completely chemically stable, but because that not necessarily is always the case, we'll put it as a want as opposed to a go/no-go issue, correct?

A Yes.

Q You also under the list of wants is that it's not hydroscopic?

A Yes.

Q Also on the list of wants is that it doesn't cause any kinds of processing problems?

A Yes.

Q Also under the list would be it dissolved quickly?

A Right, and there's an example where I would disagree with Gould.

Q And why is that?
A Dissolution properties of salts can be tailored for tailoring bioavailability.
Q So there might be times when you want to tinker with the dissolution properties of a pharmaceutical salt?
A The dissolution properties of a pharmaceutical salt are very important, so those things are considered in the development of a pharmaceutical product.
Q And correct me if I'm wrong, but you could have a type of salt in which you vary the dissolution properties of that salt by considering different forms of that salt, correct?
A Yes.
Q And determining the changes to the salt form, to achieve the ideal dissolution properties, would be a matter of experimentation as to the form of the salt to see what it -- how that altered the dissolution properties?
A It's a little bit more complicated than just the form of the salt. You have to look at the -- it's more complicated than the form of the salt. You have to look at the whole package of the drug product how it's dosed, the other excipients,

where in the GI tract would you like the material to be absorbed, all these things matter.

Q Gould suggests starting with the hydrochloride ion, correct?

A Yes, he does.

Q And do you know why he makes that suggestion?

A I don't. He explains in some other parts of a paper why hydrochloride has good compatibility with respect to physiology. But this is an area where I disagree with Gould. One should not limit the salt screen to the hydrochloride initially, and then branch out to other things when the hydrochloride fails.

There are also particular examples where hydrochloride would be avoided, and I think that either Berge or Gould actually goes into that in some detail later on.

Q When you talk about the hydroscopic nature of the salt form, can you vary the hydroscopic nature of a salt form by considering the hydrate forms of salts?

A Presuming the different hydrate forms even exist for salts, those different hydrate forms may have different hygroscopicities. But this is

not something that you can rationally engineer. You would have to first of all see if you can make those hydrates and then test their hygroscopicities.

Q If you will go to Paragraphs 40 and 42 of your rebuttal report, and if you need the Johansson patent to answer this question, let me know. But my question is: Would you agree that Johansson gives a shorter list of acids that were stated to be effective in forming a salt of 5-HMT than the lists that appear in Gould and Berge?

A No.

Q Why not?

A Because my recollection from Johansson is otherwise.

Q Specifically what's your recollection if it says it's more than those listed in Gould and Berge?

A If you provide me with a copy of Johansson, I can show you.

(Whereupon, Exhibit 9 was marked for Identification.)

(Whereupon, Exhibit 10 was marked for Identification.)

THE WITNESS: On Page 6 of Johansson the paragraph -- the last paragraph, it says,

"In accordance with the present invention, the compounds of Formula 1 in the form of free bases or salts with physiologically acceptably acids can be brought into suitable galenic forms." So there's no shortness there.

BY MR. HOLLOWAY:

Q So it's your view that Johansson doesn't narrow from Gould and Berge a list of possible salts for a person of skill in the art to try making a fesoterodine salt form?

A Of course not. This patent doesn't even concern fesoterodine.

Q Earlier we talked a little bit about your statements that the inventor's own work shows it would not have been predictable to make a salt. Do you recall our conversation?

A Yes.

Q Does it work the other way? If the inventor's work suggested a relationship between the fumarate salt of 5-HMT and the R-enantiomer fesoterodine, would you agree that a person of ordinary skill in the art could reasonably narrow the genus of starting salts for salt screening?

A No.

Q Why not?

A Because of the fact that changes in structure will change outcomes of salt-forming reactions. Salt stability is a function of how these molecules come together to form solids, either crystalline or amorphous solids. Also, how these compounds are going to be reactive toward humidity in the air, oxygen in the air. So there's all kinds of considerations that relate to the specific structure of the active ingredient.

So the fact that 5-HMT salt can form a fumarate -- and I don't know if there's any evidence that that's true. But if there was evidence that that's true, that would not provide any indication of what would be stable for fesoterodine.

Q So a person of ordinary skill in the art would put no weight on the structural similarity of two molecules in determining a genus of starting acids to find a pharmaceutically acceptable salt?

MS. MEDINA: Objection.

THE WITNESS: I think no weight is probably a little -- a little too severe in that characterization. The fact that both compounds contain amine functional groups indicates that that amine functional group can react with acids. But there the similarities

really end.

The differences in substitution of all the other parts of the molecule will have an effect on the salt formation reaction. So if you generally understand that amines react with hydrochloric acid and you identify an amine in one compound and amine in another, it's not unreasonable.

But to say in advance that this particular amine is related in structure to that particular amine, therefore I expect it to work, is not good science.

BY MR. HOLLOWAY:

Q Based on what you have seen as an expert in this case, do you think the inventors randomly selected acids to try, or do you think they thought about it and said let's start with this subset?

MS. MEDINA: Objection.

THE WITNESS: The inventors had initially identified some things to try, and I know that their work extended into the dozens of compounds. And I also know that their work extended into hiring another lab at a university to put that lab's hands on the

problem as well.

So in my experience it isn't like one goes off at it from -- at the endeavor of salt screening with a parallel type of process where you're going to try everything at once. Things are stepped through sequentially.

BY MR. HOLLOWAY:

Q I believe you said in your report that the inventors tried hundreds of possible acid residues; is that correct?

A Yes. That's based on Dr. Meese's testimony.

Q And you would agree with me that Gould and Berge show that at the time of the invention, the vast majority of compounds on the market were comprised of 50 acid residues?

A No.

Q Why do you a disagree with that statement?

A Because of the tables from the '70s and the time of the invention. This is the late '90s.

Q When was Gould published?

A 1986, but keep in mind that Gould is just reproducing the table from Berge, which was

published in 1973, I believe.

Q So a person of ordinary skill in the art who read the paper in 1986 should sit there and say, even though he published it in '86, the fact that there are about 50 listed in here doesn't mean anything?

MS. MEDINA: Objection.

THE WITNESS: I don't agree with that characterization.

But I would say that a skilled person is definitely going to look at the table for what it is, a list that was compiled from the '70s.

BY MR. HOLLOWAY:

Q The claims of the '650 patent, do any of them concern how the salt or salts are made?

A I don't remember.

Q Are you going to look?

A If you'd like me to, I can.

Yes, they do.

Q The asserted claims in this case, are any of the asserted claims in this case, in the '650, have anything to do with how the salt is made?

A I will have to refresh myself as to what the asserted claims are.

Q I'll represent to you if Counsel agrees, that it's 1 through 5 and 21 through 24.
A None of those claims concern the methods of manufacture.
Q So for the purposes of our obviousness analysis in this case, the difficulty or the -- let me start that question over again.
For the purposes of the obviousness analysis in this case, the manner in which the inventors came up with the claimed salt form is not relevant to the obviousness analysis. Would you agree with that?
A No.
MS. MEDINA: Objection.
BY MR. HOLLOWAY:
Q Why not?
A Because the inventors' trials and tribulations, if you will, in coming up with salts demonstrate that -- the difficulties associated with this type of work. The hydrochloride salt in particular is something I discussed in my report.
Q The method of making that hydrochloride salt for Claim 5, that's not claimed, is it?
A Not in Claim 5, no.

Q Do you disagree with the Gould paper's suggestion that a person of skill in the art in conducting its no-go/go analysis would consider things such as the PKA of the pharmaceutical base?

A Assuming they had that information, they should consider it, yes. But whether they do or not is going to really depend on the particular person.

Q How difficult is it to ascertain PKA value for a base?

A To know for certain what the value is, you have to do a rather specialized experiment. This is an experiment that I have relied on on a subcontract lab to do for me on occasions. PKA measurement is -- is something that can be done, but it's a rather difficult experiment. And there's one company that I use. They have a -- have a small cottage industry, if you will, in measuring it.

In the absence of a physical measurement, then you can make some estimates as to what a PKA was based on similar structurally related compounds. But those estimates would be just that, they would be estimates, and you could be off by certainly a couple PKAs.

Q In fact, Gould on Page 202 of his

paper, Gould actually shows some of those estimates based on structural similarity, correct?

A Yes. This is a very short list of amines -- yes, of amine bases, right.

Q And I'm assuming at the time of the invention longer lists agreed -- longer lists existed of structural estimates for PKA values?

A Yes.

Q And a person of ordinary skill in the art at the time would have been able to go and find those?

A Yes. It would depend on the compound that they're investigating, as well as to whether that PKA could be reliably predicted based on what's known in the literature.

Q A second ago when you talked about the experimentation and determinations necessary to determine PKA, is that something that would be within the skill set of a person of ordinary skill in the art at the time of this invention?

A Not necessarily so. It's a touchy metric titration type of technology. It's a very specialized area of electrochemistry. And if your molecule has solubility issues, then that results in a layer of complexity. And in my experience in

doing salt screens on behalf of clients, typically the clients don't have those measurements and they are relying on estimates of PKA based on things that have been measured.

Q In your examples talking at the beginning of the day about what you did at SSCI -- and then I'm going to caveat that by saying I think somewhere along the way today you said we can't consider SSCI to be a person of skill in the art; is that correct?

A Yes.

Q Does that mean anyone at SSCI, or the company as a whole, we can't consider as a person of skill in the art?

A It relates to the work that that lab does. The technicians that work in that laboratory are under the direction of experts, so the technicians develop a high level of expertise. But with respect to carrying out protocol work, the protocols, the research protocols are designed by experts.

So the technician is really doing the work of an expert in conducting salt screens, for example.

Q So at SSCI the people who -- I believe

earlier you may have said this was at the director level -- people will say, okay, let's try this set of acid residues for this base that's been brought to us. The people who say try these acid residues, those are not people of ordinary skill in the art?

A Some are beyond ordinary skill.

Q Are all of them beyond ordinary skill?

A By proxy, yes, because the protocol works are designed by experts.

Q So leaving the SSCI world, where would I ever encounter a person of ordinary skill in the art in the salt screening process?

A The pharmaceutical companies that don't have a great deal of in-house expertise would be one example that comes to mind. A lot of the work that I did at SSCI involved contract research for start-up companies, companies that were good on the medicinal chemistry side, designing that really nice active molecule that will provide the right therapeutic effect, but just didn't have the necessary skill to take it a step further in a fruitful salt selection.

Q So the person that's ordinary -- in taking this example of one of the startup companies you described, you're saying that the person of

ordinary skill in the art would have been good at designing an active compound but have no experience in salt selection?

MS. MEDINA: Objection.

THE WITNESS: That's not what I said.

BY MR. HOLLOWAY:

Q Well, how did I get that wrong?

A Because what I talked about is that that hypothetical person would be approaching salt screening and salt selection from a basis that's not as advanced as an expert such as myself would, and their approach would differ than mine.

Q So would they have had any experience in trying salt screening to be a person of ordinary skill in the art in the time of this invention?

A They could have, but I don't believe it's necessary that they do.

Q Okay. And isn't it fair to say that if you -- if it's your opinion that a person of ordinary skill in the art, at issue in this invention, had no experience in salt screening.

Wouldn't you say, okay, the likelihood of this person finding an acceptable salt is just a shot in the dark?

A The skilled person has access to prior

art. So at the time of this invention, the skilled person certainly would have been aware of Berge and Gould. It's my understanding from the attorneys that the skilled person is aware of all relevant prior art, so I consider Berge and Gould to be part of that.

It would be somewhere greater than a shot in the dark, but certainly less than the expert lab at SSCI among other experts in the area.

Q So your position, as you have said several times, is that you're beyond the skill of an ordinary skill artist and you are an expert in this field. As an expert in this field, do you possess the capability to predict for a given pharmaceutical base whether an acid residue will yield an acceptable product?

A No.

MR. HOLLOWAY: Pass the witness.

MS. MEDINA: No questions.

(Whereupon, the deposition concluded at 12:28 p.m.)

C E R T I F I C A T E

STATE OF Indiana :

COUNTY/CITY OF Tippecanoe :

Before me, this day, personally appeared LEONARD CHYALL, Ph.D., who, being duly sworn, states that the foregoing transcript of his/her Deposition, taken in the matter, on the date, and at the time and place set out on the title page hereof, constitutes a true and accurate transcript of said deposition.

Leonard J. Chyall
LEONARD CHYALL, Ph.D.

NOTARY PUBLIC SEAL INDIANA

JESSE C. REYES
Resident of Tippecanoe County, IN
My Commission Expires: April 2, 2022

SUBSCRIBED and SWORN to before me this 5th day of October, 2016, in the jurisdiction aforesaid.

April 2, 2022
My Commission Expires

Notary Public

DEPOSITION ERRATA SHEET

RE:
FILE NO.
CASE CAPTION: PFIZER vs. MYLAN
DEPONENT: LEONARD CHYALL, Ph.D.
DEPOSITION DATE: August 23, 2016

To the Reporter:
I have read the entire transcript of my Deposition taken in the captioned matter or the same has been read to me. I request for the following changes be entered upon the record for the reasons indicated. I have signed my name to the Errata Sheet and the appropriate Certificate and authorize you to attach both to the original transcript.

Page 7 Line 1:	Change: moments	To: moment
Page 11 Line 23:	Change: needs be	To: needed
Page 20 Line 22:	Change: AMAR	To: NMR
Page 27 Line 8:	Change: Correct	To: Correctly
Page 36 Line 7:	Change: claim and those	To: claim in those
Page 41 Line 7:	Change: R's	To: Arth's
Page 51 Line 2:	Change: Mr. Art's	To: Mr. Arth's
Page 54 Line 10:	Change: acid-based	To: acid-base
Page 57 Line 9:	Change: tubouterine	To: 2-butanone
Page 61 Line 24:	Change: Burgie	To: Berge
Page 78 Line 16:	Change: acid-based	To: acid-base
Page 79 Line 25:	Change: acid-based	To: acid-base
Page 80 Line 9:	Change: acid-based	To: acid-base
Page 86 Line 15:	Change: acid-based	To: acid-base
Page 89 Line 8:	Change: the search setting	To: a research setting
Page 93 Line 11:	Change: ad-ups	To: adduct
Page 114 Lines 21-22:	Change: touchy metric	To: potentiometric

All changes due to: transcription error

SIGNATURE: Leonard J. Chyall DATE: October 5, 2016

LEONARD CHYALL, Ph.D.

C E R T I F I C A T E

I, Jamie I. Moskowitz, a Shorthand (Stenotype) Reporter and Notary Public, do hereby certify that the foregoing Deposition, of the witness,LEONARD CHYALL, Ph.D. , taken at the time and place aforesaid, is a true and correct transcription of my shorthand notes.

I further certify that I am neither counsel for nor related to any party to said action, nor in any way interested in the result or outcome thereof.

IN WITNESS WHEREOF, I have hereunto set my hand this 23rd day of August 2016

_____

Jamie Ilyse Moskowitz
License No. XI01658