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

Case IPR2016-00510
Case IPR2016-00512
Case IPR2016-00514
Case IPR2016-00516
Case IPR2016-00517

MYLAN PHARMACEUTICALS INC. and
MYLAN LABORATORIES LIMITED,

Petitioner,

vs.

UCB PHARMA GMBH,

Patent Owner.

DEPOSITION OF
STEVEN E. PATTERSON, Ph.D.

Atlanta, Georgia

Tuesday, October 4, 2016

Reported BY: Michelle M. Boudreaux, RPR

Job No: 113362

October 4, 2016

9:10 a.m.

Deposition of STEVEN E. PATTERSON, Ph.D., held at the offices of Hunton & Williams, Bank of America Plaza, Suite 4100, 600 Peachtree Street, Atlanta, Georgia pursuant to Agreement before Michelle M. Boudreaux, a Registered Professional Reporter in the State of Georgia.

APPEARANCES OF COUNSEL

On behalf of the Petitioner:

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On behalf of the Patent Owner:

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STEVEN E. PATTERSON, Ph.D.,
being first duly sworn, was examined and testified as follows:

MR. TRAINOR: So just to clarify for the record, this deposition is being taken in conjunction with four pending inter partes reviews before the United States Patent Office. The -- these reviews -- these IPRs are numbered Case No. IPR 2016-0516, also 0510, 0512, 0514, 0517. And I believe 510 is the '650, correct?

MS. WOOTEN: Yes.

MR. TRAINOR: Okay.

EXAMINATION

BY MR. TRAINOR:

Q Now, good morning, Dr. Patterson.

A Good morning.

Q Sorry for the circus here. Before we get started, I wanted to hand you the declarations that have you here today submitted in support of the aforementioned IPRs. I'm handing you now what is, in IPR 510, the declaration you submitted, and that IPR, the number is Exhibit 1003.

A Uh-huh.

Q And I'm also handing you a second declaration submitted in support of the remaining IPR numbers. In all of those IPRs, this is also designated as Exhibit 10003 [sic].

Now, if I could just ask your assistance, this is probably the one document -- these are the two documents that don't have the numbers on them, so maybe we could just take a quick second and put the sticker on these. The rest of them should all be marked, if that's all right.

(Discussion off the record.)

(Exhibit 1003 marked for identification.)

Q (By Mr. Trainor) All right. Now, first of all, Dr. Patterson, I take it you've had your deposition taken before?

A This is the first time I have testified in court, but not --

Q Testified at a deposition?

A I'm not sure. Actually in a court proceeding before the judge. Not for this case, though. I'm sorry. I guess that's what you're asking.

Q Let me just back up.

A Okay.

Q Have you testified before in a court

proceeding?

A Yes, sir.

Q Okay. How many times?

A Once.

Q Okay. And in that proceeding, did you give a deposition before you testified at trial or in court?

A I don't recall doing that, no, sir.

Q Okay. In that case, I'll just let you know, I'm going to make a record today of some questions that I'm going to have for you, and hopefully you can answer those to the best of your ability. If anything is unclear, please let me know. I'll try to clarify for you.

If you'd like to take a break at any time, please just let me know. We can take as many breaks as you'd like. Just please don't ask for a break while a question is pending.

A Sure.

Q Okay. So, Dr. Patterson, with regard to the two exhibits numbered 1003 in front of you, are those exhibits -- are those declarations that you recall preparing?

A Yes.

Q Okay. Is it fair to say -- to try to make

things easy today, is it fair to say that the substance of those two declarations is more or less the same?

MS. WOOTEN: Objection, form. You still can respond.

THE WITNESS: I'm sorry. Oh, okay.

Q (By Mr. Trainor) I mean, are there any material differences in the declaration testimony you provided?

A Without taking time to review them carefully, I believe -- the differences that I remember are simply just correction of typos from one to the other.

Q Okay. Okay. So, I mean, my take on this is that they're really quite similar. If there's an occasion today where you think that may not be the case, let me know, and if there's any occasion where I think that might not be the case, I'll let you know. But to make things easy, why don't we just work with one of the documents, and why don't we work off of the -- let's see what I have here. We'll work off of the one that is -- the one that is actually pre-stamped, okay, so this is the one in the --

A The one that we do not have the sticker on?

Q Yeah, the one that says '650 patent at the top.

A Okay.

Q So the stickered one you can put aside.

A Okay.

Q And again, I'm not trying to --

A I understand.

Q -- pull anything over you. I just think they're more or less the same document, so -- right down to the paragraph numbers, so hopefully that will make it easy to make the record here today.

Okay. Now, Dr. Patterson, in the court proceeding that you testified in previously, what was the nature of that dispute, if you recall?

A It was a dispute involving my work in industry between Gilead and Idenix.

Q And I'm sorry?

A And Idenix.

Q Okay. Which was your previous employer?

A My previous employer was Pharmasset. Pharmasset was acquired by Gilead.

Q Okay. So you testified in that proceeding as a fact witness as opposed to as an expert witness?

A Yes, sir.

Q Okay. Have you ever consulted as an expert witness or as an expert consultant for litigation prior

to this proceeding?

A Not in the same way that we're doing now.

Q In what different way?

A I've had people call me for comments about one thing or another. This is the first time where, you know, I've been so involved as to prepare, you know, documents and such.

Q Uh-huh. In the prior consultations that you referred to, were you working with attorneys or --

A Yes.

Q -- non-attorneys?

A Attorneys.

Q Okay.

A My understanding is that they were attorneys, in any event.

Q Okay. In-house attorneys at a company or external counsel; do you recall?

A I don't recall.

Q That's fine.

Okay. Now, Dr. Patterson, please feel free to refer to Exhibit 1003 at any time. And we'll be looking at it together for a good part of the day. But if I ask you questions that aren't directly related to what's set forth in the declaration, you know, you can

always feel free to refer to that.

And I'd also like to invite you to ask me at any time if you see another exhibit referenced in there, which I should have here, and you'd like to see it, just let me know, because what we're here to do today is give me the opportunity and my clients the opportunity to sort of cross-examine the substance of this declaration.

So given that, you've got a number of citations in there. I should have copies of all of them. I might show them to you on my own volition, but if you say, "Hey, I'd like to see this," please feel free to let me know --

A Okay.

Q -- because we want to know what your take on that stuff is.

So, Dr. Patterson, without looking at the declaration for a moment, in the time frame of 1998 and 1999, could you describe for me in your words what you understood to be the state-of-the-art in the field of OAB drug development?

A There were very few treatments out there approved. There were some issues with many of them regarding selectivity such that many of -- you know, at

least one of them, you know, some of the patients, as I understood, or the persons treated with the drug, you know, discontinued treatment because of some of the side effects.

Q And putting aside the OAB treatments that you referred to as approved, was there research and development ongoing that was publicly known that may or may not have led later to an approved drug?

A According to reviews that I recall -- you know, recall looking at, there were multiple -- let's call them classes or drugs that were thought that might work by different, you know, mechanisms under investigation.

Q And they were being reported in the prior art as of that time?

A I believe so.

Q Okay.

A I think so.

Q Okay. Why don't I show you Exhibit --

MR. TRAINOR: I'm going to show the witness what's been marked as Exhibit 1006 in all of the proceedings. This is a publication with the lead author Andersson.

Q (By Mr. Trainor) Now, Dr. Patterson, feel

free to review that exhibit. Is this the review, Exhibit 1006, that you were just referring to?

A I believe it is. I recall the tables on the second -- or the -- yeah, the table. That's a single table, actually. It goes from the second to the third page of the paper.

Q Uh-huh.

A And that's what I was thinking about.

Q Okay. And maybe if it helps, in your declaration, Exhibit 1003, if you turn to page 4, beginning on page 4, you set forth a comprehensive chart of the materials that you considered. Do you see the Exhibit No. 1006 --

A Right.

Q -- "Andersson Review"?

A Right.

Q Okay. So if you ever need to refer to -- we'll try to cross-reference one of the documents I'm showing you. I'm fairly certain that all of the documents I'll show you are exhibits to your declaration. So this might refresh what they are, and here's the Exhibit No. 1006 on page 4 of your declaration.

So, first of all, how was it that you came

upon this Andersson review, Exhibit 1006?

A It was either referenced by counsel or I did a literature search on my own and found it. Both could, in fact, be true.

Q Okay. So is it fair to say that in the preparation of this declaration, some documents were provided to you by counsel?

A It is. That is true.

Q And other documents were procured by you independently?

A I recall doing a literature search.

Q Okay.

A And I recall discussing the -- well, I shouldn't say that. Sorry.

Q Okay.

A I recall doing a literature search, I think, in order to protect our private discussion.

Q That's okay. Okay. Well, right now I'm not as concerned about, you know, the source. What was the -- do you have an understanding as to how the search was conducted, what search terms were used or something of that nature?

A I can't tell you what counsel did, but I can tell you the terms I -- as best I can recall, because

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it was nearly a year ago, but I can -- I went to PubMed and did a keyword search. I don't recall the exact keywords.

Q Okay. Okay. Do you recall why you did that search given that you were being provided documents by counsel?

MS. WOOTEN: Objection, form. Go ahead.

THE WITNESS: Should I answer? Oh. That's my practice. I prefer to be, you know, aware of what's out there.

MR. TRAINOR: Okay.

Q (By Mr. Trainor) Now, are you aware of any other publications that were prior art as of 1999 or 1998 that, in substance, disclosed the goings-on in the research and development in the OAB field, or was it just this Andersson paper?

MS. WOOTEN: Objection, form.

THE WITNESS: What I remember -- should I answer?

MS. WOOTEN: Yes.

THE WITNESS: Okay.

MS. WOOTEN: When I make objections, it's just for the record. Unless I instruct

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you not to answer --

THE WITNESS: You will tell me?

MS. WOOTEN: I will tell you.

THE WITNESS: All right, good. Thank you. I appreciate that.

I remember the Andersson paper best because -- I think, because I don't remember much others, it was just a nice review. I don't recall that I found other reviews that were useful in the way Andersson was.

MR. TRAINOR: Okay.

Q (By Mr. Trainor) Useful for what purpose?

A To help demonstrate what was -- what had been in the literature previous to 1999.

Q Okay. But you understand if there are other review papers besides the Andersson paper that were in publication at or before that time, they would also be considered within the prior art?

A That's my understanding, yes.

Q Okay. Okay. Now, the Andersson paper -- let's take a look at that here.

Now, is it fair to say that a skilled artisan, reading the Andersson paper at the time of its publication, would have understood at least the

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disclosure that the primary pharmacotherapy in the field of OAB to date had been antimuscarinic drugs?

A Yes.

MS. WOOTEN: Objection, form.

MR. TRAINOR: Okay.

Q (By Mr. Trainor) Now, did you understand the Andersson paper to suggest that the current research, with respect to antimuscarinic drugs, was focused on antimuscarinics that were selective for M3 receptors?

A My -- I'm not certain that Andersson suggested that, but that's sort of a lesson that I remember, you know, that -- you know, that that seemed to be a very reasonable way to proceed.

Q Uh-huh. And why was that?

A Many of the side effects from the existing were due to poor selectivity, and thus you would conclude that you'd get improved selectivity and have a better profile.

Q Okay. And poor selectivity for the various antimuscarinic subtypes would lead to side effects why?

MS. WOOTEN: Objection, form.

THE WITNESS: These muscarinic receptors are involved in other processes not related to the desired. Alternatively, you know, one

might look for tissue selectivity.

MR. TRAINOR: Okay.

Q (By Mr. Trainor) Now, are you familiar with tolterodine?

A Yes.

Q How about atropine?

A Yes.

Q Okay. And do you understand that drugs such as tolterodine and atropine were nonselective antimuscarinics?

A Yes.

Q Meaning that they bound to muscarinic receptors everywhere they could be found in the body, correct?

A The studies had the multiple muscarinics expressed in cell culture. And so, yeah, you might expect that there would be found -- you know, that this would happen. But the data showed that in these culture models, you know, such agents were not selected.

Q Uh-huh.

A Now, what happens in vivo might, in fact, be slightly different because the drug might not be equally distributed across the body.

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Q Okay. Now, the thinking at the time was that the M3 subtype was most responsible for activity in the bladder; is that right?

MS. WOOTEN: Objection, form.

THE WITNESS: I'm sorry, could you repeat that?

MR. TRAINOR: Yes.

Q (By Mr. Trainor) The thinking at the time was that M3 receptors predominated the bladder as opposed to other subtypes, correct?

A I believe the line of thought at that time was that the M3 was important for bladder function.

Q Okay. And so it was understood at the time that one direction of research would be to develop drugs that selected only for that M3 receptor, correct?

A Yes.

MS. WOOTEN: Objection, form.

MR. TRAINOR: Okay.

Q (By Mr. Trainor) Now, the Andersson paper goes on to talk about other mechanisms of action that had been investigated and reported at least up till that time, correct?

A Yes.

Q So besides antimuscarinic drugs -- and

perhaps it's best if we can look at the table that you have in your declaration, which begins on the second page of the -- well, in your declaration, that would be -- let's get there anyway.

A Okay.

Q That's a good idea. So in your declaration, this is around --

A If you prefer Andersson, that's fine.

Q No, they're both the same, but just for the record, we can make clear.

Okay, if you go to -- yeah, page 39 of Exhibit 1003 --

A Yes.

Q -- I believe is a reproduction of Table 2 in the Andersson paper, which is Exhibit 1006, correct?

A Yes.

Q Okay. So looking at either one, this might be the best bird's-eye view of the other research that was being reported. So besides antimuscarinic drugs, Andersson reports on drugs acting on membrane channels. Do you see that?

A Uh-huh. Let me --

Q It's in italics. So the first italic is "antimuscarinic."

A Yeah, "adrenoceptor." I'm just trying to find -- there it is. It's the -- yes.

Q Okay. And Andersson also discloses investigation of drugs with mixed actions, correct?

A Yes.

Q And it also discloses investigation of the use of alpha-adrenoceptor antagonists, correct?

A Right.

Q And beta-adrenoceptor antagonists [sic]?

A Right.

Q Antidepressants?

A Right.

Q Prostaglandin synthesis inhibitors?

A Right.

Q Vasopressin analogue?

A Right.

Q And then a number of other sort of uncharacterized drugs, including Baclofen and capsaicin. Do you see that?

A Yes.

Q And then there's -- and all of those mechanisms of action fall under the greater heading of "Bladder Hyperactivity." Do you see that?

A Right.

Q Okay. And then there's a mention of a number of investigations for treatments of stress incontinence, and I'm not sure that really falls within the definition of OAB or at least the indication for Toviaz, which is why we're here today. But if you jump down to "Overflow Incontinence," you see that there's a further investigation of alpha-adrenoceptor antagonists?

A (No audible response.)

Q Yes?

A Yes. Oh, yes.

Q Again, muscarinic receptor agonists; do you see that?

A Yes.

Q And on the following page, continuing on, anticholinesterase inhibitor?

A Yes.

Q And again, a number of other drugs. Do you see that?

A Yes.

Q Okay. And so for bladder hyperactivity, which you understand to encompass these symptoms of OAB, correct --

A I think so.

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Q -- there are nine mechanisms of action that were investigated, or eight in addition to antimuscarinic drugs, correct?

MS. WOOTEN: Objection, form.

THE WITNESS: I haven't counted, but if that's your count, I won't argue with it.

MR. TRAINOR: Okay.

Q (By Mr. Trainor) And for overflow incontinence, which you understand to be a symptom of OAB, correct, that's actual incontinence?

A Clinically, it might be difficult to tell them apart.

Q Okay. In any event, the Andersson paper reports on the investigation of four different mechanisms of action, correct?

MS. WOOTEN: Objection, form.

THE WITNESS: If that's your count --

MR. TRAINOR: Okay.

THE WITNESS: -- I won't -- yeah.

Q (By Mr. Trainor) Now, under each of these mechanisms of action which are detailed beyond this table in the text of the Andersson paper, there are a number of specific compounds falling as within affecting that mechanism of action, correct?

A I'm sorry, say again.

Q So for each mechanism of action, such as antimuscarinic activity, the Andersson paper reports the degree of investigation with respect to a number of different compounds falling under that mechanism of action. Do you see that?

A Yes, I do.

MS. WOOTEN: Objection, form.

Q (By Mr. Trainor) So, for example, atropine, propantheline --

A Yes.

Q -- emepronium, and so forth, correct?

A Yes, I see the columns there.

Q Now, is it fair to say that this table summarizes, with respect to each of the compounds that are reported, whether those compounds have, in the first column, shown efficacy, by the letter E, or have been shown to be effective, rather? If you see the legend on the following page --

A Yes.

Q -- it says E means effective.

A You mean the --

Q First column.

A Right, the first column after the drug

column.

Q Right.

A Yes.

Q Okay. So for Table 2 in the Andersson paper, E means that the compound has been shown effective, and U means it's been shown -- unproven that it's effective, correct?

A Yes.

Q All right. Now, in the next column of Table 2, under the heading "Clinical," there are one of four designations, and A meaning that a good quality RCT has been undertaken. Do you see that?

A Yes.

Q And RCT means random controlled trial, correct?

A I believe that's correct.

Q And that's sort of the gold standard of clinical trials, correct?

MS. WOOTEN: Objection, form.

THE WITNESS: The FDA desires -- actually requires, you know -- and there are exceptions to that, however.

MR. TRAINOR: Okay.

Q (By Mr. Trainor) And I'm not sure you

completed the thought, so since we have to get the record completely, the FDA requires, generally, RCT-type clinical trials?

A Yes.

Q Okay. Now, continuing on, the designation A in Table 2 under "Clinical" suggests that -- excuse me, we just did it.

The designation B means that there have been some clinical studies and, by inference, not necessarily RCT level, but some clinical studies, correct?

MS. WOOTEN: Objection, form.

THE WITNESS: Yes, that's what the table appears to say.

Q (By Mr. Trainor) Right. And if the designation C appears under "Clinical," would you understand it to mean that no actual clinical study has ever been conducted, but there's some expert opinion out there that supports the claim of effectiveness?

A I think that's a reasonable interpretation.

Q Okay. So I don't know that you need to necessarily count them, but with respect to all of the mechanisms of action and all of the subsidiary compounds that have been investigated and reported in

this Andersson paper, I believe that -- count for yourself, but I believe that it's about 27 of the compounds have been reported as showing effectiveness in treating either bladder hyperactivity or overflow incontinence. Does that seem fair?

MS. WOOTEN: Objection, form.

Q (By Mr. Trainor) You're free to count.

A Would you like me to count?

Q No.

A Okay. If that's your count, I --

Q Okay.

A No dispute with that.

Q Great. And some smaller number -- I believe it's about 20 -- have been in either an RCT or other clinical study as opposed to not having been examined in a clinical itself. Does that seem about right, just eyeballing this chart?

MS. WOOTEN: Objection, form.

THE WITNESS: That seems close, I suppose.

MR. TRAINOR: Okay.

Q (By Mr. Trainor) So -- and that would include -- among the compounds that would fall into the category of having being shown effective and have been

the subject of a clinical trial are a number of the antimuscarinic drugs -- do you see that -- propantheline, emepronium, trospium, and tolterodine?

A I see that.

Q Okay. And oxybutynin is not classified as an antimuscarinic per se. He reports it as a drug with mixed action. Do you see that?

A I see that.

Q But you understand that oxybutynin, among its actions, has antimuscarinic action, correct?

A Correct.

MS. WOOTEN: Objection, form.

Q (By Mr. Trainor) So the question that I have is: The person of ordinary skill in the 1998 or 1999 time frame would have a number of research options available if the endeavor was to develop a new OAB drug, correct?

MS. WOOTEN: Objection, form.

THE WITNESS: Correct.

MR. TRAINOR: Okay.

Q (By Mr. Trainor) And in your declaration -- let's turn back to that. I believe it begins around -- you addressed the Andersson paper around paragraph 71. And there you're just sort of describing Andersson.

But if you turn to paragraph 76 of your declaration, paragraph 76 appears under a new heading that says "Selection of a Compound for Obviousness Analysis." Do you see that?

A I have found it.

Q Okay. Now, the sentence reads that you were first asked to look at the market for overactive bladder compounds as a skilled artisan in drug design and development and determine where a person of ordinary skill would begin possible development. Do you see that?

A Yes.

Q Okay. So I take it the "asked" refers to being asked by counsel?

A No, sir. I was thinking being asked by a director as a scientist in a laboratory.

Q Uh-huh. So that being the case, that paragraph should read, "I would have first been asked," or something like that; is that right?

A Oh, I'm sorry. I misunderstood the -- I was -- in this case, yes. Yeah, the -- yeah, I was asked by counsel. I'm sorry.

Q Okay.

A Yes.

Q Now, is it your view that a person of ordinary skill in drug development at the relevant time would have only considered the compounds that were available on the market at the time in terms of a platform for research?

MS. WOOTEN: Objection, form.

THE WITNESS: Not only, but as a starting point.

MR. TRAINOR: Uh-huh. Okay.

Q (By Mr. Trainor) So just so I have the record correctly, in your opinion, a person of ordinary skill in the art charged with trying to develop a new OAB drug would have begun looking for lead compounds exclusively among those that were on the market at the time; is that right?

MS. WOOTEN: Objection, form.

THE WITNESS: Not exclusively, but as a starting point.

MR. TRAINOR: Okay.

Q (By Mr. Trainor) Well, where else might you look for a starting point?

A I would look for compounds in my institution's library.

Q Even if they had nothing to do or no previous

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relation to urology?

A Indeed, yes.

Q Okay. And if you were to go about doing that, separate from looking at the drugs on the market, what types of compounds in your library would you be looking for?

A I would look for molecules that bear structural similarity to what I would perceive as a structure -- from the structures that were known.

Q Uh-huh. Okay. Okay. And that would be the case, again, even if some structural analog in your library had never been experimented with before for the purpose, in this case, of uses in OAB treatment, correct?

A Yes.

MS. WOOTEN: Objection, form.

MR. TRAINOR: Okay.

MS. WOOTEN: Pause and give me a moment to make an objection.

THE WITNESS: Okay. Sorry. Yeah, you're right. Okay.

Q (By Mr. Trainor) And would you or the person of ordinary skill in the art at the time also consider the literature irrespective of whether the literature

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published about marketed products exclusively?

A Yes.

MS. WOOTEN: Objection, form.

THE WITNESS: Sorry.

MR. TRAINOR: Okay.

Q (By Mr. Trainor) Would the Andersson paper be an example of such literature, a review paper like that?

A It would.

Q It would, okay, and so would it be -- would it be at least as reasonable to investigate compounds with different mechanisms of action other than those currently marketed as it would be to look at those compounds that were presently marketed?

MS. WOOTEN: Objection, form.

Q (By Mr. Trainor) As starting points?

A I'm not -- so could you ask that again to make sure I understand you correctly?

Q Okay. So when I asked you where a skilled artisan would look to try to find a starting point for a new OAB drug at the relevant time, in 1998 or 1999, and correct me if I'm wrong, one place you would look is at the currently marketed products in the field, correct?

A Correct.

Q A second place you would look, to the extent that you had access, was a library with compounds having structural similarity to compounds known to have --

A Yes.

Q -- been effective?

A Yes.

MS. WOOTEN: Objection, form.

Q (By Mr. Trainor) And from your last answer, I'm just asking, would it be just as reasonable to look for a starting point in a review article like Andersson that is proposing novel approaches to the problem, although not necessarily with drugs in the class of compounds that were presently marketed?

MS. WOOTEN: Objection, form.

THE WITNESS: I disagree that Andersson is proposing novel approaches. Andersson is merely reporting what's been described in the literature.

Q (By Mr. Trainor) Fair enough. And what's being described in the literature is that a great number of researchers were, in fact, at the time researching and trying to develop new OAB treatments

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that employed mechanisms of action other than classic antimuscarinic treatment, correct?

MS. WOOTEN: Objection, form.

THE WITNESS: My opinion is that the skilled artisan would look -- would look to find out what's already known and then proceed from there --

MR. TRAINOR: Right.

THE WITNESS: -- and choose what would be perceived -- what that person perceived as the easiest approach first.

Q (By Mr. Trainor) Why the easiest?

A Why begin with something difficult? It's the easiest, but it's the most efficient way to work.

Q Well, how else does medicine progress if everybody just looks for the easiest solution?

A It's where you begin.

Q I see.

A It's not always --

Q Okay. Okay. Be that as it may, in terms of what's known, I think you said, there are at least 20 different compounds reported in Andersson that were known, reported as effective, and had actually been in clinical trials, correct?

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MS. WOOTEN: Objection, form.

THE WITNESS: If that's your count.

MR. TRAINOR: Okay.

Q (By Mr. Trainor) Well, all I'm saying is, wouldn't they all be reasonable starting points?

MS. WOOTEN: Objection, form.

Q (By Mr. Trainor) Inclusive of tolterodine, and I'm just saying wouldn't all of the compounds reported as effective and having been through clinical studies be as reasonable a starting point as tolterodine, which is also reported in Andersson?

A The skilled artisan would then look and choose a good starting point and select, right, from -- the skilled artisan can't do all of them simultaneously.

Q Uh-huh. Isn't it the case that in research and development, there's a motivation to arrive at something different than what's already on the market?

MS. WOOTEN: Objection, form.

THE WITNESS: I believe the motivation is a successful campaign to get something successful to the market. The skilled person would seek to avoid reproducing something that's known.

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Q (By Mr. Trainor) Uh-huh. So -- okay. Now, in the -- in paragraph 81 of your declaration, just a little further down, you talk about "the analysis of the overactive bladder treatment area began with a review of the compounds and commercially available products possessing known efficacy or proposed efficacy in treating the disorder." Do you see that?

A Yes.

Q Would you agree that a great number of the compounds other than tolterodine reported in Andersson meet that description?

MS. WOOTEN: Objection, form.

THE WITNESS: Yes, the...

MR. TRAINOR: Okay.

THE WITNESS: "Great many" might be an exaggeration, but there are compounds there, right.

MR. TRAINOR: Okay.

THE WITNESS: It's a nice set.

MR. TRAINOR: Okay.

Q (By Mr. Trainor) Now, let's look at a few of these compounds specifically, and this will actually, I think, require us to go back a little bit in your declaration --

A Okay.

Q -- to -- the section begins around -- on paragraph 26, which is on page 13.

A Paragraph 26?

Q Uh-huh. And there's an intro paragraph, but then at paragraph 27, you discuss oxybutynin, correct?

A Yes.

Q That's reported in the Andersson paper?

A (No audible response.)

Q Yes?

A Yes.

Q And I note that in the last sentence, you say, "Oxybutynin was approved for treating overactive bladder in 1997." Do you see that?

A I see that.

Q Okay. Is that your understanding of when oxybutynin was first approved?

A My understanding is that it was on the market at that time. I don't recall the date it received FDA approval.

Q Okay. Would it surprise you that it was in the '70s?

A It would not.

Q Okay. And do you understand that the

approval of oxybutynin in 1997 was for a new dosage form of immediate release oxybutynin? I misspoke. Do you understand that the approval of oxybutynin in 1997 was in a new dosage form, which was a controlled-release dosage form?

A I don't remember all of the details --

Q Okay.

A -- of that approval.

Q Okay. Now, in Andersson's discussion of oxybutynin, which he calls a mixed-action drug -- back to the Andersson paper, Exhibit 1006, it's page 7 of the exhibit, page 929 of the paper. There's a heading at the top of the second column that says "Drugs with mixed actions." And as you move down to the next paragraph, the discussion beginning with the italics is of oxybutynin. Do you see that?

A Yes.

Q Okay. Now, if you go down to the next paragraph about oxybutynin, in the middle of the paragraph, staying on Exhibit 1006, do you see the sentence that begins "Oxybutynin has an active"?

A I see it.

Q Okay. And I'll just read it. It says, "Oxybutynin has an active metabolite,

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N-desethyl oxybutynin, which has pharmacological properties similar to those of the parent compound, but which occurs in much higher concentrations." Do you see that?

A I see that.

Q Okay. Now, that's somewhat similar to the metabolism of tolterodine, correct?

MS. WOOTEN: Objection, form.

THE WITNESS: My understanding is tolterodine is also dealkylated -- or is dealkylated at the amino moiety.

Q (By Mr. Trainor) Uh-huh, but I should ask the question this way: But this passage reflects that oxybutynin, like tolterodine, has an active parent compound, as Dr. Andersson uses it, and an active metabolite, correct?

MS. WOOTEN: Objection, form.

THE WITNESS: I believe that is true for both molecules.

MR. TRAINOR: Okay.

THE WITNESS: An active parent and an...

MR. TRAINOR: Okay.

Q (By Mr. Trainor) And if you move down to the last sentence in that paragraph, it says, "The

occurrence of an active metabolite may also explain the lack of correlation between the plasma concentration of oxybutynin and side effects in geriatric patients, reported by Ouslander." Do you see that?

A I see that.

Q Okay. So does that reflect that the dual active metabolism of oxybutynin can cause some issues or drawbacks with that drug? Is that what's being reported here?

MS. WOOTEN: Objection, form.

THE WITNESS: It's difficult for me to answer that question without a careful review of the Ouslander paper.

MR. TRAINOR: Okay.

Q (By Mr. Trainor) Okay. Without a review, does it suggest that this metabolism and the presence of two actives in oxybutynin make for variable pharmacokinetics in certain parts of the patient population?

MS. WOOTEN: Objection, form.

THE WITNESS: That might be the case.

MR. TRAINOR: Okay. Okay.

Q (By Mr. Trainor) Now, in any event, oxybutynin -- well, let me ask you this question: Why

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would oxybutynin not have been a reasonable starting point for the skilled artisan in 1998 to develop a new OAB drug?

A I wouldn't have chosen that as a starting point because of -- it's, you know, reported that many people discontinue use due to, you know, off-target effects, undesirable.

Q Uh-huh. So that was one drawback. And potentially the variable pharmacokinetics caused by two actives, would that be another drawback?

MS. WOOTEN: Objection, form.

THE WITNESS: It would be something to think about.

MR. TRAINOR: Uh-huh.

Q (By Mr. Trainor) But -- and let me step back and ask you --

A Uh-huh.

Q -- so would you describe yourself as a medicinal chemist?

A Yes.

Q Okay. What would you say is the authoritative treatise in the field of medicinal chemistry?

MS. WOOTEN: Objection, form.

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THE WITNESS: I'm not certain there is a single --

MR. TRAINOR: Right, sorry.

THE WITNESS: Right. The text I prefer if I'm teaching is Foye's Medicinal Chemistry.

MR. TRAINOR: Okay.

Q (By Mr. Trainor) Are there any other leading treatises in medicinal chemistry?

A Limited to textbooks, Silverman has a good one.

Q Who is it?

A Silverman.

Q Okay.

A But some people prefer Kerns and Di, is another that some people prefer. It's difficult to say leading. There are texts that people like.

Q All right. How about Burger's, is that --

A Burger's Medicinal Chemistry is a good one. I don't know anyone who uses it. Doesn't mean it's not used, but Burger is -- you know, if you're talking about leading -- you know, the founder of medicinal chemistry is often referred to as Paul Ehrlich.

Q Okay.

A But you don't go wrong to mention Burger.

Q Okay. So anyway, I was just curious, but my question, coming back to oxybutynin, is: Your testimony was that you wouldn't have started with that one because of the -- at least the dry mouth reports, but isn't that what a medicinal chemist does, is look at ways to modify compounds in any number of ways in an effort to, you know, address a drawback like that?

A It is.

MS. WOOTEN: Objection, form.

THE WITNESS: Oh, sorry. It is.

MR. TRAINOR: Okay.

Q (By Mr. Trainor) And how is that any less reasonable an option than making a prodrug of 5-HMT, for example?

MS. WOOTEN: Objection, form.

THE WITNESS: 5-HMT would be preferred for me because it had a better reported tolerability profile.

MR. TRAINOR: Okay. Fair enough.

Q (By Mr. Trainor) I understand what you're saying.

A Right.

Q But my question is, really, irrespective of

the relative favorability of the compound that a medicinal chemist is modifying, aren't there techniques that are employed regardless of the problem in the hopes of addressing that problem and arriving at a novel compound?

A There are.

Q Okay. And those could have been employed to address the concerns with oxybutynin, correct?

MS. WOOTEN: Objection, form.

THE WITNESS: I think a reasonable person might disagree with me on the starting point.

MR. TRAINOR: Okay.

THE WITNESS: But that -- right.

MR. TRAINOR: Okay.

THE WITNESS: That's...

Q (By Mr. Trainor) Okay. So does the -- so is it your testimony that the ease of developing a new compound is a function of the profile of the base compound, if you will?

MS. WOOTEN: Objection, form.

THE WITNESS: That might help --

MR. TRAINOR: Uh-huh.

THE WITNESS: -- the...

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Q (By Mr. Trainor) And -- but separately, some drawbacks with some compounds are challenging, more challenging than others, correct?

A Correct.

Q And a medicinal chemist would employ techniques to address those drawbacks, you know, as a routine part of what a medicinal chemist does, right?

MS. WOOTEN: Objection, form.

THE WITNESS: Correct.

MR. TRAINOR: Okay.

Q (By Mr. Trainor) Now, the -- and the problems with oxybutynin and its dry mouth profile were known well before the Andersson paper was published, correct?

A That appears to be the case.

Q Okay. And do you understand that the formulation of oxybutynin that was approved in 1997 and referenced in your declaration was an attempt to address that drawback?

MS. WOOTEN: Objection, form.

THE WITNESS: I know that formulations chemists can be very good at solving --

MR. TRAINOR: Okay.

Q (By Mr. Trainor) Is it fair to say that

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reformulating an existing drug can be a solution to drawbacks with that existing drug?

MS. WOOTEN: Objection, form.

THE WITNESS: It can be.

Q (By Mr. Trainor) So, for example --

A It has been done.

Q Right. So, for example, with oxybutynin, formulating it as a controlled-release or a slow-release drug addressed the drawback to some extent of the dry mouth side effect?

MS. WOOTEN: Objection, form.

THE WITNESS: I think that might be the case.

MR. TRAINOR: Okay.

Q (By Mr. Trainor) All right, let's keep going through your report here --

A Okay.

Q -- and the section of the prior art drugs.

A Uh-huh.

Q Now, the next compound is hyoscyamine. And you indicate here at paragraph 28 that it had shown some benefit in decreasing bladder contractions, but was associated with systemic side effects; is that right?

A Correct.

Q Okay. And again, it wouldn't be beyond the skill of an ordinary medicinal chemist to try to modify the hyoscyamine compound to address those side effects, correct, as of 1998?

MS. WOOTEN: Objection, form.

THE WITNESS: I think that's within the skillset.

MR. TRAINOR: Okay.

Q (By Mr. Trainor) Now, propantheline is the next compound, and this is also addressed in -- this page is out of order -- in the Andersson paper, Exhibit 1006, as well, right? Sorry to make you jump back and forth.

A No, that's okay.

Q Let me have you go to that table.

(Discussion off the record.)

Q (By Mr. Trainor) And it's on page 4 of the exhibit, page 926 of the paper.

A At the bottom of page 4?

Q Yeah, yeah. Now, propantheline bromide is a quaternary ammonium compound, correct?

A Let me look at the structure. Yes, that is a quaternary.

Q Okay. And the problem with quaternary ammoniums like propantheline is that they were poorly absorbed because of their quaternary nature; is that right?

MS. WOOTEN: Objection, form.

THE WITNESS: That can be true.

MR. TRAINOR: Okay.

Q (By Mr. Trainor) And is it fair to say that it was understood at the time that one possible way to address the absorption of quaternary ammonium compounds was to esterize the compound?

MS. WOOTEN: Objection, form.

THE WITNESS: I'm not sure -- ester --

Q (By Mr. Trainor) Or esterify?

A Okay, are you --

Q I'm just asking you in general.

A Well, you're speaking about formation of an ester with a quaternary ammonium salt.

Q Uh-huh. Had that been employed to try to improve absorption in these quaternary compounds?

A I'm having a problem with a quaternary -- with a quaternary ammonium and the term "ester" applied to that moiety --

Q Uh-huh.

A -- such --

Q Okay.

A Do you understand?

Q Sure. Well, you've got the -- you've sketched out the compound in your report, page 15, is that right, propantheline? But you would agree with me that, in general, one of the problems with quaternary ammonium compounds is that they were poorly absorbed; is that right?

A That is often true.

Q Okay. As a medicinal chemist, how could you have attempted to solve that problem in 1998?

A Start somewhere else.

Q If you started with propantheline, though?

A If I started with propantheline, I might -- you know, if I'm looking at this, you know, the propantheline molecule, you know, when I look at something that's highly polar, right, in this case, the extreme polarity, right, it's charged, I look for a way to make it more lipophilic.

Q Uh-huh.

A I would quite possibly -- you know, if I were instructed, as you just did, to improve this one's availability, I would try to modify the quaternary. I

would try to find out does this particular pharmacophore require quaternary ammonium moiety.

Q Okay. We'll come back to that.

Would you make a prodrug of propantheline to solve the absorption problem?

A A prodrug of this one would be very difficult because there are -- you know, the nitrogen is quaternized, there are no free OHs, there are no primary or secondary amines present.

Q Uh-huh. Are you familiar with the term "soft drug"?

A Could you let me know what you mean by "soft drug"? I've heard the word.

Q As it has been used in the literature --

A I've heard the term.

Q -- relating to prodrugs. You've heard of it?

A I've heard of it, yes.

Q What's a soft drug?

A At this time, I can't think of it.

Q Okay. Let's come back to it.

A Yeah, yeah.

Q All right. In paragraph 30 of your declaration, Exhibit 1003, you address terodiline, okay, which Dr. Andersson reports in the Exhibit 1006

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as a mixed-action drug having -- no, I'm sorry -- yes, mixed-action drug.

Now, I take it that terodiline would not be a reasonable starting point in your view because it had been withdrawn from the market due to concerns of the prolonged QT interval; is that right?

A Yes.

MS. WOOTEN: Objection, form.

MR. TRAINOR: Okay.

Q (By Mr. Trainor) All right. Now, do you recall what the thinking in the art at the time, at least by 1998, was as to the cause of the reported prolonged QT interval?

A I can't remember exactly if that was, in this case, due to the effect of the calcium channel or its muscarinic activity.

Q Uh-huh.

MR. TRAINOR: We've been going for an hour. Why don't we take a quick break.

(Recess taken.)

Q (By Mr. Trainor) Okay, Dr. Patterson, when we broke, I had you at paragraph 31 of your declaration, 1003 -- excuse me, paragraph 30, concerning terodiline.

A Okay.

Q Are you back there?

A Yes.

Q Okay. Now, there's a citation there to Exhibit 1008, which I'm going to hand to you, citation being the discussion of terodiline in paragraph 30. And this is also a publication. The lead author is Thomas, for the record, Exhibit 1008.

Now, it appears that -- well, this is published in 1995, so this was in the prior art, correct?

A Correct.

Q Okay. Now, it appears that you cited this paper for general propositions of the mixed mechanisms of action and also for the fact that it was withdrawn from the market, European markets, in 1991, due to concerns of the prolonged QT interval. Do you see that?

A Yes.

Q Okay. Now, do you recall reading this paper? And let me just -- maybe it's easier if I just direct you to the conclusions on the front page under the abstract.

A Okay.

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Q And the conclusion says, "Terodiline increases QTc and QTd in a concentration dependent manner. It's not clear whether this is a stereoselective effect and, if so, which enantiomer is responsible." Do you see that?

A Yes.

Q Okay. So do you understand that terodiline, as it was once marketed, was a racemate?

A That appears to be what this author is saying.

Q Okay. And what the author is concluding is that the prohibitive effect on QT may be attributable to one or the other of the enantiomers, the R and S, correct?

A Yes.

Q Okay. So assuming that terodiline may have been a reasonable starting point in 1998, wouldn't it have been routine to separate those enantiomers and test them for efficacy and safety as a means to develop a new OAB drug?

MS. WOOTEN: Objection, form.

THE WITNESS: It might be.

MR. TRAINOR: Okay.

Q (By Mr. Trainor) Well, it would certainly

have been within the skill to attempt that, correct?

A Yes.

Q Okay. Now, going back to your declaration, the next compound that you reference in paragraph 31 is trospium --

A Yes.

Q -- which is now marketed in the U.S. as Sanctura?

A Uh-huh.

Q Okay. Now, you indicate in paragraph 31 that as of the relevant time in 1998, it was not approved for use to treat OAB. Do you see that?

A Yes.

Q Okay. Do you understand that while it was not approved in the United States, it had been approved in Europe by that time?

A I think that's true. I'm not entirely certain, but I think that's true.

Q Okay.

A I just don't remember all of the approval dates.

Q Okay. Now, regardless of whether it was approved in the U.S., if my representation is correct and it had been approved at least in Europe to treat

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OAB, why would that be any less promising a starting point for development of a new OAB drug than tolterodine, for example?

MS. WOOTEN: Objection, form.

THE WITNESS: Some drugs used in Europe never make it to the United States.

Q (By Mr. Trainor) But do scientists really develop drugs with borders in mind?

MS. WOOTEN: Objection, form.

THE WITNESS: There are cases when we do.

MR. TRAINOR: Okay.

Q (By Mr. Trainor) Can you think of any reason why trospium, having been approved to treat OAB by 1998 and shortly after approved in the U.S. for the same, would not have been as promising a starting point for a new OAB drug as tolterodine?

MS. WOOTEN: Objection, form.

THE WITNESS: I worry with trospium about the unsubstituted phenyl rings, not a universal, but I -- you know, they tend to have some undesirable -- in my experience, some undesirable properties, so...

MR. TRAINOR: Okay.

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Q (By Mr. Trainor) Well --

A So I -- but also I think that more was known about tolterodine.

Q Uh-huh. Well, trospium certainly has an OH group, correct?

A Right.

Q That could be esterified to make a prodrug?

A Right.

Q Yes?

A That's correct.

Q Okay. And if absorption was a problem with trospium, would that have been a reasonable option to try to optimize trospium?

MS. WOOTEN: Objection, form.

THE WITNESS: No.

Q (By Mr. Trainor) No, it would not have been? Okay. Why not?

A There are no hydroxyls.

Q In trospium?

A I'm sorry, I'm looking at the wrong --

Q Paragraph 31.

A I'm sorry, I'm looking at the wrong molecule. I'm sorry.

Q Okay.

A Sorry, I was looking at the -- now that I'm on the right molecule now --

Q Yes, sir, now that you're on the right molecule, this is a diphenyl molecule?

A Uh-huh, right.

Q With the free OH group?

A Right, right. Okay.

Q Uh-huh.

A Right.

Q So my question is -- well, let me reask the question because I think you may have been looking at the wrong molecule.

Why would this have been any less a reasonable starting point than tolterodine for a developer looking to design an improved OAB drug?

MS. WOOTEN: Objection, form.

THE WITNESS: I think, you know, a developer looking to improve it might use it as a starting point. I'm not aware of a readily addressable issue with trospium.

MR. TRAINOR: Okay.

Q (By Mr. Trainor) If we could look back at the Andersson review, Exhibit 1006.

A Right.

Q And trospium is an antimuscarinic, so that is discussed at 928, which is page 6 of the Exhibit 1006. Now, it's the third paragraph and first column.

A Okay.

Q You can read it to yourself.

A Okay.

Q But...

A Okay.

Q Okay. So does Andersson teach that trospium had no drawbacks?

MS. WOOTEN: Objection, form.

Q (By Mr. Trainor) Well, let me --

A Yeah, I'm just --

Q -- let me speed it up. The second sentence says it's got no selectivity for muscarinic receptor subtypes.

A Right.

Q That's similar to tolterodine, correct?

A Correct.

Q And it says it's biological availability is low, at less than 5 percent. Do you see that?

A Yes.

Q That's pretty low, right?

A Yes, that's...

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Q And that would suggest to you or to the skilled artisan in reading this that that's a function of poor absorption; is that right?

A Low absorption, yes.

Q Uh-huh. And as we discussed previously, poor absorption is a drawback typical to quaternary ammonium compounds, correct?

A Correct.

Q So having read that and looking back at the structure in paragraph 31, I'll just ask again: In an effort to improve absorption and bioavailability, wouldn't trospium be a promising compound to modify?

MS. WOOTEN: Objection, form.

THE WITNESS: It could be.

MR. TRAINOR: Okay.

THE WITNESS: The -- you know, Andersson reports they found efficacy through oral dosing.

MR. TRAINOR: Uh-huh.

Q (By Mr. Trainor) Fewer side effects than oxybutynin, correct?

A That appears -- let me make sure, but I think that's what he says, yeah.

Q At the end.

A Yes, he does, right.

Q Okay. Okay. Okay. So as I understand the basis for your opinion, trospium chloride more or less fits the same profile that you suggest is what called for starting with tolterodine or 5-HMT, correct?

MS. WOOTEN: Objection, form.

THE WITNESS: There are similarities, but since it had demonstrated clinical efficacy through oral dosing, that appears a solution has been found.

Q (By Mr. Trainor) Uh-huh. Same with tolterodine, correct?

A Tolterodine is effective by oral dosing.

Q As well, yes?

A Yes.

Q Okay. Okay. Now, back at your report, after trospium, the next two compounds, paragraphs 32 and 33, back on Exhibit 1003, solifenacin and darifenacin.

A Okay, yes. Okay, I'm at paragraph 32.

Q Okay. Now, are you familiar with those two drugs, solifenacin and darifenacin?

A I know the names and I know that they're used for treatment of OAB.

Q Okay. Do you understand that by 1998, while

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they had not yet been approved, they were understood to have been designed as M3-specific OAB drugs?

MS. WOOTEN: Objection, form.

THE WITNESS: That's my -- that's what I remember, I think.

MR. TRAINOR: Uh-huh. Okay.

Q (By Mr. Trainor) So at least with respect to these two drugs, they reflect that by 1998, at least certain teams of researchers were focused on developing antimuscarinic OAB treatments that were specific to muscarinic receptor subtypes, correct?

MS. WOOTEN: Objection, form.

THE WITNESS: I'm sorry, say again.

Q (By Mr. Trainor) These two drugs would reflect that -- as of 1998, you know, the reality that researchers were, in fact, pursuing a design of M3-specific antimuscarinics for treating OAB, correct?

MS. WOOTEN: Objection, form.

THE WITNESS: Pursuing, yes.

MR. TRAINOR: Yes.

Q (By Mr. Trainor) Okay. Now, there is another compound that I don't believe you specifically address in your declaration, but it's also reported in Andersson, and I just want to have a look at that

before we close this part out. The name of the drug is propiverine.

So looking at Andersson 1006, propiverine is listed in that table as a drug with a mixed action, and there's a discussion in the text of Andersson about propiverine. Sorry, let me just note -- you see in the table of -- the Andersson table that you reproduce in your declaration that propiverine, in the table, is disclosed to have been reported to be effective in treating bladder hyperactivity. Do you see that?

A Yes.

Q And also had been subject to an A-level or RTC clinical trial, correct?

MS. WOOTEN: Objection, form.

THE WITNESS: That's in the table.

Q (By Mr. Trainor) That's correct?

A Correct.

Q Okay.

A I see it in the table.

Q Yep. So now, sorry, going back to the text, this is page 9 of Exhibit 1006 and page 931 of the Andersson paper. Now, the italicized "Propiverine" begins in the second full paragraph. I just want to take you down two paragraphs with the sentence which

begins, "Propiverine has a documented beneficial effect in the treatments of detrusor hyperactivity." Do you see that?

A Yes.

Q And it goes on to say "and seems to have an acceptable side effect profile." But then it continues, "Its place in therapy is difficult to evaluate and requires further comparative studies." And then the end of the section about propiverine concludes, "Its complex pharmacokinetics, with several active and not very well characterized metabolites, needs more attention." Do you see that?

A Yes.

Q Okay. So if you were a skilled artisan in 1998 considering whether propiverine might be a reasonable starting point for the development of a new OAB drug, what would that suggest to you, the disclosure about the complex pharmacokinetics?

MS. WOOTEN: Objection, form.

THE WITNESS: About the complex pharmacokinetics?

Q (By Mr. Trainor) Well, let me ask it to you this way: That last passage I read, would that dissuade you from using propiverine as a starting point

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as opposed to some of the other compounds, including tolterodine that we've discussed?

MS. WOOTEN: Objection, form.

THE WITNESS: What might dissuade me from that molecule is the call for additional research. That tells me somebody is probably already doing it, and that might dissuade me from...

MR. TRAINOR: Okay.

Q (By Mr. Trainor) What about the part about it having several active and not very well characterized metabolites?

A That sounds like speculation to me, that several actives, so that's unknown, hence the call for further investigation.

Q You believe it was unknown that it had several active metabolites?

A No, that the actives -- I think it was known that it had several metabolites. I think there was some degree of uncertainty whether all of them are active --

Q Well --

A -- based on the comments here.

Q Right. Well, we'll turn to this shortly, but

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as I understand your declaration, one of the reasons that, starting with tolterodine, the skilled person would have attempted to modify 5-HMT was in large part due to the fact that you had two actives with tolterodine, correct?

MS. WOOTEN: Objection, form.

THE WITNESS: Yes.

Q (By Mr. Trainor) And that, in your view, rendered the pharmacokinetics of tolterodine problematic; is that right?

MS. WOOTEN: Objection, form.

THE WITNESS: The problem I saw wasn't such -- so much that it had two actives. It was that one of the metabolic pathways was variable in humans.

MR. TRAINOR: Right.

Q (By Mr. Trainor) Well, isn't that always more probable than not when you are dealing with two active agents in a drug?

A I'm not certain. It's -- I'm not certain.

Q Okay. I guess let me ask the question this way: Why would the complex pharmacokinetics, including several active metabolites with propiverine, not be considered a drawback in 1998 on the one hand, but

tolterodine, with its multiple active agents, present a drawback to the skilled artisan on the other?

A I'm not -- I don't mean to suggest that the multiple metabolites are not a drawback. What I'm suggesting is that when I see a review that says this merits additional research, that tells me somebody is probably doing it.

Q Uh-huh.

A And so I might be directed to do something else if I were not already, you know, doing it. Right?

Q So did you just mean by that last testimony there that one factor in determining what lead compound to attempt to optimize is the knowledge that other researchers may be doing the same thing?

A In some cases, it is. If I'm in industry, I would be concerned about, you know, taking a parallel path, and even in academia, I'm concerned about taking a parallel path. Right?

Q Uh-huh.

A And so statements like that make me cautious.

Q Okay. Are you aware that at the time, in 1998 and 1999, others were working to improve tolterodine?

MS. WOOTEN: Objection, form.

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THE WITNESS: That would not surprise me.

MR. TRAINOR: Okay.

Q (By Mr. Trainor) And if that were the case, how would that impact your opinion that the skilled artisan would be drawn to tolterodine as a lead compound among others?

A Okay, so what I'm saying is that if I'm in industry and we -- let's say I was a competitor of the pharma company that owned tolterodine, I might be cautious about working there.

Q Okay.

A Right? Now, if I am -- I think that's sufficient.

Q Okay. Well, in any event, to move on from this, would you agree that what Exhibit 1006, the Andersson paper, discloses is that in reality, at that time, a number of different mechanisms of action, including but not limited to antimuscarinic action, were being pursued in an attempt to develop a new OAB drug?

A Yes.

Q And do you understand that at least certain of those approaches were suggested as promising in the

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prior art at that time?

MS. WOOTEN: Objection, form.

THE WITNESS: Andersson reports that some of the molecules had demonstrated clinical efficacy as well as pre-clinical evaluation.

Q (By Mr. Trainor) That being the case, would a skilled artisan take from that reporting that there were promising avenues of research separate and apart from nonspecific antimuscarinic treatment?

MS. WOOTEN: Objection, form.

THE WITNESS: Someone might.

MR. TRAINOR: Okay.

Q (By Mr. Trainor) But you can't say one way or the other whether the hypothetical skilled person would view these reports as promising new areas of research?

MS. WOOTEN: Objection, form.

THE WITNESS: Some might, certainly.

MR. TRAINOR: Okay.

Q (By Mr. Trainor) Okay. Now, let's turn to tolterodine, okay, and maybe we can just try to tee up where we are in your declaration. So, let's see, at the end of that last section we were running through,

we get to page 18 of Exhibit 1003. And beginning with paragraph 35 and, I would say, running through maybe paragraph 55 --

A Okay.

Q -- you dedicate discussion in your declaration to your view that skilled artisans would recognize that tolterodine could be improved. So just to -- you're there. And before I get to that, earlier on in your declaration, and I'm paraphrasing here, but let me know if this sounds familiar --

A Okay.

Q -- you suggest that those skilled in drug development typically face two options, one being to develop a completely novel compound, the second being to improve upon an existing drug or compound. Is that about fair?

A I think that's reasonable.

Q Okay. And can you tell me in what instances would the skilled drug developer pursue the completely novel compound approach?

A In a case where it's a new target.

Q Meaning?

A A recently validated drugable target, something for which there's no known treatment. Right?

Q Okay. And is it then the case that in all other instances, drug developers are just looking to improve upon existing compounds?

MS. WOOTEN: Objection, form.

THE WITNESS: I believe that's an overstatement, all other cases to improve on.

Q (By Mr. Trainor) How about in most other cases?

A In many other cases -- I think you're overstating it in two areas.

Q Okay.

A You know, just looking to improve upon, right, we -- I'm not suggesting that we improve upon a known active to the exclusion of all other approaches.

Q Uh-huh. Okay. Well, in any event, it's your view that assuming the skilled artisan identifies tolterodine as a starting point for a new drug development project, that we're talking about the second approach here, which is optimizing the compound tolterodine or its analogs, correct?

MS. WOOTEN: Objection, form.

THE WITNESS: Yes.

MR. TRAINOR: Okay. Okay.

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Q (By Mr. Trainor) Now, the references, which are particularly important in these proceedings, that you point to for the proposition that a person of skill would identify tolterodine as needing improvement include this Postlind reference; is that right? Let me show you it to you.

MR. TRAINOR: So I'm going to hand the witness what's Exhibit 1010 in all of the IPR proceedings, and it's a publication. The lead author is Postlind, P-O-S-T-L-I-N-D.

Q (By Mr. Trainor) And you recall that reference, Dr. Patterson?

A Yes.

Q Okay. Now, how does Postlind suggest or contribute to the suggestion that the skilled artisan would recognize that tolterodine could be improved in 1998, or as of the date of the publication anyway?

MS. WOOTEN: Objection, form.

THE WITNESS: Postlind identifies a single active metabolite.

Q (By Mr. Trainor) Well, that's the case with a lot of drugs, right?

A Right. And there are multiple metabolic pathways. So the expression of the CYP2D6, isoform is

variable in humans, and that could lead to some, you know, dosing problems, unpredictable effects, so --

Q Let me ask you about that. You used the word "dosing" or "dosing problems" quite a bit talking about tolterodine in the declaration. What do you mean by that?

A In that a safer example, a poor metabolizer might require a different dosing protocol than an extensive metabolizer.

Q Okay. And so in the Postlind reference, I direct your attention to the end of the text of that reference.

A Uh-huh.

Q Before we do that, the existence of multiple metabolic pathways is common to a lot of drugs, no?

A I believe it is.

Q Yeah. Now, in this Postlind reference, at the end of the discussion, the last paragraph begins "Clinical studies have demonstrated that individuals with reduced CYP2D6-mediated metabolism represent a high-risk group in the population with a propensity to develop adverse drug effects." Do you see that?

A Yes.

Q Is that what you were referring to?

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A It's one potential issue, right, that, you know, there are -- you know, if there are multiple metabolic pathways, then that increases the possibility of such drug-drug interactions.

Q Uh-huh. And with any drug that has multiple metabolic pathways, the FDA requires studies be done to ensure that any drug-drug interactions don't have adverse effects, correct?

MS. WOOTEN: Objection, form.

Q (By Mr. Trainor) I mean, isn't that the case?

A There are drugs marketed such that, you know, combinations are contradicted, so the FDA wants -- my understanding is that the FDA wants such things known.

Q Uh-huh. And that's because whatever entity is responsible for metabolizing the drug or further metabolizing its metabolite can be inhibited by certain other drugs that are taken concomitantly by the patient, correct?

MS. WOOTEN: Objection, form.

THE WITNESS: That is a consideration. It's a concern.

Q (By Mr. Trainor) And isn't it fair to say that when that's the case, the FDA will ask you to run

a study to ensure that inhibiting that metabolizing agent won't give rise to adverse events in deficient populations?

MS. WOOTEN: Objection, form.

THE WITNESS: I am aware of -- I guess I'd say I'm reluctant to issue a blanket statement of that because I have seen, you know, these warnings that caution should be exercised in, you know, use of one drug with another drug.

Q (By Mr. Trainor) Okay. How about this way: Let's assume -- forget about the FDA.

A Uh-huh.

Q Wasn't it the case in 1998, as now, that to the extent multiple metabolic pathways present the concerns of Postlind, that there are studies that can be done with known inhibitors of the metabolizing agent?

A Yes, that can be done.

Q Okay. And that was done in connection with tolterodine, correct?

MS. WOOTEN: Objection, form.

THE WITNESS: I believe that's correct.

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MR. TRAINOR: Okay.

Q (By Mr. Trainor) And so, I'm sorry, back to the reference, your summary of the references around paragraphs 41 and 42 just so -- I know I have you all over the place, but the Postlind description by you in your declaration begins at paragraph 40, and this entire last paragraph of the discussion is set forth there, correct?

A Could you remind me which paragraph?

Q So paragraph 40.

A Forty, okay. Yeah, the -- are you referring to the citation to the abstract -- of the abstract at the bottom of the page, the bottom of page 20 of the declaration?

Q Yes.

A Okay.

Q Now, so continuing on paragraph 41 in your declaration, is it fair to say what you're saying, at least in the first instance, is Postlind tells you how tolterodine is metabolized, that's where that is in the art; is that correct? I'm just on 41 now.

A He does -- I'm sorry, you're at paragraph 41, did you say? All right, he identifies three major metabolites.

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Q Uh-huh. Okay. And then just moving down to paragraph 43, that is -- aside from your little intro, that is the last paragraph of the Postlind reference, Exhibit 1010, reproduced in your declaration in paragraph 43?

A I see that.

Q Okay. So my question is: To one skilled in the art, what is the significance of this paragraph in Postlind in connection with your opinion that those of skill would have recognized the need to improve tolterodine?

MS. WOOTEN: Objection, form.

THE WITNESS: Postlind identifies it -- identifies it, "it" being the CYP2D6, as a high-risk group.

MR. TRAINOR: Uh-huh.

THE WITNESS: If I can easily avoid that, I would be motivated to do so.

MR. TRAINOR: Okay.

Q (By Mr. Trainor) Now, that assumes that you need to avoid that, correct?

A I think a caution would motivate me. He seems to identify a need here.

Q Okay.

A So...

Q Well, if we look at the second-to-last sentence, it says, "The possibility of clinical drug interaction at the enzyme level thus exists." Do you see that?

A Certainly.

Q And then in the next sentence, he says, "However, the large amount of 34a [sic] in the liver and the fact that tolterodine is predominantly eliminated via oxidation by CYP2D6 makes it less likely that clinically significant drug-drug interactions would occur with CYP3A."

A You said -- I think you said CYP4A [sic] --

Q Did I?

A -- and then I got lost at that point.

Q Okay.

A So could you --

Q Well, let me just strike that and say the first sentence I read indicates that at this point in time, as of this report, it's just a possibility that those who are CYP2D6 deficient and take tolterodine are at high risk, right?

A Yes.

MS. WOOTEN: Objection, form.

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Q (By Mr. Trainor) At this time -- at the time of this publication, it was a possibility, correct?

MS. WOOTEN: Objection, form.

Q (By Mr. Trainor) Yes?

A Yes.

Q Okay. Now, is there anything else about the Postlind reference, other than the teaching that CYP2D6 deficient patients may be at risk if they take tolterodine, that is significant to your opinion?

A The metabolite from that pathway is active.

Q Okay. Okay. Now, the -- a second reference that you cite in support of your opinion that tolterodine would have been recognized as needing improvement are two papers authored by Brynne. So if we go to -- okay, now...

Okay, sorry. Now, here we go. Sorry. Back to your declaration, page 22, paragraph 44, there's a reference to Brynne 1997, which you identify as Exhibit 1007.

MR. TRAINOR: I'm handing the witness Exhibit 1007 to both of his declarations. It's a publication. The first author is Brynne, B-R-Y-N-N-E. This one has a publication date of 1997.

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Q (By Mr. Trainor) Now, I'm sure it's difficult for you to parse these things out, and it's more than one Brynne, but it's difficult for me because I need to know, you know, where in these references you're getting the support for your opinion.

So let me suggest this: There is a -- in your paragraph 44, where you begin the discussion of Exhibit 1007, this Brynne '97 paper, you again have a large block of text that you cut out from Brynne. The identification of the metabolic pathways of tolterodine is set forth in paragraph 45, as taken from Brynne. Do you see that?

A I see it.

Q Okay. And that's really already reported in that Postlind reference, right?

MS. WOOTEN: Objection, form.

THE WITNESS: The --

MR. TRAINOR: Let me strike that.

Q (By Mr. Trainor) That was also reported in the Postlind reference, just the metabolic pathway?

A Some of the metabolites are reported in Postlind.

Q Uh-huh. Okay. Okay. So the Brynne '97 paper is more comprehensive with respect to the

metabolites produced by tolterodine than Postlind; is that right?

A Yes.

Q Okay. Now, I want to direct your attention to what I believe to be sort of the contribution of Brynne, as proposed in your declaration, and that is if you look at this block quote in paragraph 44 where it carries over from page 22 to page 23 --

A I'm there.

Q Yeah?

A I'm on page 23.

Q Great. So the first full sentence says, "The absolute bioavailability was highly variable, ranging from 10 to 70 percent." Do you see that?

A I have not found it yet. You said the -- are we --

Q I'm in your declaration.

A Right, right.

Q Page 23.

A Oh, okay. I'm on the wrong page, then. All right. I was looking at the -- okay, I was looking at the first sentence in what we quoted. You mean the first complete sentence on page 23?

Q Right.

A I'm with you now. Sorry.

Q I'll just read it again so the record is clear. "The absolute bioavailability was highly variable, ranging from 10 to 70 percent." Do you see that?

A Yes.

Q And that's a quotation from Brynne, Exhibit 1007, right?

A Yes.

Q Now, I take it from your declaration that you believe that that's significant with respect to your opinion. Is that fair to say, or no?

MS. WOOTEN: Objection, form.

THE WITNESS: It's a piece of information that informed my opinion.

Q (By Mr. Trainor) Okay. How did it inform your opinion?

A In that the exposure to the parent tolterodine was variable.

Q Uh-huh. Okay. And that would be significant if tolterodine itself was the only active agent, correct?

A No.

Q Okay. Why not?

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A I would be concerned with some adverse events due to higher exposure of the parent resulting from the variable. So such -- you know, the persons who are poor metabolizers may experience adverse events not seen in the people who metabolize it more efficiently.

Q Uh-huh. And that assumes that tolterodine carries more serious adverse events than 5-HMT, right?

MS. WOOTEN: Objection, form.

THE WITNESS: No, I don't believe that's entirely right.

MR. TRAINOR: Okay.

Q (By Mr. Trainor) Well, in this Brynne paper in 1997, is it fair to say that when the bioavailability measurements were being made, they were not being made with respect to the sum of both active agents?

A The statement regarding the absolute bioavailability appears to be made to the parent, tolterodine.

Q Right. Now, as far as therapeutic effect goes, that variability -- well, strike that.

That variability, if you were to sum tolterodine and 5-HMT and measure that bioavailability, would be or is a lot less variable, correct?

A That's my recollection.

Q So isn't the range of variability reported in Exhibit 1007 really just a function of the fact that this drug exhibits polymorphism?

MS. WOOTEN: Objection, form.

THE WITNESS: You mean -- what do you mean by "polymorphism"?

MR. TRAINOR: Sorry, that's inartfully stated.

Q (By Mr. Trainor) The variability reported in Brynne and recited in your declaration is attributable to the fact that some of the patients or subjects in this study were poor metabolizers and some were extensive metabolizers?

A Oh, I see. That appears to be the case.

Q And would you agree that at the time that this Brynne, Exhibit 1007, was published, that phenomenon of polymorphism was just starting to come into focus?

MS. WOOTEN: Objection, form.

THE WITNESS: There -- about the time, there were some reported adverse events due to such variable expression of the CYP2.

Q (By Mr. Trainor) Let's take a look at the

discussion in this paper, 1007. This begins on page 7 of the exhibit, page 293.

A Begins on page which? I'm sorry.

Q It's page 7 of the exhibit on the bottom right.

A I'm there.

Q And I'll read it. The discussion begins, "The finding that the absolute bioavailability of tolterodine was highly variable (ranging from 10 to 74 percent) and independent of dose showed either that the drug was incompletely absorbed, or that tolterodine was subject to pre-systemic elimination." Do you see that?

A Yes.

Q Today we know that tolterodine is not poorly absorbed, correct, or incompletely absorbed?

MS. WOOTEN: Objection, form.

THE WITNESS: Today I would -- tolterodine -- I would express it tolterodine is well absorbed.

MR. TRAINOR: Yeah, okay.

Q (By Mr. Trainor) But the reader of this publication in 1997 would understand that these authors are trying to make sense themselves of this -- what's causing this high variability, correct?

A Yes.

MS. WOOTEN: Objection, form.

THE WITNESS: Yes.

Q (By Mr. Trainor) Okay. And then as we move over in the discussion to the very end of the next column, the sentence that begins "However," very end.

A Okay, the second --

Q Yeah.

A -- sentence in the last paragraph [sic]?

Q Right. So it says, "However," and then it continues on the next page, "the estimated bioavailability (10 to 70 percent) clearly suggested variable first-pass elimination, which may reflect differences between subjects with respect to metabolic capacity." Do you see that?

A I believe I was -- I was looking at the second sentence in the last paragraph, "However, less than 1 percent of the administered dose," so the last sentence in -- "However, the estimated" -- okay, so the last sentence that begins on that page. Okay, I found it. Sorry. Variable first pass. I see that sentence.

Q So what Brynne is suggesting here in this '97 paper is that they're starting to realize that bioavailability is being affected by some differences

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in metabolic capacity across subjects, right?

MS. WOOTEN: Objection, form.

THE WITNESS: They're beginning to report it at this time.

MR. TRAINOR: Right, right. Okay.

Q (By Mr. Trainor) So in any event, the report from this paper about the bioavailability of tolterodine comes, you know, just as the researchers are figuring out that there is an issue with respect to certain phenyl types, right?

MS. WOOTEN: Objection, form.

THE WITNESS: It's hard to know what's truly on their mind, but what they are reporting is their findings here of variable.

MR. TRAINOR: Right.

Q (By Mr. Trainor) So, now, if you were a skilled artisan in 1998, and I understand you're a medicinal chemist, but, you know, probably dangerous enough with pharmacology, and you're one of these researchers or inventors and you're starting to realize this through this data, what do you do, you know, midway through this drug development, what is the next thing that you do?

MS. WOOTEN: Objection, form.

Q (By Mr. Trainor) And I should say when I ask what is the next thing you do, I'm speaking to this differences in metabolic capacity for now. I'm sure there are other issues here, but what do you do next?

A Okay. I think about ways to avoid these concerns, right, is there a ready solution that I can come up with to make some or all of the concerns go away or at least be reduced.

Q Uh-huh. Even if you are that far invested into a project, into Phase 2, I believe, is what's reported in Brynne?

A My opinion is that the wise drug person always has Plan B.

Q Uh-huh. Okay. But would not the wise, skilled drug developer ensure first whether or not there was, in fact, a problem in terms of ultimate efficacy and safety before going to Plan B?

A I would be concerned regarding safety. If there's a safety concern, I would prefer to solve that before taking that to humans.

Q Uh-huh. Okay. Well, certainly there were poor metabolizers in this study, which gave rise to the variable bioavailability, correct?

A Correct.

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Q And there weren't really any subjects reported in this Brynne paper to have any serious safety issues at this point, correct?

MS. WOOTEN: Objection, form.

THE WITNESS: At this point, none were discovered.

MR. TRAINOR: Okay. Why don't we take a break.

(Recess taken.)

Q (By Mr. Trainor) Now, in any event, the scientist involved with the development of tolterodine, notwithstanding any concerns, did assess the effect of differing metabolic capacities of subjects after administration with tolterodine, correct?

MS. WOOTEN: Objection, form.

THE WITNESS: So...

Q (By Mr. Trainor) Well, before the break, I was asking you whether -- after reading the Brynne paper or being one of the authors who wrote it, what would you do, and you said you would try to find a Plan B. And I'm just jumping over that and saying in any event, those researchers went on to assess the impact of polymorphism on tolterodine, CYP2D6?

A CYP2D6 polymorphism. Right, they identified

some issues.

Q Okay. What issues were those?

A The variable metabolism --

Q The variable --

A -- as a result of --

Q Well, that had been identified as far back as Postlind, right?

A Yes, you're right.

Q Okay.

A You're right.

Q And so --

A They further discuss it.

Q Right. So it's fair to say Postlind, they identify the metabolic pathways and suggest there may be a risk to CYP2D6 deficient subjects, right?

A Right, right, right.

Q And in parallel or otherwise, the researchers reporting in the Brynne '97 paper that we just looked at, they're also identifying that this may be an issue as a function of the wide variability and bioavailability that they're seeing, correct?

A Yes.

Q And then those researchers go on to assess the safety and efficacy across the entire patient

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population, irrespective of CYP2D6 capacity, correct?

MS. WOOTEN: Objection, form.

THE WITNESS: I don't think that's correct.

Q (By Mr. Trainor) Okay. Well, another of the references that you rely considerably on in your declaration is this second Brynne paper. This is Brynne 1998.

A Okay.

MR. TRAINOR: And this would be Exhibit 1011 in both declarations. So I'm handing that to the witness now.

THE WITNESS: Thank you.

MR. TRAINOR: And just for the record, this is -- 1011 is also a publication also with a lead author Brynne, but its publication date is 1998.

Q (By Mr. Trainor) Now, do you recall reviewing Exhibit 1011 in preparing your declaration?

A Yes.

Q Okay. Now, the title of the paper is "Influence of CYP2D6 polymorphism on the pharmacokinetics and pharmacodynamics of tolterodine." Do you see that?

A Yes.

Q So would you agree that Exhibit 1011 is a report on the assessment of administration of tolterodine across the entire patient population, both poor metabolizers and extensive metabolizers?

MS. WOOTEN: Objection, form.

THE WITNESS: If you mean, by the entire human population, those two groups --

MR. TRAINOR: Uh-huh.

THE WITNESS: Okay. I wouldn't be so broad as to say the entire human population.

MR. TRAINOR: Okay.

THE WITNESS: That's what I meant by...

MR. TRAINOR: Okay.

Q (By Mr. Trainor) Now, I think you refer in your declaration to the fact that poor CYP2D6 metabolizers make up about 7 percent of the population. Does that ring a bell?

A Yes, that's...

Q Okay. Now, if you would -- well, let me ask you, in your own words, you know, what do you understand Exhibit 1011, this Brynne '98 paper, to teach those of skill in the art at the time of its publication?

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MS. WOOTEN: Objection, form.

THE WITNESS: Okay. That, you know, the poor metabolism among, you know, drugs that are metabolized by the CYP2D6 form is expected in about 7 percent of the population.

They also mention that there are a large number of drugs that are metabolized by this pathway. And they teach that these considerations are important in determining the dosage, the appropriate dosage, for the population, for people -- well, not the population, the people who receive drugs metabolized by this pathway, for some drugs they say.

MR. TRAINOR: Okay.

THE WITNESS: They also, you know, even say that this can affect efficacy of the treatment in some cases.

Q (By Mr. Trainor) Where does it say that?

A It says here --

Q Can you refer us to a page number?

A Right. So, "Moreover, if a drug" -- oh, I'm sorry. It's on the first page, the second column, the

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column on the right, sentence that begins with "Moreover." It's about seven lines up from the bottom of the page.

Q Uh-huh.

A So, "If a drug is metabolized by CYP2D6 to an active metabolite, the activity of the enzyme may be an important determinant of the effectiveness of treatment." So they say there are some cases where --

Q Dr. Patterson, that's a general statement about drugs --

A So you're asking me --

Q -- metabolized by CYP2D6 in general, correct?

A Right.

Q That's not a conclusion with respect to tolterodine?

A Oh, okay, you're asking me about --

MS. WOOTEN: Objection, form. Just make sure you let him finish his question before you start talking.

THE WITNESS: All right. Thanks. Okay. So I thought you were asking me about general concepts with CYP2D6 --

MR. TRAINOR: Uh-huh.

THE WITNESS: -- not necessarily

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specific to tolterodine.

MR. TRAINOR: Okay.

Q (By Mr. Trainor) But as the title indicates, the influence of CYP2D6 polymorphism was studied on tolterodine here, correct?

A You're right.

Q Okay. Now, if we turn to the discussion of the study, begins on page 8, which is page 536 of the reference itself, and I want to direct your attention one page over, okay, and there is -- at the bottom of the first column, so the last full sentence, it begins with "Metabolism." Do you see that? "Metabolism is thus also the main route of elimination among poor metabolizers."

A I see that.

Q Okay. And then the next sentence says, "In an in vitro study, hydroxylation of tolterodine showed strong correlation with CYP2D6 activity, whereas dealkylation correlated with CYP3A activity." Do you see that?

A I see that.

Q That's essentially what Postlind had found, correct?

MS. WOOTEN: Objection, form.

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THE WITNESS: I think that's consistent.

MR. TRAINOR: Okay.

Q (By Mr. Trainor) Well, if you look at the citation there to Footnote 26 and you check the bibliography, you'll see that that corresponds to Postlind, right?

A Yes.

Q Okay. And then immediately following after that citation to Postlind, it says, "Taken together, these findings imply that tolterodine is eliminated by at least two parallel pathways: a high-affinity, low-capacity pathway (hydroxylation by CYP2D6) in extensive metabolizers and a low-affinity, high-capacity pathway (dealkylation by CYP3A) among poor metabolizers." Do you see that?

A I see that.

Q And then it continues, "In contrast to the kinetic data, the pharmacodynamics of tolterodine were not generally influenced by metabolic phenotype." Do you see that?

A I see that.

Q Okay. Now, doesn't that suggest to the person of skill reading this paper that in the end, the

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CYP2D6 polymorphism did not impact the effect of tolterodine on patients regardless of whether they were poor or extensive metabolizer?

MS. WOOTEN: Objection, form.

THE WITNESS: It does.

Q (By Mr. Trainor) Okay. And if you continue -- well, a couple other things too. And if you go to the very conclusion of this paper, the very last column before you get to the references, it says, "Despite the influence of CYP2D6 polymorphism on the pharmacokinetics of tolterodine, this does not appear to be of great pharmacodynamic importance." Do you see that?

A I do.

Q Okay. So in light of that conclusion, why, in your view, would it be so readily apparent to a skilled drug designer in 1998 that tolterodine had a metabolism problem that called for optimizing?

MS. WOOTEN: Objection, form.

THE WITNESS: In this case, they're dealing with a small population of normally -- normal, healthy persons.

My concern, since, you know, some adverse cardiac events have been reported, is

that a person who is predisposed to a cardiac condition may experience an adverse event as a result of poor metabolism of tolterodine.

Q (By Mr. Trainor) But what cardiac events have been reported about tolterodine?

A Among healthy -- oh, it caused an effect on heart rate in some persons.

Q Right. Now, let's take a look at that, then. If you have a look at -- if you turn back to just below the -- on page 9, where it had the citation to Postlind -- again, we're on Brynne, 1011 -- in that same paragraph that we read from previously, the first sentence, if we move down to the middle of that middle paragraph, it says, "In the present study, at a dosage of 4 milligrams, only a small increase in heart rate was observed in extensive metabolizers, whereas heart rate was unaffected among poor metabolizers." Do you see that?

A Yes.

Q Doesn't that suggest that to the extent one of these two active agents is responsible for effect on heart rate, that it's 5-HMT and not tolterodine?

MS. WOOTEN: Objection, form.

THE WITNESS: There's another paper that

indicated an alteration in heart rate among poor metabolizers.

Q (By Mr. Trainor) Uh-huh, okay, but how about this statement in this paper, isn't that what it suggests? It's a small dataset, I'll grant you that, but based on what we know, which is that poor metabolizers are getting tolterodine and extensive metabolizers predominantly 5-HMT, that it's 5-HMT, not tolterodine, that would be responsible for the increase in heart rate?

MS. WOOTEN: Objection, form.

THE WITNESS: My concern can't be based upon a single reference with a small N. And your question earlier was in the late 1990s.

MR. TRAINOR: Uh-huh.

THE WITNESS: Now, there were known cardiac events among other drugs reported in the late '90s. There was some with -- I believe it was the antihistamine Seldane and others with the NSAIDs, and there's a subset of population with cardiac issues that were affected by these drugs.

So this is something that was -- that would have been on my mind and sticks with me

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to this day.

MR. TRAINOR: Uh-huh.

THE WITNESS: Right? And so that would be my concern, particularly in a drug such as this that might be likely to be used in an aging population, you know, my understanding is often, you know, women of a certain age begin to be affected, right, and they might be among the target population. And so as this happens, I think there might be a subset of those women susceptible, and that would be my concern.

Q (By Mr. Trainor) Okay. Well, if that's your concern, notwithstanding the data that we just looked at with respect to heart rate, then why would you be comfortable isolating 5-HMT?

MS. WOOTEN: Objection, form.

Q (By Mr. Trainor) If you have a concern about one or the other of these entities being at elevated levels in certain populations and you don't have an educated guess as to which one is causing the effect on the heart, then what would be the basis for isolating 5-HMT?

MS. WOOTEN: Objection, form.

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THE WITNESS: That it seems to be deactivated reasonably well and with less variability than the parent drug. So that would appear to me to be easier to manage clinically.

Q (By Mr. Trainor) I'm sorry, I don't understand that. Your premise in this case is that you would recognize a problem with tolterodine based upon the fact that poor metabolizers would have excessive levels of tolterodine as opposed to 5-HMT after administration, okay?

A Yes.

Q And the premise follows that I would want to isolate 5-HMT as the safer option as between those two active agents. We just looked at data that suggests that it's the patients with tolterodine -- excuse me, with 5-HMT that are getting the increase in heart rate, not the patients with tolterodine. You say you still have a concern. If you still have a concern, then how can you be comfortable isolating 5-HMT instead?

MS. WOOTEN: Objection, form.

THE WITNESS: Because there are other references that indicate alterations in heart rate with the parent drug, right, so the --

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Q (By Mr. Trainor) Which references are you talking about?

A I believe it was another pharmacokinetics study.

Q Okay.

A I don't remember the author. And so the clinician would not necessarily know who among his population are poor metabolizers in that, and it would be difficult to predict the response of these patients.

Q Okay.

A So that would be my concern.

Q But the only way that you would confirm that is to determine which of the two agents is causing the effect, correct?

MS. WOOTEN: Objection, form.

THE WITNESS: I think based on the paper, they show -- that I'm thinking about, they show that -- or they claim that among the poor metabolizers, they showed a decrease in heart rate, right, so -- right, and in this case, I think it would make it easy to manage clinically because there would be fewer issues for the clinician to be concerned about among the patients.

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Q (By Mr. Trainor) There has to be a basis for that. Easier to manage clinically has to be grounded in some science, has to be grounded in the fact that, you know, having a single entity is not the entity that's responsible for adverse effects, correct?

MS. WOOTEN: Objection, form.

THE WITNESS: It's not the single entity that's responsible for the potential adverse effects.

MR. TRAINOR: I'm not suggesting --

THE WITNESS: It's --

MR. TRAINOR: Go ahead. Sorry.

THE WITNESS: So...

Q (By Mr. Trainor) I'm not suggesting that it is. I don't know what paper you're referring to, but I'm trying to understand because this declaration supports that the prior art renders my client's patents invalid. So if it's prior art in your declaration, I'd like to know about it. If it's not and you can't remember, fine. It could be that it's a paper from before they were understanding this, before they were measuring 5-HMT and tolterodine separately or before they had appreciated this phenomenon. I don't know.

But the real question is: The skilled

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artisan reading this paper, reading this conclusion about pharmacokinetics of tolterodine not being influenced by metabolic phenotype can only conclude that the drug is safe and effective regardless of what segment of the population you administer it to, correct?

MS. WOOTEN: Objection, form.

THE WITNESS: I would hesitate to make such a leap with such a small N.

Q (By Mr. Trainor) Okay, but what other data is there in the prior art? This is it, right? Are you aware of any other prior art that suggests that this conclusion should be conditioned?

A The -- there are other issues with other drugs among the poor metabolizers where a subset of the population -- and that would be a concern to me.

Q Okay. The subset of the population who are poor metabolizers?

A And also may be predisposed to some cardiac issues.

Q Okay. But there are warnings for all drugs with patients, for the most part, who have cardiac issues, no?

MS. WOOTEN: Objection, form.

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THE WITNESS: For -- there's a safety index for all drugs. If we can reduce that possibility, then I'm more comfortable.

Q (By Mr. Trainor) How do you reduce that possibility?

A By using a drug that's targeted by fewer metabolic pathways. That's one way that it can be done. So if you do that, then you remove the concerns expressed in the literature, right, and then --

Q Hold on. Sorry. What concerns expressed in the literature? This is not a concern, Brynne --

A But there are other --

Q -- Exhibit 1011.

A Right, but Postlind discussed that, and there are -- there is other literature on the alteration of the heart rate.

Q But, Dr. --

A And there are also fewer potential drug interactions if we only proceed with a drug that's metabolized by the CYP3 isoform.

Q Okay. Dr. Patterson, you understand that a person skilled in the art has to look at the prior art as a whole, correct, all of it, correct?

A Yes.

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Q Okay. And a person looked at Postlind -- Brynne Exhibit 1011 cites Postlind -- recognizes what Postlind suggested, that this can be an issue for certain patients, and immediately following that says, "In contrast to the kinetic data, the pharmacokinetics of tolterodine were not generally influenced by metabolic phenotype."

How is it that a person of ordinary skill in the art reads that conclusion following the citation to the statement in Postlind and says there's still a problem that's readily apparent and needs to be fixed?

MS. WOOTEN: Objection, form, asked and answered.

Q (By Mr. Trainor) I want an answer to that question. I don't think there's anything equivocal about that statement.

A Insufficient sample size.

Q Okay. That's fine. That doesn't mean -- if it's an insufficient sample size, you can't draw a conclusion one way or the other, correct, you can't draw a conclusion that, to your point, it's absolutely safe and effective for extensive and poor metabolizers, but by the same token, you can't draw the conclusion that now there's a need to isolate 5-HMT, correct?

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MS. WOOTEN: Objection, form.

THE WITNESS: What I'm saying is that that concern still exists.

Q (By Mr. Trainor) It's unsupported by any data at this point in the prior art, correct?

A I don't think I agree. We've had this discussion, so --

Q Okay.

A -- I can repeat my previous statements if you'd like, but...

Q Okay. Now, let's look at some other data. If we could turn to the previous page, on page 8, before the discussion, the end of the first column, there's a paragraph that begins, and I'll read it, "All 16 volunteers completed the study. No severe adverse events were reported. The most frequently reported adverse events were headache (two extensive metabolizers and four poor metabolizers), dry mouth (four extensive metabolizers and two poor metabolizers), abnormal visual accommodation (five poor metabolizers), and tachycardia (four extensive metabolizers)."

So again, putting the heart rate increase aside, doesn't this suggest that if either of the two

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agents is responsible for the dry mouth side effect, it would be 5-HMT, given that more extensive metabolizers reported that adverse event?

MS. WOOTEN: Objection, form.

THE WITNESS: For that particular adverse event?

MR. TRAINOR: Yes.

THE WITNESS: Yes, your rereading of that points made to, you know, abnormal visual accommodation among the poor metabolizers.

MR. TRAINOR: Okay.

THE WITNESS: That's something that might be avoided by such a pathway.

Q (By Mr. Trainor) Right, but if you avoid that, then you might exacerbate the dry mouth, correct?

A You might.

Q Well, if you're pointing to the visual accommodation data suggesting that tolterodine seems to be causing that, then by the same token, it would appear that 5-HMT is causing the dry mouth, no?

A So while we might not agree with one another's conclusion, we can both see advantages to one pathway. I don't think I agree with -- you know,

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entirely that all of the concerns are alleviated by this. I understand your point.

Q Okay.

A And I perfectly understand why you're making your point.

Q Right, and I understand your point about one pathway always being preferred if you can get it, but the question is really, in light of this data, in light of these conclusions, in light of this assessment, does the person of ordinary skill in the art say, "I am going to make a new drug by isolating 5-HMT because tolterodine is problematic enough to justify doing that"?

MS. WOOTEN: Objection, form.

THE WITNESS: I think a person of ordinary skill would be ready to do so and would be eager to do so as a Plan B.

Q (By Mr. Trainor) Now, if -- let me just ask you: If this data were extrapolated and held true and it was confirmed that as between the two agents, 5-HMT causes more dry mouth, okay, what would be the justification for isolating 5-HMT at that point?

MS. WOOTEN: Objection, form.

THE WITNESS: The justification for

isolating 5-HMT, I would say you still -- it still does not alleviate my concern about the subset of the population sensitive to cardiac events that could be caused by accumulation of 5-HMT or poor metabolism of 5-HMT.

Q (By Mr. Trainor) You're not aware of any prior art that confirms that -- I think you might have misspoke there.

A Did I?

Q Let's back up.

A Okay.

Q You said --

A I said 5-HMT, didn't I? Gosh. Thank you, sir. I meant the parent, tolterodine. Thank you very much.

Q Right, but you're not aware of any data or any reports in the prior art that concluded that there were cardiac events associated with tolterodine that were not associated with 5-HMT?

A I don't remember the author of the paper, but they report four subjects had an alteration -- among the poor metabolizers, had an alteration in their heart rate.

Q Uh-huh, okay.

A So...

Q Okay. Now, earlier, when I asked you about why oxybutynin wouldn't be a reasonable starting point, you suggested because it had severe dry mouth and caused withdrawals.

A Right.

Q And would you agree with me that in light of oxybutynin, the skilled artisan in the OAB field is looking to reduce that side effect?

A Yes.

Q Okay.

A And I'm not -- I think maybe saying it's an unreasonable starting point might be an overstatement. It's not necessarily where I would begin, knowing what I know about 5-HMT, but I think reasonable persons might be interested in modifying that molecule, maybe not the first one, but that might be among the, say, Plan B2 or something like that.

Q Okay. Let's take a look at this Detrol label, which is Exhibit 1009 is both declarations. Dr. Patterson, you understand that this is the label or package insert for tolterodine as it had been approved in early 1998?

A Yes.

Q Okay. Now, I'd like to direct your attention to the "Pharmacokinetics section" on the first actual page of the -- page 2 of the Exhibit 1009.

A Uh-huh.

Q Now, as you run through the "Pharmacokinetics" discussion, it carries over into the next column. There's a heading that says "Variability in Metabolism."

A Yes.

Q Do you see that?

And there's a discussion of the 2D6 and 3A4 pathways in extensive and poor metabolizers, as we've been discussing now for a while. And I direct your attention to just a little more than midway through that paragraph, and it says, "Because of differences in the protein-binding characteristics of tolterodine and 5-HMT, the sum of unbound serum concentrations of tolterodine and the 5-HMT metabolite is similar in extensive and poor metabolizers at steady state. Since tolterodine and the 5-HMT metabolite have similar antimuscarinic effects, the net activity of Detrol tablets is expected to be similar in extensive and poor metabolizers." Do you see that?

A I see that.

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Q Okay. So in this label, that's more or less the same conclusion that we read from the Brynne '98 paper, Exhibit 1011, set forth in the FDA-approved labeling, correct?

MS. WOOTEN: Objection, form.

THE WITNESS: It appears to follow the same line of reasoning, yes.

Q (By Mr. Trainor) Okay. And that's the conclusion that both poor and extensive metabolizers get similar antimuscarinic effects and net activity of Detrol regardless of their phenotype, right?

MS. WOOTEN: Objection, form.

THE WITNESS: Yes.

MR. TRAINOR: Okay.

Q (By Mr. Trainor) So this -- the FDA did not see a problem or a concern with this polymorphism as it related to tolterodine, correct?

A With efficacy, I agree.

Q Uh-huh. Well, net activity would encompass adverse events too, no?

A Usually when I speak about activity, I differentiate that from off-target -- the activity against the -- you know, for the desired, and then I'll talk about, you know, off-target affects or adverse

events separately. That's usually what I do. So that's usually how I interpret that versus the -- so...

Q Okay. So in terms of the polymorphism first identified in Postlind, the Brynne paper, Exhibit 1011, concludes that it's not a problem, and the approved FDA labeling, Exhibit 1009, concludes that it's not a problem, correct?

MS. WOOTEN: Objection, form.

THE WITNESS: They don't identify an issue among otherwise normal, healthy subjects who participated in the clinical trial.

Q (By Mr. Trainor) Okay. And are you aware of any other prior art that identifies an issue among otherwise normal, healthy subjects?

A Only the potential adverse events we discussed previously that were not dose-limiting.

Q That's the paper you can't remember or identify?

A And we also discussed -- which was it? I think it was the Brynne paper where they list, you know, some alterations in vision and such.

Q Okay, but my question was: Are you aware of any prior art that makes a conclusion contrary to these

conclusions about the impact of polymorphism on tolterodine that is set forth in Exhibits 1009 and 1011?

MS. WOOTEN: Objection, form.

Q (By Mr. Trainor) Anything else?

A No.

Q Okay. If you turn to the next page of the Detrol label, in the second column, there's a heading that says "Drug-Drug Interactions."

A Yes.

Q Okay. And underneath that, it says "Fluoxetine."

A Yes.

Q Okay. Now, do you understand why a study with fluoxetine was reported or required in the FDA labeling?

MS. WOOTEN: Objection, form.

THE WITNESS: I think so.

Q (By Mr. Trainor) Okay, and why is that?

A Because it's a known inhibitor of CYP2D6.

Q And what was the result?

A Would you like me to read the --

Q No, I mean, is the conclusion that even if poor metabolizers are taking CYP2D6 -- excuse me, in

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anybody who's taking CYP2D6 inhibitors, no dosage estimate is required?

A Well, they report here that it inhibits the metabolism in extensive metabolizers, and it alters the pharmacokinetics in such papers. They do say among the population studied, no dosage estimate is required.

Q Right. And when you administer a CYP2D6 inhibitor like fluoxetine to an extensive metabolizer, would you agree that you're mimicking the situation of the poor metabolizer with the drug?

A Yes.

MS. WOOTEN: Objection, form.

Q (By Mr. Trainor) Okay. So this test with fluoxetine reported in the Detrol label is further support for the fact that poor metabolizers are not at risk; would you agree?

MS. WOOTEN: Objection, form.

THE WITNESS: That doesn't change my concern that there may be a subset, you know, prone to cardiac events that could be sensitive.

Q (By Mr. Trainor) But how would the skilled artisan reading this in 1998 understand the conclusion in the Detrol label?

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A That, you know, such an event hadn't yet been reported. I think, you know, these types of things would be in the forefront of a skilled artisan's mind at that time because some of these have been described --

Q How big would the patient population --

A -- in other drugs. Sorry.

Q I'm sorry, I didn't mean to interrupt you.

A I'm sorry, I interrupted you. Go ahead.

Q How big would the patient population need to be in a study, like this fluoxetine study, to give you comfort that no incidents had been reported?

MS. WOOTEN: Objection, form.

THE WITNESS: Well, to be confident that no incidents had been reported, I would just have to say they -- you would just have to see they didn't report the incidents. Not being a statistician, in order to answer that, I would have to consult with a statistician.

MR. TRAINOR: I see.

Q (By Mr. Trainor) How about a rough ballpark, I mean, would it have to be more than 50 patients, more than 100 patients?

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MS. WOOTEN: Objection, form.

THE WITNESS: Yes, I would -- honestly, since I'm concerned about a specific subset, I would like to see that --

MR. TRAINOR: Okay.

THE WITNESS: -- that specific.

Q (By Mr. Trainor) So -- and just to wrap this up, although I understand that you have concerns, you're not aware of any prior art that contradicts the conclusions in the Detrol label and the Brynne Exhibit 1011 that polymorphism does not adversely impact patients administered tolterodine?

A Right, the events -- right, the events reported weren't such that caused a halt in further development.

Q Okay, but in view of these conclusions, with respect to the role of the differing metabolic capacities, it is nonetheless your opinion that one of skill in the art would recognize that tolterodine had a problem, requiring improvement?

MS. WOOTEN: Objection, form.

THE WITNESS: I would recognize that some of the concerns could be addressed and you should have a Plan B.

Q (By Mr. Trainor) And in terms of looking at the prior art, the person of skill, recognizing the need for improvement, would recognize that from this publication concerning cardiac events in poor metabolizers; is that right?

MS. WOOTEN: Objection, form.

THE WITNESS: That would be something that would highlight the concern, I believe.

MR. TRAINOR: Okay.

Q (By Mr. Trainor) Is there anything else that would highlight the concern or the need to improve in the prior art?

A I think, again, some of the events reported with the NSAIDs, that such things happen among, you know, subsets of the population, would just make me cautious.

Q Okay, but that prior art about NSAIDs is not specific to tolterodine, correct?

A It is not.

Q Okay. So that wouldn't draw the skilled artisan's attention to a problem with respect to tolterodine any more than it would any other drug that's got complex metabolism, right?

A I think so.

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MS. WOOTEN: Objection, form.

Q (By Mr. Trainor) You think I'm correct?

A I think you're correct.

Q Okay.

MR. TRAINOR: You want to break for lunch now?

(Discussion off the record and lunch recess taken.)

Q (By Mr. Trainor) So, Dr. Patterson, welcome back.

A Thank you.

Q I actually just have a couple of last questions before we move to chemistry.

On the Detrol label, Exhibit 1009, just very quickly, if you turn to the second-to-last page, which is page 6 of the exhibit --

A Okay.

Q -- and I'm focusing on the chart here that takes up the bottom two-thirds of the page, this is a report in the label of reported adverse events in the Phase 3 clinical studies. Do you see that?

A Yes.

Q Okay. My only question is: For each of these events, whether they rise to the level of adverse

or not, you would agree that there's no way to distinguish the agent as between 5-HMT and tolterodine that may be responsible for any one of these symptoms or events listed here, correct?

A The way this study is conducted, I don't think you would discern between the -- you know, the parent drug and its metabolites.

Q Okay. And other than that small dataset that we looked at in the Brynne 1998 paper, are you aware of any report in the prior art that distinguishes as between 5-HMT and tolterodine as the source of a particular pharmacokinetic effect?

MS. WOOTEN: Objection, form.

THE WITNESS: So pharmacokinetic effect, I think of that as ADME, and those are, in fact, you know, the --

MR. TRAINOR: Oh, fair enough, fair enough. Let me rephrase the question.

Q (By Mr. Trainor) Other than the Brynne 1998 paper, Exhibit 1011, are you aware of any report in the prior art that parses between 5-HMT and tolterodine as the source of a particular pharmacodynamic effect?

MS. WOOTEN: Objection, form.

THE WITNESS: Source of -- still -- I'm

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not sure -- just to make sure we're on the same page, right, so ask the question again, because I'm --

MR. TRAINOR: Sure.

THE WITNESS: Yeah, right.

Q (By Mr. Trainor) I just asked you about the label.

A Right, right, right, the label.

Q You said you couldn't contribute these adverse events that are reported to being a function of 5-HMT or tolterodine, one way or the other.

A Right.

Q Then I asked you about Brynne, Exhibit 1011, which does that to a limited extent. As you said, it's a very small dataset. So my question is simply: Other than that Brynne paper, are you aware of any reporting in the prior art that similarly parses between 5-HMT and tolterodine for a given effect?

A Besides the ones we've already discussed, no.

Q Okay. And when you say "already discussed," this is the cardiac reference that you can't remember?

A I wish I could --

Q Okay.

A Yeah.

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Q Okay. You can put the label aside.

And then in the prior art as of 1998, would you agree that there were a number of examples of compounds with multiple actives that were subject to CYP2D6 polymorphism that were determined to be safe and effective?

MS. WOOTEN: Objection, form.

THE WITNESS: I think there were -- well, there were known drugs that are metabolized by that pathway, and some examples are listed in the --

MR. TRAINOR: Okay.

Q (By Mr. Trainor) Oxybutynin would be one, right? We looked at that earlier.

A (Witness nods head affirmatively.)

Q I think you have to say yes for the --

A Yes. Oh, I'm sorry.

Q How about the drug encainide, have you ever heard of that?

A Encainide, can you spell that for me?

Q I think it's E-N-C-A-I-N-I-D-E.

A I don't recall very much about that drug.

Q Okay. Propafenone?

A Propafenone? Not propiophenone, right?

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That's not a drug.

Q Okay. And in your view, did the prior art teach generally that in the situation where you have a drug with multiple active ingredients mediated by CYP2D6, that an assessment should be made as to whether to further develop or modify?

MS. WOOTEN: Objection, form.

THE WITNESS: Okay, so just to make sure I answer the right question, can you give it to me one more time?

MR. TRAINOR: Yeah.

Q (By Mr. Trainor) I mean, would you agree that in the prior art, it was taught that in the instances like tolterodine, where you have multiple actives and multiple metabolic pathways, including being mediated by CYP2D6, that an assessment should be made before terminating the development of that drug or electing to modify it?

MS. WOOTEN: Objection, form.

THE WITNESS: My assessment of the art is that at every step in development, you should be prepared to -- right, prepared for a no-go or a Plan B at every step. And so seeing variable, you know, mechanism would

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be -- maybe put me on a slightly higher alert.

MR. TRAINOR: Okay. Fair enough.

Q (By Mr. Trainor) And one other thing that you mentioned this morning or the first half of the day was I thought you mentioned a therapeutic index.

A Yes.

Q Okay. What is a therapeutic index?

A A therapeutic index is a ratio of the desired effect to the -- usually a toxic effect.

Q Uh-huh.

A Right?

Q Okay.

A Usually referred to in a cell culture assessment. Sometimes we broaden that, you know, to an animal study or human study, in which case we often say -- you know, call a safety index.

Q Okay. In your review of the prior art, did you discern any teaching or suggestion about the therapeutic index of tolterodine -- Detrol, tolterodine?

MS. WOOTEN: Objection, form.

THE WITNESS: I do not recall seeing a cytotoxicity assessment.

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Q (By Mr. Trainor) Okay. And putting aside whether you saw anything in the art, how -- what would you -- how would you define -- this is an inartful question. I don't want to know what the therapeutic index is, but if you were to say the therapeutic index of tolterodine is a ratio of what?

MS. WOOTEN: Objection, form.

THE WITNESS: I can't answer that because I don't --

MR. TRAINOR: Okay.

Q (By Mr. Trainor) I take it from your answer -- well, I take it from your answer that depending upon the effect you're defining as toxic, there could be a number of therapeutic indexes for any drug, right?

MS. WOOTEN: Objection, form.

THE WITNESS: There are a number of alternatives to assign a safety index or therapeutic index.

MR. TRAINOR: All right.

Q (By Mr. Trainor) I guess what I'm asking is: Does toxic always mean toxic in the conventional sense of the word, or can toxic be just an unpleasant adverse event in the context of therapeutic index?

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A I would -- you know, if -- people may say that in the terms of an -- but I would say it's more properly addressed as something that we would all recognize as, you know, toxicity --

Q I got you.

A -- in cell culture, cell death.

Q Okay. Okay, so I want to move to the next phase of your declaration, I guess, for lack of a better description, which is now we're going to assume that you've identified tolterodine and wish to isolate 5-HMT. First question is: Would you agree that there were a number of other design alternatives -- strike that.

Would you agree that there were design alternatives for trying to accomplish the isolation of 5-HMT other than prodrug?

MS. WOOTEN: Objection, form.

THE WITNESS: Well, prodrug wouldn't be isolation of 5-HMT.

MR. TRAINOR: Okay.

Q (By Mr. Trainor) How so?

A Well, isolation means you have a pure sample of your target molecule.

Q Oh, okay. I guess what I meant was we talked