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component as well, in my opinion.

Q. Mm-hmm.

A. Nor did I state that these -- that this would be the only factor.

Q. No. I understand.

A. That would be a consideration. And, in fact, in my experience, it's always a consideration, and it should be a consideration with respect to any drug that has significant, enough CNS exposure to have any nervous system-related effect.

Q. How does an agent -- how does a central nervous system become exposed to an agent?

A. There are three general ways. Basically, though, the physiology is by crossing the blood-brain barrier.

Q. Okay.

A. It is a membrane system that delimits the central nervous system; specifically, the brain --

Q. Mm-hmm.

A. -- from the blood circulation. There are active transporters, both -- that can alter this transit across the membrane.

Q. Mm-hmm.

A. And there are also situations where the physiochemical property of the compound, small molecule, will be favorable for its partitioning into that membrane system and then partitioning potentially out of it into the nervous system compartment.

Q. Okay. Now, you would agree with me that tolterodine, in the vast majority of patients, metabolizes into the active 5-HMT. Correct?

MS. WOOTEN: Objection. Form.

A. In the vast majority of patients, yes.

Q. Okay. So isn't it fair to say that the reports of adverse events with respect to the central nervous system are a function of 5-HMT crossing into the central nervous system?

A. Based upon these data, no.

Q. No?

A. The 5-HMT would have to be tested independently, under the same conditions, at the same dosing regimen, with the same vehicle, independently of tolterodine, to make some sort of conclusion, comparative conclusion in that

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regard, in my opinion.

In other words, tolterodine, alone, would have to be profiled.

Q. Okay.

A. I'm sorry. 5-HMT would have to be profiled.

Q. But a person of ordinary skill in the art, in 1998, would have understood the probability of any of these effects to be attributable to 5-HMT in the majority of patients? No?

MS. WOOTEN: Objection. Form.

A. I could not say in the majority of patients.

Q. Okay. If -- so your testimony is that a person of ordinary skill in the art, familiar with tolterodine and its pharmacology and its metabolism, in 1998, did not understand that in the majority of patients, 5-HMT was the active agent? Is that right?

MS. WOOTEN: Objection. Form. Mischaracterizes testimony.

A. No. That's not correct.

Q. That's not right?

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A. No. The understanding, in my opinion, would have been that the parent compound, tolterodine, is metabolized into 5-HMT, and the antimuscarinic effect of the parent, Detrol, tolterodine, is a consequence of both of these agents as active drugs.

Q. Mm-hmm. And what is the percentage of the population that are extensive metabolizers?

A. I don't remember, offhand.

Q. Does 93 percent ring a bell?

A. They may be extensive metabolizers.

Q. Mm-hmm. Yes.

A. That simply means they have the capacity to do so.

Q. Okay. Isn't it well reported in the prior art that in extensive metabolizers, the active agent is 5-HMT?

A. But tolterodine also has activity as well.

Q. Correct. But -- so you're saying that one of ordinary skill in the art would not assume that in the majority of those patients, whatever might be crossing into the central nervous system is tolterodine?

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A. In terms of mesh action, yes. But in terms of having -- initiating or effecting a side effect or an event profile, we don't know.

Q. Okay. Okay. And with respect to dry mouth, are you aware of any evidence which suggests that the activity leading to dry mouth is attributable to 5-HMT or tolterodine?

MS. WOOTEN: Objection. Form.

A. I don't believe 5-HMT, itself, has been tested in humans to that endpoint -- with that clinical endpoint. I am aware of the cat study I alluded to earlier in vivo by Nilvebrant, et al --

Q. Mm-hmm.

A. -- that did look at, did compare 5-HMT and tolterodine in terms of effect on salivation --

Q. Mm-hmm.

A. -- and found that tolterodine had more of an effect than did 5-HMT in terms of affecting salivation, saliva production in the cat model in vivo.

Q. Okay. Did you not review the human data --

A. Mm-hmm.

Q. -- in the Brynne paper?

A. I have. I may not remember it. But if you have the paper, I'll be glad to do it now.

Q. We'll get to that. Let me just stick with the CNS --

A. Sure.

Q. -- concern for a moment.

If it's the case that you didn't know whether it's 5-HMT or tolterodine which may be causing any CNS effects --

A. Mm-hmm.

Q. -- then why would you be so readily -- motivated to isolate 5-HMT at the time?

A. To isolate 5-HMT?

Q. That's what you're trying to do. Right? They're both active. You're trying to segregate 5-HMT to deliver it only by a prodrug. Correct? That's the theory?

A. That would be true. Yes.

Q. Right.

A. That would be, yes. Yes.

Q. So how can I be motivated to improve upon the CNS profile of tolterodine if I'm not

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sure whether it's tolterodine or 5-HMT that's causing the CNS effects?

MS. WOOTEN: Objection. Form.

A. That may not be the sole factor in terms of the motivation. As I alluded to earlier, there could have been many other factors, many other factors. And one may, indeed, show that by a prodrug, there may be a different pharmacokinetic, pharmacodynamic profile that might benefit a number of these aspects.

Q. Okay.

A. The data would tell.

Q. Okay.

A. But, a priori, I could not forecast that.

Q. Okay. This is what I'm trying to do, is understand the basis for your opinion.

A. Mm-hmm.

Q. And we've got to the point where you say the skilled artisan would have been motivated to improve upon tolterodine in 1998 or 1999, and I'm trying to understand what about tolterodine needed to be improved.

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I believe that you said the CNS profile, the dry mouth issue and the polymorphism issue?

A. Right.

Q. If there are other factors, I'd like to know what they are. But if there aren't, then I want to take these one by one --

A. Sure.

Q. -- and ask you, you know, what the basis would be for each of them respectively.

A. To me, the polymor- -- the polypharmacology issue generating two active agents from one would be, to me, a prime motive --

Q. Okay.

A. -- of the three listed.

Q. But you would agree with me that, just sticking with the CNS factor --

A. Mm-hmm.

Q. -- if, as you say, you can't be sure which agent is responsible for the CNS effects, then you, therefore, wouldn't be sure whether that is something that needed to be improved upon with tolterodine. Correct?

A. Unless directly --

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MS. WOOTEN: Objection to form.

A. Unless directly tested. I agree. The only way to answer that question would be, as I mentioned earlier, a direct test of the various agents.

Q. Okay. But you're not aware of any direct testing that was done or available at the time in 1998. Correct?

A. In humans, I'm not aware of any.

Q. Okay.

MR. TRAINOR: Why don't we take a break. Let's go off.

THE VIDEOGRAPHER: The time now is 12:27, and we're off the record.

(Lunch recess was taken.)

THE VIDEOGRAPHER: The time now is 13:17. We're back on the record.

BY MR. TRAINOR:

Q. Sorry. Okay, Dr. Janero, welcome back.

A. Thank you. Pardon me.

Q. So we were talking before about the areas for improvement of tolterodine that you identified. Just to set the context, we had the CNS concerns, the dry mouth concern, the

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polymorphism concerns and patent concerns?

A. Mm-hmm.

Q. We just talked about the CNS. I want to turn to the dry mouth issue.

A. Actually, I do want to finish one point about that, if I may.

Q. About which?

A. The nervous system related.

Q. That's the central nervous system. Okay.

A. Well, it could be in general, because the autonomic nervous system also has a component of control of, neuro control of salivary secretions, so that affects dry mouth. So I'm going to --

Q. Okay.

A. -- put them together for the sake of time and for the sake of discussion. The basic -- the question, I believe, that was posed is basically why -- why, in essence, would one find 5-HMT attractive in terms of improving some of these profiles. Is that correct?

Q. Right now, I'm just sticking to the part about why one of ordinary skill would have

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recognized a need to improve tolterodine.

A. Okay. Then we'll save that.

Q. Okay.

A. Thank you. Sorry.

Q. So turning to improving the dry mouth profile --

A. Mm-hmm. Mm-hmm.

Q. -- of tolterodine, the improvement in dry mouth was really sort of the breakthrough with tolterodine, to begin with, at its launch. Right? Would you agree with that?

A. It still had that as a side effect that is considered to be a common effect for antimuscarinic agents because of the population of receptors in the oral mucosa that are there. So it had a -- I'd have to look at the numbers to refresh my memory, but certainly it was a shared side effect in this class.

The extent to which it was expressed versus others in the class, that, I don't remember.

Q. Okay. And you're aware that it's just a matter of a couple of months, right, between the time that tolterodine or Detrol was approved and the first priority date of these patents in

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1998, right, roughly?

A. Roughly. Yes.

MS. WOOTEN: Objection. Calls for a legal conclusion.

A. But I --

Q. Okay. So this is Exhibit 11, the label.

A. Yes, I have that.

Q. Okay. Now, under the autonomic nervous system as you're just --

A. Yes.

Q. -- referring to, that's where they list dry mouth as --

A. Yes.

Q. -- an adverse event. And I think, as you pointed out, in the text of this label there are also some textual comments about dry mouth being the frequently reported adverse event.

My question is similar to the CNS-related question, is isn't it also true that based upon what was available at the time, in 1998, including this label, it was not known which chemical entity 5-HMT, on the one hand, or tolterodine, on the other hand, was responsible

for the dry mouth side effect. Correct?

A. I believe so, because to my knowledge, 5-HMT was itself not directly studied in this paradigm, in the clinic.

Q. Okay. So this is just the report of you administer tolterodine, and most of the population is extensive metabolizers, there's some poor metabolizers, but the events don't discriminate between tolterodine and 5-HMT?

A. I couldn't say that from this, from this table.

Q. From the label. Right?

A. From the label. Right.

Q. Okay. So irrespective of the label, are you aware of any evidence or information that was available to a skilled artisan at that time that would have allowed them to recognize which of the two active entities was responsible for the dry mouth side effect?

A. There was the -- there is the preclinical study that was published by Nilvebrant, et al, in vivo in the cat.

Q. Mm-hmm.

A. Which was shown -- which I believe

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showed that both agents, both tolterodine, Detrol, and 5-HMT, did affect salivation in that model.

Q. Mm-hmm.

A. But the differential between the potencies at which relaxation was affected in the bladder and salivation was affected was less differential for tolterodine versus 5-HMT, despite the fact that 5-HMT was around, as I recall, around sevenfold more potent, a smooth muscle relaxant, an antimuscarinic smooth muscle relaxant.

Q. Mm-hmm. So relevant to my question, what is the implication? Do you believe a person of ordinary skill would have understood tolterodine to be more responsible for dry mouth as distinguished from 5-HMT?

A. I think from those data, the person of ordinary skill in the art, at that time, would have concluded that 5-HMT could have less propensity to induce dry mouth.

Q. Okay. And so, therefore, that would support your opinion that tolterodine's dry mouth profile could be improved upon by isolating

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5-HMT. Is that right?

MS. WOOTEN: Objection. Form.

A. That would be -- that could be one possible route, but not the only possible route.

Q. I understand. But --

A. Right.

Q. -- just on this issue of dry mouth.

A. Right.

Q. Okay. By the way, can we have that Nilvebrant paper? I think -- I hope I have the one that you're referring to, because I don't want you to be operating in a vacuum here.

There was a Nilvebrant paper, Exhibit 8, I showed you before. You said that was not the one --

A. I have it here. I have it here.

Q. -- that you had in mind and that you referenced here. So let me show you this.

MR. TRAINOR: This will be number 12, I believe.

(Document Bates-stamped MYLB_FESO_00027129 through -7132 marked Exhibit 12.)

A. This is the paper to which I was

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referring. Yes.

Q. Okay. Let me just introduce it for the record.

A. Oh.

Q. I asked the court reporter to mark as Janero Exhibit 11 a publication entitled "Antimuscarinic Potency and Bladder Selectivity of PNU-200577, A Major Metabolite of Tolterodine." The lead author is Nilvebrant, copyright date 1997. It bears Mylan Bates numbers 27129 through 32.

And I'm sorry, Dr. Janero, you were saying that this is the paper you had in mind?

A. Yes, it is the paper. Yes.

Q. If you look at Paragraph 14 of your opening report, Exhibit 1, would you just confirm this is the Nilvebrant paper that's referenced there?

A. From pharmacology and toxicology, yes. Pharmacol, toxicol.

Q. Okay. Now, it's a short paper, but -- you can take a minute to review it, but I want to ask you: Where in this paper is there a disclosure that you're referring to with respect

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to -- let's start with the potency issue?

A. I was referring specifically to the in vivo study in the cat model.

Q. Okay.

A. And that's on Page 171, left column, about a third down under the heading "In Vivo Studies."

Q. Okay.

A. The second sentence gives the mean ID50. That means mean inhibitory dose, 50 percent inhibition for acetyl, for PNU, of 15 nanomole per kilogram. And that's for acetylcholine-induced urinary bladder contraction.

(Reporter clarification.)

A. For acetylcholine-induced urinary bladder contraction.

So that's one piece of data.

Q. Okay. Okay. For the record, can we note PNU 200577 is 5-HMT. Correct?

A. Yes. Yes. That is correct.

Q. Okay.

A. I'll refer to it subsequently as 5-HMT. Sorry.

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Q. Now, what does that tell us about the relative potencies of 5-HMT in tolterodine?

A. Now, if we retain that figure --

Q. Right.

A. -- and we proceed on to the -- in the article --

Q. Yup.

A. -- and we go to Page 172, left column, first paragraph --

Q. Mm-hmm.

A. -- third line in that, "Although 5-HMT is more potent than the parent compound in vivo, ID50 values for tolterodine were 101 nanomole per kilogram respectively for inhibition of urinary bladder contraction and salivation."

Q. Mm-hmm.

A. "A likely explanation for the higher potency of 5-HMT in vivo is that available percentage of tolterodine is unbound in serum, whereas over 30 percent of 5-HMT exists as the unbound drug."

So I compare the 101 nanomole per kilogram ID50 for tolterodine with the stated, on the previous page, 15 nanomole per kilogram, as mean

ID50 for 5-HMT to conclude that 5-HMT is about sevenfold more potent than tolterodine in this model, as an antimuscarinic bladder-relaxing agent in response to acetylcholine-induced bladder contraction."

Q. Okay. But at the conclusion of that paragraph that you were just reading from on 172 --

A. Uh-huh.

Q. -- the next sentence discusses the likely explanation for the higher potency in vivo --

A. Yes.

Q. -- is the very low percentage of tolterodine in unbound serum relative to the percentage of 5-HMT that is unbound. Correct?

A. Yes.

Q. Okay. Doesn't that mean that pound-for-pound, if you will, the potency is the same?

A. We can't -- we can't equil- -- we can't make equivalent the bound component of either drug to the free, because only the free will be a ligand, will be able to bind to muscarinic

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receptor.

Q. Mm-hmm.

A. That portion that is sequestered in any plasma protein, plasma lipoprotein will not be able to bind as that complex. It must be freed.

Q. Right.

A. So they're not -- so we can't say pound-per-pound, because they're in different states in terms of drug ability.

Q. Mm-hmm.

A. So in terms of the less than 5 percent versus greater than 30 percent of 5-HMT that's available as an active agent in vivo --

Q. Right.

A. -- they're different.

Q. Well, the free is what is unbound in serum. Correct?

A. And that, in the case of 5-HMT, is greater than 30 percent. In the case of tolterodine, it is less than 5 percent.

Q. Right. And is it just a coincidence that that's also a factor of six or seven?

A. It may be. I don't have all of those -- those data --

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Q. Mm-hmm.

A. -- to look and see what the absolute kinetics would be --

Q. Mm-hmm.

A. -- and what the distribution of those kinetics would be, what the distribution of both compounds would be over time.

The important point here, I think, is that both compounds were looked at. 5-HMT, in particular, was examined separately.

Q. Now --

THE WITNESS: Excuse me.

Q. -- does it surprise you that given the same dose to the same subject, in this case, in animal, that the value of potency that is measured is greater for the entity which has a higher free percentage by a factor of six or seven?

MS. WOOTEN: Objection. Form.

A. Those two factors would correlate, but the higher free need not translate into greater efficacy --

Q. Mm-hmm.

A. -- or higher potency.

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Q. But you would agree that, at least according to this author, that's the likely explanation for the difference in potency in vivo. Correct?

MS. WOOTEN: Objection. Form.

A. Actually, I refer to the sentence that follows that --

Q. Mm-hmm.

A. -- that begins "since," and after the comment, "the response observed in vivo following oral administration of tolterodine is likely to be, in part, the result of the activity of unbound 5-HMT."

So it would be difficult, in the case of tolterodine, where we have the polypharmacology, we have two active agents going on, to parse out quantitatively the way you're suggesting. It would be difficult for me, at least, to do that quantitatively.

Q. Okay.

A. Because we have the same effect; in other words, relaxation of acetylcholine-induced bladder contraction. In one case, we're looking at 5-HMT. In another case, we're looking at some

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dynamic combination of bound-unbound tolterodine and bound-unbound 5-HMT, either one of which has different proportions of bound and unbound.

Q. Okay. Now, if you assume that all things being equal, the two agents are equipotent, then that would explain the difference in the potency measure, that being the difference in percentage bound. Correct?

MS. WOOTEN: Objection. Form.

A. I don't believe that's an explanation, because there are other factors involved, one of which that's not -- that's not dealt with in this paper, in the discussion, is the idea that the bound portion is not -- is dynamic.

Q. Mm-hmm.

A. It can enter and exit plasma proteins, plasma lipoproteins. So although it is true that the muscarinic receptor, muscarinic receptors cannot bind drug that's bound to plasma protein or plasma lipoprotein, that doesn't mean that it's permanently bound there.

There are on and off, so-called "on and off rates" associated with this -- with this -- with these complexes.

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Q. Okay.

A. And this happens to be one of the -- one of the areas I studied in my -- my postdoc at Hopkins.

Q. Okay. Now, in that next paragraph, the first sentence indicates that, in vitro, the potency -- the potencies of 5-HMT and tolterodine are identical. Correct?

A. I don't read that statement. I read the statement to say "that the pharmacological profile in vitro."

Q. Mm-hmm.

A. The pharmacological profile goes much beyond, but may include potency and efficacy.

Q. Okay. If you look at the next paragraph, at the bottom of the column, the sentence says, "In summary, the pharmacological in vitro and in vivo profiles of 5-HMT are identical to those of tolterodine, the parent compound."

Do you see that?

A. Yes. That is almost identical to those. Yes. I see that.

Q. Okay. So do you have any understanding

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why the author would conclude that the pharmacological profiles are identical?

MS. WOOTEN: Objection. Form.

A. I believe the next sentence gives a clue, because both compounds have high antimuscarinic potency. They both have protein bound, but one has a different degree of protein, of plasma protein, lipoprotein binding. And they have good serum concentrations in humans after oral administration.

The conclusion is that, as stated here by the authors, that 5-HMT may contribute to the therapeutic action of tolterodine. So, in other words, both the 5-HMT and tolterodine are acting to effect the muscarinic relaxation in response to acetylcholine contraction in the bladder.

That's how I would interpret that.

Q. Can you look at the abstract on the first page.

A. Yes.

Q. The second to last sentence in the abstract.

A. Yes. I see.

Q. It says, "Thus, 5-HMT is similar to

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tolterodine in terms of antimuscarinic potency." Do you see that?

A. Yes, I do.

Q. As a reader, how would you reconcile that with your conclusion that the data suggests 5-HMT is more potent?

MS. WOOTEN: Objection. Form.

A. The data --

Q. Tolterodine -- sorry.

A. Yes. The data I'm referring to are in the in vivo study. They're not referring to the radioligand binding studies or the in vitro studies, where it could be a similar -- there could be a similar potency or similar profile there.

In other words, in the in vitro testing, biochemical testing, differences or similarities need not quantitatively transfer into the intact animal.

And that's why I would put myself, in terms of drug discovery and development, in terms of pharmacology, more weight on the difference in vivo than I would in a binding study, because both of these, we know both of these compounds

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are, indeed, muscarinic receptor agents with good ligand binding properties.

Q. Are you aware of any evidence, other than this cat data, which speaks to the relevant -- relative potencies of 5-HMT and tolterodine that was available in 1998?

A. I have not looked at that point extensively. My impression, generally, has been that 5-HMT itself has rarely been tested.

Q. Mm-hmm. Now, can you just -- my question is: As to the relative potencies of the two entities, are you aware of anything else, as you sit here, other than this cat data, which speaks to the relative potencies?

MS. WOOTEN: Objection. Form.

A. Let me just say in terms of this particular data set or in terms of any other?

Q. Anywhere. I mean, I see what you're saying here. I see this paper.

A. Yes.

Q. I just want to know if -- are you aware of anything else that you read or reviewed that suggests that 5-HMT is more potent than tolterodine?

A. In vivo?

Q. In vivo, in vitro. Anything?

A. As I say, my focus was on in vivo in studying this, and in vivo, I, at this moment, don't -- cannot cite any other references --

Q. Okay.

A. -- than this.

Q. In your opening report, Page 17, Paragraph 55 --

A. Yes.

Q. -- in that paragraph, you're providing a couple of different reasons as to why, in your view, a person of ordinary skill in the art would have been motivated to improve upon 5-HMT.

I'm not sure if you meant tolterodine there, but the second reason that you provided, it says, "It was known that 5-HMT's affinity for the M3 receptor was comparable to tolterodine."

A. Mm-hmm.

Q. Do you see that?

A. Yes, I do.

Q. Okay. So if you thought -- if your view of the prior art was that 5-HMT was more potent, why would you suggest that they were

comparable in your report there, at Paragraph 55?

A. The data, in terms of the biochemical parameters, in terms of competition binding to the receptor, shows that within, in my opinion, statistical error, they are comparable.

They are both high-affinity ligands for the muscarinic type, Subtype 3 receptor.

Q. Okay.

A. And that -- pardon me, I'll just conclude by connecting my point earlier, as I say, but the -- that in vitro affinity in an isolated biochemical, not a living system, need not quantitatively translate to a complex mammal in vivo, such as a human or experimental animal.

Q. A skilled artisan in drug development setting out to dedicate resources into developing a new drug in 1998, in your view, how much weight would they put on that cat data, in the absence of other data speaking to the potency of 5-HMT?

MS. WOOTEN: Objection. Form.

A. As an outsider who was not at -- in the development or discovery stream in the company, I do not know that there were no -- I would not know there would be no other data. But I'll take

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it as an assumption that I would not know.

My experience as a drug discovery and development person has taught me over many decades that internal data need not appear in publications, in print, in any form.

Q. Right.

A. So, given that, and given the fact that -- and we'll set that aside -- the fact that these data in this particular paper, in this particular model, address the very -- the fundamental basis for bladder contraction; namely, acetylcholine-induced smooth muscle relaxation via an antimuscarinic mechanism, I believe that these data would hold significant credence in terms of a drug discovery campaign.

Q. Okay. My question was simply: If you were going to develop a new drug and the idea was that to target an entity because it had shown better potency than what existed at the time, would you really undertake that endeavor on the basis of a study in cats?

MS. WOOTEN: Objection. Form.

A. I would need to know the whole context in order to answer your question.

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Q. Okay.

A. Specifically, I would need to know any other data.

On the other hand, I realize again from my experience in drug discovery and development, that we're operating here at a more sophisticated level of in vivo animal than is usually done in pre-clinical; namely, mouse, rat, rodent.

Q. Mm-hmm. You do know that, in terms of invalidating the patent, that it's not really the perspective of these inventors or this company. It's what this hypothetical ordinary person would do with the information that's available. Correct?

A. Yes. I'm simply taking those data, for example --

Q. Okay.

A. -- at face value.

Q. All right. Let's move on to the polymorphism issue. Where in the art or what evidence do you have to support the fact that -- or the supposition that the polymorphism exhibited by those given tolterodine was, in fact, a problem or something that needed to be

improved upon?

MS. WOOTEN: Objection. Form.

A. I suggest that we want to clarify. I was talking about polypharmacology. I was not equating that with polymorphism. We can discuss polymorphism, but my point was different.

My point was the idea that when a mammal, man, administered tolterodine two active agents result. That is what I was calling polypharmacology.

Q. Mm-hmm.

A. The polymorphism is the genetic variance in metabolizing enzymes, so we're talking about the latter.

Q. Okay.

A. Are we? I just want to be sure.

Q. Well, let's just -- let's just step back and say the fact -- we agree that there are two active agents with tolterodine. Correct?

A. We agree. Yes.

Q. That's a little unique. Correct?

A. I haven't done a complete survey of all known drugs in the pharmacopeia, so I would not know how unique it is.

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Q. Are you familiar with any other drugs that exhibit that type of double agent activity?

MS. WOOTEN: Objection. Form.

A. I have certainly encountered drugs that have active metabolite.

Q. Mm-hmm. And the parent or the starting compound is also active?

A. Yes.

Q. Are those compounds that are commercialized?

A. They probably would be. I can't name any, but I know I've run into them in my own drug discovery and development.

Q. Okay. Maybe we should start out with this: Can you explain to me what the difference is between polypharmacology and polymorphism?

A. Yes. Polypharmacology, as I'm referring to, is the condition whereby we have multiple active agents effecting the same therapeutic result.

Q. Mm-hmm.

A. The specific example here is tolterodine and 5-HMT.

Q. Mm-hmm.

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A. Polymorphism is a genetic difference among subjects, whereby variance in enzymes can result in disparate enzyme activities that then can manifest themselves in differences in metabolism, differences in metabolic products, differences in rates of metabolism, differences in sensitivity to a compound, a drug.

Q. In essence, the person asking the question was very inartful. So I understand what you're saying.

A. I just wanted to be clear that because they are very different things, in my opinion.

Q. I understand.

A. Okay.

Q. Drugs are not polymorphic. All right. That's your point. Drugs themselves aren't polymorphic?

A. In the context that we just laid out, that is a separate concept.

Q. That's my bad. Okay. So --

A. I --

Q. -- the polypharmacology of tolterodine -- well, let's just say the poly-- in the instances where -- forget about tolterodine.

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You've got a drug that itself is active and has an active metabolite --

A. Yes.

Q. -- giving rise to polypharmacology. Correct?

A. Yes.

Q. Is that always a problem?

MS. WOOTEN: Objection. Form.

A. I haven't surveyed every instance, so I can't say always. I do know, in my own personal experience, some -- a major problem can occur as a result of the active metabolite having a toxicity profile or other profile that would be unwarranted, that could lead to adverse events in and of itself.

Q. Mm-hmm. So a person of skill, in 1998, how, if at all, would they have recognized that to be a problem with tolterodine?

A. I didn't say that it would be a problem with tolterodine. I said that would be a general instance to exemplify an answer to your question.

Q. Okay. And the prior art is clear that this was something that was recognized, correct, prior to 1998?

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MS. WOOTEN: Objection. Form.

A. "This" being?

Q. "This" being the polypharmacology of tolterodine?

A. If we define that as the ability of tolterodine to be metabolized in vivo by a common cytochrome enzyme to result -- 2D6 -- to result in an active product, 5-HMT, correct. Yes.

Q. And it was investigated by researchers, including the researchers at Pharmacia. Correct?

MS. WOOTEN: Objection. Form.

A. I have no direct knowledge of that since I was not at Pharmacia.

Q. Well, certain of the art that you cite in your report is reflective of that investigation. Correct?

A. Yes. From what I have read and from what I have gleaned from published literature, the common knowledge at that time would have been that tolterodine administered to a mammal, to a human, results in production of 5-HMT.

Both of these chemicals act as high-affinity antimuscarinic agents in vivo.

Q. Mm-hmm.

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A. Yes.

Q. So the question is: The fact that there are two active agents with tolterodine, why was it a problem?

MS. WOOTEN: Objection.

Q. That required improvement of tolterodine?

MS. WOOTEN: Objection. Form. Mischaracterizes prior testimony.

MR. TRAINOR: I'm not mischaracterizing anything.

Q. Tell me -- you said one of the reasons that you would improve upon tolterodine is because of this polypharmacology that it exhibits. And I'm asking, you know, what evidence supports that a person of ordinary skill would look at that fact and say, That's problematic, that's a reason to improve upon tolterodine?

MS. WOOTEN: Objection. Form.

A. One aspect would be the fact that metabolizing tolterodine to 5-HMT in vivo --

Q. Mm-hmm.

A. -- by two cytochromes, in particular,

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results in more extended metabolism and actually produces a metabolite that is tolterodine specific.

Q. Mm-hmm.

A. So the metabolism is more complex.

Secondly, a person in the art, at that time, would likely recognize the difference between tolterodine and 5-HMT structure; the latter, 5-HMT, being a dialcohol; tolterodine being monoalcohol.

We're talking at the 2 position, both tolterodine and 5-HMT. The 5 position is the dialcohol, 5-hydroxymethyltoluene.

This would suggest readily that 5-HMT is more hydrophilic, less lipophilic, and, therefore, less -- has less proclivity to cross the blood-brain barrier, enter the nervous system passively.

This, to me, would be an attractive feature to capitalize from 5-HMT in terms of the adverse event profile that we had -- that we had discussed earlier.

The other factor that we also discussed earlier is the idea that in the mammalian

system's per-unit dose, there's more free 5-HMT available to bind to muscarinic receptor target than there is tolterodine.

Q. Mm-hmm.

A. This would also, to me, lend an attractive feature for focus on 5-HMT in terms of potential improvements over tolterodine.

Q. Okay. Let's talk about the first issue you identified, which is that the metabolism is complex. That's true for a lot of drugs.

Why was that problematic?

A. Here we have a means to simplify that with an agent that effects the same therapeutic result as tolterodine. So we have a chance to simplify that.

Q. I understand that is the solution. Right?

A. Right.

Q. But I'm asking you, before you get to how you solve it, the question is: Why do you need to solve it? What indicated that the complex metabolism compromised tolterodine in any way?

A. I don't see that it did. But I see, in

terms of basic tenets of drug discovery and development, simpler metabolism with less intermediates is generally preferred.

Q. Okay. But you wouldn't apply general rules to embark on a drug development program, would you?

A. I would apply them if they -- if they are general rules that stood the test of time, and based on experience, yes.

Q. Well, what about -- would you apply the general rule when you had a lot of specific observation about that very issue and in-depth investigation about the metabolism? Which would you turn to, the general rule or what you knew about the pharmacology of tolterodine at that point?

A. Both.

MS. WOOTEN: Objection. Form.

A. Both, because all of these compounds, including tolterodine, are foreign -- they're xenobiotics. They're foreign agents in living systems.

And in treatment, one wants to minimize that as much as possible. They're foreign chemicals.

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Q. Mm-hmm. Okay.

A. There's no -- right.

Q. Okay. So let me just make sure that I have this correctly.

A. Sure.

Q. Is it your opinion that the fact that tolterodine has two active agents compromised the efficacy or side effect profile of tolterodine such that one of skill would have recognized it needed to be improved?

MS. WOOTEN: Objection. Form.

A. I cannot say that it -- that the presence of both metabolites compromised, because I don't have data for 5-HMT in virtually any of the studies, alone, as an agent.

Q. Mm-hmm.

A. So I don't have the comparator necessary to answer that question.

Q. Mm-hmm. And isn't it one of the fundamental principles of prodrug design that you should design a prodrug based on an entity that you do have data for, that you do fully understand? In this case, 5-HMT?

A. Some knowledge, yes.

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Q. So --

A. So --

Q. So you don't have enough information to know whether or not it's a problem, but you have enough information to solve the problem, if, in fact, it's a problem?

A. Whether what's a problem?

Q. The motivation for eliminating two active agents in tolterodine is something I believe that you said you can't speak to, because you don't have enough data about 5-HMT to know whether, in fact, the two-agent issue compromised tolterodine as an agent.

A. Mm-hmm.

Q. But when you turned to prodrugs and you look at Bundgaard, for example, and it says, the first thing you need to do when you're designing a prodrug is have as much information as you can about the entity which you're trying to convert to. Correct?

A. Mm-hmm.

Q. So I'm just trying to make sense of that. There's not enough information to know whether, in fact, it was a problem with

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tolterodine, but it is enough information to justify making a prodrug?

MS. WOOTEN: Objection. Form.

A. We know that there are two active agents that effect the clinical outcome, the therapeutic outcome when tolterodine is administered. Both agents are effective, high-efficacy antimuscarinic ligands.

Q. Mm-hmm.

A. 5-HMT, the structure of 5-HMT, would present to someone, in my opinion, skilled in the art in -- at the time, certain advantages as a starting point in terms of designing a proprietary prodrug that gave the benefits, the pharmacological profile of 5-HMT because of its decreased propensity to be sequestered by plasma proteins, lipoproteins, and its dialcohol profile, which would increase its hydrophilicity; and, therefore, decrease its propensity to cross the blood-brain barrier passively.

Q. If the polypharmacology, as you referred to it, was not determined to be problematic for tolterodine, is it your opinion that one of skill would, nonetheless, make a

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prodrug to isolate 5-HMT?

MS. WOOTEN: Objection. Form.

Q. Is that how rational drug companies work? I mean, would you really --

A. That question ignores the other factors that I mentioned, as well as the fact that the 5-HMT, being a dialcohol, would have less propensity to cross the blood-brain barrier, to enter the nervous system, and, therefore, to have less potential for side effects than tolterodine -- nervous system side effects than tolterodine.

So if we're on a drug campaign leveraging the -- your drug that you have out there on the market that's an accepted therapy for that therapeutic space, and you have an active metabolite therefrom that shows certain potential for benefit, to extend the franchise, then, yes, that would be an attractive combination of -- of circumstances and properties to go forward, in my opinion.

Q. Okay. But when you say "benefit," that assumes a baseline of something that needs improvement. Correct?

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MS. WOOTEN: Objection. Form.

A. We have the -- we have the -- we have the side effect profile of tolterodine in the prescribing information.

Q. Yes.

A. And any side effect, any adverse event could be improved upon, could be ameliorated or reduced.

Q. That may be true, but we've already established that since you didn't know whether it was 5-HMT or tolterodine that was causing those side effects, and because you don't have enough data to know whether the polypharmacology is a problem, what is the justification for doing that?

A. But we also have data in vivo, at least published data -- there may be more that I don't know -- of the greater potency, the better potency of 5-HMT as an antimuscarinic agent in the mammalian bladder that's contracted by the natural agent that is the contractile agent, acetylcholine.

Q. Okay. Why don't we just sort of maybe stick to the specific bases for invalidity that

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you have in your report.

As I understand it, and I believe the claim-by-claim analysis begins around Page 42 of Exhibit 1.

A. Okay.

Q. And if you look at Paragraph 133, just starting out with Claim 1, the combination of references that you suggest would have rendered these patent claims which cover fesoterodine obvious are Postlind and Bundgaard, in view of the Detrol label, and Berge; or, alternatively, Brynne, Bundgaard, and Johansson.

Do you see that?

A. I do.

Q. So let's start with Postlind.

MR. TRAINOR: Can I mark that, please. This will be 13.

(Document Bates-stamped MYLB_FESO_00026898 through -6902 marked Exhibit 13.)

Q. I've asked the court reporter to mark as Janero Exhibit 13 a publication entitled "Tolterodine, A New Muscarinic Receptor Antagonist, Is Metabolized By Cytochromes P450

2D6 and 3A in Human Liver Microsomes." This has a copyright date of 1998. The lead author is Postlind, Mylan Bates numbers 26898 through -902.

Now, you recognize this reference, right, Dr. Janero?

A. I do.

Q. And I think you'll agree with me that the crux of this publication in relation to your opinions is -- comes at the end of the publication, the very last paragraph. And I'll just read that -- the first sentence. "Clinical studies have demonstrated that individuals with reduced CYP2D6 mediated metabolism represent the high-risk group in the population with a propensity to develop adverse drug effects."

Do you see that?

A. I do.

Q. And further down in the paragraph, it says -- a little more than halfway through the paragraph, it says, "The possibility of clinical drug interaction at the enzyme level thus exists, especially if tolterodine is administered at the same time as a compound that is preferentially metabolized by CYP2D6 or to individuals

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associated with the CYP2D6 poor metabolizer phenotype." Do you see that?

A. I do.

Q. Isn't it the case that you cite this reference because, in your view, this suggested that the -- in certain members of the population who are CYP2D6 deficient, would not metabolize tolterodine to 5-HMT, and, thus, high levels of tolterodine may create side effects?

MS. WOOTEN: Objection. Form.

A. That was one consideration. They're higher levels, yes. But whether they're absolutely high levels to cause adverse events, that I cannot say.

Q. Why don't you just tell me in your own words --

A. Yup.

Q. -- why a person of ordinary skill in the art would read this reference and be motivated to make a prodrug for 5-HMT?

A. It show -- the reference, the data show and the reference show that tolterodine is metabolized to 5-HMT --

Q. Mm-hmm.

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A. -- by the cytochrome system that is well established to do the -- to effect these chemical transformations.

So it defines the main metabolic pathways of tolterodine in human liver microsomes. So that's -- the first point is that we have the metabolite identified.

Q. Mm-hmm. But what about this reference motivated one of skill in the art to improve upon tolterodine by making a prodrug of 5-HMT?

A. But then we can go to the fact that now we have the two chemical entities --

Q. Mm-hmm.

A. -- and we have the possibility that in a subpopulation, they could be treated differently.

Q. Mm-hmm. How so?

A. And that you identified or you read portions of the last paragraph, saying that if there are changes or deficiencies in the enzymes they're metabolizing, the parent compound, tolterodine, this could result in a differential distribution of tolterodine and its active metabolite --

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Q. Okay.

A. -- 5-HMT.

Q. So just to be clear, in terms of your proposed reasons that one of skill would want to improve upon tolterodine, this -- this reference does not speak to the dry mouth issue. Correct?

A. I haven't read it in a while, but I don't believe it does.

Q. And it doesn't speak to the --

A. I don't believe it does.

Q. It doesn't speak to the CNS concern. Correct?

A. I don't believe it can speak to any biological concern, because I don't see any in vivo or animal data in this paper at all.

Q. So this speaks to the polypharmacology concern. Correct?

A. And also the fact that the metabolite is generated by the CYP mechanism, and the mechanism by which it's generated is one that is found in humans.

Q. And it's fair to say that Postlind is setting forth this general rule that it stood the test of time, you say, that as a general matter,

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having two actives can be problematic. Yes?

MS. WOOTEN: Objection. Form.

A. He says the possibility of a clinical drug interaction at the enzyme level could exist --

Q. Mm-hmm.

A. -- what you read. So there's a possibility of that. There are no data here showing that, but it is raised in that paragraph as a possibility.

Q. All right. But this reflects that general rule. Yes?

MS. WOOTEN: Objection. Form.

A. The general rule that?

Q. The general rule that having two active agents can be problematic. Can be?

A. In this particular case, yes. It's -- it opens the possibility.

MR. TRAINOR: Okay. Now, can I see this? This one.

Q. And just while we're still on Exhibit 13, the Postlind reference, this -- your understanding is that this was published by Pharmacia, the same people who made tolterodine.

Correct?

A. Pharmacia, Upjohn. Yes. I would have to concluded that.

Q. Okay.

A. Although it does say in the reprint request "Hans Postlind, Department of Drug Metabolism, Pharmacia and Upjohn, Upsala, Sweden."

Q. Yes.

A. I would imagine that was so, based upon the contact information, alone.

Q. And in your experience over the course of drug development as things are discovered, these -- events like this would be published, not necessarily, but, you know, a group of researchers might serially publish what's going on in their development. Correct?

MS. WOOTEN: Objection. Form.

A. They would publish, in my experience, select data, not necessarily serially, with respect to the time course at which it evolved.

Q. Okay.

A. That also occurs in terms of any type of research, in my experience.

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MR. TRAINOR: Okay. Mark this one as 14.

(Document Bates-stamped PFE01847326 through -7372 marked Exhibit 14.)

THE WITNESS: Thank you.

Q. I've asked the court reporter to mark as Janero Exhibit 14 another publication, the title of which is "Role of pharmacokinetics and metabolism in drug discovery and development." It is -- the lead author is Lin, L-Y-N -- excuse me, L-I-N. Copyright date of 1997. This bears Pfizer Bates numbers -1847326 through -7372.

Now, Dr. Janero, as far I can see, this is not a publication that you cite or reference in your report. But I'll ask you: Are you familiar with this publication?

A. I believe I have seen it in the past, but you're right, I have not cited it in the report.

Q. Okay. Now, in the front page of this, there's a little table of conte- -- contents, excuse me. And you see the Roman Numeral V --

A. I do.

Q. -- at the bottom. It says,

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"Interindividual variability: A critical issue in drug development."

Do you see that?

A. I see that.

Q. So I want to turn to -- and one of -- the subheading B is "Pharmacogenetics of Drug Metabolism."

Do you see that?

A. I do.

Q. The proposition from the Postlind reference that we just looked at that concerns pharmacogenetics of drug metabolism. Correct?

A. It does.

Q. Okay. Now, if you go to that section on pharmacogenetics of drug metabolism, this is at Page 436 of the reference --

A. I have it.

Q. -- okay, and the -- if you look -- this is a discussion underneath heading B, about midway through the second paragraph, it says, "The major polymorphisms that have clinical implications are those related to the oxidation of drugs by CYP2D6 and CYP2C19."

Do you see that?

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A. I do.

Q. Okay. And is that consistent with your experience? CYP2D6 has been pretty well studied --

MS. WOOTEN: Objection. Form.

Q. -- in the art?

A. My impression is it's a very well-recognized metabolic oxidation pathway for drug elimination. Yes.

Q. Okay. And if you look at the last sentence of that same paragraph, it says, "Individuals who inherit an impaired ability to catalyze one or more of these enzymatic reactions may be at an increased risk of concentration-related adverse events and toxicity."

Do you see that?

A. I do.

Q. Is that more or less consistent with the statement from Postlind that we just looked at?

MS. WOOTEN: Objection. Form.

A. That would depend upon the specific drug.

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Q. Okay. Okay. And then it's -- then there's a subheading one, "Polymorphism and Drug Oxidation."

A. I see that.

Q. In fact, the first sentence says, "CYP2D6 polymorphism is perhaps the most studied genetic polymorphism in drug metabolism."

Do you see that?

A. I do.

Q. Do you agree with that?

A. I have no direct databases to -- to support it or disagree with that.

Q. Okay. Now, that paragraph ends, "To date, more than 50 drugs, including antidepressants, antipsychotics, and cardiovascular drugs, are known to be catalyzed primarily by CYP2D6."

Do you see that?

A. I do.

Q. Does that sound reasonable to you?

A. I have no reason to doubt that. In fact, my experience in cardiovascular and in central nervous system-acting drugs would tend to support that as well as a very common oxidative

pathway.

Q. Okay. And, again, in the next paragraph, there's a mention that those who are poor metabolizers (PMs) of the CYP2D6-mediated drugs have a propensity to develop adverse effects, or there's a high risk.

Do you see that?

A. I do. I see that sentence.

Q. Now, then there's a discussion about some practical experiences with the drug going on to the next page, and it says -- on the second full paragraph, it begins, "The effects of CYP2D6 polymorphism on pharmacological responses can be quite complex, depending on whether the parent drug or metabolite or both are pharmacologically active."

Do you see that?

A. I do.

Q. Okay. And then there's a discussion on Encanide. Do you see that?

A. I do.

Q. And as you move further down, there's another discussion of a different drug, propafenone, and it's 5-hydroxy propafenone.

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Do you see that?

A. I do. It's the middle of the paragraph, yes.

Q. And this reference indicates that propafenone and its metabolite are similar to tolterodine -- is similar to tolterodine, a drug where both the parent and the metabolite are active. Yes?

MS. WOOTEN: Objection. Form.

A. In that general term, yes. But I don't know the activity. They're not -- they're not muscarinic agents, as far as I know. So they may have pharmacological activity.

That's the extent of similarity that I would see.

Q. Mm-hmm. And moving back up in that first case of Encanide, the conclusion is that, in both PMs and EMs, that drug produces similar therapeutic responses. Correct?

A. That is so stated. Yes. That's stated.

Q. And then moving back down to this propafenone example, it says -- I think in that second to last sentence -- the same conclusion.

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Differences between extensive and poor metabolizers, there's no significant difference?

MS. WOOTEN: Objection. Form.

A. In terms of propafenone --

Q. Mm-hmm.

A. -- and its metabolite.

Q. So these represent two examples of precedent for a drug, which is both active and having an active metabolite, also being mediated by CYP2D6, where in the end, and after investigation, there was -- it was not problematic that you had this polypharmacology. Correct?

MS. WOOTEN: Objection. Form.

A. I don't know to what extent the differential activities of the metabolite in the original compound in either case here parallels quantitatively the situation with respect to tolterodine and 5-HMT.

Certainly, these are different agents, without question. They're not muscarinic agents whatsoever. They have different therapeutic profiles.

They have different targets, different

therapeutic results, different pharmacologies. So without all of those details, I couldn't draw a parallel among these three, other than the simple statement that all three compounds we're discussing are good CYP -- appear to be facile CYP2D6 substrates and that CYP2D6 converts them to at least one active metabolite.

Q. Okay. If you turn to the next page on 438, just before this section closes, the second full paragraph, it -- I'll read it. It says, "In view of the examples presented above, it is clear that genetic polymorphism in drug metabolism could lead to clinically significant differences in pharmacokinetics and pharmacological responses of some patients and, therefore, might result in adverse effects or therapeutic failure."

Do you see that?

A. I do.

Q. Again, that's more or less in line with the Postlind statement. Yes?

A. Could lead to. Yes.

Q. Okay.

A. Raises the possibility.

Q. But then it goes on to say, two

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sentences down, "However the development of a drug is sometimes prematurely terminated based solely on the fact that its metabolism is polymorphic."

Do you see that?

A. I do.

Q. And then there's a disclosure in the next sentence that says, "To avoid premature termination, the clinical relevance of genetic polymorphism must be assessed carefully."

Do you see that?

A. I do.

Q. Do you agree with that?

MS. WOOTEN: Objection. Form.

Q. Do you agree that the clinical relevance should be assessed carefully?

A. I would agree with that, to avoid termination of the development.

Q. Okay.

A. Yes.

Q. And then it goes on to say, "Pharmacokinetic differences between phenotypes are most relevant for drugs with narrow therapeutic indices."

Do you see that?

A. I do.

Q. Do you agree with that?

A. I would, yes.

Q. And did you ever determine what the therapeutic index of tolterodine is or was?

A. I don't know it, offhand. It must be -- it must be in the literature, certainly in the corporate information. But I don't know it, nor do I know it for 5-HMT.

Q. Mm-hmm.

A. Again, my impression is 5-HMT itself would not be known, because it would not perhaps have been studied directly. But, no, I don't know those data.

Q. Okay. And the last sentence of this section says, "If the benefit of a drug is significantly greater than its risk and dosage can be titrated by direct clinical monitoring, then polymorphic metabolism is of less consequence."

Do you see that?

A. I do.

Q. Do you agree with that?

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A. Operationally, I agree with it. However, in practice, what this would do, it would tend to decrease the range over which dosing could be titrated.

Q. How about the first part? I mean, do you agree that the benefits that were presented by tolterodine upon its launch in 1998 were greater than any risk that was presented by the polypharmacology?

MS. WOOTEN: Objection. Form.

A. I don't know to what extent the polypharmacology, per se, contributed to any of the risk. So I really couldn't answer that question --

Q. Okay.

A. -- alone, per se.

MR. TRAINOR: Okay. Now, can I see -- just a few more questions, and we can take a short break. We've been going about an hour. This will be 15. Right?

COURT REPORTER: Yes.

(Document Bates-stamped MYLB_FESO_00026903 through -6913 marked Exhibit 15.)

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THE WITNESS: Thank you.

Q. I asked the court reporter to mark as Janero Exhibit 15 another publication entitled "Influence of CYP2D6 polymorphism on the pharmacokinetics and pharmacodynamics of tolterodine."

The lead author is Brynne, and it bears Mylan Bates numbers -26903 through -913.

Dr. Janero, is this the Brynne paper that's referred to in Paragraph 133 of your report that we were just looking at, Page 44 of Exhibit 1?

A. Forty-four. I believe it is, yes.

Q. Okay. Have you reviewed this paper since you submitted your report?

A. I have not.

Q. Now -- well, let me ask you: What is about, if you know, in Paragraph 133, I guess independent of the Postlind reference, this, in combination with some other references, supports your view that the patent claims are invalid?

Can you tell me what particular teaching or teachings of Brynne support that opinion?

A. One is that the paper teaches me that CYP2D6 transforms tolterodine into 5-HMT in

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humans, in male subjects. And allied with the previous data, 5-HMT is a good antimuscarinic agent that's effective in relaxing acetylcholine contracted bladder.

Q. Okay. Now, you see the conclusion in the abstract, the last sentence says, "Despite the effect on pharmacokinetics, the CYP2D6 polymorphism does not appear to be of great importance in the antimuscarinic effect probably because of the addited action -- additive action of the parent drug and active metabolite."

Do you see that?

A. Yes, I do.

Q. Okay. Would you agree that that conclusion is supported by the data that are presented in this paper?

MS. WOOTEN: Objection. Form.

A. In these particular subjects, that would appear to be so.

Q. Okay. Could you turn to -- it's Page 5 of this Brynne paper.

A. Yes.

Q. It's in the discussion. And at the very end of the first column, there's a sentence

that carries over. It says, "In an in vitro study, hydroxylation of tolterodine showed strong correlation with CYP2D6 activity, whereas dealkylation correlated with CYP34A activity."

Do you see that?

A. I do, but I believe it's CYP3A activity.

Q. Sorry. CYP3A activity. Then there's a citation to reference No. 26. Do you see that?

A. I do.

Q. And if you look at the references, you'll see reference 26 is the Postlind reference?

A. Yes.

Q. Okay. Now, right after, there's a following sentence and then the next paragraph says, "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. So does that suggest to you that the possible problem posed by the metabolism of tolterodine that was reported in Postlind had

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subsequently been considered, addressed, and determined not to be problematic for tolterodine?

MS. WOOTEN: Objection. Form.

A. It would not lead me to conclude that it was -- that the -- that the polymorphism was not problematic.

I concluded from that, and the previous quotes from this paper, that the pharmacodynamics of tolterodine were not generally influenced by the difference in enzymatic phenotype.

MR. TRAINOR: Mm-hmm. I see. Okay. Now, why don't we take a quick break.

THE VIDEOGRAPHER: The time now is 14:27, and we are off the record.

(A recess was taken.)

THE VIDEOGRAPHER: The time now is 14:35, and we are back on the record.

BY MR. TRAINOR:

Q. Okay. Dr. Janero, just staying with Exhibit 15, this Brynne paper, on Page 534 there begins a section on pharmacokinetic-pharmacodynamic relation?

A. I see that.

Q. And then on the next page, in the

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left-hand column, that begins a discussion with respect to salivation. It's the sentence that begins, "Tolterodine caused a decrease in salivation among all subjects."

A. I see that.

Q. Okay. And it goes on and carries over into the next paragraph -- next column. And it says, "A distinct drug effect was nevertheless obtained for four of eight extensive metabolizers and most of the poor metabolizers after oral administration."

Do you see that?

A. I do.

Q. Okay. And it says, "For extensive metabolizers, the effect was equally pronounced after intravenous, compared with oral, where salivation was less affected among poor metabolizers after the infusion."

Do you see that?

A. I do.

Q. Doesn't that suggest to you or the reader that of the two agents, the agent most influencing the dry mouth side effect is actually the 5-HMT?

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MS. WOOTEN: Objection. Form.

A. I actually -- if you go back to the sentence, please, that begins, "A distinct drug effect was nevertheless."

Q. Mm-hmm.

A. I read that as saying, mean number 50 percent of extensive metabolizers and most of the poor metabolizers, after oral administration, had a drug effect on saliva secretion.

So I would interpret that as saying that the poor metabolizers of tolterodine, more of them had the adverse effect on saliva secretion than did the extensive metabolizers, who would have converted more of the tolterodine to 5-HMT.

Q. Mm-hmm. Okay. But as you mentioned before, when we looked at the label, you can't be sure which agent is really responsible. Correct?

A. Unless 5-HMT itself were tested directly, at equidose and so on, that is correct.

Q. Okay. Turning on to the next page, about seven lines down, it says, "The relation between salivary effect and unbound serum concentrations of tolterodine and 5-HM for extensive metabolizers is shown in 5A." And then

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it says, "There was a weak correlation between tolterodine concentration and effect on salivation."

A. Mm-hmm.

Q. "A stronger correlation was seen with 5-HM concentration and effect."

Do you see that?

A. I do.

Q. So does that suggest to you that of the two agents, the 5-HMT is more responsible for the effect on salivation?

A. No, because the correlation study never establishes causality.

Q. Okay. Okay. How about in the next paragraph? It says, "All 16 volunteers completed the study. No severe adverse events were reported."

And then it says, "The most frequently reported adverse events were headache (two extensive metabolizers and four poor metabolizers), dry mouth (four extensive metabolizers and two poor metabolizers)."

Do you see that?

A. I do.

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Q. Does that suggest to you given that poor metabolizers have almost all tolterodine and extensive metabolizers convert primarily extensively to 5-HMT, that 5-HMT is the more responsible agent for the dry mouth?

MS. WOOTEN: Objection. Form.

A. Pardon me. No. I read this because of -- I read this sentence in terms of the frequency of report. And if we go on and we take this sentence, as a whole, my impression is that, in terms of the quantitative tally, that poor metabolizers, especially with respect to abnormal visual accommodation, can have basically an exclusive side effect, if you will, in this -- again, in this population of 16 male subjects who do not suffer from a urinary problem.

Q. Right. By the same token, the tachycardia is only experienced by those converting to 5-HMT. Correct?

A. According to this, yes. The four out of the 16 male subjects.

Q. Right. Doesn't that suggest that if you isolate 5-HMT, you're more likely to have patients exhibit tachycardia?

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MS. WOOTEN: Objection. Form.

A. A reported adverse event does not equate with a clinically significant event, so I cannot answer that question.

Q. Okay.

A. In fact, the next sentence does say most events were judged as mild. Again, I don't know what the spectrum of clinical outcome would be. Therefore, I can't -- I can't quantify the effect in any of these cases.

Q. Okay. Well, are you aware of anything, other than the results reported in this Brynne study, that even attempt to segregate adverse effects as between 5-HMT and tolterodine?

MS. WOOTEN: Objection. Form.

A. I don't believe that this study segregates between the two. As I mentioned before, pharmacological segregation of effect would involve parallel analysis of 5-HMT, alone, under exactly the same conditions with exactly the same dosing protocol, exactly the same route of dosing, exactly the same subject or subject population, head-to-head, under the same conditions. That was not achieved in this study.

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Q. Mm-hmm. And if no such head-to-head study existed, then how would you -- would one of ordinary skill ever have the expectation that 5-HMT would reduce side effects?

MS. WOOTEN: Objection. Form.

A. As I mentioned before, the chemical nature of 5-HMT, as a dialcohol versus tolterodine, would indicate that it would have less propensity to cross passively the blood-brain barrier because of its relatively greater hydrophilicity, lower lipophilicity, and also the attraction of 5-HMT, the amount of available drug, available antimuscarinic to effect the clinical outcome would be greater, because of its lower binding capacity to serum protein and lipoproteins.

Q. But when I asked you before as to CNS effects that would be caused by a crossing of the blood-brain barrier, whether it was reasonable to infer that, if anything, 5-HMT is responsible, given that that is what is most exposed in the majority of patients, you said you can't draw that conclusion, even based on data.

Are you suggesting to me that you can draw

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that conclusion and develop a drug based on a two-dimensional diagram of the chemical structure?

MS. WOOTEN: Objection. Form.

A. No. I'm simply saying that the potential to do so, to me, would exist because of the dialcohol property of the 5-HMT versus tolterodine.

Q. Mm-hmm.

A. The experimental data -- as I've alluded to, the data would be necessary to answer that question definitively.

Q. Right. And the data was not available. Correct?

A. Not in the public domain that I have been able to access.

Q. Mm-hmm.

A. I cannot speak for internal documentation or studies.

Q. Now, the chemical structure of tolterodine, does that suggest to you that it, in fact, has an unsafe or risky propensity to cross the blood-brain barrier and cause side effects, as a practical matter?

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MS. WOOTEN: Objection. Form.

A. In and of itself, no.

Q. Okay. And I guess I'd just like to know what the expectation would have been of a person of ordinary skill in the art who did decide to make a prodrug or otherwise deliver 5-HMT, per se, if you will, what the expectation would be with respect to the benefit of that prodrug or that administration over tolterodine, as it was reported in the prior art?

MS. WOOTEN: Objection. Form.

A. Let me understand the question. You're saying either as a prodrug or the actual agent? 5-HMT would be the only active agent we're talking about now.

Q. Correct.

A. Okay.

Q. What benefit would you expect to gain by administering it solely?

A. Well, one expectation would be, as I say, you would have -- compared to tolterodine administration, you would have less propensity to cross the blood-brain barrier passively, because you would have a more hydrophilic, less

lipophilic agent.

You would expect to have the potential for greater efficacy, because you would have more free compound than bound, more free -- free component being able to bind and interdict in terms of the acetylcholine bladder contraction and have a therapeutic effect thereof.

You would also have the ability to deliver one active agent doing essentially the same -- effecting the same therapeutic outcome, rather than having two active agents that could have variability among patient populations, among subjects --

Q. Right.

A. -- in the clinic.

Q. But the conclusion of the Brynne paper is that having two active agents does not create any problems with respect to tolterodine?

MS. WOOTEN: Objection. Form.

Q. Correct?

A. I'm looking at the text in the conclusion. In the antimuscarinic effect, probably because of the additive action of parent drug and active metabolite.

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Q. Mm-hmm.

A. So this is a conjecture, probable, because of the additive action of parent drug and active metabolite. So I would submit that that also could compel someone to focus on the active metabolite as a sole agent for delivery or for -- as a therapeutic small molecule, as a chemical therapeutic.

Q. Would there be any practical difference between the biological effects of 5-HMT, in isolation, and extensive metabolizers' administered tolterodine?

MS. WOOTEN: Objection. Form.

A. There is -- there is the possibility. I don't know the data. But, again, we'll go back to the Brynne paper that we're looking at, at the moment. The implication from the data, "The findings imply that at least 80 percent of a systematically available dose of tolterodine is metabolized by CYP2D6 to 5-HM in extensive metabolizers."

So in that very patient population, there's perhaps, according to this quantification, 20 percent or so of tolterodine still there and

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still active.

Q. Right.

A. So --

Q. And what are the consequences of that? Is there any evidence that that would be problematic?

MS. WOOTEN: Objection. Form.

A. Without data comparing tolterodine versus 5-HMT, alone, under exactly the circumstances, I don't know how that could be parsed out to answer that question.

Q. And the CYP34A enzyme metabolizing the unmetabolized tolterodine. No?

A. It does. It, in fact, creates a unique metabolite as a result of that enzymatic transformation.

Q. Which is inactive. Correct?

A. As far as the literature says. Yes, it is inactive.

Q. And that remaining 20 percent is pretty extensively metabolized, you would conclude, would you not, when you look at Page 537 at the bottom of the first column, and it says that, "Only 2.5 percent of intact tolterodine is

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excreted."

Do you see that?

A. Is that "only minimum amounts"? Starting at that? Where, exactly, are we?

Q. The last complete sentence in the column, it says, "Metabolism" --

A. Ah, yes. Sorry. I've got it. Yes, basically tolterodine, as well as 5-HMT, are -- share the elimination route through that 3A, the CYP3A.

Q. So that being the case, what would be the risk of unmetabolized tolterodine?

A. If it were -- being relatively more lipophilic than the dialcohol 5-HMT, if it were to have a greater permeability across the blood-brain barrier, that could be a potential risk, and that could underlie some of the adverse event profile.

And not having a direct comparison with 5-HMT, alone, we don't have the data to make that conclusion quantitatively.

Q. Okay. Now --

(Discussion off the record.)

Q. Now, let's -- I'll assume now, for a

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moment, that -- well, probably for the rest of this deposition, that one of ordinary skill would start with 5-HMT as a lead compound.

My question is: Why would one use a prodrug to deliver 5-HMT rather than some other vehicle?

MS. WOOTEN: Objection. Form.

A. In my opinion, knowing that 5-HMT is not only an effective antimuscarinic, but also a component of the efficacy of the parent compound, tolterodine, this, to me, would provide a very effective lead, in terms of simple chemical elaboration, to maintain 5-HMT's therapeutic effect at the target organ of interest, the bladder.

Q. Mm-hmm. And I'm saying -- I'm assuming that now. I want to know why not deliver it -- why not just administer 5-HMT orally?

A. I believe that, my understanding of the proprietary field, the patent art, is that 5-HMT was already a proprietary -- it was already claimed by another party.

Q. Is that the only reason to believe why one wouldn't administer it directly?

A. If I were in a drug company that --

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who's depending upon -- that depended upon revenue to support my ongoing R&D and to establish a product line, that could be a very important factor.

Q. What is an important factor?

A. The ability -- the inability to market the drug, to market the compound as a drug.

Q. Okay. Because of the patent situation?

A. Because of the inability to penetrate the market with an agent that you would, in essence, own and gain revenue from.

Q. Okay. I'm not sure if I understand the answer. But let me just ask you this: Let's just assume there was no patent coverage anywhere on 5-HMT, so they didn't have that constraint --

A. I understand.

Q. -- why wouldn't a person of skill in the art of drug development just administer 5-HMT, per se?

MS. WOOTEN: Objection. Form.

A. Under the circumstance where there was no prior disclosure of 5-HMT other than it was a metabolite, an active metabolite of tolterodine, offhand, I don't see any reason why one wouldn't

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administer that, at least test it preclinically.

I believe regulatory authorities would not allow its direct administration as a substitute or proxy for tolterodine, even though it were an active metabolite.

It would still have to go through the development and -- the development process.

Q. Right. You'd have to --

A. Right.

Q. -- demonstrate to the regulatory authorities?

A. Right. Yes. That's it.

Q. But certainly the reasonable drug developer would at least try to administer it orally, before going to the trouble of a prodrug. Correct?

MS. WOOTEN: Objection. Form.

A. That would, to me, be a logical experiment. Perhaps that was the basis for the experiment, the in vivo experiments, Exhibit 12, that Nilvebrant, et al, in the cat model, in the feline model, where it was administered separately.

Q. Okay.

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A. Again, I have no knowledge of internal experiments. Therefore, I cannot say whether there have been other experiments. But in the public literature, that is one example.

Q. Okay. Now, I think in your expert report, I don't believe that was the reason that you suggested one would try to make a prodrug of 5-HMT.

Let me see. I believe that what you had suggested was that you would make a prodrug because a person of ordinary skill in the art would expect that 5-HMT, administered orally, would not be absorbed.

I'm just jumping around here. If you go to Paragraph 48, Page 15.

(Witness complies.)

Q. And you've got this first paragraph --

A. Mm-hmm.

Q. -- that says how to avoid the complications of tolterodine, "maintain positive attributes of 5-HMT."

And then in the next paragraph, it says, "A person of ordinary skill in the art would recognize that it's more hydrophilic than

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tolterodine, seek to avoid the potential limitation of 5-HMT absorption across the gut and into the systemic blood circulation."

Do you see that?

A. I do.

Q. So which is the reason, you wouldn't attempt to administer it orally because of the patent restraints, or one wouldn't try to administer it orally because the limitation of absorption?

A. Both could play a part. We're talking here about absorption across the gut into the systemic circulation.

Q. Mm-hmm.

A. Without that absorption, the active agent would not reach the target organ; namely, the bladder.

Q. Mm-hmm.

A. So there has to be a balance here along the hydrophil- -- hydrophobic scale so that you could leverage the physical properties of 5-HMT so that they would be hydrophilic enough, more hydrophilic than tolterodine so as to limit the nervous system exposure. But not so much as to

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compromise absorption across the gut so that the agent would enter -- could enter the systemic blood circulation and reach the target organ.

Q. Okay. Well --

A. If --

Q. -- what if you didn't alter 5-HMT at all, then you wouldn't increase the propensity to cross the blood-brain barrier, as long as you could get it absorbed through the gut?

MS. WOOTEN: Objection.

Q. Why not do that?

MS. WOOTEN: Objection. Form.

A. Theoretically, that would be possible, but in light of the comparative data, I can't answer that question. Theoretically, it's possible.

Q. Well, I mean, it's kind of an important point. Right? Because my understanding, from your report, is that the reason you make a prodrug, as opposed to any other design alternative or as opposed to administering 5-HMT, per se, is because you don't expect that it would get across the gut wall and get absorbed?

A. That could be one consideration. But

the other consideration, for example, to leverage, in another chemical form, the properties of that active metabolite, that active agent; the other chemical form being the prodrug that would then be converted to that active agent; the prodrug being a new chemical entity. That would be another factor.

Q. Well, didn't you testify earlier that the objective is to simplify the process, simplify the metabolic pathway, when possible?

A. Yes.

Q. Is that always preferred?

A. And that's why I believe, in this case, a prodrug of 5-HMT simplifies, we know, the tolterodine metabolic pathway, but also continues, preserves, leverages the profile of 5-HMT as an effective muscarinic agent that binds to the M3 and other receptors with high affinity.

Q. I understand that. But what I'm asking is: Why -- what you've just described certainly is not -- strike that.

What you've just described is not more simple than just administering 5-HMT.

A. No.

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MS. WOOTEN: What -- objection. Form. I'm not sure if that was a question.

A. It is more simple, in my opinion, than altering the basic structure of 5-HMT to arrive at another compound with 5-HMT-like pharmacological and therapeutic properties.

Q. You mean --

A. That was my point.

Q. -- making an analog?

A. Yes. A different -- yes.

Q. I understand.

A. Not an ester.

Q. I understand.

A. Right.

Q. Just making a different 5-HMT analog, like tolterodine, you're saying that would just be no less complicated, maybe more complicated. I understand that.

What I'm saying is making a prodrug of 5-HMT is not less simple than just administering 5-HMT or at least trying. Correct?

A. I agree.

Q. Okay. And so why would you not expect -- why would you not try to just

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administer 5-HMT orally, per se, instead of making a prodrug?

MS. WOOTEN: Objection. Form.

A. If I could not obtain a marketable entity out of that 5-HMT, alone, as 5-HMT, the active agent, as a marketable chemical therapeutic, this, to me, would not be attractive in terms of drug discovery and development -- commercial drug discovery and development.

Q. I understand that.

A. That would be, to me, a driver. And, as I understand the situation, more globally, that is the case in this scenario.

Q. Okay. I understand. What I'm saying is Paragraph 49 does not suggest that that's not why you would not first try to administer 5-HMT orally.

It's suggesting that you would make a prodrug because a person of skill did not expect 5-HMT would be absorbed sufficiently, if administered, per se; is that correct?

A. That could be one -- that could be an expectation, because it could be a bit too hydrophilic to cross or to be absorbed by the gut

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mucosa, not the blood -- not across the blood-brain barrier. This is a possibility.

Q. In your experience, assuming you don't have these patent restrictions, wouldn't you certainly attempt that administration, per se, and see whether it gets absorbed sufficiently before going to the trouble and expense of making a prodrug?

MS. WOOTEN: Objection. Form.

A. I would be surprised if that had not been done. I do not know the results, though, if it had been done.

Q. Would you expect a person of ordinary skill in 1998 to attempt to administer 5-HMT, per se, before going to the time and expense of making a prodrug?

MS. WOOTEN: Objection. Form.

A. I would have.

Q. Okay. And the -- a prodrug, assuming it works -- I understand everything you suggest with regard to its benefits. But you would agree with me that there are a great number of variables and uncertainties in prodrug design. Correct?

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MS. WOOTEN: Objection. Form.

A. In general, yes. But those variabilities and uncertainties are tempered and restricted by knowledge of, in this case, 5-HMT structure and what 5-HMT does and what it -- what its profile is pharmacologically.

These, to me, represent great advantages in design of a 5-HMT prodrug versus design of prodrugs perhaps in other areas, where the profiling were not as -- as extensive for the parent compound or the models were not as well established, for example.

Q. Okay. And according to --

(Discussion off the record.)

Q. I think the support for your opinion with regard to the obviousness of making a prodrug; in other words, support for the obviousness of that design approach, you rely primarily on this Bundgaard reference. Is that right?

A. It was certainly one of the most comprehensive.

Q. Okay. And we can look at this --

MR. TRAINOR: We can mark this.

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Q. We can look at this, but would you agree with me that among the many things in this text, that Bundgaard text, there's a suggestion that if you're going to make a prodrug, you need to understand what problem it is that you're trying to solve. Correct?

MS. WOOTEN: Objection. Form.

A. That's one possibility. Another possibility is you would like to see what potential improvements you could make or what potential new chemical entity you could market.

Q. Okay. Well, the first part of that is the other side of the coin.

In other words, if my problem is absorption, I would follow teachings about prodrugs that were made to overcome an absorption problem. Correct?

A. Yes. And perhaps you would, as I allude to here in Paragraph 49, you might alter the hydrophilicity a bit by making an ester, for instance. For instance.

Q. I understand. But the -- right. And the point is that you're trying to make the prodrug more lipophilic than the metabolite, if you will, in the instance where absorption is

what you're trying to resolve. Correct?

A. Resolve, improve, differentiate.

Q. Right. You wouldn't necessarily always try to make a more lipophilic prodrug if that wasn't the issue with the metabolite compound you're trying to convert to?

MS. WOOTEN: Objection. Form.

A. I could see where there would be cases where you would. For example, suppose you had a dosing regimen that was limited by a limited absorption. For example, your dose range was very, very limited.

You might then want to develop a prodrug that would have a wider dose range so that, potentially, if it reached the clinic, you would be able to prescribe various dosing regimens for a wider patient population than simply one dose for perhaps a more circumscribed patient population.

MR. TRAINOR: Okay.

Q. Now, all I was really trying to just sort of establish for these questions with the prodrug is the assumption in following the prodrug teachings is that absorption is the issue

that needs to be resolved with 5-HMT. Correct?

MS. WOOTEN: Objection. Form.

A. I don't believe that it's an issue that needs to be resolved. I think the potential avenue for improvement because of the dialcohol nature of the compound could invite limitation for absorption across the gut into the blood circulation. Without that, there is no pharmacological activity.

Q. Right. But if it's sufficiently absorbed, there is no reason to go to the complexity of a prodrug at all. Correct?

A. No. There could be. As I've just alluded to, the idea that if you have sufficient absorption to give a pharmacological effect, but that absorption is such that the efficacious dose is limited in some way --

Q. Okay.

A. -- then you might wish to enhance, alter the gut absorption to improve that parameter, enhance that parameter so that you could increase the dose range, increase the dynamic range over which you could give the drug, to have an effect over a wider range of

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population.

Q. Okay. What evidence are you aware of that 5-HMT's absorption was such that there was room for improvement or insufficient bioavailability?

MS. WOOTEN: Objection. Form.

A. I do not know of any study that looked specifically at the bioavailability of 5-HMT, alone.

Q. Mm-hmm. Okay.

A. So I cannot answer that question.

Q. Well, then how can you come to the opinion that one would simply make a prodrug of 5-HMT without having the data to provide that justification?

A. If you're in a situation where 5-HMT, which this is, is an effective antimuscarinic, effectively produces relaxation of the acetylcholine contracted bladder, and we're putting aside, as I understand it, an important factor here, that prior art basically prohibits 5-HMT from reaching the marketplace for this particular commercial entity we're discussing, as a drug.

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Q. Mm-hmm.

A. Then one would -- in my opinion, it would be very attractive to leverage the pharmacological properties of 5-HMT as an antimuscarinic agent, active at the bladder, in terms of a prodrug design approach.

Q. All right. But how much more are you leveraging it over the administration of 5-HMT, alone, if 5-HMT is sufficiently absorbed?

MS. WOOTEN: Objection. Form.

A. We would need the data to show, but if 5-HMT is sufficiently absorbed, is ultra-absorbed, if I don't have a drug, if I don't have a commercial entity out of the situation, at the end of the day, I have nothing, regardless of its pharmacological profile, in terms of the marketplace, in terms of therapy, in terms of the pharmacopeia, in terms of the clinic.

(Document Bates-stamped MYLB_FESO_00026925 through -7120 marked Exhibit 16.)

Q. Mm-hmm. Okay. Now, the Bundgaard paper that I just marked, I'm sorry, marked as

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Exhibit No. 16, Janero 16, is a multi-page publication that we've been referring to here as the "Bundgaard publication."

This is -- it looks like a copy of an actual textbook on the first page, the title of which is "Design of Prodrugs." The editor is Bundgaard. And these are Mylan Bates numbers -26934 through -27120.

Now, Dr. Janero, you recognize this text?

A. I do.

Q. Is this -- is this something that you pulled up in your search for prior art?

A. I believe I obtained it through counsel.

Q. Okay. Now, if you look at -- if you turn a few pages in, there's an introduction, and it just sort of walks through, with a sentence or two, a description of what each of the following chapters concerns.

A. I see that.

Q. And that's followed by a table of contents. Do you see that?

A. I do.

Q. If I'm not mistaken, your reliance on

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this Bundgaard text is limited to the first chapter, "Design of Prodrugs: Bioreversible Derivatives or Various Functional Groups and Chemical Entities."

Do you see that?

A. That's correct. Yes, I do.

Q. And if we turn to that chapter, okay, there is an introduction and then there is a section on -- well, before you get to the Section 2, on Page 2 of the reference, I believe that you have -- if you look at almost -- about three lines up from the end of the text, it says, "In the past, esters mostly have been considered as prodrug types, and the best known prodrugs are, in fact, esters of drugs containing hydroxyl or carboxyl groups."

Do you see that?

A. I do.

Q. I think you relied on that statement in your report, in your opinions. Right?

A. Yes.

Q. And then it goes on to say, "Various reviews have dealt with esters, and, therefore, this important class will only be briefly treated

herein." And I think that treatment is in this following Section 2 on esters as prodrugs.

Do you see that?

A. I do.

Q. Okay. Now, the fact that esters had been historically used and best known for drugs containing hydroxyl and carboxyl groups doesn't mean that there are not other promoieties that were available to one of skill in the art at the time. Correct?

MS. WOOTEN: Objection. Form.

A. Correct.

Q. Okay. Now, the Table 2 here on Page 3, there is a great number of different esters that could be used. Correct?

A. Correct.

Q. So let me just ask you: Why is it your opinion that one of ordinary skill in the art, at the time, would not have considered other promoieties besides esters?

MS. WOOTEN: Objection. Form.

A. The person skilled in the art, I believe at that time, would leverage the known distribution, the known activities and the known

promiscuity of esterases in the human body, as well as in other mammals, to convert prodrug into active agent, in the classic definition of a prodrug.

This is why I believe, as stated by Bundgaard, esters have mostly been considered as prodrug types, and the best known prodrugs are, in fact, esters of drugs containing hydroxyl, carboxyl groups, because these are readily transferred, very rapidly, catalytically, into active agent.

Q. Okay. And is what you're referring to the fact that esterases are ubiquitous in the body?

A. Esterase activity is ubiquitous in the body. Yes.

Q. Okay. Now the -- keep that open.

If you look at the figures of tolterodine, 5-HMT, and fesoterodine you've got here nicely on Page 7 of your report.

A. I see that. Yes.

Q. Okay. Now, fesoterodine's ester group has got a little circle around it there?

A. I see that. Yes.

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Q. What type of ester is that?

A. That's a hydrocarbon ester, simple hydrocarbon ester.

Q. Okay. Now --

A. Isopropyl, to be exact.

Q. Mm-hmm. Now, the fact that esterases are ubiquitous in the body and available to convert an ester prodrug means that it's possible that the prodrug will convert quick -- too quickly before it even reaches the systemic circulation. Correct?

A. That's a possibility. However, that would depend upon the local esterase activity with respect to this specific prodrug as substrate at the level of the gut.

Q. Okay. Well, what would stop it from being converted in the GI tract by all the esterases that are there?

MS. WOOTEN: Objection. Form.

A. If the compound presented the esterases, did not or was limited in terms of its engaging the catalytic, the active site of the enzyme, it would, therefore, have limited ability to be converted, because the enzyme would have

limited recognition of that agent, as substrate.

In other words, just because esterases are ubiquitous doesn't mean that they are -- that they -- that any esterase will recognize any substrate.

There is a substrate specificity associated with esterases.

Q. Okay. Well, what esterases would this prodrug that you proposed would recognize the prodrug -- I mean, I'm not sure I understand. I thought esterases are esterases, wherever they are in the body.

A. Right.

Q. Okay. Go ahead.

A. An esterase, no matter what its substrate, introduces the elements of water, hydrogen and OH --

Q. Mm-hmm.

A. -- across an ester bond. That's why, for example, fesoterodine, an esterase, acts on a fesoterodine, we obtain back as product the dialcohol 5-HMT. In other words, the 2 position is reconverted to the alcohol.

Q. Mm-hmm.

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A. So, in general, that is so. All esterases are protein machines that catalyze that activity.

However, the esterases vary in terms of enzyme type. They vary in terms of tissue concentration. They vary in terms of plasma concentration.

They're promiscuous, in the sense that most enzymes will recognize a very limited number, perhaps one, substrate.

Q. Mm-hmm.

A. Mammalian esterases have more of a variety which they'll recognize. However, they won't recognize all esters.

Q. Mm-hmm.

A. So they have their limitations with respect to what molecules they'll turn over from substrate to product.

So, therefore, they have limitations as to what prodrugs they can convert to active agent.

Q. Right.

A. That's my meaning.

Q. A person of ordinary skill in the art, who is developing, in 1998, a prodrug of 5-HMT,

which esterases does he know are going to recognize that prodrug?

A. In general, the basic principle is that the more chemically delimited, the smaller the ester group, the general tendency is for esterases to be more able to recognize that ester functionality, because the group has to fit into the active site pocket of the esterase or esterases that may interact on that.

Q. I understand. So back to my initial question, which is: How did you know to design a prodrug that would avoid premature conversion by virtue of the esterases that come before the gut?

MS. WOOTEN: Objection. Form.

A. I don't -- I don't know that that would have been a necessary specific consideration.

Q. Why not? Esterases are ubiquitous, are they not? Are they not found in the GI tract?

A. They are. In fact, the esterase there in the GI tract, that's -- one is relying on that to get the prodrug into the blood, and perhaps blood esterases could do that as well.

Q. Okay.

A. One would have to do, and one would do

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experimentally in vitro studies looking at potential drug candidates, potential hits, potential leads, as esterase substrates. And that's a typical, routine biochemical assay, usually done with a liver supinate preparation.

And, in fact, investigators across various publications cited here and elsewhere use that assay. It's a very routine assay with a human supinate.

Q. Okay.

A. So one would -- one would gauge this type of activity in drug discovery, this propensity in drug discovery in the preclinical stage.

Q. Okay. But without the benefit of the testing and the assays, is there anything in the prior art that teaches the type of esters that can be used to avoid premature conversion?

A. Not that I can cite.

Q. Okay. And sometimes, depending on what you're trying to do with the prodrug, you may not want rapid conversion. Correct?

A. The kinetics of conversion are really complex, because the rapidity of conversion or

the retardation of the conversion in terms of the enzyme kinetics do give exposure of the system to the drug, but not need -- they need not correlate absolutely with the efficacy of the drug in vivo.

As long as there's sufficient turnover, the drug should be active, if, indeed, we're talking about the classic prodrug definition, the prodrug being inactive.

Q. Mm-hmm. Right. What I'm saying is, there are times, depending on your objective, where you want very quick conversion. There are times -- there are other times, depending on your objective, where you may want to delay the conversion of the prodrug. Correct?

A. I agree.

Q. One example would be if your objective is to arrive at a once-daily drug. Correct?

A. I agree.

Q. With respect to design of once-daily drugs, you don't necessarily want immediate and rapid conversion. Correct?

A. Not necessarily. Correct.

Q. Okay. And the same would be true with respect to prodrugs designed to be target

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specific. Correct?

A. Not necessarily. No.

Q. Okay. The prodrug that one of ordinary skill would have designed of 5-HMT, would that design have attempted to target receptors in the bladder?

MS. WOOTEN: Objection. Form.

A. Target the receptors with the prodrug?

Q. In other words, would you be trying to target conversion at or near contact with that tissue or location?

A. You could, but I would believe the preferential route would be to target so that you obtain sufficient therapeutic level of 5-HMT in the blood.

Q. Okay.

A. Now, I should mention, in terms of this discussion, that there are many other factors in vivo that impinge upon our discussion of rates --

Q. Mm-hmm.

A. -- one of which is, for example, suppose we have very rapid conversion at the gut of a prodrug into an active metabolite, but that active metabolite is subsequently very rapidly

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eliminated, as the intact metabolite even.

(Court reporter clarification.)

A. If it's rapidly eliminated as the active metabolite then, yes, you have rapid activation of the prodrug, of a fair amount of prodrug, but basically your exposure can still be very limited --

Q. Mm-hmm.

A. -- even with the rapid conversion.

So a rapid conversion need not necessarily translate into a flood or a quantum of active agent in the circulation.

Q. Okay.

A. It's a balancing act.

Q. But what effect would the design of the prodrug have on that phenomenon? Wouldn't that just purely be a function of how the metabolite is eliminated, no matter how you deliver it?

MS. WOOTEN: Objection. Form.

A. You could design the prodrug, though, for example, to have a slower turnover with respect to the esterases. I'm just -- I just used that example to say that the in vivo situation, in terms of these kinetics, in terms

of these dynamics, the output being therapeutic effect, is complicated.

What we're discussing here in terms of the kinetics, the enzyme kinetics of esterase action is one component. It's an important essential component, but it's not the only determinant, by any means. That's all I wish to say.

Q. So would the person of ordinary skill, at the time in 1998, need to have an understanding of how 5-HMT is eliminated?

A. To? A need to then, a need to?

Q. In other words, to avoid the exposure problem that you were just alluding to?

A. Not necessarily, no.

Q. Okay.

A. No.

Q. Okay. Now, what teachings in the art suggest which esters provide the requisite stability for 5-HMT?

A. In terms of chemical stability of the compound?

Q. Right. In other words -- well, let's step back.

If you want to have an effective prodrug --

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A. Mm-hmm.

Q. -- the prodrug has to be stable. Correct?

A. As a chemical entity, yes.

Q. Yes. It's got to convert. Yes?

A. Yes.

Q. It's got to be inactive. Correct?

A. In terms of the classic definition of a prodrug, yes.

Q. That's --

A. In terms of this definition, yes.

Q. "This," meaning Bundgaard's definition?

A. Yes.

Q. Okay. And the prodrug itself, to the extent not metabolized, cannot be toxic. Is that right?

A. That would be essential. Yes.

Q. And the promoiety, in this case, the ester, itself, cannot be toxic and have off-target effects. Correct?

A. Correct.

Q. Okay. Now, are there any teachings as to what ester will accomplish those things, or you just have to test?

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A. There are two ways to answer that -- to derive it, that information along those lines. One is the empirical route, which is simply designing, making compounds and testing them against an esterase preparation, for example.

Q. Mm-hmm.

A. Another is to appreciate that various chemical, various moieties, various groups, chemical groups can carry their own reactivities. And even if separated, if hydrolyzed from the parent compound, the ester, yes, one would derive the active agent desired from the prodrug.

But one could also invite a complication due to potential chemical reactivity, instability, metabolism of that agent. For example -- I'll give one specific example. If we had an ester of an unsaturated fatty acid, an unsaturated fatty acid is susceptible to oxidation. That's a rancid fat that's not metabolized very well, and, actually, that can be toxics.

So one would tend to avoid certain possibilities as a result of not wishing to invite further reactivity metabolism transformations, post de-esterification.