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about separating tolterodine from 5-HMT and trying to administer a single active moiety. How would you feel comfortable describing that so I don't --

A Okay.

Q That's what I meant by --

A How about let's just say isolation of 5-HMT.

Q Okay.

A In the development of tolterodine, you have this known metabolite. Your synthetic chemist will make that in order to perform the analytical chemistry properly so that an authentic standard exists.

Q Okay.

A That's all the motivation necessary to prepare it and isolate it.

Q Uh-huh.

A Having that in hand, then you have the synthetic method, that facilitates further investigation of the molecule.

Q Okay. So maybe let me ask it this way: Why would a person of ordinary skill in the art in 1998 not have tried to formulate 5-HMT in a formulation for delivery as distinguished from designing a prodrug?

MS. WOOTEN: Objection, form.

THE WITNESS: A medicinal chemist would

prepare a prodrug. That would be a formulation exercise, right, so that's not what we do.

A medicinal chemist looking at the hydroxyls would recognize that esterification is not a particularly difficult task for most of us. It's relatively easy, and that's a method that's known to increase lipophilicity. So that's almost a knee-jerk response, prepare a set of esters, evaluate them.

MR. TRAINOR: Okay.

Q (By Mr. Trainor) And was that a knee-jerk response in 1998?

A Such chemistry has been known for decades previous to 1998.

Q Okay. Let me be a little more articulate, I hope. If the goal is to deliver 5-HMT -- well, let's step back.

As I understand your declaration -- and maybe just to get us all at a right point, I think the discussion of prodrug design begins around paragraph 105 --

(Interruption in the proceedings.)

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THE WITNESS: Pardon me. Let me turn this thing off so it doesn't bug us. Okay. Thanks for putting up with that.

MR. TRAINOR: No, no.

THE WITNESS: I am at paragraph 105.

Q (By Mr. Trainor) Well, I guess I'm trying to -- what is the reason, in your view, that a skilled drug developer would have had to make 5-HMT more lipophilic?

MS. WOOTEN: Objection, form.

THE WITNESS: The log D value that was known of tolterodine, and so I would -- you know, that's relatively low. The log D value at around pH 7 was -- of that molecule was between 1 and 2.

So we have now a more polar substrate of something with a relatively log D value [sic]. I might be -- I would be concerned that we would see a decrease in the hydroxymethyl's ability to decrease the gut.

I wouldn't necessarily predict that such permeability would be zero, but I would predict that the permeability would be decreased; therefore, I would be ready to

attempt to increase that by increasing its lipophilicity, and the more lipophilic molecules to a point are known to be better candidates for oral absorption.

Q (By Mr. Trainor) Okay. So do I understand that the hypothetical developer at that time would recognize from the lipophilicity that 5-HMT, if you try to deliver it per se, if you will, would not be sufficiently well absorbed? Is that --

A It would recognize that's a possibility.

Q Okay. So coming back to my first question: Wasn't one available solution for that to put it in a dosage form that would permit delivery of the 5-HMT notwithstanding concerns about its absorption?

A That might be -- that might be an approach. A medicinal chemist would look to modify it chemically in order to solve that problem.

Q Okay. Are there other members of the makeup of the skilled drug developer besides medicinal chemist who might look more toward the new dosage form?

A A form --

MS. WOOTEN: Objection, form.

THE WITNESS: Sorry. Yes, I think so.

MR. TRAINOR: Okay.

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Q (By Mr. Trainor) And a formulation chemist, is that what you were going to say?

A (Witness nods head affirmatively.)

Q Okay.

A Sorry, I'm nodding. Yes.

Q That's okay.

So one alternative option would be to formulate 5-HMT per se in, for example, a controlled-release formulation; is that right?

MS. WOOTEN: Objection, form.

THE WITNESS: I'm not sure a controlled release would be the way to go.

MR. TRAINOR: Okay.

THE WITNESS: I'm -- not being a formulation chemist, it's difficult for me to say what formulation would work.

MR. TRAINOR: Okay.

Q (By Mr. Trainor) Well, without being a formulation chemist, do you believe that some type of formulation would work to achieve delivering 5-HMT per se --

MS. WOOTEN: Objection, form.

Q -- even if it's not a controlled-release formulation?

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MS. WOOTEN: Sorry. Same objection. Objection, form.

THE WITNESS: Difficult for me to say not being a formulation chemist.

MR. TRAINOR: Okay.

THE WITNESS: And I don't advocate sole -- you know, chemical modification as a sole response to solve a problem. A project manager might want to look at -- right, so this is just simply the first thing just simply because the relative ease of esterification of the molecule that you would already have because you made it knowing it's a metabolite.

Q (By Mr. Trainor) But if you do that, you're creating a new chemical entity, right?

A That's probably going to be the case. There probably would not be known esters of that molecule.

Q Okay. Now, what about administering 5-HMT per se, wouldn't you attempt to do that before going to the trouble of a prodrug?

MS. WOOTEN: Objection, form.

THE WITNESS: I would perform a KCO2 assay for oral availability or have someone

do it for me.

Q (By Mr. Trainor) And depending on the results, the simplest method would be just administer it per se, correct, 5-HMT?

MS. WOOTEN: Objection, form.

THE WITNESS: If the results predicted low oral availability, I would commence preparation of prodrug.

MR. TRAINOR: Right.

Q (By Mr. Trainor) If the results were sufficient for oral availability, then you would agree it would be much simpler just to administer the 5-HMT per se, correct?

A I would -- right.

Q Yes?

A Yes, yes.

Q Okay. And a drug developer at the relevant time -- strike that.

Would the drug developer at the relevant time attempt to do that before jumping to an analog or a prodrug approach just in case it worked?

MS. WOOTEN: Objection, form.

THE WITNESS: Are you asking me if the synthetic lab would make such a prodrug

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before performing a KCO2 predictor or before doing an oral availability?

MR. TRAINOR: Yes.

THE WITNESS: Okay. Maybe.

MR. TRAINOR: Okay.

Q (By Mr. Trainor) Okay. Why would that be reasonable in terms of resources?

A It would depend on how certain you were that you were going to need to do it.

Q Okay.

A That's why I say maybe.

Q Okay. Now, the absorption of 5-HMT was not known prior to 1998, correct?

MS. WOOTEN: Objection, form.

THE WITNESS: I don't know the answer to that. It was not -- yeah, I don't know the answer to that. I don't think it was reported in the literature.

MR. TRAINOR: Okay.

Q (By Mr. Trainor) And you would agree that lipophilicity can be an indicator of oral absorption, but that's not always the case, correct?

A It can -- it can, yes, it can be an indicator of whether or not a compound is likely to get in,

right.

Q Okay, but it's not always the case?

A There are exceptions where molecules are transported in. There are cases, though may understanding is they're quite rare, where it passes between the cells to get in.

Q Okay. Now, based on the calculated lipophilicity -- did you do that? I'm looking at the section -- in any event, your view of the calculated or theoretic lipophilicity of the 5-HMT structure itself was that it would not be sufficiently absorbed; is that right?

MS. WOOTEN: Objection, form.

THE WITNESS: Are you referring to Professor Rouse's calculation?

MR. TRAINOR: Did you do a calculation?

THE WITNESS: I did not.

MR. TRAINOR: Okay.

Q (By Mr. Trainor) So without doing the calculation, how would you arrive at the conclusion that 5-HMT needed to be more lipophilic?

A Because the parent, tolterodine, isn't particularly lipophilic; its log D is less than 2. And so you make the thing more polar by putting hydroxy

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group on there, the lipophilicity is going to go down. My experience with polyols is that many of them don't get in passively very well.

Q Okay. Was that routine, in 1998, to extrapolate the propensity to be absorbed from one analog to another based on lipophilicity?

MS. WOOTEN: Objection, form.

THE WITNESS: So based on structure, it was to predict a relative. So you put a polar moiety on the thing, you would predict it would have a lesser lipophilicity than its parent molecule.

MR. TRAINOR: Okay.

Q (By Mr. Trainor) I think earlier you agreed that tolterodine seemed to be well absorbed.

A Yes.

Q So even if the -- even if 5-HMT structure suggested a lower lipophilicity, how could you conclude that 5-HMT would not itself be sufficiently orally absorbed?

A I wouldn't conclude with certainty as you expressed it. I would say it might not be adequately absorbed.

Q Okay, but wouldn't you want to go on more

than the possibility before going to the process of designing a prodrug?

A Well, design of an ester is really quite easy, and that's routinely done with polyols. I would do the KCO2 assay before initiating a synthetic effort.

Q Okay. And what about the option of making analogs of 5-HMT that aren't necessarily prodrugs, but just chemical analogs to --

A Right.

MS. WOOTEN: Objection, form.

THE WITNESS: I'm sorry. The reason I wouldn't consider that as a first-pass approach or first approach -- let's not say first pass, so I apologize for that, but as a first approach, is that it's known that 5-HMT is quite potent, it's equipotent to a molecule that was taken to the clack [phonetic]. So the structural modifications, what if that, you know, abolishes the activity.

MR. TRAINOR: Okay.

THE WITNESS: Right? Now, that might be something I would be interested in doing had I enough people in my lab to prepare

synthetic analogs, but that wouldn't be my first approach.

Q (By Mr. Trainor) But it's equally possible that you could make an analog that would actually increase 5-HMT's potency, correct?

MS. WOOTEN: Objection, form.

THE WITNESS: That might be -- yeah, that might be the case. If you're making analogs, ideally that's what you want to do.

MR. TRAINOR: Okay.

Q (By Mr. Trainor) Now, just sticking again with the absorption part of it, would you agree that the theoretical log P of -- I'm sorry, let me reask the question. Is it log P or log D that is the preferred indicator of lipophilicity?

A Both are used. I think both are very similar.

Q Okay.

A I think both can be used, you know, in, you know, ranking, right.

Q Okay. So how about I ask it this way: However appropriately measured, would you agree that the calculated lipophilicity for 5-HMT, based on its

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structure, fell within the range of other compounds that had been deemed to be sufficiently absorbed?

A Can you --

MS. WOOTEN: Objection, form.

THE WITNESS: Oh, I'm sorry. Can you show me an example where someone calculated the --

MR. TRAINOR: I can. I sort of didn't have that in my order here, so maybe we'll come back to it.

THE WITNESS: I'll be happy to rest a minute or --

MR. TRAINOR: Okay.

THE WITNESS: -- whatever is most convenient for you.

MR. TRAINOR: Okay, okay.

Q (By Mr. Trainor) All right. So about the prodrugs, you said it's relatively easy for a medicinal chemist to make an ester, correct, and that was the case in 1998, 1978, probably?

A Yes, sir.

Q Okay, but just making an ester of a compound does not mean that it will be a prodrug, correct?

A I think -- well, the enzymes that hydrolyze

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esters are widely distributed. They're in pretty much -- they're in serum, they're in liver, they're in most cells. So it's reasonable to expect that if you make an ester, the esterases will cleave that ester.

Q Okay. But, again, even if you make an ester and esterases cleave that ester, that doesn't necessarily mean that you've made a prodrug, correct?

MS. WOOTEN: Objection, form.

THE WITNESS: Well, now, if the drug is cleaved in vivo, I would say that you have a prodrug.

MR. TRAINOR: Okay.

THE WITNESS: It may not be a perfect prodrug.

MR. TRAINOR: Okay.

THE WITNESS: But it is, in fact, if it releases the active.

Q (By Mr. Trainor) Well, according to Bundgaard, which is another one of the papers that you rely on -- let me get that for you. Exhibit 1012. Let me keep talking and I'll hand it -- the accepted definition by those skilled in the art in 1998 of a prodrug was one where the delivering molecule is inactive, correct?

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MS. WOOTEN: Objection, form.

THE WITNESS: If you wish to argue that, you know, that doesn't affect what you're trying to accomplish, in my opinion. You can call it something else if you like. If your modified derivative has some affinity for your target receptor, it still, you know, crosses, the drug is liberated, the desired drug is liberated by the esterases, and you've accomplished your task.

So the -- you may say that, well, by the strictest definition, this isn't a prodrug, but what we've done is made our target molecule appropriately bioavailable.

MR. TRAINOR: Okay.

THE WITNESS: And that's our goal.

Q (By Mr. Trainor) I understand that that's the goal, but I want to figure out what the definition was, to your understanding, in 1998 to skilled artisans.

MR. TRAINOR: So just for the record, I've handed Dr. Patterson what is Exhibit 1012 to both of his declarations. This is a series of chapters, maybe the whole

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book, but first author is Bundgaard.

Q (By Mr. Trainor) And I believe -- do you have reason to believe that Bundgaard, in this treatise that you rely upon, does not define a prodrug as inactive?

MS. WOOTEN: Objection, form.

THE WITNESS: You know, I don't recall if Bundgaard defines prodrugs as active or inactive. What I will say is that people are very often sloppy because we talk about prodrugs as being active -- or inactive, I'm sorry, until, you know, some activation event happens, either metabolic or spontaneous.

Nucleosides are molecules that require metabolic activation in order for them to inhibit the polymerases for which they're designed. People don't usually refer to nucleosides as prodrugs, but if we accept that strict definition, they are, in fact, prodrugs. I won't argue, you know, such small points.

Q (By Mr. Trainor) Okay. Well, I don't think it's a small point because the majority of your opinion as to the obviousness of making a prodrug of 5-HMT

stems from this Bundgaard reference, who's published a whole book on prodrugs. I have it here. If you turn to the very first page --

A Okay.

Q -- page 8, Chapter 1, "Design of Prodrugs," in the very first paragraph.

A Page 8 of the exhibit or page 8 of the reference?

Q I'm sorry, it's page 8 of the Exhibit 1012. Sorry.

A Okay. There I am, okay.

Q In the middle of that introductory paragraph, it says, "The prodrug per se is an inactive species, and therefore, once its job is completed, intact prodrug represents unavailable drug." Do you see that?

A Okay.

Q So is it fair to say that at least according to this prior art reference, the definition of a prodrug is one that remains inactive even if it's not -- if it doesn't convert?

MS. WOOTEN: Objection, form.

THE WITNESS: Okay. According to Bundgaard, the way he defines it there.

MR. TRAINOR: Okay.

Q (By Mr. Trainor) So is it your view that that is not the appropriate definition that's used in this treatise?

A I'm okay with that even if my attempt to -- or my attempt isn't to make an inactive; it's to get the target molecule into the blood and have the target molecule released by the esterases.

Q Right. That is a --

A You're right.

Q That is a goal?

A So if you wish to say that's not a prodrug, I'll accept your correction.

Q Okay. Well, let's say that you esterify a compound and it cleaves, but a certain percentage of that prodrug doesn't convert. It's quite important that that prodrug remain biologically inactive, correct; otherwise, we're just back at the problem that we had with tolterodine that you wanted to eliminate, no?

A That might present some concern.

Q Okay.

A But the main problem to eliminate by prodrugging is the variable metabolism by CYP2A.

Q Understood.

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A Uh-huh.

Q And prodrugs are designed for all sorts of reasons, correct?

A Yes.

Q Including improving absorption?

A Yes.

Q But so my point was simply, you would agree with me that just esterifying a compound and confirming that it cleaves does not necessarily mean that you have made a successful prodrug to the extent that the prodrug is active, correct?

MS. WOOTEN: Objection, form.

THE WITNESS: What I would say is, you know, just because of an ester, what -- my response to that is if that becomes a concern, I think that among a -- you know, a selection of esters, I would find one with the desired properties.

MR. TRAINOR: Right.

THE WITNESS: So...

Q (By Mr. Trainor) And until you find one that meets that definition of a prodrug, correct?

MS. WOOTEN: Objection, form.

THE WITNESS: If I care about that,

so...

Q (By Mr. Trainor) Well, if you don't care, then you might end up with what you termed a prodrug-like compound like tolterodine, correct?

A Yes.

Q And then we now have three entities: the promoiety, the potentially active prodrug, and the metabolite. In that event, doesn't that further exasperate the concerns you had with the complex metabolism of tolterodine?

A Well, the esterases are typically efficient, so I would be less concerned that the ester were metabolically stable.

Q I understand that preliminarily, at least, that's got to be your first concern; if it doesn't cleave, it doesn't convert, then you're on to the next one. But my question is: If your prodrug is not inactive, then you haven't solved the very problem that you've identified as tolterodine having, correct?

MS. WOOTEN: Objection, form.

Q (By Mr. Trainor) You haven't eliminated a pathway, you haven't eliminated an active, correct?

A Well, I wouldn't say that I haven't eliminated a pathway because I've eliminated the CYP2D6

pathway of concern.

Q Okay.

A Okay?

Q But you -- in that example that I just provided, you would still have two active ingredients, correct, or two active moieties, correct?

A You know, if it were active and it would -- I think it would also depend on the degree of activity. You know, some actives we define, you know, have activity that's so low that it's not clinically relevant.

Q Okay, but you have to confirm that, correct?

A It would be a matter of routine testing.

Q Is that right? How routine would that be?

MS. WOOTEN: Objection, form.

THE WITNESS: Well, since the assays are established in this case, you use the existing assays.

Q (By Mr. Trainor) Well, but in order to confirm that you have an inactive prodrug, you've got to test that in humans, no?

A You would know that what -- by the cell culture methods discussed with the CHO cells, whether it had an affinity for the M3 -- or the muscarinic

receptors.

Q Why don't you turn to page 4 of Bundgaard, please.

A Four of the --

Q I'm sorry, page 4 of Bundgaard, page 10 of the exhibit.

A Okay. I thought you said page 4 of the actual text. I just want to make sure we're on the same page.

Q Okay. Now, in this first full paragraph that begins "Sometimes," this paragraph is reporting about these penicillin esters that I want to get to. You mentioned them in your declaration.

For the moment, I just want to focus your attention on -- if you look at the second sentence -- third sentence, rather, it says, "Although various simple alkyl and aryl esters of the thiazolidine carboxyl group hydrolyzed rapidly to the free penicillin acid in animals, such as rodents, they proved to be far too stable in man to have any therapeutic potential. This illustrates also, as do many other examples, the occurrence of marked species differences in the in vivo hydrolysis of ester prodrugs." Do you see that?

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A Yes.

Q And that would suggest to you that you would have to take your prodrug all the way into humans to determine whether or not it has therapeutic potential or therapeutic drawbacks, correct?

A Certainly not.

MS. WOOTEN: Objection, form.

THE WITNESS: Oh, sorry.

Q (By Mr. Trainor) No?

A Certainly not, no.

Q How do you reconcile that with this --

A The comment --

MS. WOOTEN: Hold on.

THE WITNESS: Okay. Sorry.

MS. WOOTEN: Whatever the question is, just be clear about who's talking.

THE WITNESS: Okay. Sorry.

MR. TRAINOR: Sorry.

THE WITNESS: I didn't mean to step on you.

MR. TRAINOR: That's okay.

THE WITNESS: I'm eager to answer because this is -- routinely is. You use human serum. Esterases are abundant in human

serum. In addition, they're abundant in human liver, so you could use, for example, the S9 fraction or the cytosolic fraction of liver homogenates without going in vivo.

Q (By Mr. Trainor) Right, but that's not going to tell you anything about whether that unmetabolized prodrug binds to certain off-targets, correct?

A Which you also and big pharma also have established assays in order to measure those.

Q Which are? What were those in 1998?

A I don't have a laundry list of them, but, you know, you would use the same established assays that -- used as a routine to translate for clinical translation of the parent drug.

Q Okay, but can you just explain that to me? How do you assay for activity at nontarget receptors without administering the prodrug to subjects?

MS. WOOTEN: Objection, form.

Q (By Mr. Trainor) Can you just explain the assay to me?

A There is a -- since I'm not an entomologist, I'm not going to attempt to go into the technical details.

Q Okay.

A These things exist. There is a Chinese hamster ovary cell model that exists for the muscarinic ones.

Q Okay. In any case, can we just talk about the -- let's just talk about the properties that are required of a prodrug in your view or in your opinion as of the view of the skilled artisan in 1998. So it needs to convert, correct?

A (No verbal response.)

Q You may be looking for a certain rate of conversion, correct? Yes?

A Yes.

Q Sometimes you want a very rapid rate of conversion, correct?

A Yes.

Q Other times not so rapid?

A Depending on your reason for it.

Q Okay. And if your reason is to improve absorption, what rate of conversion are you looking for?

A I would look for a relatively rapid rate of conversion.

Q Okay. Now, let's just continue on. So then the prodrug needs to be stable pre-administration,

correct?

A Yes.

Q And would you describe lability as the same thing as conversion rate?

A That would depend on the context. We could discuss enzymatic lability, chemical lability, right?

Q Uh-huh. Okay. You need to ensure that the prodrug is inactive; we discussed that. You would also need to ensure that the promoiety is not itself toxic or active, correct?

A Yes.

Q And are there any other properties of a prodrug that you're looking for in designing one?

MS. WOOTEN: Objection, form.

THE WITNESS: You covered the major ones, I believe.

MR. TRAINOR: Okay.

Q (By Mr. Trainor) So -- and in the prior art by 1998, it was known that simple alkyl esters often had poor stability, correct?

A Well, poor enzymatic stability can isolate most simple alkyl esters. Put them in a bottle.

Q Okay. So you do not agree that the prior art reported simple alkyl esters were not always stable?

A Well, were not always stable, that I think is true.

Q Okay.

A Most of them, the simple alkyl ones, you can isolate and put in a bottle, keep in a lab. They're reasonably stable.

Q Okay. And would you agree that in the prior art prior to 1998, there were a number of examples where simple alkyl esters did not sufficiently convert?

MS. WOOTEN: Objection, form.

THE WITNESS: Bundgaard mentions some specific examples.

Q (By Mr. Trainor) Are these the Ampicillin -- the penicillin prodrugs?

A That's one.

Q Okay. So now let's look back at the reference. So if you look at the table of --

A Is it page 4?

Q Yeah, well, I'll just go back to the first page because I got caught up looking at the rat issue with you.

So the introduction, he's discussing, you know, use of prodrugs and active drug species containing hydroxyl groups can be converted. And as he

gets down to page 2 with this brief intro, it says -- at the end of the text on page 2, before the table, it says, "Various reviews have dealt with esters as prodrug types, and therefore this important class will only be briefly treated herein." Do you see that?

A Right, past esters have been considered as prodrug types.

Q Right.

A Yes, I see that.

Q Did you -- did you ever review those references that he cites as previously treating, you know, basic ester prodrugs, 6 and 7 there? I think the author is Bodor or something like that, B-O-D-O-R.

A I don't recall looking at those specific --

Q Okay. So then he transitions to say -- I could paraphrase -- here's what's new or what's going on with the ester prodrugs, and he gets into that in Section 2. And then it carries over onto page 4, and as you just suggested, there's a discussion of these penicillin esters. Do you see that?

A Okay.

Q And there are three examples, I believe, of penicillin esters that have been made and are being reported on. I think you referenced them in your

declaration. But in any case, what Bundgaard teaches here is that the simple alkyl esters for use as penicillin prodrugs didn't quite work, correct?

A Uh-huh.

Q And so the solution was to make these special double esters; is that right?

A Is that Scheme 1?

Q I'm reading the middle of the paragraph there. It says, "A solution to the problem was found in 1965...who showed that a double ester type" -- "a special double ester type of benzylpenicillin was hydrolyzed rapidly."

A Okay.

Q So what do you understand him to be reporting there about the simple alkyl esters and the need for double esters?

A In this specific case, the simple alkyl ester didn't work, so he used a different type of ester in order to solve the problem.

Q Okay. So this would be at least one example where the simple alkyl ester just won't work with a particular compound as a prodrug, correct?

A For the these beta lactam -- or the beta-lactam penicillin, that appears to be the case.

Q Okay. Now, if you have to make a double ester, is it -- is the resulting prodrug any less beneficial than a simple alkyl ester?

MS. WOOTEN: Objection, form.

THE WITNESS: You've accomplished the prodrugging task. I might be, in this case, a little concerned about the release of formaldehyde, depending on the dose, but you've still accomplished the task.

Q (By Mr. Trainor) Okay. Now, the double ester that he's describing here -- I'm trying to see -- I think it's Scheme 1, like you said.

A Uh-huh.

Q So that is a two-step metabolic process, correct?

A No.

Q No?

A The first step is enzymatic, and the second is spontaneous.

Q I see. But in any event, that's more complicated than your simple one-step --

A Right, this is a case where -- and keep in mind, organic chemists like me sometimes say it's steric. In this case, I think it is, in fact, steric.

That position is rather sterically -- is very sterically congested, and Bundgaard says, well, what you do is you get the promoiety a little bit further away and then let the second step happen spontaneously. And that's a special case, you know, given as an exception, and I don't think that's meant to be interpreted as a general example.

Q Right, but it nonetheless is an example of how you design a prodrug in instances where a simple alkyl ester or simple aryl ester may not work?

A That's right.

Q Okay. Now, does the double ester penicillin prodrugs -- strike that.

Do the double ester penicillin prodrugs have more carbons than the simple alkyl esters?

A I haven't sat down to count that. I think it would depend on the -- in this case, the type of alcohol used to make the simple ester and then the type of acid used to make, you know, what you refer to as a double ester.

Q Okay.

A So some of them might; some of them might not.

Q Okay. In some cases, would they exceed six

carbons?

A Bundgaard doesn't give an example of an alkyl ester here that does.

Q No, no, no, no. I'm just asking about the special double ester penicillin prodrugs.

A Right, the -- these carboxymethyl esters that Bundgaard lists here, none of them contain -- the alkyl ones don't contain more than six carbons, the alkyl moiety of that, so there's a four-carbon one and a two-carbon one listed here.

Q When you say "listed," can you direct me --

A Okay, I'm sorry. It is the top of page 5.

Q You mean the illustration?

A Yes.

Q Okay.

MS. WOOTEN: Page 5 of the book.

THE WITNESS: Thank you, page 5 of the book.

MR. TRAINOR: Page 10 of Exhibit 1012?

THE WITNESS: Yes, sir, page 10.

Q (By Mr. Trainor) Okay. Now, just to -- turning back for a minute to the -- well, one of the things that you say, for the predictability of the alkyl esters that one would experiment with, is the

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Lipinski rule of five. Do you remember that?

A Yes, I do.

Q Okay. Let me hand you that.

MR. TRAINOR: And this is -- what I'm handing the witness is Exhibit 1019 in all of his -- in both of his depositions.

THE WITNESS: After we complete this question, is it okay if we have a bathroom break?

MR. TRAINOR: Of course.

THE WITNESS: Okay. Thank you.

MR. TRAINOR: Actually, I don't have a question. I was just giving you the document, so we can go off the record. That's fine.

THE WITNESS: Okay. Thank you.

MR. TRAINOR: Of course.

(Recess taken.)

Q (By Mr. Trainor) So before we broke, I handed you Exhibit 1019, but I actually -- for now I want to ask you a few more questions about Bundgaard, which is 1012, so sorry for the confusion.

A That's okay.

Q So in Bundgaard, there is a table, Table 2,

which is at page 9 of the exhibit and page 3 of the document that I believe you reproduced in your declaration. I'm certain of it. And there are -- this is a -- why don't you explain what this table reflects, Table 2.

A These are specific examples of ester-type prodrugs of hydroxy compounds, so phenols and alcohols.

Q Okay. So all of the drugs in the left-hand column of Table 2, those are successful prodrugs; is that right?

A They have been on the market at one time. I'm not sure if all of them are -- well, you know, here in "Drug" it says phenols, so that's a class of molecules; that's not a specific drug.

Q Okay.

A Right? So we don't want to issue such a broad, blanket statement.

Q Okay. And the middle column describes the type of ester that was used to esterify the corresponding drug in the left-hand column; is that right?

A Yes.

Q Okay. Now, there are a number of different types of esters in this table, correct?

A Yes.

Q Okay. And they're not all simple alkyl esters, correct?

A That's right.

Q Okay. There are carboxylate and carbonate, phosphatase esters, monoesters, diesters, and so on and so forth.

Now, are all of the esters that are listed as examples of esters in these known prodrugs esters having less than six carbons?

A Many of them are, but not -- and some of them, you know, carbonate esters, for that we don't know. Your phosphate ester, that's not a -- that's an inorganic phosphate ester. Many of them are, but not -- let's see. I'm looking through. Aromatic, the aromatic ones would have at least seven, so not all of them.

Q Okay, but it's fair to say that this Bundgaard reference teaches a number of successful ester prodrugs where the ester group comprised more than six carbons?

MS. WOOTEN: Objection, form.

MR. TRAINOR: I don't know what's wrong with the form, but I can ask the question

again.

Q (By Mr. Trainor) Is it fair to say that this Bundgaard reference teaches a number of examples of known prodrugs where the ester group comprised more than six carbons?

A Some do.

Q Some do, so --

A Some are -- some contain more than six carbons.

Q Okay. So the answer is yes?

A Yes.

Q Okay. Now, a person of skill in 1998 could have tried to esterify 5-HMT, assuming they wanted to make a prodrug, with a number of these esters in Table 2, correct?

A The person could, yes.

Q Are there any of these ester groups listed in Table 2 that, for reasons beyond my skillset, would not -- would not be available as potential ester groups?

A I don't think so.

Q Okay. Now, if you page through the rest of this chapter in Bundgaard, and we're only going to focus, I believe, on this first chapter, after the

discussion of esters in Section 2, we get to, on page 10 of the reference, page 13 of Exhibit 1012, a new section on "Prodrugs for amides, imides and other NH-acidic compounds."

A I'm sorry, I lost the page here.

Q So page -- if you're looking at the bottom numbers, it's page 13.

A Okay, I'm there.

Q Okay. Now -- and then there are a number of examples in this next section. The first is N-Mannich bases.

A Okay.

Q Could a person of skill have attempted to make a N-Mannich base prodrug of 5-HMT in 1998?

A I think so, yes. The -- in this case, though, I don't think they would be -- you know, according to the description here, I don't think they would really be -- because they're talking about NH-acidic compounds, so amides, imides, carbamates, hydantoins for aliphatic and aromatic amines, right? That's not the class of molecule that we're dealing with.

Q Okay, so this teaching of -- well, that's a fair point. So this section is discussing the

application of N-Mannich bases to specific classes of compounds of which 5-HMT would not fall --

A Right.

Q -- nonetheless, in your experience, would it be possible to make a N-Mannich base prodrug of 5-HMT?

A Since it's a tertiary amine, I think that would be a bad choice.

Q Okay. Now, how about if you turn to page 16 of both the reference and the exhibit.

A Okay, I'm there.

Q There's a discussion of N-hydroxymethyl derivatives.

A I see that.

Q Could N-hydroxymethyl derivatives be conjugated with 5-HMT to make a potentially viable prodrug?

A Okay, sorry, ask the question again. I'm sorry.

Q Could you make a prodrug of 5-HMT by making it an N-hydroxymethyl derivative?

A N-hydroxymethyl? Since it's a tertiary amine, I think that would be a bad choice.

Q Okay. Impossible or bad choice?

A It would be very difficult to -- in this

case, you would be quaternizing that tertiary amine.

Q Right.

A I think that would likely give you an unstable --

Q Got it. Okay.

Now, if you go to the next N-Mannich base example, this is at page 18 of Exhibit 2012 [sic] and page 21 of the reference.

A Okay.

Q These are N-acyloxyalkyl derivatives.

A Okay.

Q Now, you would agree that these would be possible prodrug constituents for 5-HMT, correct?

A In the context of this, no, I do not, because once again, the example here is for prodrugging a primary or secondary amine.

Q Well, I'm looking at 3.3. Unless I'm reading this incorrectly, it says, "In recent years, N-acyloxyalkylation has become a commonly used approach to obtain prodrugs of various amides, imides, hydantoins, uracils, tertiary or N-heterocyclic amines." See that?

A Okay, yes.

Q So would you agree that in 1998, one option

for a prodrug of 5-HMT would have been N-acyloxylalkyl derivatives?

A That would be one option.

Q Okay. Certainly according to --

A According to --

Q -- Bundgaard?

A -- Bundgaard.

Q Okay. Now, if you go to page 21 of Exhibit 1012, and this is page 27 of the chapter --

A Okay.

Q -- there's a section that begins at No. 4. The heading is "4. Prodrugs for amines." Do you see that?

A Okay.

Q So would you agree that 5-HMT, being an amine, would be capable of being made into a prodrug by, for example, N-acyl derivatives?

A No.

Q No. Okay.

A It's a tertiary amine.

Q Okay. And let's see. If you go to page 25 of Exhibit 1012, and it's page 35 of the chapter, "Quaternary Derivatives of Tertiary Amines."

A Uh-huh.

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Q Now, we've been across this a few times today. Could you explain to me why making a quaternary derivative of a tertiary amine would not be useful as a prodrug?

A In this case, the idea is to make it more lipophilic. You're putting a charge on that nitrogen that's not going to accomplish that.

Q I see. And that's because this method at 4.3, the quaternary derivatives of tertiary amines, would be useful to make a prodrug to solve a solubility problem as opposed to an absorption problem; is that right?

A I would use it --

MS. WOOTEN: Objection, form.

THE WITNESS: Oh, I'm sorry. I would use it for such a reason.

MR. TRAINOR: Okay.

Q (By Mr. Trainor) Okay. Now, just flipping over here, page 36 and -- yeah, 36, there is a separate section on Mannich bases, I guess Mannich bases under the greater heading of "Prodrugs for amines."

A Uh-huh.

Q So I guess consistent with what you had mentioned earlier, you'd agree that according to

Bundgaard, N-Mannich bases are -- would have been available as alternatives to esters as prodrug substituents of 5-HMT?

A I suppose you could attempt to do that at the ammonium moiety.

Q Well, there's no ammonium moiety in 5-HMT.

A In water, it's going to be proteinated, so that's what I was referring to, so the tertiary -- the amino moiety, then.

Q I see. So if you were to design a prodrug using an N-Mannich base, according to Bundgaard, of 5-HMT, you would be making the substitution on the amino group?

A Yes, sir. In fact, in Scheme 16, he gives the example as an amide.

Q Scheme 16?

A I'm sorry, Scheme 15, about three-quarters of the way down, he gives that as an example of, you know, using an amide, and the examples given in Table 12, you know, Mannich base formation of amines.

Q Okay. And so in your declaration, you provide your view that the person designing a prodrug of 5-HMT would have had to select between the two and five or both positions of the phenyl ring.

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Does this disclosure in the Bundgaard reference at page 36 and 37 change your view about the possible locations for the location of the pro substituent?

MS. WOOTEN: Objection, form.

THE WITNESS: It doesn't change my view about the possible locations, and it doesn't change -- it doesn't change my view about the ones to begin with first, the ones for which I would select.

Q (By Mr. Trainor) Okay. So is it your testimony that you would begin with the hydroxyl groups on the phenyl ring as a matter of first course in designing a 5-HMT prodrug, but it would also be possible to substitute a Mannich base on the amino group even if you didn't try that first; is that right?

MS. WOOTEN: Objection, form.

THE WITNESS: I think it would be a bad idea to -- I certainly wouldn't try to derivatize that tertiary amine as a first course of action.

Q (By Mr. Trainor) Why not?

A Because the ester formation is simpler, and we derivatize that tertiary amine, then we're typically

going to end up with a clot, and then that's not going to help me get it across the gut, I don't believe.

Q Okay. Okay. And how about these other examples on page 38 and 39 of Bundgaard, the Schiff bases at 4.5 and the enaminones at 4.6?

A Right, those wouldn't be appropriate because a Schiff base is the result of reaction between a primary amine and a ketone.

Q Okay. I got you.

All right. Let's see if there's anything else here. Now, at page 51, Bundgaard is disclosing a new type of prodrug. This is No. 6 in the sequence of the chapter. It says "Ring-opened derivatives as prodrugs for cyclic drugs."

A Uh-huh.

Q Would 5-HMT be characterized as a cyclic drug?

A Well, there are phenyl rings on it.

Q That's why I ask.

A So you might -- I wouldn't consider that cyclic in the same way as the example given here, as the barbiturate.

Q Okay.

A Right.

Q And I suppose if we get to page 62 of the chapter, which is page 39 of the Exhibit 1012, that your answer would be the same as to cyclic prodrug derivatives?

A Under 7.1, lactones?

Q Uh-huh.

A Right.

Q That's for compounds with open chains?

A Right.

Q I see. Okay.

Okay. And just one more. When you get to page 76 of the chapter, page 45 of Exhibit 1012, there's a short discussion here about "Enzyme-specified Prodrugs for Acyclovir."

A Uh-huh, I see that.

Q I wanted to ask you about that. You see acyclovir come up in a lot of these prodrug references. Can you just explain what Bundgaard is teaching there? Is this an instance where -- I'll let you explain. Sorry.

A Okay. Let me take a few minutes to see what Bundgaard says about the molecule.

So in this case, Bundgaard describes poor oral availability because of poor water solubility,

right, and also low lipophilicity, and then -- so there are some prodrug approaches. So the Molecule No. 151 here is one such example, so it's -- you know, Bundgaard tells us it's more water soluble, and then there's an adenosine deaminase that converts it to the drug that way, so it dissolves better in the gut. And so the examples here are given as examples to improve water solubility so that it gets in better.

Now, acyclovir is one of those that those of us who have experience in nucleosides look to a lot, and there's a valacyclovir prodrug, which is a valerate ester, and there's a different approach to that --

Q Right.

A -- right, so in that case, you solve that molecule -- solve that issue -- so in that case, you're working on the poor lipophilicity with that one.

Q Okay. Is what's being described here the design of a prodrug of acyclovir to target a specific enzyme like CYP2D6 as opposed to just targeting esterases?

A It depends on which approach you're taking. So valacyclovirs get -- once it gets in, right, so this is one of these nucleoside-type molecules where we discussed earlier where one might say valacyclovir is

itself a prodrug, though that's not -- often not the case.

So that molecule is phosphorylated by a kinase that's in the virus. And then that gets converted to the triphosphate, and then that becomes a substrate for the viral polymerase, and that gets incorporated in the copy of the viral genome. And then when it's there, there's -- it can't elongate the chain, so it inhibits viral replication that way.

Q Okay.

A I'm not sure that --

Q No, no, no, no, I get it.

A Yeah.

Q So just to -- I want to sum up on Bundgaard here. Let me just go back to that table that is reproduced in your declaration at paragraph 61.

A I'm working on it.

Q Can you tell whether any of the ester groups in Table 2 are or could be mixed diesters?

A Mixed diesters? He doesn't specify mixed diesters. With epinephrine, there's a dipivaloate, which is -- in this case, they're using the same pivaloate for two hydroxyls.

Q Uh-huh, okay, but in any event, this --

Bundgaard discloses a number of esters that can and had been previously used as ester substituents on known prodrugs, correct?

A Yes.

Q And there's nothing -- I think we've just gone through the whole chapter in Bundgaard, but there's nothing in Bundgaard that teaches the isobutyryl ester specifically, correct?

A I think so, yes. I don't recall seeing a mention.

Q Okay. So the answer is that's correct?

A That's correct. I'm sorry.

Q And the opinion that you have that the person of skill in designing a 5-HMT prodrug would start with simple alkyl esters is based on the ease of synthesis; is that right?

A That, and it would appear that -- to me, that they would give us the desired increase in lipophilicity, right, so -- and they're commercially available, they're similar examples to the pivaloate described in Bundgaard, the valerate, you know, esters that have been used for nucleosides.

Q Uh-huh. The same would be true for carbonates, though, correct?

A A carbonate is an alternative approach.

Q All right. What I meant was ease of synthesis, commercially available would give you more lipophilicity?

A That could be done, yes.

Q Carbonates could accomplish that as well?

A They could.

Q Carbamates could accomplish that as well?

A They could.

Q How about ethers?

A I would select away from ethers.

Q Why is that?

A Because I would -- I might be worried that they wouldn't be as labile as an acyl derivative. And the ethers I'm aware of are frequently oxidized to the corresponding -- or to an ester and then are cleaved by the esterase.

Q Okay. How about carbonyls, would they be available as alternatives?

A Can you describe what you mean by a carbonyl?

Q Let's come back to that when we get to the patent.

A Okay.

Q But in any event, carbonates, carbamates, and

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alkyl esters would be available as alternatives, easy to synthesize, commercially available, and could increase lipophilicity; is that right?

A Yes.

Q What about phosphate esters?

A That -- a monoester, I would -- right, or a diester, I would steer away from. A triester could be done. I would steer away from that because such things are a little more difficult to do.

Q In what way, the synthesis?

A The synthesis and isolation.

Q Okay, okay. Okay. And for the esters that are disclosed in Table 2 of Bundgaard here, and I know that they're stated very generally -- diacetyl ester, mono and diesters, carbonates, and so on and so forth -- my question is: While Bundgaard discloses these as having been used successfully in the past, there's no teaching in here that correlates a particular ester with, for example, stability, correct?

MS. WOOTEN: Objection, form.

THE WITNESS: He doesn't say much about stability except in a few specific cases where the stability wasn't desired.

MR. TRAINOR: Okay.

Q (By Mr. Trainor) Okay. So he doesn't teach any sort of general correlation between a particular type of ester and a particular level of stability, correct?

A Right.

Q And it doesn't teach anything about a particular ester type and a level rate of conversion, correct?

A Uh-huh.

Q Yes?

A Right.

Q Same would be true if I said it doesn't -- Bundgaard doesn't teach any correlation between a specific ester type and a penetration rate, correct?

A Right.

Q And Bundgaard doesn't teach any correlation between any specific ester type and the activity or inactivity of any unconverted prodrug, correct?

A Right. What he does teach is that it's a mature formation of these esters. These are mature --

Q Understood.

A Right, right.

Q Understood. So it's well known how to make all of these esters, is what you're saying?

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A Right, that it's -- yeah, that type of prodrug is relatively mature.

Q Okay. But the skilled artisan at the time, would you agree, would have to make a number and screen them and see which of the ester prodrugs has the most ideal properties as a prodrug, correct?

MS. WOOTEN: Objection, form.

THE WITNESS: I would do such a thing with the expectation that one of them or maybe multiple ones would have properties good enough.

MR. TRAINOR: Understood, understood.

Q (By Mr. Trainor) But in advance of making them and understanding that you would have that expectation, in advance of doing so, there's no teaching in Bundgaard as to which specific ester conjugated to a particular compound would end up being one or more of the successful ones that you made, correct?

A Correct.

Q Okay. Now -- you good or you want to take a minute?

A I'm comfortable.

MR. TRAINOR: Are you okay?

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MS. WOOTEN: Yeah.

MR. TRAINOR: Okay. We can put the Bundgaard aside.

(Discussion off the record.)

Q (By Mr. Trainor) Now, I had previously handed you Exhibit 1019, this Lipinski paper.

A Okay.

Q And to give you some context, so if you go to paragraph 121 of your declaration, Exhibit 1003, it's paragraph 121, page 54.

A Okay.

Q There is a discussion of the Pfizer rule of five disclosed in this Lipinski publication; is that right?

A Yes.

Q And just so the record is clear, if you now look at that Lipinski -- Exhibit 1019, page 7 of the exhibit, page 9 of the publication.

A Okay, Lipinski, page 9.

Q Okay. And in the left-hand column, in the middle, there's sort of a bunch of text offset that begins, "There are more than five hydrogen-bond donors." Do you see that?

A Yes.

Q Is it fair to say that that's the Lipinski rule of five right there?

A Yes.

Q Okay. So can you explain to me how, if at all, the person of skill would utilize this Lipinski rule of five in conjunction with Bundgaard to design successful prodrugs of 5-HMT?

A Okay. I would use that to limit my choice of acyl groups to those that would not exceed the lipophilicity. And the reason is that, you know, not just simply because Lipinski writes against it, but when you do that, you end up with poor dissolution, poor solubility, and so it doesn't get in. So Bundgaard teaches, you know, that the esters are a viable approach.

Q Right.

A And I would select for simple acyl groups first because they tend to be more stable than carbamates and carbonates. Many of those are acid labile, and so I would be concerned, you know, upon dissolution in the stomach, they may not be as stable as, you know, a simple ester.

Q Okay. Now, would it be fair to say that looking at the catalog of esters that can be used for a

prodrug, as we just did in the Bundgaard Exhibit 1012, that ester groups other than simple alkyl esters could be used to make a 5-HMT prodrug and still fall within the Lipinski rule of five?

A Yes.

Q Okay. Are there any types of esters or other prodrug substituents that we looked at, like the N-Mannich bases and things like that, that would be more likely not to meet this rule of five?

A I don't think so.

Q Okay. And would you agree or have you considered -- strike that.

Have you considered whether 5-HMT per se, not in prodrug form, itself meets the Lipinski rule of five?

A It doesn't violate the rule of five, but since it's so polar, it violates -- it's a -- it raises a flag saying -- you know, in the same way that nucleosides raise a flag, right; they're so polar, right, they just don't get across the membranes very well. And that would be my concern, that it's so polar that it doesn't get across membranes very well. That's not discussed in Lipinski, however.

Q Uh-huh. Because isn't it the case that

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Lipinski teaches these five rules because they are indicative or inform permeation and solubility but permeation?

A Right.

MS. WOOTEN: Objection, form.

THE WITNESS: I think that's true, and I would use it in modifying the 5-HMT.

MR. TRAINOR: Okay.

Q (By Mr. Trainor) So is it your view that the Lipinski rule of five should not apply when you're dealing with a polar molecule or not be used or relied upon?

A I think those sometimes are exceptions.

Q Okay. Now, so let me ask you -- are you sure you're good? I could actually use just a quick run to the restroom.

(Recess taken.)

Q (By Mr. Trainor) Dr. Patterson, I don't know the answer to this. Do you know whether or do you have a view as to whether if 5-HMT was delivered per se or otherwise, whether it undergoes first-pass metabolism?

A Since it's metabolized in the liver, right, and this depends on the mode of administration, so since that -- you know, it's administered orally, I

presume, right --

Q Right.

A Right. So since it's metabolized in the liver, I would expect there is -- that's the first-pass organ, I would expect some first-pass metabolism occurs.

Q Okay. So tolterodine, we know, undergoes first-pass metabolism?

A Uh-huh.

Q With tolterodine, in extensive metabolizers, if it metabolizes into 5-HMT in the liver and then 5-HMT is metabolized into whatever it gets metabolized into by the 3A, that's still considered first pass metabolism even though it's the second to metabolize in the sequence of things?

A I think -- and keep in mind I'm not a pharmacokinetics guy.

Q I understand.

A I look at first pass as what happens to the -- with oral, right, is -- so it gets in through -- and then it goes from the vein to the liver. So what happens when it hits the liver first and then becomes distributed, right, and then, of course, it gets distributed to the tissues and sees the liver again,

and then additional metabolism can happen. So I look at what happens when it goes right through that vein into the liver before it gets...

Q All right. So the rule of thumb is if it's metabolized in the liver, it's first-pass metabolism?

A It can --

MS. WOOTEN: Objection, form.

THE WITNESS: It can be.

MR. TRAINOR: Okay.

Q (By Mr. Trainor) Okay. Anyway, so I want to bring you to paragraph, say, 123 of your declaration, Exhibit 1003. And the second sentence, it says, "First, it was known that conversion of tolterodine to a diester would likely create an overly lipophilic compound leading to a greasy or oily compound depending on the nature of the acyl group." Do you see that?

A Yes, I see that.

Q Did you mean to say tolterodine, or was that 5-HMT?

A That was -- that is an error. I meant to say 5-HMT because tolterodine only has one hydroxyl.

Q Okay. Okay, so when you say "conversion" here, you mean --

A Synthetic.

Q -- it was known that making a prodrug of 5-HMT using a diester would create an overly lipophilic compound?

A Depending on the nature of the acyl groups.

Q Okay. I see. So there would be certain -- there will be certain diesters that would be adequately lipophilic; is that right? Is that how to read that?

A There are, yeah, certain diesters that -- I think -- well, what I meant to say in this case is there are certain diesters that would exceed the lipophilicity expected to give good oral, you know, penetration, oral availability.

Q Right. And what is the consequence if you make a compound overly lipophilic?

A It's poorly absorbed. It can also be, you know, difficult to handle in the lab in that you get this waxy, you know, oily molecule, and the synthesis people don't like to -- and the formulation process people don't like to handle such molecules.

Q Okay. So is there some sort of ceiling on lipophilicity where a compound becomes too lipophilic to cross the blood-brain barrier?

A The rule that we like to look at is similar to the rule of five, but usually, you know,

lipophilicity of around between 2 and 4.

Q Uh-huh. Okay.

A That's outside of Lipinski, but I don't guess we're talking about Lipinski any longer.

Q Okay. In any event, back to that sentence that it was -- now that it's corrected, it should read, "First, it was known that conversion of 5-HMT to a diester would likely create an overly lipophilic compound depending on the nature of the acyl group," correct?

A Yes.

Q Okay. When you make a reference to it being known, how was that known?

A It would be guided by Lipinski is what I meant.

Q I see. So it was not -- no prodrug of 5-HMT had been made before 1998, so that's not what you meant, correct?

A Exactly.

Q Okay. So based on Lipinski, the supposition is that diesters with certain acyl groups would be too lipophilic?

A Right.

Q Correct?

A That's correct.

Q Now, it continues on, "In the art, it was known that these compounds did not have the best oral availability and were not the easiest to work with in terms of processing and storage."

And I take it that was the explanation you just provided, poor absorption and greasy and difficult to handle?

A (Witness nods head affirmatively.)

Q Okay, I understand now.

A Uh-huh.

Q Okay.

A Thank you for the correction.

Q No, that's okay.

A Pointing out my typo. No, thank you.

Q I have my moments.

A Yeah.

Q Okay. So then we get to paragraph 124, and you suggest that a monoester would be attempted by one setting out to make a 5-HMT prodrug because it would provide for a one-step process; is that right?

A Yes.

Q Okay. And so, again, it's not that a diester -- strike that.

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It's not that a 5-HMT prodrug that is a diester would not work; it's just that, in your view, a monoester is simpler and easier to make. Is that right?

A That would be one reason for doing it. It would be where I would start.

Q Uh-huh. Okay. That doesn't mean that a diester would not work as a prodrug, correct? It's just not where you would start?

MS. WOOTEN: Objection, form.

THE WITNESS: It's not necessarily where I would start, and I might say that would be more likely, you know, apriori to have some problems, as I -- as I mentioned in there, you know, two steps to release the target 5-HMT as opposed to a single step.

Q (By Mr. Trainor) But, again, there were a number of examples, for example, in Bundgaard where diesters had been perfectly fine, correct?

A That is correct.

Q Okay. Now, then you move in the next paragraph to, assuming I desire a monoester, you faced the choice of substituting at either the two or five position where the hydroxyls are located on 5-HMT,

correct?

A Yes.

Q All right. And the concern that you have that informs your opinion that the person of skill would select the two position is transesterification; is that right?

A Yes.

Q Okay. Now, in this discussion here about selecting the two position over the five and the transesterification possibility, I don't see any cites to any particular prior art. So can I ask what is the -- what is it in the art that suggested selecting the two position over the five position, if anything?

A It's known that a sterically bulky ester is more difficult to hydrolyze than one of less sterical -- from organic synthesis. You know, Bundgaard cites an extreme example where we have -- in the penicillin, it's so stable that it was undesirable.

Q Uh-huh.

A Right, right. And that, I think, is due to the steric bulk adjacent to the position that's modified, and similar here. So if I choose that position and put some substitution on the alpha carbon of that alkyl acid, I'm likely to find an ester that's

chemically stable, but still enzymatically labile.

Q Uh-huh. But I thought that teaching from Bundgaard was that the simple aryl ester failed to convert?

A That was an aryl, and I'm talking about an alkyl. I don't think the steric bulk at this is as great as that in penicillin.

Q Uh-huh. Okay. Just on -- you don't think that the steric bulk is as great with penicillin, just looking at the structure?

A Yes. In penicillin, there are two groups adjacent to the one being modified, and that's not a planar molecule. It's this lactam that's kind of a cup shape, right, so there's, you know, steric bulk, you know, around a good portion of that acid.

Here I have a carbon group, ortho to the phenol, that's substituted with a phenyl group and an amino alkyl group, so there's some steric bulk, and then -- that's a flat molecule, so we can approach from above or below. And then there's a hydrogen that's unsubstituted at the other ortho position to the hydroxyl. So that leaves it -- you know, there -- leaves it a little less sterically congested, I think, than the penicillin example we discussed.

Q Okay. But is there anything other than the penicillin example in Bundgaard that, in your view, suggested this selection of two versus five?

A One example that is mentioned in Bundgaard is acetylsalicylic acid, and that is acetylated at the phenolic position.

Q Uh-huh. Okay. Weren't there examples in the prior art of esters at the phenol position not being sufficiently labile?

A I don't recall phenolic ones.

Q Okay. Okay. Well, is there any specific teaching in the prior art as to the preferred position of the substitution in the case of diphenylpropylamines?

A I don't recall seeing that.

Q Okay. And would you agree that if you were to -- I'm getting sloppy. Would you agree that if you were to make a 5-HMT prodrug by way of homologous diester, then transesterification would not be a concern?

A Yes, I agree.

Q You would agree?

A Yes.

Q Okay. And you said something about -- I

think about 5-HMT being a planar molecule; is that right?

A The phenol moieties are planar.

Q I see.

A I didn't mean to say the entire molecule is planar.

Q Okay.

A Or planar or -- you know, the phenol is flat or very nearly flat, so...

Q Okay. Now, if the -- if it was understood how the 5-HMT or analogs of it, for example, tolterodine, bound to the muscarinic receptor, and from that understanding, it was understood that, you know, a particular position on the ring or a particular hydroxyl was important to that binding, would that impact your choice as to where to substitute the promoiety?

A It might, but I would look for, you know, relatively rapid release of the target drug. So I don't think it would have much impact on that.

Q Okay. And is there a correlation between the size of the ester group or the size of any promoiety and the ability to be -- strike that.

Let's stick with esters for a minute.

A Okay.

Q Is there any correlation between the size of the ester group and the amenability to being cleaved by the enzyme?

A I think it depends on what you mean by "size." If we're talking about steric bulk around the acyl group, like, greater steric bulk would be expected to increase difficulty in cleavage.

Q Why is that?

A Okay, so I may need to -- when you're talking to an organic chemist, it's only a matter of time before paper and pencil comes out. Let's see if we can form a mental picture.

In order to cleave the enzyme, there's a group on the esterase that has to come in and attack the carbonyl moiety, right, and so if you put a bunch of mess around it, right, a bunch of -- whatever word, then it's difficult to do. And, in fact, t-butyl acid esters are quite base stable such that they're cleavable by acid, readily cleavable by acid, but for this type of, you know, nucleophilic attack mediated cleavage, they're quite stable to that.

Q Okay. So basically, the more you crowd the base of the tree, the harder it is to cut the tree

down?

A That's --

Q Is that right?

A That's a good lay example.

Q All right. Okay. So in the -- just to make sure I get your testimony, I asked you whether there was any actual disclosure or teaching in the prior art with regard to transesterification in forming the position. Did you say that the Ampicillin or the penicillin prodrugs were an example, or did I have that --

A No, that's just an example of steric bulk --

Q Okay, okay.

A -- leading to increased stability.

Q Okay. Can you think of any examples from the prior art that describe the vulnerability to transesterification as driving the location of the promoiety substitution?

A Not from prior art with respect to HMT.

Q Okay. All right. Now, moving on to the isobutyryl ester specifically, the -- I think we -- I think you testified that there was no specific disclosure of isobutyryl in the Bundgaard textbook that we looked at, correct?

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A I think that's correct.

Q And then -- but there is this citation to a Bundgaard patent, which is Exhibit 1020. I'm looking at paragraph 129 of your report now.

A Okay. Okay.

Q Now, I believe -- let me give that to you. I'm sorry. You know what, let's hold that for a minute while I find that. Let me ask you about something else.

A Okay.

Q Let me ask you to look at...

MR. TRAINOR: You know what, we will stick to this. Bundgaard patent, Exhibit 1020, I'm handing to the witness now. It was Exhibit 1020 to both his declarations.

THE WITNESS: Okay. Uh-huh.

Q (By Mr. Trainor) Now, in paragraph 129 of your declaration, it says, "Focusing on the phenolic moiety, a skilled drug designer or developer would have started with simple acids of two to six carbons, as suggested by Bundgaard and other prior art publications such as Lipinski, and Exhibit 1020, which disclosed a group of about eight esters to try."

So that's what this is, Exhibit 1020, which,

for the record, is a PCT application or publication where the lead inventor is Bundgaard, and it's dated May 1992.

Now, I just want to get your understanding of how this Bundgaard patent teaches making prodrugs with simple carbons of two to six esters.

Are you looking at me?

A I thought you were going to -- I didn't hear a question.

Q Oh, I'm sorry.

A No, that's okay.

Q Are you familiar with this patent or this patent application?

A I'm familiar with -- I remember certain aspects of it. I certainly haven't memorized all of it.

Q Okay. Well, if you look at, let's see, page 7 of the Exhibit 1020, which is page 5 of the application --

A Okay.

Q -- it looks -- let's back up.

A Okay.

Q This is a patent directed to morphine prodrugs --

A Okay.

Q -- correct?

A I believe that's the case.

Q If you look at the cover page, right above the figure there, it says, "Title: Topical Compositions for Transdermal Delivery of Prodrug Derivatives of Morphine."

A Right.

Q Okay. So if you go back to page 5, and correct me if I'm wrong, what's being described at the bottom are a series of esters that -- and it continues on to page 6 -- that Bundgaard, in this patent, is disclosing as preferred promoiety groups at either or both of the free hydroxyls. Would that be right?

A Yes.

Q Okay. On the molecule. And this is a good -- if you look at the last set on -- first of all, are these all esters, these preferred groups from --

A They're preferred -- if I remember correctly, they're preferred -- methoxycarbonyl, ethoxy, yeah -- so they're, yeah, acyl groups used to put on the hydroxyl, and then, of course, the resulting derivative would then be an ester.

Q Okay. So the set that is on page 6, you

asked me before what I meant by carbonyl --

A I see. Okay, I understand you now. Yes, so that's the acyl group used to form the ester. Okay. Thank you.

Q Would you consider those ester groups, or no?

A Well, I would say they're the acyl part of the ester group, so --

Q Okay.

A -- for simplicity, we can refer to them as esters.

Q Is it incorrect to call them carbonyl esters?

A I would say call them acyl groups, might be the more correct way to do that. I'll try not to pick on you too much if you're not perfectly specific with chemical terms.

Q Okay. So let me just ask you, then: Are acyl groups like the ones exemplified on page 6 of Exhibit 1020, for example, the methoxycarbonyl, would those groups also have been alternative substituent groups in making a 5-HMT prodrug?

A They're certainly possible ones. In this case, the one you mentioned, the methoxycarbonyl, would be a carbonate ester. And, you know, as we discussed earlier, for the first round, I would probably select

away from that, but they are, in fact, possibilities.

Q Okay.

A I would just select away from those.

Q Okay. Then if you -- so this disclosure without any examples of these groups on 5 and 6, and then if you go to page 7 of the PCT, which is page 9 of Exhibit 20 [sic], there Bundgaard sets forth, beginning on page 7 and over to the next page, five specific examples of these prodrugs that he made. Do you see that?

A Yes.

Q Okay. Is it fair to say that of the five prodrugs he made, three were diesters, two were monoesters? Do you see that?

A That sounds about right.

Q Okay.

A Let's see. Propionyl, that's a monoester. There's the diesters. There's another monoester. So I think you're right.

Q Okay. Now, is there anything in particular about morphine that would suggest to a person of skill that diesters are among the first choice along with monoesters?

MS. WOOTEN: Objection, form.

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THE WITNESS: So --

Q (By Mr. Trainor) Well, my question was -- basically, you said you would start with a monoester because it's simple.

A Right.

Q And Bundgaard's got this patent where he makes a few monoesters, but the slight majority of these prodrugs that he makes are diesters, and I'm just wondering whether there's anything in particular about morphine that makes diesters more promising than monoesters relative to 5-HMT.

MS. WOOTEN: Objection, form.

THE WITNESS: Not that I remember.

MR. TRAINOR: Okay.

Q (By Mr. Trainor) So the -- Example 3 is a diisobutyryl.

A Okay.

Q And can you tell from the table on page 8 of the PCT -- I understand that the solubilities of these prodrugs that were made is being compared, but what does that data reflect in terms of the relative solubility of these various prodrugs?

A Well, there's a general trend, you know, with increasing log P(a), there's a decreasing solubility.

Q I see.

A There appears to be one exception, but that's a general trend.

Q Okay. So the diisobutyryl morphine is next-to-last in this solubility comparison --

A Uh-huh.

Q -- but would that teach one of skill in the art anything about the application of isobutyryl or diisobutyryl to 5-HMT?

A I'm not sure. Since the central pharmacophore is a little different, I'd hesitate to try to extrapolate the log P(a) or the solubility to, you know, this diphenylpropylamine.

Q Just because they're different structures, right?

A Right. Right.

Q I see. So the properties of a prodrug substituted with a certain ester group can't be extrapolated to the properties of a different compound substituted with the same ester group?

A Right, you could do it, but I think you need to be careful about it. I look at that and say, oh, well, the diisobutyryl, we're focusing on that, isn't, you know, extremely lipophilic, right, but if I look at

the dihexanoyl, well, gee, that's greater than four, and so I might say, well, maybe -- but I would want to be careful, but maybe if I use a diisobutyryl on this or an isobutyryl on this, I'm not going to exceed the -- you know, the log P of 5, right, maybe. You know, I would be careful, but it wouldn't -- you know, it wouldn't tell me, oh, gee, that's going to be too lipophilic or...

Q Would the data for the diisobutyryl morphine prodrug tell you to any reasonable certainty what the lipophilicity or other properties of a diisobutyryl 5-HMT would be?

A Again, I would be careful in doing that, but it -- you know, you might say, well, gee, you know, maybe this isn't going to be, you know, so lipophilic that -- right, so...

Q Okay.

A Now, my experience with others, when we start, you know, putting -- you know, doing these other molecules, sometimes it does, sometimes it gives us something more lipophilic.

Q Okay. And if you -- how often is it, when you or a skilled artisan in 1998 is designing a prodrug or a number of prodrugs, how typical is it for that

person to look to the properties of a proposed promoiety when used in a different compound or a different class of compounds?

A I think that's probably relatively common. I'll say, oh, I saw somebody do this, so I'm going to do it here. I think it's relatively common.

Q Okay. If you're dealing with an antimuscarinic diphenylpropylamine, what, if anything, would motivate that person to look to a publication on morphine?

A Similar esters, right, similar way to, you know, increase lipophilicity. I would -- you know, in my experience with, you know, nucleosides, would do the same thing with the nucleosides.

Q But this is a prior art reference that is directed to transdermal delivery of a prodrug.

A Right.

Q So how would that be relevant when you're trying to develop an oral prodrug?

A Well, we still see an increase in lipophilicity, and the -- this was cited as an example of limiting the choice of our acyl group, right, and so, you know, your first time around, if you're being aware of this, you would say, well, maybe I'll take the

same or some similar groups used here and do it and, you know, in particular for synthesis. We often apply synthetic methods from different classes of compounds provided -- you know, if it's a hydroxyl, right, you used it for that, let's see if it works here.

Q But you said you would be careful.

A I would be careful, but I would -- you know, you've got to start somewhere.

Q Right, but any -- one of the core premises of your view is that, you know, any esterification of any molecule is likely to increase lipophilicity, correct?

A Not necessarily any. If we're talking about an alkyl group, that's likely to increase lipophilicity, an alkyl group substituting on the acyl, right. Now, if it's a diacid, let's use succinate, for example, and I make a monosuccinate ester, what I end up with is an ester that's also a carboxylate. That's relatively hydrophilic, so I'm not likely to accomplish my goal of increasing lipophilicity with such an acid.

Q Well, wouldn't a person of the skill in looking for such suggestions look for alkyl-substituted compounds, you know, for the same purpose or in the same class as opposed to -- you know, why would you look to morphine as opposed to any other example in the

art where you have used alkyl groups to increase lipophilicity? You could look anywhere for that, correct?

A Right. Well, in this case, the thinking is that we want to be concerned about the possibility of transesterification. So we want to find something that's branched alpha to the acyl moiety. And so we go for the literature, and you find an example where this was done and you think, well, maybe I want to be careful, but maybe this would be a reasonable place to start as well. Right?

Q Okay. But you would agree that there would be any number of references which would also be good places to start for that sort of analogous suggestion?

A There might be. I'm sure -- well, there are other examples of branched-chain acyl groups used to make esters.

Q Uh-huh. Okay. Now, just a couple of other things. One is there's a mention in your declaration somewhere about -- ah, here it is, I think this is it -- about -- that's not exactly it -- the motivation to use -- to make a prodrug of 5-HMT because 5-HMT had been studied to some degree already with tolterodine, correct?

A Uh-huh.

Q And then there is a citation to -- I'm sorry, I can't pinpoint it to you, but I'm going to hand to you -- this is Exhibit 1026 in both declarations, and this is FDA guidance, and it's dated July -- October 1999. And my question is -- well, first of all, have you ever filed or participated in the filing of a 505(b)(2) application?

A I have not.

Q Okay. Do you know of any precedent for applying for approval of a prodrug like fesoterodine by way of a 505(b)(2) application?

A None come to mind.

Q Okay. Okay. Now, you can put that aside.

I wanted to also ask you about what I started asking you about, Exhibit 1018 to your declaration, which I'm handing to you. And for the record, Exhibit 1018 is a short publication with first and only author, Ashworth. So if you want to look at your declaration, the reference to this is at paragraph 109 --

A Okay.

Q -- which is at page 51 of Exhibit 1003.

Okay, so this Ashworth publication concerns

the approval of terfenadine; is that right?

A Yes.

Q And terfenadine -- excuse me, of fexofenadine. Sorry.

A That's right.

Q So this concerns the approval of fexofenadine, which was the active metabolite in terfenadine. So Seldane was the name of the drug with terfenadine, and Allegra is terfenadine, right?

MS. WOOTEN: Objection, form.

THE WITNESS: Did you misspeak? Allegra is fexofenadine, is it?

MR. TRAINOR: Allegra is fexofenadine.

THE WITNESS: Okay.

Q (By Mr. Trainor) And it is the metabolite of terfenadine, which was formerly Seldane; is that right?

A Yes, I think that's right.

Q Okay. Now, earlier you were referring to concerns with other drugs, including antihistamines and NSAIDs. Do you recall that?

A I do.

Q Is this the -- is this what you were referring to when you were thinking about the antihistamines?

A It is.

Q Okay. Now, originally, terfenadine, or Seldane, was marketed and approved, correct?

A Yes.

Q And there were some safety concerns after it was marketed for a while; is that right?

A Yes.

Q Which led to its removal from the market; is that right?

A Yes.

Q Okay. And was terfenadine active, as well as its metabolite; do you know?

A I'm trying to remember. I don't remember if it was.

Q Now, if you -- well, what's being disclosed in this paper, right, is that terfenadine, which was the carrier molecule, if you will, was reported to be causing Torsades de pointes. That's the same thing that terodiline that we discussed earlier was removed for, correct?

A Yes.

Q Okay. Now, isn't it fair to say that terfenadine, the carrier molecule, the former Seldane, had some activity if it was responsible for these

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cardiac arrhythmias?

MS. WOOTEN: Objection, form.

THE WITNESS: Well, it had at least an undesirable activity, an off-target effect.

Q (By Mr. Trainor) Right, and the problem was that it is also metabolized by CYP2D6, correct?

A Yeah.

MS. WOOTEN: Objection, form.

Q (By Mr. Trainor) And for those poor metabolizers who did not metabolize Seldane into fexofenadine, there were unsafe levels of the Seldane which were believed to be causing these arrhythmias, correct?

A Yes.

Q And so the solution was to just administer the active metabolite, fexofenadine, which was believed to drive the therapeutic action and did not cause these adverse effects, correct?

A Yes.

Q Okay. So this is a fairly analogous set of facts with Seldane and Allegra to the concern that you have or had, I suppose still have, with tolterodine; is that right?

MS. WOOTEN: Objection, form.

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THE WITNESS: Correct.

Q (By Mr. Trainor) And doesn't this Ashworth paper suggest, then, to the extent that your concern with tolterodine or the skilled artisan's concern with tolterodine is a legitimate one, then the solution is administration of 5-HMT per se as opposed to developing a prodrug?

A That is -- it's one example that informed my opinion, yes.

Q Okay. Well, it's inconsistent with your opinion that you would design a prodrug as opposed to a attempt to first administer the active metabolite per se, correct?

A Not necessarily. If there were problems with oral administration due to low penetration of the gut, then it would be the same case.

Q Okay. But you would agree that as of 1998, the oral absorption of orally administered 5-HMT was not known one way or the other, correct?

MS. WOOTEN: Objection, form.

THE WITNESS: It had not been disclosed.

MR. TRAINOR: Okay.

Q (By Mr. Trainor) Now, are you okay -- I'm

just going to have a last few questions on a couple of documents, but I also wanted to give you the opportunity to look at -- I want to make sure if the reference that you had in mind is something that we have, if we could take a look at it.

A It might be and I'll be glad to scan the papers, if that's what you're asking me.

Q I haven't given it to you yet.

A Oh.

Q So that's kind of what I just wanted to use the rest of the time to do.

A Okay.

Q So if you want to take, like, five minutes and then we'll finish after that, or I'll finish.

A I think that's a good idea.

Q Great, okay. Good, we'll do that, then.

(Recess taken.)

MR. TRAINOR: Okay, I'm going to hand the witness Exhibit No. 1013 to both of his declarations. This is a multipage publication, the lead author of which is Berge, I believe, B-E-R-G-E.

Q (By Mr. Trainor) Now, Dr. Patterson, toward the end of your declaration, there's a discussion about

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the obviousness of the fumarate salt of fesoterodine. I don't know if you recall that, but page 58 of your declaration, Exhibit 1003, and it begins at paragraph 131.

A I am there.

Q All right. So in this near final section of your declaration, is it a fair characterization that you were addressing the specific bases for your view that the fumarate salt of what we know now as fesoterodine was obvious? Is that a fair characterization, paragraphs 131 through, I guess, 137?

MS. WOOTEN: Objection, form.

THE WITNESS: Beginning at paragraph 131, I don't know how long it is --

MR. TRAINOR: Okay.

THE WITNESS: -- but there is discussion of that.

Q (By Mr. Trainor) All right. And so the first reference that you discuss as supporting your view that the fumarate salt of fesoterodine is obvious is this Berge reference that I handed to you, Exhibit 1013. It's not a lengthy discussion about that particular reference, but I just want to ask about the reference because you said it here.

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Now, in paragraph 132 of your declaration, you reproduce what you can confirm is at page 3 of Exhibit 1013 -- sorry -- yes, that's right.

A I think it is, yes.

Q Actually, the page is reproduced twice, but page 2 and 3 of the exhibit are the same. Oh, no, they're not. It's the same table.

MS. WOOTEN: It's just page 2 is twice.

MR. TRAINOR: Yes, there you go. In any event, rather, it's page 2 or page 3.

THE WITNESS: That's right.

MR. TRAINOR: The table that's referenced is reproduced in your declaration.

Q (By Mr. Trainor) And Table 1 of this Berge reference, Exhibit 1013, is a list, at least as of 1977, of salts that -- commercially marketed salts that had been previously approved by the FDA; is that right?

A That is correct.

Q Okay. And there are quite a few salts. I won't try to count them, but fumarate is listed there sort of a little more than halfway down in the left-hand column. Do you see that?

A I see it.

Q Okay. Now, I haven't been able to find it,

but if you think otherwise, could you tell me whether the fumarate salt is mentioned anywhere else in this reference other than in that table?

A I don't remember.

Q Okay. Okay. In any event, the -- in the right-hand column for the salt in Table 1 of the reference, Exhibit 1013, there's a percentage of times -- there's a number that represents the percentage of approved salts that that particular salt takes in the market. Do you see that?

A I see it.

Q Okay. And the indication is that fumarate salts had been marketed and approved one quarter of one percent -- one quarter of one percent of the approved salts at that time; is that right?

A Yes.

Q Do you know whether that number -- that percentage increased between 1977 and 1998?

A I don't know whether it increased.

Q Okay. And there are maybe 60 other salts here, give or take, something like that, that I'm counting in this table.

A I haven't counted.

Q Okay. That's all right.

Now, beyond the table, at the beginning of this reference, there's a bunch of text, and is it fair to say that the text of the reference teaches about specific salts that had been used with respect to specific compounds, highlighting their utility in certain circumstances, for example, to address stability, solubility, things of that nature?

MS. WOOTEN: Objection, form.

Q (By Mr. Trainor) Does that seem about right to you?

A There's much about this paper that I've forgotten, but he discusses, you know, much about the salts that have been used and some of the desirable properties trying to -- you're trying to generate with salts, if I remember correctly.

Q Okay. So, for example, if you turn to page 12 of Exhibit 1013, there's a section that begins in the second column under the heading "Absorption Alteration."

A I see the heading.

Q Okay. And just taking, for example, the discussion in that section under the first paragraph, it begins, "Several years ago, clinicians claimed that certain salts of theophylline were therapeutically

preferable to other salts or to the free acid." Do you see that?

A I see that.

Q And then what follows is, you know, citations to the literature where various salts of theophylline were experimented with or observed for purpose of evaluating the effect of those salts on those compounds of absorption; is that fair to say?

A They mention, you know, difference in oral absorption of ethylenediamine salt and compare to, say, a choline salt.

Q Okay. Now, my question about this reference is really -- taking that sample as an example, if you assume that I'm correct that the fumarate salt is not mentioned anywhere in this reference as conjugated with any particular compound for any particular purpose, if you make that assumption, my question is: Why would a person of ordinary skill in the art predict that the fumarate salt of fesoterodine or any 5-HMT analog would be any more viable as a drug than any of the other salts that are listed in the table or discussed in the text?

A Well, my position is that it's among a limited set of approved drugs that are obvious ones to

try and, you know, among a set for which at least one is likely to give the desired properties.

Q And assuming that you're correct, and I'm not suggesting that you are, but assuming that you're correct that you could test all of these salts and expect one to be useful as a pharmaceutical, that -- there's no specific teaching as to which particular salt among them or salts would, in fact, be commercially viable, correct?

MS. WOOTEN: Objection, form.

THE WITNESS: I don't think I could predict which one would have -- you know, would be the best of the set. But I would say that's among a set that are obvious to do, and it's likely to find one among them. We do similar salt formation in my lab among similar -- salt forming, you know, in my lab. Right?

Q (By Mr. Trainor) But isn't the reasonable expectation of -- strike that.

Isn't the reasonable expectation that one of these salts that you would try would be effective as a fesoterodine salt -- strike that.

Isn't the expectation that one of the salts

among this list or described in this reference would work for a particular compound informed by the properties of the compound that you're conjugating with the salt?

A I think both are likely to be important. I guess to reiterate, you know, what I've said before, there's a set, and I would expect at least one or maybe more to have desirable properties, but I wouldn't say -- these -- I would say that these are obvious things to try. I wouldn't say, you know, based on what I know about this structure, oh, yeah, I know exactly the perfect one to try. I don't necessarily need perfect. I need good enough.

Q Okay. Now, based on what one would know about the structure of 5-HMT or any of its analogs or proposed analogs, is there anything in particular about that structure that would suggest that any particular salt form would be more compatible than others?

A Not a single salt form.

Q Is there something about the structure of 5-HMT and its analogs that would suggest a particular compatibility with a group of salts in this paper?

A I would say the carboxylate salts in that paper would be good ones to try, in addition to

hydrochloride salt and -- right, they would all be obvious ones to try in that they've been used before.

Q But other than the fact that they've been used before, what is it about 5-HMT and its analogs that suggest compatibility with the carboxylate salts in particular?

A Well, it's an amine, and the idea would be to improve its solubility and dissolution by preparing the salt.

Q Okay. Now, if you look at the first page of Exhibit 1013, the very second sentence of the reference at the bottom of the first column says, "Choosing the appropriate salt, however, can be a very difficult task, since each salt imparts unique properties to the parent compound." Do you see that?

A Yes.

Q Do you have a view as to whether that statement held true as of 1998?

MS. WOOTEN: Objection, form.

THE WITNESS: As of 1998, when I was practicing, if we needed to make a salt form, we weren't concerned about finding one that would work. If that statement were, in fact, an absolute, then there would be great

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concern that you would find one that would be acceptable. In my career, I've never encountered a worry that, oh, my gosh, we need a salt, nothing is going to work.

MR. TRAINOR: Okay.

Q (By Mr. Trainor) Was there any development reported in the prior art between 1977 and 1998 that made choosing the appropriate salt something less than a very difficult task?

MS. WOOTEN: Objection, form.

THE WITNESS: I don't think it's as difficult as the authors present here. I wasn't practicing in 1977. Maybe it appeared that way in 1977. But making salts is very easy to do.

MR. TRAINOR: Okay. Okay.

Q (By Mr. Trainor) Now, in the next paragraph of this opening page of Exhibit 1013, in the middle of that paragraph, it says, "Unfortunately, there is no reliable way of predicting the influence of a particular salt species on the behavior of the parent compound."

A Okay. I'm having trouble finding that.

Q The very first page.

A Oh, okay, the very first page. Sorry. Okay.

Q Right column.

A Right column, okay.

Q First paragraph.

A Okay, I see it now. Yeah, yeah.

Q So, again, it says, "Unfortunately, there is no reliable way of predicting the influence of a particular salt species on the behavior of the parent compound." Do you see that?

A Yes.

Q Do you agree with that statement?

A If the authors are saying that, you know, you can look at the compound and say this is the exact salt I want to make, I agree with it, but that you -- you'll have no way of saying I'm going to -- am I going to be able to find an acceptable salt, I don't disagree with that interpretation of the comment, of the author's comment.

Q So you agree that still today there's no reliable way of predicting the influence of a particular salt species on the behavior of the parent compound?

A For a single one, but I do believe that preparing and selecting, right, for one is routine

among a set of analogs. And, you know, given a set, like I say, I would not be able to tell you that's going to be the one apriori, but I would say among this set, we'll find one.

MS. WOOTEN: It makes it a lot easier for the court reporter if you let him finish his question.

THE WITNESS: Oh, I'm sorry. You're right, I keep -- I've done that a few times.

Q (By Mr. Trainor) Okay. So the other reference that you said in your declaration in support of your view that the fumarate salt of fesoterodine is obvious is another PCT patent application where the lead inventor is Johansson. So if you want to go back to around paragraph 133 or so, you might see that.

A I'm there.

MR. TRAINOR: So I'm handing the witness Exhibit No. 1005, same exhibit number for both declarations.

Q (By Mr. Trainor) Now, following on your discussion of the Berge reference, 1013, in paragraph 133 of your declaration, Exhibit 1003, it says, "Making the fumarate salt of esterified 5-HMT even more obvious and predictable was that Johansson describes the

fumarate salt of 5-HMT." Do you see that?

A Yes.

Q Okay. Now, in the next -- over the next page, page 60, of your declaration, you describe, I believe, how Johansson discloses 5-HMT. And on page 3 of Exhibit 1005, the Johansson application, there's a figure there of a chemical genus next to Roman numeral I that's reproduced in you declaration at paragraph 134. Do you see that?

A Yeah, I see it in my declaration. Oh, I see it in the patent as well.

Q Okay. So would you agree with me that in terms of the number of possible permutations of that genus, that 5-HMT is one of at least tens of thousands?

A It's one of many.

Q Okay. And aside from making the variable substitutions provided for in Exhibit 1005 that would arrive you at 5-HMT, would you agree that there's no specific disclosure in the Johansson application of the 5-HMT molecule?

A I don't remember, but it is -- I would look at that and say that it's covered or included among the structures mentioned.

Q It's covered by that genus?

A Right.

Q But would you agree that the 5-HMT species of that genus is not specifically disclosed anywhere in this application?

A I don't -- it has N as the same tertiary amine at line 30. I don't recall seeing it specifically there.

Q Okay. And if you assume that it is not -- if that species at 5-HMT is not specifically disclosed anywhere -- and hold that assumption for a moment and turn to page 2 of the Johansson application, which is page 4 of the Exhibit 1005.

A Okay.

Q Okay. And in the first full paragraph, it says, "The compounds of Formula 1" -- and that's the Formula 1 in your declaration -- "can form salts with physiologically acceptable acids, organic and inorganic, and the invention comprises the free bases as well as the salts thereof." And then it follows, "Examples of such acid addition salts include the hydrochloride, hydrobromide, hydrogen fumarate, and the like." Do you see that?

A Yes. Until -- it's on page 4 of the exhibit -- yes, I'm sorry, I found it now.

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Q That's okay.

A Yeah.

Q And so would you agree with me that if you factor in these three salts that are specified at -- in the passage we just read from Exhibit 1005, hydrochloride, hydrobromide, and hydrogen fumarate, that the hydrogen fumarate species of that genus of compounds is much larger, even three times whatever the great number is of species that are covered by that genus?

MS. WOOTEN: Objection, form.

Q (By Mr. Trainor) It's one of tens of thousands of potential salts?

A It's one of many covered.

Q Okay. And given that -- well, my representation and the assumption that the 5-HMT species is not specifically disclosed anywhere in this Johansson application, if you assume that, then it is also true that the fumarate salt of 5-HMT is also not specifically disclosed here, correct?

MS. WOOTEN: Objection, form.

THE WITNESS: Not specifically enclosed, but it's there -- or disclosed, but it's there.

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MR. TRAINOR: Okay. Now, just hang with me for a minute.

THE WITNESS: Okay.

Q (By Mr. Trainor) If you go to page 8 of the application, which is page 10 of Exhibit 1005 --

A Okay.

Q -- you'll see that there is an Example 1.

A I see Example 1, yes.

Q Okay. And Example 1, would you agree, is one species of that genus of Formula 1 made as a mandelate salt?

A It is.

Q Okay. Now, you can confirm this if you'd like, but as you page through the rest of this document, that is the only example, other than the other enantiomer, of that same salt. And so my question for you is: Why would a person of ordinary skill in the art be directed to fumarate salt when the prior art reference only provides a working example and data for the mandelate salt?

MS. WOOTEN: Objection, form.

THE WITNESS: Because that's specifically mentioned, and the position of skill would notice that and include that. I

would be certain to include that in the ones that I prepared in my search for one acceptable.

MR. TRAINOR: In search for what?

THE WITNESS: In my search for a salt that would have acceptable properties, I would be certain to include the ones mentioned.

Q (By Mr. Trainor) Okay. The ones mentioned in the --

A In this particular patent.

Q Okay.

A Even though he does not specifically characterize one here, he does mention it.

Q Okay. This compound, this mandelate salt, specific Example 1, it's a 5-HMT analog, would you agree?

A Appears to be the case, yes.

Q Okay. So let me ask the question this way: If I'm trying to predict which, among many salts, might be commercially viable or clinically viable for use with a 5-HMT analog, wouldn't this reference suggest that I look to the mandelate salt, which had data and which had been provided and synthesized as an example,

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as opposed to any other salt?

MS. WOOTEN: Objection, form.

THE WITNESS: That might be one that I would include as a benchmark. I might be cautious about doing that one because it's specifically disclosed.

Q (By Mr. Trainor) But --

A But I still might do it.

Q But as a prior art teaching, wouldn't this suggest, among others, the mandelate salt as opposed to any salt that was not provided for in an example?

A There would be a reason the inventor specifically mentioned the others, so I might be -- I would wonder why he mentioned it earlier and didn't include an example later. And that's something that might motivate me even more to make the ones not specifically described.

Q But you would agree that that Berge reference that we just looked at taught that the properties of a salt are a function of the properties of the underlying compound, correct?

A He seems to say that. I think both the acid and the free amine are important.

Q But the properties of a particular salt are

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going to be a function of the compatibility of that particular salt or that particular acid with the underlying compound, correct? That's always going to be the case, correct?

MS. WOOTEN: Objection, form.

THE WITNESS: I hesitate to say always.

MR. TRAINOR: Okay. Okay.

Q (By Mr. Trainor) In any event, there's no specific example of a 5-HMT analog made into any salt other than the mandelate salt, correct, in this patent?

A It's not disclosed in this patent. I don't remember seeing it in that patent.

Q Okay. So no teaching about the compatibility of any salt, other than the mandelate salt, with any particular 5-HMT analog can be drawn from this prior art reference, correct?

A Since the fumarate is specifically mentioned, there has to be a reason the inventor mentions it, so that would direct me to want to prepare that salt.

Q What does a mention without an example conjugating that salt to the compound teach a person of ordinary skill?

A That there has to be a reason the inventor mentioned it.

Q So that's all it teaches, is that there has to be a reason, correct?

A And the reason would likely be there's something -- he found something about that that maybe he's not ready to disclose.

Q And if he's not yet ready to disclose it, then none of the properties of such a fumarate salt of a 5-HMT analog could be known until such time as it's disclosed, correct?

A Or made in another lab, right.

Q Right, until it's made and reported?

A Yeah. But my position is that for this reason, that would be one of the ones that I would include in my search for an acceptable salt.

Q And I understand that.

A Okay.

Q All I'm saying is that that fumarate salt conjugated with a 5-HMT analog has not been made, and therefore no teachings about the properties of that combination could be drawn from this Johansson reference?

A Okay.

Q Correct?

A Okay.

Q Yes?

A Yes.

Q Okay. Now, the only other thing that I wanted to do -- I'm done here, but I -- there is one other publication that you reference that I hadn't shown you today. This is Exhibit 1015 to both of your declarations. It's a publication, the lead author Nilvebrant, and it's got a publication date of 1997.

And before we close, I just wanted to give you an opportunity to look at it and let me know if this might be the prior art that you had in mind where you thought concerns mirroring your own about tolterodine were reported somewhere.

A I don't think it is.

Q Okay.

MR. TRAINOR: Okay, well, that being the case, I have no further questions.

THE WITNESS: Okay.

MR. TRAINOR: Appreciate your time very much.

MS. WOOTEN: And I do not have any follow-up questions for you.

(Deposition concluded at 4:58 p.m.)

C E R T I F I C A T E

STATE OF GEORGIA

COUNTY OF COBB

I, MICHELLE M. BOUDREAUX, do hereby certify that STEVEN E. PATTERSON, Ph.D., the witness whose deposition is hereinbefore set forth, was duly sworn by me and that such deposition is a true record of the testimony given by such witness.

I further certify that I am not related to any of the parties to this action by blood or marriage and that I am in no way interested in the outcome of this matter.

IN WITNESS WHEREOF, I have hereunto set my hand this 15th day of October 2016.

_____

MICHELLE M. BOUDREAUX, RPR

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EXAMINATIONS

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EXHIBITS

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ERRATA SHEET FOR THE TRANSCRIPT OF:

Case Name: Mylan Pharmaceuticals vs. UCB Pharma GMBH

Deposition Date: October 4, 2016

Deponent: Steven E. Patterson, Ph.D.

Pg.	Ln.	Now Reads	Should Read	Reason
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Signature of Deponent

SUBSCRIBED AND SWORN BEFORE ME
THIS _____ DAY OF _____ 20___.

_____
(SIGNATURE OF NOTARY PUBLIC)
MY COMMISSION EXPIRES:_____