STEPHEN G. DAVIES, D.PHIL.

patent, column 7, where we were at before.

MS. LEBEIS: I think you're looking at the '984.

Q Yes, I'll get there in a minute. You can have that one open.

A Which exhibit number?

Q It's the one that you have open in front of you, I believe.

A This one, okay.

Q Yes.

A '560, got it.

Q '560, yes. So if you look at the '560 patent --

A Yes.

Q -- as we just discussed, in the '560 patent we see a report of a formulation of diclofenac, BAC, and octoxynol forming no precipitate after storage, right?

MS. LEBEIS: Objection to the extent it mischaracterizes the document.

A After 41 days at 4 degrees.

Q Right.

A In that particular formulation, there's no precipitate, it says.

Petitioner InnoPharma EX 1061-C
IPR2015-00902
IPR2015-00903

STEPHEN G. DAVIES, D.PHIL.

Q Then if we look back at EP '984, page 9, likewise, there was a -- there's a report in this patent of a clear solution with no precipitate of ketorolac, benzalkonium chloride, and octoxynol 40 after storage at various conditions, right?

MS. LEBEIS: Objection to the extent it mischaracterizes the document. Objection to the form of the question.

A Well, they're two different formulations for two different drugs.

Q Right. So in each of these patents we see a formulation of an NSAID, benzalkonium chloride, and octoxynol 40 showing no precipitate after storage at 4 degrees, right?

MS. LEBEIS: Objection to the form of the question.

A We haven't seen any evidence of anything ever forming, a precipitate of benzalkonium chloride and an NSAID.

Q I'm not asking about a precipitate of benzalkonium chloride and an NSAID. I think my question was simpler than that. I'm just asking, in each of these patents, the '560

patent and the '984 patent, we see a formulation of an NSAID, benzalkonium chloride, and octoxynol 40 showing no precipitate after storage at 4 degrees, right?

MS. LEBEIS: Objection to the form of the question. And objection, mischaracterizes the documents.

A 4 degrees isn't one of the temperatures of -- in example 5 of the '984.

Q Let me change the question then. So in each of EP '984 and the '560 patent, we have formulations of an NSAID, benzalkonium chloride, and octoxynol 40 showing no formation of a precipitate after storage at all the conditions tested in each of these patents, right?

MS. LEBEIS: Objection to the form of the question and to the extent it mischaracterizes the documents.

A I don't think you can take an experiment out of one patent under one set of conditions and compare it to an experiment in -- under a different set of conditions in another patent but a different drug.

STEPHEN G. DAVIES, D.PHIL.

Q I wasn't asking you to do any comparison here. I was just asking you whether or not you agree that, in each of the '560 and EP '984 patents, we have a formulation of an NSAID, benzalkonium chloride, and octoxynol 40 showing no formation of a precipitate after storage at each of the conditions tested in those patents.

MS. LEBEIS: Objection to the form of the question and to the extent it mischaracterizes the documents and asked and answered.

A I don't think you can make a comparison. There were conditions where you have a clear solution in the '984 patent, and there's -- for a completely different experiment with different actives. There's apparently no precipitate in the '560.

Q When you say that these are completely different experiments, can you explain what you mean by that?

A Well, the temperature raisings are not the same. The active ingredient is not the same. I haven't looked at the -- all the

ingredients, so I have to look at the ingredients.

(Document review.)

The ingredients in the '984 seem to include sodium EDTA, which doesn't appear to be in the comparative example C in the '560. Sodium chloride appears to be in the '984 and not in the comparative example C in the '560 so they're not comparable conditions.

Q Are you -- are you assuming that the ingredients listed in example 4 are the ones that are in the formulations tested in example 5?

MS. LEBEIS: Objection to the extent it mischaracterizes prior testimony.

A I'm looking at all of the examples on page 8, and all the -- and 7 and 6 all contain those ingredients.

Q So you're making the assumption that those ingredients are in the formulations tested in example 5?

MS. LEBEIS: Objection to the extent it mischaracterizes prior testimony. Asked and answered.

STEPHEN G. DAVIES, D.PHIL.

A Well, example 5 says the -- in the '984, it says, "The formulations of the present invention have proven to be stable," and that is the data for that. And every formulation that's in that '984 has those ingredients.

Q Okay. So you're assuming again that the ingredients in the formulations tested in example 5 are the same as the ingredients listed in the other examples on pages 7 and 8?

MS. LEBEIS: Objection to the extent it mischaracterizes prior testimony and mischaracterizes the document. Asked and answered.

A I'm reading the document for what it is, and it seems to me to state that they're testing the formulations that are in the invention, all of which contain those ingredients.

Q In your view, the experiments in the '560 patent and in the experiments in the -- the experiment in the EP '984 patent aren't comparable, at least in part because the active ingredients are different; is that right?

MS. LEBEIS: Objection to the extent

it mischaracterizes prior testimony.

A They have different active ingredients, and they have many other things that are different as well.

Q So, in your view, you can't learn anything about one from the other; is that right?

MS. LEBEIS: Objection to the extent it mischaracterizes prior testimony. Asked and answered.

A I don't think you can make a comparison between them.

Q Is there anything you can learn from one of these examples that would be relevant to the other?

MS. LEBEIS: Objection to the extent it mischaracterizes prior testimony. Calls for speculation. Asked and answered.

A So many things. More than one thing has changed. In fact, several things have changed. So you can't make a direct comparison between the two.

Q Are you familiar with the textbook Remington: The Science and Practice of

Pharmacy?

A I know of it, yes.

Q It's a well-known reference in the field of pharmaceutical formulation?

MS. LEBEIS: Objection. Calls for speculation.

A It is a textbook in that field, yes.

Q It's a recognized authority in pharmaceutical science, right?

MS. LEBEIS: Objection. Calls for speculation. Asked and answered.

A It's a textbook within that field.

Q You don't think it's a recognized authority?

MS. LEBEIS: Objection to the extent it mischaracterizes prior testimony. Asked and answered.

A It's a textbook within that field.

Q But you disagree that it's a recognized authority in pharmaceutical science?

MS. LEBEIS: Objection to the extent it mischaracterizes prior testimony. Asked and answered.

A It's one of several textbooks that

STEPHEN G. DAVIES, D.PHIL.

are in the field.

Q It's a leading pharmaceutical textbook, right?

MS. LEBEIS: Objection to the extent it mischaracterizes prior testimony. Asked and answered.

A It's one of several textbooks in the field.

MS. RAPALINO: I'm going to ask the court reporter to mark as Davies Exhibit 10 an excerpt from the 20th edition of Remington: The Science and Practice of Pharmacy.

(Exhibit 10 was marked for identification and attached to the deposition transcript.)

BY MS. RAPALINO:

Q You would agree that a person of ordinary skill in the art would be familiar with the Remington's textbook, right?

MS. LEBEIS: Objection. Calls for speculation.

A I expect they would have heard of it.

Q And it would be a textbook they'd

consult in the course of doing their work in pharmacy?

MS. LEBEIS: Objection. Calls for speculation.

A They may or may not.

Q If you turn to page 831 and the excerpt from Remington's in Exhibit 10.

A Yes.

Q You see there's a section entitled "Quaternary Ammonium Compounds"?

A I see that.

Q And Remington states that "Benzalkonium chloride is a typical quaternary ammonium compound and is by far the most common preservative used in ophthalmic preparations."

Do you see that?

A That's what it says.

Q You don't disagree that BAC is by far the most common preservative used in ophthalmic preparations, do you?

MS. LEBEIS: Objection. Calls for speculation.

A I haven't done the analysis.

Q So you don't have a basis to disagree

with Remington's?

MS. LEBEIS: Objection. Calls for speculation. Asked and answered.

A It doesn't give me anything to go by, and I haven't done the analysis, so I don't know whether it's correct or not.

Q And Remington's also states that "Over 65 percent of commercial ophthalmic products are preserved with benzalkonium chloride."

Do you see that?

A That's what it says.

Q And then Remington's goes on to say that "Despite this broad use, the compound has definite limitations."

Do you see that?

A That's what it says.

Q Could you read the next sentence in Remington's.

A "As a cationic surface active material of high molecular weight, it is not compatible with anionic compounds."

Q So how would a person of skill in the art understand that sentence?

STEPHEN G. DAVIES, D.PHIL.

A Well, it's saying that there's supposed to be supposedly an incompatibility between the benzalkonium and anionic compounds. But, again, there's no evidence being put forward to that effect. The examples that are given are with salicylates and nitrates but, again, no reference.

Q In your opinion, would a person of skill in the art ignore this explicit guidance from Remington's regarding incompatibility of benzalkonium chloride and anionic compounds?

MS. LEBEIS: Objection.

Mischaracterizes the document.

Argumentative.

A Well, without encountering a problem, they wouldn't be looking at this. So you do an experiment and, if you see a problem, maybe you would go out and look for some explanation. But I haven't seen any evidence that there is a problem.

Q If a person of skill in the art formulating an NSAID reviewed this section of Remington's, is it your opinion that they would ignore this guidance regarding the

incompatibility of anionic compounds with benzalkonium chloride?

MS. LEBEIS: Objection to the extent it mischaracterizes prior testimony, mischaracterizes the document.

A They would do the experiment to see what happened.

Q They would have to check to see whether there was an incompatibility, right?

MS. LEBEIS: Objection to the extent it mischaracterizes prior testimony. Argumentative.

A They would do the experiment, and all the experiments that have been done so far that I have seen don't show a problem of the benzalkonium ammonium and the NSAID.

MS. RAPALINO: I'm going to ask the court reporter to mark as Davies Exhibit 11 an excerpt from the declaration of Shirou Sawa submitted in IPR 2015-902 and IPR 2015-903.

(Exhibit 11 was marked for identification and attached to the deposition transcript.)

STEPHEN G. DAVIES, D.PHIL.

MS. RAPALINO: For the record, that's Exhibit -- Senju Exhibit 2098 in those IPRs.

BY MS. RAPALINO:

Q Dr. Davies, you participated as an expert in inter partes review proceedings for some of the patents-in-suit, right?

A Can you repeat the question.

Q You've participated as an expert in inter partes review proceedings for some of the patents-in-suit in this case, right?

A I said early on today that I didn't know what that meant. So I've participated in patent office proceedings.

Q Okay. So you participated in --

A I've never heard them called what you -- what you've just said.

Q Understood. Let me use that terminology. So you've participated in patent office proceedings regarding the patents-in-suit in this case, right?

A I have, yes.

Q You submitted one or more declarations in those patent office

proceedings?

A Yes, I have, yes.

Q Have you reviewed a declaration submitted by one of the inventors in -- one of the inventors of the patents-in-suit, Mr. Sawa?

A I've reviewed this one before, yes. So I may have misspoken earlier then because I didn't understand what IPR was when I said I hadn't read anything in the I -- well, as far as I knew, I hadn't, but now you explained it. I have seen this one.

Q Understood. We won't hold that against you. I know we use some complicated acronyms to talk about those patent office proceedings.

Okay. So if you look at page 2 of this translation of Davies Exhibit 10 -- do we have 10?

MS. LEBEIS: I think it's 11.

Q 11, I'm sorry. 11.

You understand that Mr. Sawa, who submitted this declaration, is the first named inventor on one or more of the patents-in-suit?

A Yes.

STEPHEN G. DAVIES, D.PHIL.

Q If you turn to page 3, you see that he -- in paragraph 7, he attests that he prepared and tested the stability of bromfenac sodium formulations and he references Appendix A for that testing. Do you see that?

MS. LEBEIS: Objection.

Mischaracterizes the document.

A Well, he says the specific formulation is disclosed in table 1 of the '431 and '290 patents.

Q Right. And then he goes on to reference Appendix A in the next sentence. Do you see that?

MS. LEBEIS: Objection.

Mischaracterizes the document.

A Well, there's a lot of other words in between there about what actually they looked at, but it does say Appendix A.

Q Then if you look at paragraph 8, the following paragraph --

A Yes.

Q -- he says, "As reflected in the laboratory notebook of Appendix A, the stability of these bromfenac sodium

formulations was tested after adjusting the pH of the formulations to 7."

Do you see that?

MS. LEBEIS: Objection --

A I see that.

MS. LEBEIS: -- mischaracterizes the document.

Q So do you understand that he's characterized Appendix A as a laboratory notebook?

MS. LEBEIS: Objection. Mischaracterizes the document.

A Well, it's not a laboratory notebook. It might be a translation of a laboratory notebook.

Q Okay. So Appendix A is a translation of a laboratory notebook.

A I don't know that. That's what this says.

Q So you think that Mr. Sawa is mistaken here in his declaration?

A No, I --

MS. LEBEIS: Objection. Mischaracterizes -- to the extent it

mischaracterizes prior testimony, argumentative.

A I think you're asking me do I know it's a translation of a laboratory notebook. I don't know other than what Mr. Sawa says.

Q No, to be clear, my question was, do you see that he's characterized Appendix A as a laboratory notebook?

MS. LEBEIS: Objection to the extent it mischaracterizes the document.

A He is suggesting that Appendix A is a laboratory notebook, yes.

Q So let's look at Appendix A, which starts at page 28 of this excerpt.

A Sorry, page?

Q 28.

A 28, okay.

Q And if we look -- and you see that page 28 is the beginning of Appendix A, right?

A Yes.

Q Then if you look at page 30 in Appendix A --

A Okay.

Q -- you see that the top of the page

-- well, first of all, the page is dated February of 2000, right?

A February of 2000, yes.

Q And there is a name of the test here. It says, "Study of the formulation of Bronuck ophthalmic solution at pH 7."

Do you see that?

A Yes.

Q Do you understand that Bronuck is a formulation of bromfenac sodium?

A Yes.

Q And you see that the study director listed here on this page is Shirou Sawa, right?

A That's correct.

Q That's the inventor on the patents-in-suit, right?

A Yes.

Q And you see that in the paragraph in the middle of the page that start with the word "Purpose" --

A Yes.

Q -- he writes five lines from the bottom of that paragraph, "Although the addition of counterions to control the acetic

acid group has been considered, bromfenac sodium forms insoluble complexes due to the addition of quaternary ammonium salt and becomes cloudy."

A I see that.

Q So do you understand that Mr. Sawa, the inventor, understood that bromfenac sodium forms insoluble complexes with the addition of a quaternary ammonium salt?

MS. LEBEIS: Objection. Calls for speculation.

A I don't agree with that. So that's not what he says.

Q How do you understand what Mr. Sawa is saying in this declaration?

A Well, first of all, this is a laboratory notebook, apparently, of one of the inventors, which I don't think is normally regarded as part of the common general knowledge. And what this actually says is that a precipitate -- the solution becomes cloudy due to the addition of a quaternary ammonium salt does not mean that the quaternary ammonium salt is part of the precipitate. So unless

Mr. Sawa, Dr. Sawa actually analyzed the precipitate, there's no way of knowing that it's -- contains the quaternary ammonium salt.

Q Okay. So you understand Mr. Sawa just to be saying that in a formulation containing bromfenac sodium, the addition of the quaternary ammonium salt -- after addition of the quaternary ammonium salt, insoluble complexes were formed, but he didn't know what those complexes were. Is that what -- how you understand that?

MS. LEBEIS: Objection to the extent it mischaracterizes prior testimony.

A He doesn't know that. He doesn't know what they are and he doesn't know that they contain the quaternary ammonium salt.

Q Okay. But you would agree that Mr. Sawa does know that when you formulate bromfenac sodium and benzalkonium chloride in a formulation, the formulation becomes cloudy?

MS. LEBEIS: Objection to the extent it mischaracterizes prior testimony and to the extent it mischaracterizes the document.

STEPHEN G. DAVIES, D.PHIL.

A I can only repeat what I've said. There is no evidence that any cloudiness involves the interaction of the benzyl ammonium cation with anything.

Q Right. But there is evidence from this declaration of cloudiness in a bromfenac formulation that contains benzalkonium chloride, right?

MS. LEBEIS: Objection to the extent it mischaracterizes the document.

A Well, actually, there's no evidence that bromfenac is involved in the cloudiness either. There is evidence that the solution goes -- his observation is the solution goes cloudy, but he provides no evidence that bromfenac has anything to do with the cloudiness or that the benzyl ammonium has anything to do with the cloudiness.

Q Okay. So he has a formulation that contains bromfenac and benzalkonium chloride and sees that it goes cloudy, right?

MS. LEBEIS: Objection to the extent it mischaracterizes the document.

A He has a formulation that contains

those two and sees it go cloudy, yes.

Q In fact, if you turn the page to page 33 --

A Okay.

Q -- there is a table there that reports the results of his observations of these formulations, right? Do you see that?

MS. LEBEIS: Objection to the extent it mischaracterizes the document.

A I don't know how do I know that's related to that experiment.

(Document review.)

I'm trying to see how I know whatever the analysis is on page 33 has to do with the experiment.

Q So you don't think that what's on page 33 has to do with the bromfenac formulation?

MS. LEBEIS: Objection to the extent it mischaracterizes prior testimony and to the extent it mischaracterizes the document.

A Okay. It would appear to be from that experiment.

STEPHEN G. DAVIES, D.PHIL.

Q And you see that in the chart on page 33, there are columns labeled "Turbidity" and "Foreign Insoluble Matter"?

A Yes.

Q Those columns -- the results in those columns suggest that the formulations of bromfenac -- the formulations containing bromfenac and benzalkonium chloride show turbidity and show the presence of foreign insoluble matter, right?

MS. LEBEIS: Objection to the extent it mischaracterizes the document.

A What I recall is that they're labeled "Turbidity" and "Foreign Insoluble Matter," yes, with plus and minuses.

Q Right. So in nearly every one of those formulations, there was -- in nearly every one of the results reported in that table there was the presence of turbidity and the presence of foreign insoluble matter, right?

MS. LEBEIS: Objection to the extent it mischaracterizes the document.

A Well, with a little data available to go on, that would appear to be the case.

There's also quite a lot of color change, I see.

Q Let's go back to Davies Exhibit 1. That's your expert report. And if you would turn, please, to paragraph 26.

A Yes.

Q You say in the first sentence of paragraph 26 that "The sodium salt of bromfenac is freely water soluble," right? Do you see that?

A I see that.

Q And you conclude that -- at the end of that sentence that "Thus, any solubilizing effect of polysorbate 80 or tyloxapol would not be required to dissolve or solubilize bromfenac sodium," right?

A That's what I say, yes.

Q You would agree that the solubility of the salt depends on the nature of both the anion and the cation, right?

MS. LEBEIS: Objection. Incomplete hypothetical.

A If you take a particular salt of a particular anion and cation, then the

solubility overall would depend on some balance between the two.

Q So the solubility, for example, of bromfenac sodium would be different from the solubility of a salt of bromfenac and benzalkonium ion, right?

MS. LEBEIS: Objection, incomplete hypothetical.

A Without experimentation, I can't answer that.

Q So you don't know whether the solubilities would be the same or different?

MS. LEBEIS: Objection to the extent it mischaracterizes prior testimony. Incomplete hypothetical.

A Well, what I know is that sodium bromfenac is freely water soluble. So both the anion and the cation of that are likely to be highly solvated, and that's what makes the salt soluble, freely solid. I don't know about -- I know that benzyl ammonium salts are soluble in water, but I don't know to what extent relative to sodium.

Q Benzalkonium ion is more hydrophobic

than sodium, right?

MS. LEBEIS: Objection, incomplete hypothetical. Calls for speculation.

A It's more hydrophobic, yes.

Q And benzalkonium has alkyl chains in its structure, right?

A It does, yes.

Q And alkyl chains are hydrophobic, right?

MS. LEBEIS: Objection, incomplete hypothetical.

A They are, and the plus charge is hydrophilic.

Q These formulations -- strike that.

Why don't we look at U.S. Patent 4,910,225, which we will mark as Exhibit -- Davies Exhibit 12.

(Exhibit 12 was marked for identification and attached to the deposition transcript.)

BY MS. RAPALINO:

Q This is a patent you reviewed in connection with rendering your opinions in this case, right?

STEPHEN G. DAVIES, D.PHIL.

A It is, yes.

Q You understand that experimental example 6 at column 8 of this '225 patent at Exhibit 12 contains the same ingredients as the Bronuck bromfenac sodium product?

MS. LEBEIS: Objection. Calls for speculation.

A I haven't actually compared them so I don't know that.

Q Actually, I think I misspoke. It's example 6 at column 10 of the '225 patent that has the same ingredients as the Bronuck product.

Have you had a chance to look at that?

A No.

Q You would agree that the Bronuck bromfenac product contained polysorbate 80 as one of its components, right?

MS. LEBEIS: Objection. Calls for speculation. Asked and answered.

A I haven't reviewed in detail the ingredients of the bromfenac patent. So what were you asking me to compare?

STEPHEN G. DAVIES, D.PHIL.

Q Oh, I was asking about the Bronuck formulation.

A Bronuck. I haven't reviewed in detail.

Q You're familiar with the Bronuck product, that there was a Bronuck product on the market in Japan as of 2003?

MS. LEBEIS: Objection, no foundation.

A I know that -- I don't know the date, but I know that Bronuck contains bromfenac.

Q And that was a commercial product in Japan?

MS. LEBEIS: Objection, no foundation. Asked and answered.

A I don't know that.

Q Let's look at example 6 of the '225 patent. This is at column 10. Are you there?

A Yes.

Q You see that that formulation contains polysorbate 80?

A It does, yes.

Q What's the -- what is polysorbate 80?

A It's a -- I drew a picture of it in

my review. It's a polyethoxylated derivative of sorbic acid.

Q It's used as a surfactant, right?

MS. LEBEIS: Objection, incomplete hypothetical.

A You have to look at the particular case where it's employed as to whether it's been a surfactant or not.

Q Have you seen polysorbate 80 used in pharmaceutical formulations for some other purpose?

MS. LEBEIS: Objection. Calls for speculation. No foundation.

A I haven't done that analysis.

Q But you're aware that polysorbate 80 is used in a surfactant?

MS. LEBEIS: Objection to the extent it mischaracterizes prior testimony. No foundation.

A In some instances it has been, yes. But in this particular patent, I don't recall any -- any comment as to why they put polysorbate 80 into these formulations.

Q And, in your view, a person of skill

in the art wouldn't know what the function was of polysorbate 80 in these formulations; is that right?

MS. LEBEIS: Objection to the extent it mischaracterizes prior testimony.

A Well, I would expect to be informed, but I'm not informed. So I don't know why they put it in there.

Q So a person of skill in the art wouldn't know what polysorbate 80 was doing in the formulation?

A Well, since they don't tell you, you can't tell why they put it in there.

Q A person of skill in the art couldn't look at the literature that was available as of the time of the patent to determine the function of an excipient like polysorbate 80?

MS. LEBEIS: Objection. Calls for speculation, to the extent it mischaracterizes prior testimony, asked and answered.

A The author of the patents doesn't -- don't tell you why they put the polysorbate 80 in there so you can't be sure.

STEPHEN G. DAVIES, D.PHIL.

Q So you don't know why it was put in there?

A I don't know why, no.

Q So, in your view, a person of skill in the art would have known that bromfenac sodium was relatively water soluble?

MS. LEBEIS: Objection to the extent it mischaracterizes prior testimony.

A Would you like to repeat the question.

MS. RAPALINO: Could you read that back, please.

(Record read.)

MS. LEBEIS: Objection. I'm not sure you read the question back exactly as it was read before.

MS. RAPALINO: Let me withdraw it --

MS. LEBEIS: Can you ask it again.

MS. RAPALINO: -- and ask it again.

BY MS. RAPALINO:

Q But, in your view, a person of ordinary skill in the art would have known that bromfenac sodium was relatively water soluble?

MS. LEBEIS: Objection to the extent

STEPHEN G. DAVIES, D.PHIL.

it mischaracterizes prior testimony.

A As I say in my report, it was known that the sodium salt of bromfenac was freely water soluble.

Q In forming your opinions in this case, did you consider how many nonionic surfactants had been used in approved ophthalmic formulations as of 2003?

A I didn't do that analysis.

Q You also didn't do the analysis to consider how many polyethoxylated octylphenol surfactants had been used in approved ophthalmic solutions as of 2003, right?

MS. LEBEIS: Objection to the extent it mischaracterizes prior testimony.

A I didn't do the analysis.

Q Now, in rendering your opinion that a person of ordinary skill in the art would not expect tyloxapol to be interchangeable with polysorbate 80, you rely at least in part on the different three-dimensional chemical structures of tyloxapol and polysorbate 80, right?

MS. LEBEIS: Objection to the extent

it mischaracterizes the document.

A The question was between which ones?

Q Tyloxapol and polysorbate 80.

I'm looking at -- it's about page 32 of your expert report.

A Well, I start on page 28.

Q Okay.

MS. LEBEIS: Take your time to review as needed.

A (Document review.)

So I start off by saying that tyloxapol and polysorbate 80 are structurally and chemically dissimilar. So a person of ordinary skill in the art would not expect to substitute one for the other.

Q Now, just -- I want to just make sure that I remember your earlier testimony. You've never formulated any pharmaceutical products with either polysorbate 80 or tyloxapol, right?

MS. LEBEIS: Objection to the extent it mischaracterizes prior testimony.

A I haven't formulated a product with either of these materials.

Q And you've never selected one or the

other of these surfactants as the appropriate surfactant to use in an ophthalmic formulation, right?

A I haven't been involved in formulating that ophthalmic formulations, so, no.

Q Okay. So, again, in your -- in expressing your opinions about how a person of skill in the art would -- would or would not substitute tyloxapol for polysorbate 80, you rely at least in part on the three-dimensional structures of those two compounds, right?

MS. LEBEIS: Objection to the extent it mischaracterizes prior testimony.

A Well, I describe what I rely on in the -- in the paragraphs on pages 28 through to 33. And there are many things so -- I list examples of where their properties are different as in the critical micelle concentration, molecular weight. Their shapes, indeed, means that they will interact with things differently. The different numbers of ratios, if you like, of head group to arms and the like.

STEPHEN G. DAVIES, D.PHIL.

Q Right. And one of the things you rely on is the difference in their three-dimensional structure, right?

A One of the things, yes.

Q You depict those three-dimensional structures on page 32 of your report, right?

A I do, yes.

Q Likewise, for the comparison of tyloxapol, octoxynol 9, and octoxynol 40, you also rely on the differences in the three-dimensional structures of those surfactants in rendering your opinions that they would function differently, right?

A Only --

MS. LEBEIS: Objection to the extent it mischaracterizes the document.

A You have to read my whole comparison because it includes other things than just the structures.

Q I know. We can get to those other things later, but I want to take them one at a time. So right now we're talking about the three-dimensional structure. That's one of the things you relied on in forming your opinion

that these -- that these surfactants would function differently, right?

A It's one of a set of things.

Q And you depict the three-dimensional structures of tyloxapol, octoxynol 9, and octoxynol 40 on page 37 of your expert report?

A Yes.

Q You would agree that the three-dimensional structures you've depicted on pages 32 and 37 of your expert report are not the three-dimensional structures of the surfactants in solution, right?

MS. LEBEIS: Objection, no foundation.

A They may well be, but you can't be sure. There will be different structures, a mixture of structures in solution, at least for tyloxapol.

Q And, in fact, these long hydrophobic chains on these surfactants in solution would look quite different. They wouldn't be extended in solution the way they are in your diagrams; isn't that right?

MS. LEBEIS: Objection. Calls for

speculation, foundation.

A Can you repeat the question, please.

Q And, in fact, these long hydrophobic chains on each of these surfactants in solution wouldn't be extended in solution the way they are in your three-dimensional diagrams in your expert report, right?

A They're not hydrophobic.

Q In your view, the ethoxylated tails of these surfactants are not hydrophobic?

MS. LEBEIS: Objection to the extent it mischaracterizes prior testimony.

A They're not hydrophobic.

Q Now, you're aware that each of these surfactants in solution forms micelles above the critical micelle concentration, right?

A Yes.

Q And the three-dimensional structures you've depicted in your diagrams on pages 32 and 37 are not the structures of these compounds as they would appear in a micelle, right?

MS. LEBEIS: Objection, no foundation, calls for speculation.

STEPHEN G. DAVIES, D.PHIL.

A Well, the micelle is made up of numerous molecules of each of these.

Q And you didn't depict what the three-dimensional structure of these compounds would look like in -- when -- in a micelle?

MS. LEBEIS: Objection to the extent it mischaracterizes prior testimony.

A I did not depict them in the micelle, no, but I depicted them as individual molecules when they pack together. Just by looking at the shape, a person of ordinary skill would know that they were packed differently.

Q You didn't address in your expert report how the three-dimensional structures of each of these surfactants in solution might impact their properties, right?

MS. LEBEIS: Objection to the extent it mischaracterizes the document.

A I gave the measured CMC values for each of them.

Q You would agree that the CMC for tyloxapol is lower than the CMC for polysorbate 80, right? Actually, let me withdraw that question.

STEPHEN G. DAVIES, D.PHIL.

You would agree that the CMC for tyloxapol is lower than the CMC for octoxynol 9, right?

A Well, octoxynol 9 is .24 millimolar, and for tyloxapol it's 0.018 millimolar. So tyloxapol is lower.

Q The CMC for tyloxapol is also lower than the CMC for octoxynol 40, right?

A (Document review.)

Oh, there it is. It is -- octoxynol 40 is 0.810 millimolar, in millimoles, yes.

Q The CMC for tyloxapol is lower than the CMC for octoxynol 40, right?

A In millimoles, yes.

MS. RAPALINO: Let's mark as Davies Exhibit 13 a reference by author Hans Schott dated 1998.

(Exhibit 13 was marked for identification and attached to the deposition transcript.)

BY MS. RAPALINO:

Q This reference is a reference you reviewed in rendering opinions in this case?

A Yes.

STEPHEN G. DAVIES, D.PHIL.

Q You point in your report to a sentence in the introduction on the first page of the Schott reference, second paragraph, that says that "Tyloxapol is essentially an oligomer of octoxynol 9," right?

A That's what it says in the Schott paper, yes.

Q You read that sentence to say that it's not a true oligomer because of the word "essentially" in that sentence, right?

MS. LEBEIS: Objection.

Mischaracterizes prior testimony.

A Let me have a look where I say that. Remind myself which paragraph?

Q Paragraph 74 of your expert report.

A Thank you.

(Document review.)

Okay. So what was the question?

Q So you say that tyloxapol is not a true oligomer, and you point to the word "essentially" in that sentence to show that it's not -- it's not saying that it's a true oligomer; is that right?

MS. LEBEIS: Objection to the extent

STEPHEN G. DAVIES, D.PHIL.

it mischaracterizes the document.

A It's not an oligomer of octoxynol 9.

Q Schott refers to it as "essentially an oligomer of octoxynol 9," right?

A An oligomer is a repeat unit of the same thing, and tyloxapol is not a repeat unit of the -- of octoxynol 9.

Q Certainly Schott characterizes octoxynol 9 as a monomer -- as the monomer of tyloxapol, right?

MS. LEBEIS: Objection to the extent it mischaracterizes the document.

A I don't see where it says that.

Q Well, if we look at the sentence after the one we were just looking at in the introduction, referring to tyloxapol, it says, "Comparison with its monomer is of physicochemical importance."

Do you see that?

A That's what it says, yes.

Q Then this reference goes on to compare tyloxapol with octoxynol 9, right?

A It's making that comparison with things that are not oligomers, yes.

STEPHEN G. DAVIES, D.PHIL.

Q Let's look at the conclusions of the Schott paper on page 501.

A Okay.

Q The first sentence says that "From a practical viewpoint, the fact that the CMC of tyloxapol was 4.4 times smaller than that of octoxynol on a weight-by-weight basis is an advantage," right?

MS. LEBEIS: Objection.

Mischaracterizes the document.

A It doesn't say what it's an advantage for.

Q So you don't think a person of skill in the art would understand that tyloxapol, with its lower CMC, has some advantages over octoxynol 9?

MS. LEBEIS: Objection to the extent it mischaracterizes the prior testimony and it mischaracterizes the document.

A That sentence doesn't say what it's an advantage for. So a person of ordinary skill reading that sentence wouldn't know why it's an advantage.

Q If you look at the last sentence of

that first paragraph, it says, "Therefore, surfactants with lower CMCs can be formulated at lower use levels without compromising their effectiveness."

Do you see that?

MS. LEBEIS: Objection. Mischaracterizes the document.

A That's what it says, but without reading the whole paper, that can't be a completely general statement. So you have to look at what that might be referring to.

Q Do you disagree that surfactants with lower CMCs can be formulated at lower use levels without compromising their effectiveness?

MS. LEBEIS: Objection, incomplete hypothetical. Calls for speculation.

A I wouldn't make that -- I would have to look at what was actually being investigated to see in which case that statement could be made. It doesn't mean that that statement is true in every single scenario.

Q Certainly you would agree that all else being equal as between two surfactants,

the one with the lower CMC would have the benefit of being able to be formulated at a lower use level without compromising its effectiveness, right?

MS. LEBEIS: Objection to the extent it mischaracterizes prior testimony and mischaracterizes the document. Misleading and an incomplete hypothetical.

A I don't think you could take that away from that sentence. It would depend on the scenario in which you're looking as to what is more effective under what system.

Q So what are some of the factors that you would have to consider as a person of skill in the art in determining whether a lower CMC is a benefit?

MS. LEBEIS: Objection. Calls for speculation.

A Whether your formulation or whatever experiment you're looking at performs better or not.

Q So you can't form any expectation, based on the CMC of two different surfactants, as to whether -- as to what the relative

performance would be in a formulation?

MS. LEBEIS: Objection to the extent it calls for speculation and mischaracterizes prior testimony.

A CMCs are measured for surfactants on their own. You don't know -- you can't predict how they're going to perform when you put other things into the system, including other materials that they would interact with.

Q In your work over the course of your career, have you been involved in assessing CMCs of different surfactants for use in pharmaceutical formulations?

MS. LEBEIS: Objection. Vague and ambiguous.

A I personally have done no experiments.

Q Can you explain what a cloud point is for a surfactant?

MS. LEBEIS: Objection, vague and ambiguous.

A As far as I recall, it's where you first see the formation of micelles.

Q How does the cloud point differ from

the CMC?

MS. LEBEIS: Objection. Calls for speculation. No foundation.

A I don't recall.

Q So you're not very familiar with how to evaluate different surfactants?

MS. LEBEIS: Objection to the extent it mischaracterizes prior testimony. Argumentative.

A I've given you what I -- how I evaluate these particular surfactants in my report.

Q Have you ever evaluated the cloud point of any surfactants over the course of your career?

MS. LEBEIS: Objection, incomplete hypothetical. Vague and ambiguous.

A I haven't done an experiment.

Q Have you been involved in reviewing the results of experiments evaluating cloud points of different surfactants for use in pharmaceutical formulations?

MS. LEBEIS: Objection, vague and ambiguous.

STEPHEN G. DAVIES, D.PHIL.

A I haven't, no.

Q You don't know the significance of the cloud point of a surfactant in assessing its usefulness in a pharmaceutical formulation?

MS. LEBEIS: Objection to the extent it mischaracterizes prior testimony. Argumentative.

A I wasn't asked to evaluate that.

Q Do you know the significance of the cloud point of a surfactant in assessing its usefulness in a pharmaceutical formulation?

MS. LEBEIS: Objection. Asked and answered. Vague and ambiguous. Argumentative.

A I wasn't asked to evaluate that.

Q I'm not asking whether you were asked to evaluate it. I'm just asking whether you know.

MS. LEBEIS: Object --

Q Do you know the significance of the cloud point of a surfactant in assessing its usefulness in a pharmaceutical formulation?

MS. LEBEIS: Objection. Vague and ambiguous. Asked and answered.

STEPHEN G. DAVIES, D.PHIL.

A I wasn't asked to evaluate cloud points.

Q Can you not answer the question whether you know the significance of the cloud point in assessing the usefulness of a surfactant in a pharmaceutical formulation?

MS. LEBEIS: Objection. Vague and ambiguous. Asked and answered. He's answered your question already.

A I don't know the relevance of the cloud point, sitting here.

Q If a compound is known to degrade mostly by hydrolysis, would you expect addition of an antioxidant to significantly prevent that degradation?

MS. LEBEIS: Objection, incomplete hypothetical.

A I can't answer that because it would depend on the system that we're -- the specific system you were dealing with. The fact is, an antioxidant wouldn't affect the rate of hydrolysis. But there are -- any molecule has several different ways in which it can interact with other molecules and one of those other

properties could well do.

Q Are you familiar with the antioxidant BHT?

A Butylated hydroxytoluene, yes.

Q Have you ever known the antioxidant BHT to prevent degradation by hydrolysis?

MS. LEBEIS: Objection, incomplete hypothetical.

A I haven't done an analysis of that.

Q Can you think of a way in which BHT might prevent hydrolysis?

MS. LEBEIS: Objection. Incomplete hypothetical. Calls for speculation. Asked and answered.

A I haven't done an analysis of that, but there are ways it can -- you could imagine it would alter the rate of hydrolysis.

Q And how could it do that?

MS. LEBEIS: Same objections.

A Well, if it changes the environment in which the hydrolysis is occurring, then it would change the rate of hydrolysis.

Q How would BHT change the environment in which the hydrolysis is occurring in order

to alter the rate of hydrolysis?

MS. LEBEIS: Objection to the extent it mischaracterizes prior testimony. Incomplete hypothetical. Calls for speculation. Asked and answered.

A Well, you can take extremes and try and do a hydrolysis in neat BHT against no BHT, and the rate will be different between those two. So there's an infinite variation between those two extremes.

Q In that example you're just altering the amount of water to which the compound is exposed? Is that what you're saying?

MS. LEBEIS: Objection to the extent it mischaracterizes prior testimony. Incomplete hypothetical.

A In parts of that spectrum, yes. But in other parts, not significantly.

MS. LEBEIS: Do you think it might be a good time for a break?

MS. RAPALINO: Sure. Let's take a break.

MS. LEBEIS: I think we've got about an hour left on the record.

STEPHEN G. DAVIES, D.PHIL.

THE VIDEOGRAPHER: We're going off the record at 4:15 p.m.

(A brief recess was taken.)

THE VIDEOGRAPHER: We're going back on the record at 4:26 p.m. This is the start of disc number 6 in the deposition of Stephen Davies.

BY MS. RAPALINO:

Q Dr. Davies, nonionic surfactants have a polar head group and a nonpolar tail group, right?

A Yes.

Q Water is a polar solvent, right?

A Yes.

Q So in aqueous solution, the nonpolar tail group would not be extended, right?

MS. LEBEIS: Objection, no foundation.

A You would have to define which materials group you're talking about.

Q If you dissolved a nonionic surfactant in aqueous solution, you would agree that the nonpolar tail group would not be -- the structure of the nonpolar tail group would

not be extended?

MS. LEBEIS: Objection. Vague and ambiguous. No foundation. Incomplete hypothetical.

A Can you just explain that -- just ask me the question again because I think I didn't get the same question on the two times.

Q If you dissolve a non- -- it's probably my fault. I am sure that my terminology is off here, but maybe you'll correct me if I get it wrong.

If you dissolve a nonionic surfactant in aqueous solution --

A Yes.

Q -- you would agree that the nonpolar tail group of the nonionic surfactant would not be extended in aqueous solution?

MS. LEBEIS: Objection. Incomplete hypothetical, vague and ambiguous, no foundation.

A It depends entirely on what the tail group is, and whether it's extended or not would depend on a number of factors. Some tail groups can't avoid being extended, whatever

happens. Others would want to be extended if -- for other structural reasons, sterid reasons that they can't fold.

Q So let's talk about the ethoxylated octylphenol nonionic surfactants. For one of those -- and we can take octoxynol 40 as an example. For octoxynol 40 in solution, the polyethoxylated tail of octoxynol 40 wouldn't be extended in a straight line in solution, right?

MS. LEBEIS: Objection, vague and ambiguous, no foundation.

A Well, the -- on octoxynol 40, there's an aryl group as part of the tail group. That is rigid so it can't avoid being sticking straight out.

Q Where do you see the aryl group in the tail of octoxynol 40?

A Where is my picture? If you look at my picture of octoxynol 40, there's a hexagon with three lines in it. That is an aryl group.

Q That's in the head group of octoxynol 40, right?

A How did you define tail group?

STEPHEN G. DAVIES, D.PHIL.

Q How do you define tail group when it comes to nonionic surfactants?

A Well, your question -- I've defined the tail group as the hydrocarbon part, the bit that is hydrophobic.

Q So in these ethoxylated octylphenol surfactants, you would include the phenyl or aryl portion in the tail of these surfactants? Is that what you're saying?

A Yes.

Q Is that how a person of skill in the art would understand what was the head group and the tail group of these surfactants?

MS. LEBEIS: Objection. No foundation. Calls for speculation.

A I believe so. The polar -- the head groups are the polar end, and the tail groups are the nonpolar end. I've defined that in my paragraph 72.

Q Let's go back, then, to talking about what the structure would look like in solution, in aqueous solution.

So you would agree that the ethoxylated portion of the tail of octoxynol 40

would not be extended in a linear fashion in aqueous solution, right?

MS. LEBEIS: Objection to the extent it mischaracterizes prior testimony.

A I don't think I agreed to that at all because, as I was trying to explain to you, the aryl part of the tail group is rigid. It is inflexible. It has to stick straight out.

Q Okay. But my question was directed to the ethoxylated portion of the tail group of octoxynol 40. You would agree that the ethoxylated portion of the tail group of octoxynol 40 would not be extended in a linear fashion in aqueous solution, right?

MS. LEBEIS: Objection to the extent it mischaracterizes prior testimony. Asked and answered.

A The ethoxylated part of the molecule is the head group.

Q Do you have your expert report open in front of you?

A Yes.

Q Could you -- if you're looking at page 35 --

A Yes, okay.

Q -- could you point or maybe circle with a pen -- do you have a pen?

A Yes.

Q Could you circle the ethoxylated portion of octoxynol 9 on page 35.

A (Complying)

Q Okay. So, in your view, the ethoxylated portion is the head group. Is that what your testimony is?

A That's how I've defined it in paragraph 72, and I think that's how a person of ordinary skill would define it.

Q So, in your view, the single nonpolar linear tail is the portion of octoxynol 9 on page 35 that you did not circle; is that right?

MS. LEBEIS: Objection --

A That's right.

MS. LEBEIS: -- to the extent it mischaracterizes the document.

A That's right.

Q So the ethoxylated portion of octoxynol 9 is the polar region; is that right?

A Yes.

STEPHEN G. DAVIES, D.PHIL.

MS. LEBEIS: Objection, asked and answered.

Q And the octylphenol portion of the octoxynol 9 is the nonpolar region?

A That's correct.

Q When octoxynol 9 forms micelles, which portion of the octoxynol 9 molecule faces outward towards the aqueous solution?

MS. LEBEIS: Objection, vague and ambiguous.

A The polar head group.

Q So the ethoxylated portion is what faces outward towards the aqueous solution?

A Yes.

Q Let's look at paragraph 49 of your expert report.

A Okay.

Q In the second sentence of paragraph 49, you say that "The presence of a hydrolyzable amide group in pranlukast suggests that pranlukast would be mainly susceptible to chemical degradation by hydrolysis."

Do you see that?

A Yes.

STEPHEN G. DAVIES, D.PHIL.

Q Then you cite a number of references in support of that, right?

A Yes.

Q Let's talk about that first reference for a moment. It's an article by Giffney and O'Connor. Do you see that?

A Yes.

Q Now, that reference teaches nothing about pranlukast, right?

MS. LEBEIS: You're going to put the reference in front of the witness, right?

Q Can you answer my question?

A Can I check on the reference?

Q Certainly.

MS. RAPALINO: I'm going to mark as Davies Exhibit 14 an article by Giffney and O'Connor. It bears production numbers PROL332616 through 619.

(Exhibit 14 was marked for identification and attached to the deposition transcript.)

BY MS. RAPALINO:

Q This reference, Exhibit 14, it teaches nothing about pranlukast, right?

STEPHEN G. DAVIES, D.PHIL.

MS. LEBEIS: Objection to the extent it mischaracterizes the document. Vague and ambiguous. Argumentative.

A What this reference describes is the hydrolysis of substituted acetanilides, which are acyl derivatives of anilines, which pranlukast is.

Q There's no mention in this reference of pranlukast, right?

A The specific example isn't in here, but it's described in a properly -- a person of ordinary skill would expect for that.

Q Right. Because people of ordinary skill in the art can learn about properties of compounds from similar compounds, right?

MS. LEBEIS: Objection to the extent it mischaracterizes prior testimony, misleading, argumentative.

A It depends entirely on what you're looking at. So this is a functional group. You're looking at possible instabilities. We see some instability. A person would look at the structure and say, how might this be unstable. As it happens, pranlukast has a

couple of places it could hydrolyze as in a way that it would obviously oxidize. So a person of ordinary skill would take away that there may be a hydrolysis problem.

Q So a person of skill in the art would look at the functional groups on pranlukast to determine where it might react. Is that fair?

MS. LEBEIS: Object to the extent it mischaracterizes prior testimony.

A Well, they would -- if they saw a problem by doing an experiment on pranlukast and found that it was degrading, they would ask themselves what features of a molecule such as pranlukast might undergo a chemical reaction in order to destroy it. So having done the experiment, they would ask the question.

Q I'm not sure I understood that answer, but maybe let me see if I can clarify.

So a person of skill in the art would look at functional groups on a particular compound like pranlukast to determine where it might react in any potential degradation. Is that fair?

MS. LEBEIS: Objection to the extent

it mischaracterizes prior testimony.

A If you have a compound and you find it's very stable, fine. If you find a compound that is unstable, you look at the structure of the compound and try to determine from your general chemical knowledge where reactivity might be and what might be leading to it to degrade.

Q The next reference you cite in this paragraph is a reference by Karve and Kelkar. Do you see that?

MS. LEBEIS: Are you going to put the reference in front of the witness?

A I see that, yes.

Q Did you cite this reference because it was specific to pranlukast?

MS. LEBEIS: Objection. Calls for speculation. If you're going to ask him about the reference and what it contains, you should put it in front of the witness.

A I don't recall whether it actually deals with pranlukast. It certainly deals with the hydrolysis of anilides. Anilides are the acyl derivatives of anilines. It's one of the

sites on pranlukast that might -- that could hydrolyze one of the degradation sites.

Q So this is another instance of the use of a reference about a class of compounds to learn about the reactivity of pranlukast specifically?

MS. LEBEIS: Objection to the extent it mischaracterizes prior testimony. Misleading. Argumentative. And no foundation.

MS. RAPALINO: I would just ask that you limit your objections. An objection that mischaracterizes prior testimony when the question has nothing to do with prior testimony is just inappropriate, and you've made that objection to nearly every question.

So, again, these are all speaking objections. You can limit your objections to "objection" and identifying the form of the -- what form objection you have, but otherwise these speaking objections are inappropriate and disrupt the witness from understanding what the question is.

STEPHEN G. DAVIES, D.PHIL.

MS. LEBEIS: I entirely disagree. My objections have been proper. And to the extent your question mischaracterizes the prior testimony of the witness, I will object on that basis.

MS. RAPALINO: Could we read back my prior question.

(Record read.)

MS. LEBEIS: Same objections.

A I missed that even the second time.

(Record read.)

A You don't learn directly about the properties of pranlukast directly from this -- these references. If you see that there's a problem with pranlukast because you do an experiment and see degradation, then you have to look at the molecule that's degrading and ask yourself what functional groups, what type of reactivity might be there. And these types of references give you a clue as to what might be happening in order to explain that experimental result.

Q Did you say anywhere in your expert report that pranlukast is subject to

degradation?

A I don't recall, but we looked earlier at a pranlukast reference, I think. I saw -- I've seen a reference that shows it degrades. In fact, you asked me a question about it.

Q I'm just asking in this paragraph where you suggest that pranlukast would be mainly susceptible to chemical degradation by hydrolysis. Have you identified in this paragraph a problem with pranlukast that led you to suggest that it would be susceptible to degradation by hydrolysis?

MS. LEBEIS: Objection to the form of the question.

A (Document review.)

Well, I refer to the Yasueda reference at the end of paragraph 49.

Q You conclude there about the Yasueda reference in paragraph 49 that "any teaching of Yasueda regarding the chemical stability of pranlukast is irrelevant to bromfenac," right? That's what you say in the last sentence of paragraph 49?

A Because they degrade. Anilides

degrade by different mechanisms, yes.

Q So you're not making any comment there about the relevance of the physical stability of bromfenac and its relevance to pranlukast, right?

MS. LEBEIS: Objection, no foundation.

A I quite clearly state I'm talking about chemical stability.

Q Right. Okay.

Let's take a quick look at -- if we could mark as Davies Exhibit 15 the article by Karve and Kelkar bearing production numbers PROL332620 through 626.

(Exhibit 15 was marked for identification and attached to the deposition transcript.)

BY MS. RAPALINO:

Q This reference doesn't mention pranlukast, right?

A I don't believe it does, no. It's about anilides and their hydrolysis.

Q And so you cited that in support of your statement that pranlukast would be mainly

susceptible to chemical degradation by hydrolysis, right?

A Well, given that pranlukast is -- shows signs of degradation, this is one possible explanation for that. One would have to do the experiment to find out what the degradation product was to see if it's that reaction or hydrolysis of the chromanone or some other reaction, rearrangement, something.

Q Then the next reference you cite in paragraph 49 in support of your statement that pranlukast would be mainly susceptible to chemical degradation by hydrolysis is a paper by Aman and Brown, right?

A Yes.

MS. RAPALINO: Let's mark as Davies Exhibit 16 the Aman and Brown paper, with the production numbers PROL332635 through 644.

(Exhibit 16 was marked for identification and attached to the deposition transcript.)

BY MS. RAPALINO:

Q Now, Exhibit 16, the Aman and Brown

STEPHEN G. DAVIES, D.PHIL.

reference, that also doesn't mention pranlukast, right?

A I don't believe so, no, but it is to do with the hydrolysis of acetanilides -- or anilides, rather.

Q So Exhibit 16 relates, generally, to hydrolysis of anilides? Is that what you're saying?

A Of which pranlukast is one, yes.

Q But, again, Exhibit 16 doesn't mention pranlukast specifically.

MS. LEBEIS: Objection, asked and answered.

A It does not, no.

Q The next reference you cite in this paragraph is an article by Panarin and Solovskii, right?

A Yes.

MS. RAPALINO: We can mark that one as Davies Exhibit 17.

(Exhibit 17 was marked for identification and attached to the deposition transcript.)

STEPHEN G. DAVIES, D.PHIL.

BY MS. RAPALINO:

Q The Panarin and Solovskii article that you've cited also doesn't mention pranlukast specifically, right?

A It does not, no.

Q The next one you cite in this paragraph is an article by Barnett and O'Connor, right?

A Yes.

MS. RAPALINO: If we could mark as Davies Exhibit 18 the Barnett and O'Connor article with production numbers PROL332648 through 650.

(Exhibit 18 was marked for identification and attached to the deposition transcript.)

BY MS. RAPALINO:

Q Exhibit 18 also doesn't mention pranlukast specifically, right?

A It does not. It's an example of how acetanilides hydrolyze.

Q So you've cited this paper about how acetanilides hydrolyze, generally, in support of your statement that pranlukast would be

mainly susceptible to chemical degradation by hydrolysis, right?

A Well, given that it degrades, you have to look at the structure of pranlukast and ask yourself what chemical features are there there that might change. And for pranlukast you have an anilide function, an acylanilide function, which are known to be susceptible to hydrolysis. There are other parts of the molecule that could react, but it's hydrolysis that's likely to occur.

Q Let's look at paragraph 59 of your expert report.

A Yes.

Q In the first sentence of paragraph 59, you say, "It is known that many quaternary ammonium salts are water soluble and thus will not precipitate out of solution."

Do you see that?

A Yes.

Q And you cite an article by Streitwieser and Heathcock for that proposition, right?

A I do, yes. It was a textbook.

STEPHEN G. DAVIES, D.PHIL.

Q Textbook. Are you familiar with Dr. Heathcock?

A I know of him. I think I met him once.

Q Is he a respected chemist?

A Yes.

MS. RAPALINO: I'm going to mark as Davies Exhibit 19 Introduction to Organic Chemistry, 3rd Edition, by Streitwieser and Heathcock, bearing production numbers PROL332187 through 191.

(Exhibit 19 was marked for identification and attached to the deposition transcript.)

BY MS. RAPALINO:

Q This excerpt that you cited from the textbook doesn't discuss benzalkonium chloride, right?

A Doesn't discuss what, sorry?

Q Benzalkonium chloride.

A Not specifically. Structures closely related, but not specifically benzalkonium chloride.

Q And even though it doesn't discuss

benzalkonium chloride specifically, you cite this and then say that you disagree with Dr. Lawrence's statement that "In the presence of a negatively charged NSAID, such as bromfenac, it was known that the NSAID and benzalkonium chloride form an insoluble complex," right?

A Where have I said that?

Q Paragraph 59.

A 59.

That's what I say. Heathcock shows you that benzyl ammonium salts are soluble in water. So you can't make the assumption, and there's no evidence for the fact that any precipitate that's seen with an NSAID and -- a benzalkonium species is a salt of -- or complex of benzyl ammonium.

Q I'm sorry, what did you say that Heathcock showed you?

A That benzyl -- that ammonium -- quaternary ammonium salts are soluble in water.

Q But Heathcock doesn't say anything about benzalkonium chloride specifically, right?

A It doesn't about that in itself, no.

Q So, in your view, to conclude that benzalkonium chloride would be soluble, you would -- a person of skill in the art would learn from similar compounds about the properties of benzalkonium chloride? Is that your testimony?

MS. LEBEIS: Objection to the extent it mischaracterizes prior testimony. Vague and ambiguous.

A Well, the benzyl ammonium salt cations have one functional group, which is the ammonium group.

Q A person of skill in the art then would learn about the properties of benzalkonium chloride based on the functional group that it has in common with other similar compounds?

A You can make some analogy in this case because there's a single function group in the molecule.

Q Does a person of skill in the art only extrapolate properties of a compound when there is a single functional group at issue?

STEPHEN G. DAVIES, D.PHIL.

MS. LEBEIS: Objection. Calls for speculation. Vague and ambiguous.

A You have to look at -- if you're looking at -- comparing two molecules, you have to look at all of the functional groups, the whole structure, and compare the whole structure with the whole structure.

Q In pranlukast, was there only a single functional group?

A No. There are several functional groups in pranlukast.

Q And despite the existence of the presence of several functional groups in pranlukast, you concluded that pranlukast would be susceptible mainly to hydrolysis, right?

MS. LEBEIS: Objection to the extent it mischaracterizes prior testimony.

A I said given that there's a degradation seen for pranlukast, a person of ordinary skill would look at the whole structure of pranlukast and ask himself what type of reactivity might any of the parts of the structure have and would come up with a hydrolysis as the likely degradation route,

wouldn't know for sure unless the experiment is done and you analyzed the by-products in the pranlukast case.

Q Now, in paragraph 81 of your expert report, this is a section where you talk about cyclodextrins, right?

A Yes.

Q And five lines from the bottom of the page you say that "Cyclodextrins are known to form complexes with aryl groups such as the bromophenyl group in bromfenac."

Do you see that?

A Yes.

Q You cite a number of references in support of that statement. Do you see that?

A Yes.

Q The first reference you cite is an article by Breslow and Campbell. Do you see that?

A Yes.

Q It's actually a letter to the editor by Breslow and Campbell, right?

A That's the same as an article without detailed experimental.

STEPHEN G. DAVIES, D.PHIL.

MS. RAPALINO: Can we mark as Davies Exhibit 20 the communication to the editor by Breslow and Campbell, bearing production number PROL332298.

(Exhibit 20 was marked for identification and attached to the deposition transcript.)

BY MS. RAPALINO:

Q This communication to the editor doesn't mention bromfenac, right?

A No.

Q Doesn't mention any NSAID in this communication to the editor, right?

A No. It's describing the basic reactivity of aromatic groups with cyclodextrins.

Q And the second article you cite is an article by Sawada, et al.

Do you see that?

A Yes.

MS. RAPALINO: Let's mark as Davies Exhibit 21 the article by Sawada, et al., with production number PROL0332299 through 300.

STEPHEN G. DAVIES, D.PHIL.

(Exhibit 21 was marked for identification and attached to the deposition transcript.)

BY MS. RAPALINO:

Q This is the Sawada reference that you cited in paragraph 81?

A I believe so.

Q This reference also is not -- doesn't mention bromfenac, right?

A No.

Q If you look at page 40 of your expert report, you go on to say, "Such complexation is likely to affect the chemical stability of bromfenac by impacting its electronic character and making it potentially more susceptible to oxidation."

Do you see that?

A Yes.

Q And you cite an article by Aree and Chaichit for that proposition?

A Yes.

MS. RAPALINO: We'll mark as Davies Exhibit 22 an article by Aree and Chaichit with production numbers PROL0333336 through

STEPHEN G. DAVIES, D.PHIL.

343.

(Exhibit 22 was marked for identification and attached to the deposition transcript.)

BY MS. RAPALINO:

Q Is this the Aree and Chaichit article that you cited in paragraph 81?

A Yes.

Q This article also doesn't mention bromfenac, right?

A It doesn't have bromfenac in it. It discusses benzoic acid, which is an aryl group sitting in the cavity of a cyclodextrin.

Q So you cite this article in support of your statement that complexation between bromfenac and cyclodextrin "is likely to affect the chemical stability of bromfenac by impacting its electronic character and making it potentially more susceptible to oxidation," right?

A Well, the fact that it forms an inclus- -- I do cite it for that. The fact that it forms an inclusion complex at all means that there's a change in electron density

around the aromatic ring which impacts its chemical reactivity.

Q So you cite an article that doesn't mention bromfenac at all as informing you and a person of ordinary skill in the art about something -- a reaction that's relevant to bromfenac; is that right?

MS. LEBEIS: Objection to the extent it mischaracterizes prior testimony. Argumentative.

A I say it potentially would impact, and I'm responding to what Dr. Lawrence says in her report.

MS. RAPALINO: Let's take a quick five-minute break.

MS. LEBEIS: Sure.

THE VIDEOGRAPHER: Going off the record at 5:08 p.m.

(A brief recess was taken.)

THE VIDEOGRAPHER: We're going back on the record at 5:14 p.m.

BY MS. RAPALINO:

Q Dr. Davies, in selecting ingredients for use in an ophthalmic solution formulation,