IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY
CASE NO. 1-14-CV-06893

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SENJU PHARMACEUTICAL CO, LTD., :
BAUSCH & LOMB INCORPORATED, and :
BAUSCH & LOMB PHARMA HOLDINGS CORP.: :
Plaintiffs, :
:
- v - :
:
LUPIN, LTD and LUPIN :
PHARMACEUTICALS, INC. :
:
Defendants. :
:
INNOPHARMA LICENSING, INC., :
INNOPHARMA LICENSING, LLC, :
INNOPHARMA, INC., INNOPHARMA, LLC, :
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February 19, 2016
10:08 a.m.
620 Eighth Avenue
New York, New York

VIDEOTAPED DEPOSITION OF CLAYTON HEATHCOCK, Ph.D., held at the above-mentioned time and place, before Randi Friedman, a Registered Professional Reporter and Notary Public within and for the State of New York.
Job No. NJ2238541

C. Heathcock, Ph.D.

APPEARANCES:

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BY: JUSTIN J. HASFORD, ESQ.

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Attorneys for Defendants, Innopharma
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BY: JITENDRA MALIK, Ph.D.

* * *

ALSO PRESENT:
Dan McClutchy - Videographer
Terrence Kim

C. Heathcock, Ph.D.

MR. McCLUTCHY: Good morning. We are now on the record. Please note that the microphones are sensitive and can pick up whispering and private conversations. Please turn off all cellphones or place them away from the microphones, as they can interfere with the deposition audio. Recording will continue until all parties agree to go off the record. My name is --

MR. MARGOLIS: You might want to go off the record for a minute.

MR. McCLUTCHY: Okay. Going off the record. The time is 10:05.

(Whereupon there was a beverage spill.)

MR. McCLUTCHY: We are back on the record. To continue, my name is Daniel McClutchy, representing Veritext New Jersey. The date today is February 19, 2016, and the time is approximately 10:08 a.m. This deposition is being held at Goodwin Procter, located at 620 Eighth Avenue in New York, New York.

The caption of this case is Senju

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Pharmaceutical versus Lupin Ltd. and Lupin Pharma and Innopharma Licensing. This case is filed in the U.S. District Court, District of New Jersey, Case No. 1-14-CV-06893. The name of the witness is Dr. Clayton Heathcock.

At this time, the attorneys present will identify themselves and the parties they represent, and then our court reporter, Randi Friedman, representing Veritext, will swear in the witness and we can proceed.

MR. HASFORD: Justin Hasford of Finnegan, on behalf of plaintiffs. And I'm here with my colleague, Terrence Kim.

MR. MARGOLIS: Dan Margolis from Goodwin Procter, for Lupin.

DR. MALIK: Jitendra Malik of Alston & Bird, for the Innopharma defendants.

* * *

CLAYTON HEATHCOCK, Ph.D., the witness herein, having been duly sworn, was examined and testified as follows:

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EXAMINATION

BY MR. HASFORD:

Q Good morning, Dr. Heathcock.

A Good morning.

Q Would you please state your name and address for the record.

A My name is Clayton Heathcock, H-e-a-t-h-c-o-c-k. My address is Martinez, California.

Q How many times have you been deposed before?

A Something between 15 and 20. I don't know an exact number. I'm not sure.

Q Do you understand the deposition process?

A Yes, I do.

Q Let me tell you how today's deposition will proceed. I represent plaintiffs in this case. Today I will ask you questions, and I ask that you answer my questions truthfully and accurately. If you need a break, just let me know, but I would ask that if I have asked a question, please first answer the question and then we can take a break.

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If for any reason you do not understand a question that I ask, please let me know. If you answer a question, I will assume that you understood the question; is that okay?

A Yes.

Q Is there any reason why you cannot testify truthfully and accurately today?

A No.

MR. HASFORD: I am handing the court reporter what I would ask to be marked as Heathcock Exhibit 1. For the record, Heathcock Exhibit 1 is entitled "Responsive Expert Report of Clayton H. Heathcock, Ph.D." It includes Appendices A, B and C.

(Heathcock Exhibit 1 was marked.)

BY MR. HASFORD:

Q Is Heathcock Exhibit 1 your responsive report and appendices in this case?

A Yes, it is.

Q Please turn to Page 29.

A Yes.

Q Does your signature appear on Page 29 of your responsive report for this case?

A Yes, it does.

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Q Who prepared your responsive report for this case?

A I did.

MR. MARGOLIS: Objection, form.

THE WITNESS: I prepared it along with a lot of help from the attorneys that I'm working for.

BY MR. HASFORD:

Q How did the attorneys help you prepare this report?

MR. MARGOLIS: Objection. Just be careful not to reveal the substance of any communications with the attorneys, but you can answer the question.

THE WITNESS: I understand. The way this report was constructed was that we had several meetings via telephone conference. I was provided with documents to review; mainly Dr. Bailey's expert report and the art that he cited in it. And I was -- and we held conference about my responses and my opinions with regard to what he had opined.

They then took my -- my ideas.

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Put them into a draft of a report, which was provided to me. I then revised it, provided some chemical illustrations to illustrate some of the things that I said and then back and forth. That's the way it was prepared.

BY MR. HASFORD:

Q Did defendants' counsel provide you the documents on which you are relying on your opinions in this case?

MR. MARGOLIS: Objection, vague.

THE WITNESS: They provided me with Dr. Davies' report and the prior art that he cited. And as I recall, I did some limited amount of literature work on my own and turned up, I think, a couple of things that they had not provided me. But I don't remember the details of that.

BY MR. HASFORD:

Q Do you remember what those two documents were?

A I don't.

Q Please turn to Paragraph 6 on Page 2 of your responsive report for this case.

A Okay.

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Q It reads, "I am a chemist with over 50 years of experience in organic chemistry and medicinal chemistry. I am currently Emeritus Professor at the University of California at Berkeley. A copy of my curriculum vitae and list of publications is attached as Appendix A."

Do you see that?

A Yes.

Q Do you consider yourself an expert in organic chemistry and medicinal chemistry?

A Yes.

MR. MARGOLIS: Objection, vague.

BY MR. HASFORD:

Q Do you consider yourself an expert in other areas besides organic chemistry and medicinal chemistry?

MR. MARGOLIS: Objection, vague.

THE WITNESS: Yes, I do. I consider myself an expert in genealogy and an expert in breeding Ridgeback show dogs, for example.

Q Do you consider yourself an expert in any other scientific areas besides organic chemistry and medicinal chemistry?

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MR. MARGOLIS: Objection, vague.

THE WITNESS: Yeah, that would depend how you define expert. I, for about ten years, have operated a seminar in the QB3, which is a quantitative biosciences institute. I know a lot about biological science. And I do consider that I have some expertise. Not as much as inorganic chemistry and medicinal chemistry, but you know, I can carry out very comfortably conversations with people about topics in those fields as well.

BY MR. HASFORD:

Q Have you ever held yourself out to the public as an expert in any other areas besides organic chemistry and medicinal chemistry?

MR. MARGOLIS: Objection, vague.

THE WITNESS: I don't recall that I've been asked to before.

BY MR. HASFORD:

Q Have you ever been qualified by any court or by the patent office as an expert in any other areas besides organic chemistry and medicinal chemistry?

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MR. MARGOLIS: Objection, vague. Calls for legal conclusion.

THE WITNESS: Yeah. Not that I can recall. In the court appearances I have made, I have been qualified as a medicinal chemist or an organic chemist.

BY MR. HASFORD:

Q Is Appendix A to your responsive report a copy of your curriculum vitae?

A Yes, it is.

Q Does your curriculum vitae list your relevant professional experience?

MR. MARGOLIS: Objection, vague.

THE WITNESS: Yeah. I guess that would depend on what you mean by "relevant." It does list my -- the positions I've held and some but not all of the important positions I've held outside the University of California. And some but not all of the honors that I've received.

BY MR. HASFORD:

Q Does your curriculum vitae list your professional experiences as is relevant to this case?

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MR. MARGOLIS: Objection, vague.

Calls for a legal conclusion.

BY MR. HASFORD:

Q You may answer.

A Yes. I consider my contribution to this case to be in the area of organic chemistry, and it does -- my CV does give a good summary of my background in organic chemistry.

Q Please turn to your curriculum vitae at Appendix A to your responsive report.

A Yes.

Q And let me direct your attention to the first page.

A Okay.

Q Are you there?

A Yes.

Q On the first page of your curriculum vitae, let me direct your attention to the section entitled "Professional History."

A Right.

Q In particular, let me direct your attention to a line that begins "Organic Chemistry Division;" do you see that?

A Yes.

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Q Have you been a member of the Organic Chemistry Division of the American Chemical Society?

A Yes.

Q Is there a separate Medicinal Chemistry Division of the American Chemical Society?

A Yes, there is.

Q Have you ever been a member of the Medicinal Chemistry Division of the American Chemical Society?

A No.

Q Please turn to the next page of your curriculum vitae, and let me direct your attention to the section entitled "Research Interests." Do you see that?

A Yes, I do.

Q Do your research interests include drug discovery?

A No.

Q Is organic synthesis your field of specialty, and are most of your publications in that area?

MR. MARGOLIS: Objection. Vague.

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THE WITNESS: Yes. That's correct.

BY MR. HASFORD:

Q Let me direct your attention to the section of your curriculum vitae entitled "Publications." Does the "Publications" section of your curriculum vitae list all of your publications?

A Yes, it does.

Q Did you publish your last paper in 2008?

A Yes, I did.

Q How many years ago is that?

A That would be eight years ago.

Q Have you published only one paper since 2004?

A Yes.

Q Have you published only two papers in the Journal of Medicinal Chemistry?

A I don't remember that, but I could read through this list and see.

Q Please do.

A Okay, yes, you're right. Two papers on my Compactin with Levinolin(sic.), a synthetic

project.

Q Did both of the papers that you published in the Journal of Medicinal Chemistry involve statins?

A Yes.

Q Have you ever published any papers involving bromfenac?

MR. MARGOLIS: Objection, vague.

THE WITNESS: No.

BY MR. HASFORD:

Q Have you ever published any papers involving any non-steroidal anti-inflammatory drug?

A No.

MR. MARGOLIS: Objection, vague.

BY MR. HASFORD:

Q Have you ever published any papers involving tyloxapol?

MR. MARGOLIS: Objection, vague.

THE WITNESS: No.

BY MR. HASFORD:

Q Have you ever published any papers involving any non-ionic surfactant?

MR. MARGOLIS: Objection, vague.

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THE WITNESS: Yes.

BY MR. HASFORD:

Q Have you ever published any papers involving benzalkonium chloride?

MR. MARGOLIS: Objection, vague.

THE WITNESS: No, I have not.

BY MR. HASFORD:

Q Take a look, if you would, at Paragraph 22 in your responsive report. It's on page 5?

A Yes.

Q It states "During the last four years, I have testified as an expert, either at deposition or trial as set forth in Appendix B."

Please turn to Appendix B to your responsive report. Does Appendix B to your responsive report list the cases over the past four years in which you have testified at deposition and trial?

A Yes.

Q Over the past four years, have you testified at deposition and trial in 12 separate cases besides this case?

A I counted 11. Oh, 12. There's

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another page. Sorry about that. Yes, 12. Let's see -- so what was the question?

Q Over the past four years, have you testified at deposition and trial in 12 separate cases besides this case?

A Yeah. Deposition and/or trial, yes.

Q In all the cases in which you have testified at deposition and trial, have you testified on behalf of the generic pharmaceutical company?

A Yes, that's correct.

Q Have you ever testified that a pharmaceutical patent was novel and non-obvious?

MR. MARGOLIS: Objection.

THE WITNESS: I have not testified to that.

MR. MARGOLIS: Calls for a legal conclusion.

THE WITNESS: In fact, I've given that opinion to lawyers, but I have not been asked to testify in those cases.

BY MR. HASFORD:

Q Just to be clear, have you ever testified that a pharmaceutical patent was novel

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and non-obvious?

MR. MARGOLIS: Objection. Calls for a legal conclusion.

THE WITNESS: I have not testified that a patent in suit was novel. I've testified that other patents were novel.

BY MR. HASFORD:

Q Is it fair to say that your specialty in your career has been synthetic organic chemistry?

MR. MARGOLIS: Objection, vague.

THE WITNESS: Yes. Synthetic organic chemistry is involved in lots of other disciplines. Most notably medicinal chemistry. And my expertise has been in the synthesis of complex compounds.

MR. HASFORD: I'm handing the court reporter what I would ask to be marked as Heathcock Exhibit 2.

For the record, Heathcock Exhibit 2 is the transcript of the trial in AstraZeneca, et al. v. Mylan, et al. In Re, Rosuvastatin Calcium Patent Litigation, case number 08 MD 1949, Monday, February 22nd,

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2010, 9:30 a.m., U.S. District Court for the District of Delaware.

(Heathcock Exhibit 2 was marked.)

BY MR. HASFORD:

Q Doctor, turn, if you would, in Heathcock Exhibit 2, to Page 215 in the small numbered pages. It's going to be Page 55 toward the bottom of the big numbered pages.

A Okay.

Q Do you see about halfway down, it says "Cross-examination by Ms. Bourke"? And she says, "Good afternoon, Dr. Heathcock. Is it Heathcock or Heathcock?"

And you say, you answer, "Heathcock;" you see that?

A Yes.

Q Are you the Dr. Heathcock who testified at trial that was transcribed in Heathcock Exhibit 2?

A Yes.

Q Turn, if you would, to page 218. It's going to be the next page of the document. Let me direct your attention to Page 218, Line 6 through 10.

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You were asked: "Question: And in those cases that we just mentioned, you testified that your specialty in your career has been synthetic organic chemistry; is that right?"

And you answered: "That's correct."

That was your sworn testimony; correct?

A Yes, that's right, yeah.

Q You can put this document aside for now.

A I think that's what I just told you too, but...

Q Aside from your work in this case, have you ever consulted for any party on a matter involving bromfenac?

A No.

Q Aside from your work in this case, have you ever consulted for any party in a matter involving a non-steroidal anti-inflammatory drug?

MR. MARGOLIS: Objection, vague.

THE WITNESS: You have to give me time to think this over, because I've served as a consultant for almost 50 years with companies, and it is possible that one of my

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consulting appointments may have exposed me, but I can't put my finger on a specific case. It would have been with Abbott or Merck or one of these companies that may have been -- very likely core developing NSAIDs. And I probably did consult with chemists about, but I don't remember details.

BY MR. HASFORD:

Q Aside from your work in this case, have you ever consulted for any party on a matter involving tyloxapol?

A No.

Q Aside from your work in this case, have you ever consulted for any party on a matter involving any non-ionic surfactant?

MR. MARGOLIS: Objection, vague.

THE WITNESS: Not that I can recall.

BY MR. HASFORD:

Q Aside from your work in this case, have you ever consulted for any party on a matter involving benzalkonium chloride?

A No, not that I can recall.

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Q Have you ever given any presentations on any matters involving bromfenac?

A No.

Q Have you ever given any presentations on any matters involving any non-steroidal anti-inflammatory drug?

MR. MARGOLIS: Objection. Vague.

THE WITNESS: I think I probably have as a part of a chemistry course when I was teaching organic chemistry. I'm sure that I've explained NSAIDs and what they generally are and how they generally work to my students.

BY MR. HASFORD:

Q Do you remember which NSAIDs you were referring to?

A It would likely have been the most well-known ones. Probably ibuprofen and indomethacin, and, you know, examples that would have illustrated the chemistry.

Q Why are ibuprofen and indomethacin the most well-known examples of NSAIDs?

MR. MARGOLIS: Objection, form.

THE WITNESS: Because they were --

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they were compounds that were widely used both as prescriptions and over-the-counter, so...

BY MR. HASFORD:

Q Have you ever given any presentations on any matters involving tyloxapol?

A Not that I can recall.

Q Have you ever given any presentations on any matters involving any non-ionic surfactant?

MR. MARGOLIS: Objection, vague.

THE WITNESS: Not really, except perhaps as an example, when explaining how surfactants behave and what they're used for in a class.

BY MR. HASFORD:

Q Do you remember which surfactants those were?

A I don't.

Q Have you ever given any presentations on any matters involving benzalkonium chloride?

A No.

MR. MARGOLIS: Objection, vague.

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BY MR. HASFORD:

Q Are you an expert in pharmaceutical formulation?

MR. MARGOLIS: Objection, vague. Calls for a legal conclusion.

THE WITNESS: I am not. I don't hold myself out to be an expert in formulations, except to the extent that chemistry and the interaction of ingredients would be involved.

Q Have you ever held yourself out to the public as an expert in pharmaceutical formulation?

A No.

MR. MARGOLIS: Objection, vague.

Q Are you an expert in the field of pharmacy?

MR. MARGOLIS: Objection, vague.

THE WITNESS: Could you define what you mean by "pharmacy"?

Q What's your understanding of the field of pharmacy?

A Well, pharmacy to me would encompass a number of different areas. And certainly the

medicinal chemistry aspect, I consider myself an expert in. The delivery of medicinals, I certainly have sufficient knowledge to consider myself an expert in. Is that sufficient?

Q Have you ever practiced pharmacy?

A No.

Q Have you ever held yourself out to the public as an expert in the practice of pharmacy?

A No.

Q Are you an expert in pharmacology?

MR. MARGOLIS: Objection, vague. Calls for a legal conclusion.

THE WITNESS: I have some considerable expertise in pharmacology to the extent that pharmacokinetic properties of drugs are part of pharmacology. I understand that. I understand absorption, distribution, metabolism. So I do consider I have expertise in that part of pharmacology.

Q Have you ever held yourself out to the public as an expert in pharmacology?

MR. MARGOLIS: Objection, vague.

THE WITNESS: I have not been

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asked before whether -- I think you're the first person who's asked me that question.

BY MR. HASFORD:

Q So just to be clear, have you ever held yourself out to the public as an expert in pharmacology?

A Not previously.

MR. MARGOLIS: Objection, vague.

THE WITNESS: No.

MR. MARGOLIS: Dr. Heathcock, can you slow down and give me a chance to object so we're not talking over each other, thank you.

BY MR. HASFORD:

Q Have you ever held yourself out to the public as an expert in pharmacokinetics?

MR. MARGOLIS: Objection, vague.

THE WITNESS: I have not, but I would have if I had been asked.

BY MR. HASFORD:

Q Have you ever taught any courses in pharmacokinetics?

A Not where that was the single topic.

Q Are you an expert in pharmacodynamics?

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MR. MARGOLIS: Objection, vague. Calls for a legal conclusion.

THE WITNESS: No.

BY MR. HASFORD:

Q Are you an expert in ophthalmology?

MR. MARGOLIS: Objection, vague. Calls for a legal conclusion.

THE WITNESS: No, I'm not.

BY MR. HASFORD:

Q Are you an expert in any field of medicine?

MR. MARGOLIS: Objection, vague. Calls for a legal conclusion.

THE WITNESS: No, I have no medical training and no medical practice in my background.

Q Have you ever prescribed medication to a patient?

A No. Certainly I would not be allowed to do that.

Q Have you ever treated an inflammatory disease of the eye?

MR. MARGOLIS: Objection, vague.

THE WITNESS: No, I have not.

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BY MR. HASFORD:

Q Have you ever administered any bromfenac product to a patient?

MR. MARGOLIS: Objection, vague.

THE WITNESS: No, I have not.

Q Have you ever dispensed any bromfenac product to a parent?

A No.

Q Have you ever administered any non-steroidal anti-inflammatory drug product to a patient?

MR. MARGOLIS: Objection, vague.

THE WITNESS: Well, if I'm the patient, yes, I do that regularly. And I do -- I have administered NSAIDs to other members of my family. And so, yes. But not as a doctor.

BY MR. HASFORD:

Q Have you ever dispensed any non-steroidal anti-inflammatory drug product to a patient?

A Same answer.

Q Have you ever administered any product containing tyloxapol to a patient?

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MR. MARGOLIS: Objection, vague.

THE WITNESS: No, I have not.

BY MR. HASFORD:

Q Have you ever dispensed any product containing tyloxapol to a patient?

A No, I have not.

Q Have you ever administered any product containing any non-ionic surfactant to a patient?

MR. MARGOLIS: Objection. Vague. Calls for speculation.

THE WITNESS: Yeah, I don't know. I mean, I may have because I had four children and I administered all sorts of things to them that were prescribed by their doctors, and some of them may have been surfactants.

BY MR. HASFORD:

Q Have you ever dispensed any product containing any non-ionic surfactant to a patient?

MR. MARGOLIS: Objection, vague. Calls for speculation.

THE WITNESS: Only under the same sort of circumstances.

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BY MR. HASFORD:

Q Have you ever administered any product containing benzalkonium chloride to a patient?

MR. MARGOLIS: Objection, vague. Calls for speculation.

THE WITNESS: Well, again, if I am the patient, I probably have because I've used lots of eyedrops. I've had cataract surgery. And actually other eye surgery, so I've administered these things to myself, I'm sure.

BY MR. HASFORD:

Q Have you ever dispensed any product containing benzalkonium chloride to a patient?

MR. MARGOLIS: Objection, vague. Lacks foundation.

THE WITNESS: I guess it would be under the same circumstances. I've never sold it.

BY MR. HASFORD:

Q Have you ever conducted any research on any bromfenac product?

A No.

Q Have you ever conducted any research

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on any non-steroidal anti-inflammatory drug product?

A I don't think so.

Q Have you ever conducted any research on any product containing tyloxapol?

A No.

Q Have you ever conducted any research on any product containing any non-ionic surfactant?

A I don't think so, no.

Q Have you ever conducted any research on any product containing benzalkonium chloride?

A No.

Q Have you ever designed a drug in which you replaced a carboxylic acid group with a tetrazole group?

MR. MARGOLIS: Objection, lacks foundation. And vague.

THE WITNESS: In a way, yes, I've -- in my capacity as consultant to medicinal chemists who were developing new drug products, I have certainly suggested to medicinal chemists that they make that substitution because tetrazole is an

isosteric replacement for carboxyl group. I have not carried out those experiments myself. But professors usually don't carry out experiments. We usually suggest them to students, and they do it.

So in interacting with medicinal chemists, Pfizer, Merck or one of the main companies, they might make those kinds of suggestions and they do it, it's like the same as if my students had done it, so... So that's something where I can say I have had that kind of experience.

BY MR. HASFORD:

Q Just to be clear, have you yourself ever carried out a synthesis in which you replaced a carboxylic acid group with a tetrazole group?

A Not with my own hands, no.

Q Are you an expert in clinical testing?

MR. MARGOLIS: Objection, vague. Calls for a legal conclusion.

THE WITNESS: No, I'm not -- I've not done any -- I'm an expert to the extent that my expertise has to do with evaluation

of clinical testing results of our -- well, about 20 years, I was a member of advisory boards for either Abbott Laboratories or Plexxikon, and part of my responsibility was to review clinical test data. And these would be presentations that would be presented by scientists who were gathering the data. And so I understand how clinical test data is presented -- is acquired, presented and evaluated, but it's not been my responsibility to make decisions other than just make observations.

BY MR. HASFORD:

Q Take a look, if you would, again at Heathcock Exhibit 2. And let me direct your attention to Page 222 on the small numbered pages. Its Page 57 at the bottom of the large numbered pages.

A Okay.

Q Let me direct your attention on Page 222 to Lines 12 -- sorry, Lines 9 through 13.

A Yes.

Q You were asked: "Question: You do not consider yourself an expert in clinical

matters relating to statins; isn't that right?"

You answered: "No, I'm not a practicing clinician."

That was your testimony, correct?

A That's right.

Q You likewise do not consider yourself an expert in clinical matters relating to NSAIDs correct?

MR. MARGOLIS: Objection. Vague. Calls for a legal conclusion.

THE WITNESS: I'm sorry, relating to what?

BY MR. HASFORD:

Q Relating to NSAIDs.

A Oh, yes. Yes, that's correct. Same answer.

Q Okay. You can put that aside.

Are you an expert in statistics or biostatistics?

MR. MARGOLIS: Objection, vague. Calls for a legal conclusion. Compound.

THE WITNESS: No.

BY MR. HASFORD:

Q Are you an expert in the U.S.

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pharmacopoeia criteria for antimicrobial effectiveness?

MR. MARGOLIS: Objection, vague. Calls for a legal conclusion.

THE WITNESS: You're asking if I'm an expert in one particular document?

BY MR. HASFORD:

Q No. I'm asking if you are an expert in the U.S. pharmacopoeia criteria for antimicrobial effectiveness generally?

MR. MARGOLIS: Objection, vague. Calls for a legal conclusion.

THE WITNESS: Yeah, I wouldn't call myself -- advertise myself as an expert in that.

BY MR. HASFORD:

Q Are you an expert in the European pharmacopoeia criteria B standards?

MR. MARGOLIS: Objection, vague. Calls for a legal conclusion.

THE WITNESS: No, I'm not.

BY MR. HASFORD:

Q Are you an expert in stability testing of aqueous liquid preparations?

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MR. MARGOLIS: Objection, vague. Calls for legal conclusion.

THE WITNESS: No.

BY MR. HASFORD:

Q Are you an expert in patent law?

MR. MARGOLIS: Objection, vague. Calls for a legal conclusion.

THE WITNESS: You know, I know -- I know a lot about patent law, but I'm not lawyer. I'm not trained as a lawyer. I don't practice as a lawyer.

You know, being an expert, you're asking a lot of questions if I'm an expert, if I'm an expert. A lot of these things I know a lot about, but I don't advertise myself as that. I don't get paid to do that. So I think your bar is sort of, "Are you a person who could get paid to do this?" And so my answer would be no.

BY MR. HASFORD:

Q You testified you know a lot about patent law. What do you know about patent law?

MR. MARGOLIS: Objection, vague.

THE WITNESS: What do I know about

patent law? I don't think that's a question I can answer you in a simple -- a few words, but I know what I've learned in dealing with guys like you who are very interesting for, you know, 10 or 15 years. I understand the grounds for -- yeah, so --

BY MR. HASFORD:

Q You're a named inventor on a couple U.S. patents; correct?

A That's right.

Q Are you a named inventor on only two U.S. patents?

A Yes.

Q Are you a named inventor on any patents involving bromfenac?

A No.

Q Are you a named inventor on any patents involving any non-steroidal anti-inflammatory drug?

A No.

Q Are you a named inventor on any patents involving tyloxapol?

A No.

Q Are you a named inventor on any patent

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involving any non-ionic surfactant?

A No.

Q Are you a named inventor on any patents involving benzalkonium chloride?

A No.

Q Are you an expert in FDA regulatory law?

MR. MARGOLIS: Objection, vague. Calls for a legal conclusion.

THE WITNESS: Again, I know a lot about it, but I'm not -- I don't hold myself out as an expert.

BY MR. HASFORD:

Q Prior to this case, have you ever provided any opinion regarding any bromfenac product?

A No.

MR. MARGOLIS: Objection, vague.

BY MR. HASFORD:

Q Prior to this case, have you ever provided any opinion regarding any non-steroidal anti-inflammatory drug product?

MR. MARGOLIS: Objection, vague.

THE WITNESS: Let me think about

that. Well, you know, some of the cases I have worked on and I've given opinions on did involve drugs that are anti-inflammatories and are not steroids. They would not have been included in the general NSAID rubric and I'm not really sure why that is, but there are a lot of compounds that have anti-inflammatory properties that are steroids but which for some reason people don't group with the NSAIDs like the profens, for example.

So that's a complicated answer. But, yes, I have provided opinions about anti-inflammatory drugs.

Q What opinions have you provided about non-steroidal anti-inflammatory drugs?

MR. MARGOLIS: Objection, mischaracterizes his testimony. Lacks foundation.

THE WITNESS: I've said that some of the cases that I've worked on -- some of the patent cases I've worked on both on infringement and on validity of patent have involved drugs, and I can't -- I can't

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really recall the exact cases, but if you want to, I can go through and perhaps remember which ones from looking at my list. Is that something you would like me to do?

Q Let me ask you a different question for now.

A Okay.

Q Prior to this case, have you ever provided any opinion regarding any product containing tyloxapol?

MR. MARGOLIS: Objection. Vague. Lacks foundation.

THE WITNESS: Yeah, that, I think I can say confidently, no, I have not.

BY MR. HASFORD:

Q Prior to this case, have you ever provided any opinion regarding any products containing any non-ionic surfactant?

MR. MARGOLIS: Objection, vague. Lacks foundation.

THE WITNESS: Again, not that I can recall.

BY MR. HASFORD:

Q Prior to this case, have you ever

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provided any opinion regarding any product containing benzalkonium chloride?

MR. MARGOLIS: Objection, vague. Lacks foundation.

THE WITNESS: I think also no.

BY MR. HASFORD:

Q Have you ever formulated any bromfenac product?

A No.

Q Have you ever formulated any non-steroidal anti-inflammatory drug product?

MR. MARGOLIS: Objection, vague.

THE WITNESS: No, I haven't.

BY MR. HASFORD:

Q Have you ever formulated any product containing tyloxapol?

MR. MARGOLIS: Objection, vague.

THE WITNESS: No.

BY MR. HASFORD:

Q Have you ever formulated any products containing any non-ionic surfactant?

MR. MARGOLIS: Objection, vague.

THE WITNESS: No.

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BY MR. HASFORD:

Q Have you ever formulated any product containing benzalkonium chloride?

MR. MARGOLIS: Objection, vague.

THE WITNESS: No.

BY MR. HASFORD:

Q Have you ever formulated any marketed drug product?

MR. MARGOLIS: Objection, vague.

THE WITNESS: Have I ever formulated any marketed drug product? No, I think. That's correct, no.

Q Have you ever formulated any product for treating an inflammatory disease of the eye?

MR. MARGOLIS: Objection, vague.

THE WITNESS: No.

BY MR. HASFORD:

Q Have you ever authored any papers dealing with formulation of aqueous liquid preparations?

MR. MARGOLIS: Objection, vague.

THE WITNESS: That's correct, no.

BY MR. HASFORD:

Q Have you ever authored or edited any

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book chapters dealing with formulation of aqueous liquid preparations?

MR. MARGOLIS: Objection, vague.

THE WITNESS: No.

BY MR. HASFORD:

Q Have you ever measured the solubility of bromfenac?

A No.

Q Have you ever measured the solubility of any complex or salt of bromfenac and benzalkonium chloride?

A No.

Q Have you ever contributed to the content of any edition of the European Pharmacopoeia?

A No.

Q Have you ever contributed to the content of any edition of the United States Pharmacopoeia?

A No.

Q Are you aware that the United States Pharmacopoeia is a publication of the National Formulary?

A I wasn't aware of that.

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Q Have you ever consulted for the National Formulary?

A No, I have not.

Q Have you ever contributed to the content of any edition of the Japanese pharmacopoeia?

A No, I have not.

Q Have you ever consulted for the FDA?

A For the FDA? No.

Q Have you ever been hired for a permanent position at a pharmaceutical company?

MR. MARGOLIS: Objection, vague.

THE WITNESS: Yeah, I think the answer is no. Yeah.

BY MR. HASFORD:

Q Just to be clear, have you ever been hired for a permanent position at a pharmaceutical company?

MR. MARGOLIS: Objection, vague.

THE WITNESS: Yeah, the reason I paused was I did spend a two-week period once at Merck teaching a course, and I was trying to remember if they put me on the payroll for those two weeks or just gave me

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consulting money, and I think it was that they just paid me as a consultant.

BY MR. HASFORD:

Q So just so we have a clear record, have you ever been hired for a permanent position at a pharmaceutical company?

A Yeah, I'll say no.

MR. MARGOLIS: Objection, vague, asked and answered.

BY MR. HASFORD:

Q Have you ever founded or co-founded a pharmaceutical services company?

MR. MARGOLIS: Objection, vague.

THE WITNESS: No.

BY MR. HASFORD:

Q Have you ever formulated an ophthalmic product at a pharmaceutical company?

MR. MARGOLIS: Objection, vague.

THE WITNESS: That's right, no.

BY MR. HASFORD:

Q Have you ever received a research grant for the use of bromfenac in a pharmaceutical formulation?

A No.

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Q Have you ever received a research grant for the use of any non-steroidal anti-inflammatory drug in a pharmaceutical formulation?

A No.

Q Have you ever received a research grant for the use of tyloxapol in a pharmaceutical formulation?

A No.

Q Have you ever received a research grant for the use of any non-ionic surfactant in a pharmaceutical formulation?

A No.

Q Have you ever received a research grant for the use of benzalkonium chloride in a pharmaceutical formulation?

A No.

Q Have you ever published a book chapter dealing with the use of bromfenac in a pharmaceutical formulation?

MR. MARGOLIS: Objection, vague.

THE WITNESS: No.

BY MR. HASFORD:

Q Have you ever published a book chapter

dealing with the use of any non-steroidal anti-inflammatory drug in a pharmaceutical formulation?

MR. MARGOLIS: Objection, vague.

THE WITNESS: No.

BY MR. HASFORD:

Q Have you ever published a book chapter dealing with the use of tyloxapol in a pharmaceutical formulation?

MR. MARGOLIS: Objection, vague.

THE WITNESS: No.

BY MR. HASFORD:

Q Have you ever published a book chapter dealing with the use of any non-ionic surfactant in a pharmaceutical formulation?

MR. MARGOLIS: Objection, vague.

THE WITNESS: No.

BY MR. HASFORD:

Q Have you ever published a book chapter dealing with the use of benzalkonium chloride in a pharmaceutical formulation?

MR. MARGOLIS: Objection, vague.

THE WITNESS: No.

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BY MR. HASFORD:

Q Have you ever published a book chapter dealing with formulating a stable aqueous liquid preparation?

MR. MARGOLIS: Objection, vague.

THE WITNESS: No.

BY MR. HASFORD:

Q What are some of the different physical and chemical properties that different non-steroidal anti-inflammatory drugs possess?

MR. MARGOLIS: Objection, lacks foundation. Calls for speculation.

THE WITNESS: Could you say the question again?

BY MR. HASFORD:

Q Certainly. What are some of the different physical and chemical properties that different non-steroidal anti-inflammatory drugs possess?

MR. MARGOLIS: Objection, lacks foundation. Vague. Calls for speculation.

THE WITNESS: Different chemical and physical properties? Well, they can have different -- they can have different

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melting points. Boiling points. Solubilities. Densities. Refractive indices. They can have -- different colors. I think that all of the common ones that we've talked about are colors. But that's a physical property. They can have -- depending on their functional groups, they can have different chemical reactivity. Even if they have the same functional groups, the chemical -- the rates of chemical reactions could be -- could be different, either slightly different or in some cases largely different. How far would you like me to go? Is that enough?

BY MR. HASFORD:

Q Please. Continue.

A That's probably enough to give you.

Q Why do different non-steroidal anti-inflammatory drugs have different physical and chemical properties?

MR. MARGOLIS: Objection. Vague. Compound.

THE WITNESS: Well, they have different chemical and physical properties

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because they're different entities. And the physical and chemical properties of a molecule are related to the chemical structure. And generally, if two things have a different chemical structure, they have different chemical and physical properties.

BY MR. HASFORD:

Q Have you ever accurately predicted the physical and chemical properties that a non-steroidal anti-inflammatory drug based on the physical and chemical properties of a different non-steroidal anti-inflammatory drug with a different chemical structure?

MR. MARGOLIS: Objection, vague.

THE WITNESS: Yeah, I think that's kind of vague. I mean, you know, you can -- chemists routinely predict -- make predictions. I mean, that's -- especially medicinal chemistry is based on making predictions.

If you have a compound that has certain properties that you've determined, and you make a change in structure, we often

predict what that change will do to the properties. And with some confidence because we have a lot of experience. So if you make a small change in structure, you would expect a small change in properties and so forth. So the accuracy of that prediction is going to be depending on how big the change is.

BY MR. HASFORD:

Q Have you yourself ever accurately predicted the physical and chemical properties of a non-steroidal anti-inflammatory drug based on the physical and chemical properties of a different non-steroidal anti-inflammatory drug with a different chemical structure?

MR. MARGOLIS: Objection, vague. Asked and answered.

THE WITNESS: Well, yeah, I mean, I think I haven't probably been asked or confronted with the need to do that.

Q What are some of the different physical and chemical properties that different non-ionic surfactants possess?

MR. MARGOLIS: Objection. Vague.

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Compound. Lacks foundation.

BY MR. HASFORD:

Q You may answer.

A Yeah, it would be a similar answer. They would have different -- you know, they would have different melting points. Different solubilities. In the case of surfactants, they have this property of -- because they're amphiphilic and they have a hydrophobic section and a hydrophilic section, they have this property of forming aggregates both with each other and with other molecules in solution. They can even form aggregates to a sufficient size that they form what we call micelles, which is a particular kind of structure. But they can also form complexes without forming micelles with other substances in solution and therefore alter the properties of that other substance.

So I mean, it may differ because the different structures of the different surfactants will allow them to be better or, you know, or worse at interacting with each other and with other solute molecules that may be in the solution along with them.

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Q Why do different non-ionic surfactants have different chemical and physical properties?

MR. MARGOLIS: Objection, vague. Compound.

THE WITNESS: Because they have different structures, and again, the properties of a molecule are generally related to the molecular structure.

Q Have you ever accurately predicted the physical and chemical properties of a non-ionic surfactant based on the physical and chemical properties of a different non-ionic surfactant with a different chemical structure?

MR. MARGOLIS: Objection, vague.

THE WITNESS: No, I have not had -- I've not really been confronted with that problem in my own work.

BY MR. HASFORD:

Q What is pKa?

A PKa is the -- is a -- is the number that characterizes the acidity of a protic acid. It's a number that -- a measurement that tells us how likely the acid is to release a proton and become an anion.

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Q Is pKa measured on a logarithmic scale?

A Yes, it is.

Q How large a difference on a linear scale is as difference of 0.3 pKa units?

A 0.3 is about a factor of five, I think. 1.0 is a factor of ten. And 0.3, I think, is a factor of five, as I recall.

Q How large a difference on a linear scale is a difference of 0.5 pKa units?

A Well, you know, I think it would be probably about a factor of seven or so, but something between five and ten.

Q How large is a difference on a linear scale is a difference of 0.7 pKa units?

A Again, something between five and ten.

Q In connection with your opinions in this case, did you consider any biological data?

MR. MARGOLIS: Objection, vague.

THE WITNESS: Well, I mean, no, I didn't really -- I didn't really look at biological data. I don't think that was really a factor for me.

Q In connection with your opinions in

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this case, did you consider any in vitro potency data?

MR. MARGOLIS: Objection, vague.

THE WITNESS: No.

BY MR. HASFORD:

Q In connection with your opinions in this case, did you conduct any of your own testing?

A No.

Q In connection with your opinions in this case, did you consider any spectroscopic or spectrometric data?

MR. MARGOLIS: Objection, vague.

THE WITNESS: No.

MR. HASFORD: For the record, I'm handing the court reporter what I would ask to be marked as Heathcock Exhibit 3.

Heathcock Exhibit 3 is a copy of the U.S. District Court for the District of Delaware's Opinion in OSI Pharmaceuticals, et al. v. Mylan Pharmaceuticals.

(Heathcock Exhibit 3 was marked.)

BY MR. HASFORD:

Q Turn, Doctor, to Page 13 in Heathcock

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Exhibit 3. It's Page 13 on the upper right-hand corner.

A Okay.

Q And let me direct your attention to Footnote 13, which is about two-thirds of the way down the left-hand column. Do you see that?

A Yeah.

Q It says "Heathcock testified that a chloro group is non-polar and lipophilic;" do you see that?

A Right.

Q Are you the Dr. Heathcock who testified that chloro group is non-polar and lipophilic?

A Yes.

Q What did you mean when you testified that a chloro group is non-polar and lipophilic?

MR. MARGOLIS: Dr. Heathcock, take whatever time you need to familiarize yourself with the document.

BY MR. HASFORD:

Q Oh, please do.

A So what was the question again? What did I mean by non-polar and small?

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Q What did you mean when you testified that a chloro group is non-polar and lipophilic?

A Oh, non-polar and lipophilic.

This was in the context of a chloro attached to a benzene ring. And lipophilic means that a compound has a predilection for being dissolved in oil more than for being dissolved in water. We have a way of measuring that, which is an experimental technique, where you actually partition the compound of interest between an oily substance and water and you shake it up and let it find its home. And then you measure how much is in each one -- each of these two phases. And the more of it that ends up in the oil layer, the more lipophilic the compound is said to be.

And there's a property that's called the distribution coefficient that is kind of like the pKa, that is a logarithmic scale that you can then give the compound that measures how much it distributes between the oil and the water.

And in the case of the chlorine, if you do that with chlorobenzene, you find that the chlorine will make the compound prefer the oil more than if it weren't there. So it's a

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lipophilic substituent. And it's non-polar because it doesn't cause the compound to have a charge. Yeah. Is that enough?

Q Yes. Thank you.

Is a chloro group freely water-soluble?

MR. MARGOLIS: Objection, vague.

THE WITNESS: If it's a chloride ion, well, yeah, that's a question that doesn't really -- it's not a question that can be answered. You can't say that any group is water-soluble. I mean, it's -- it may have -- yeah, that's not -- kind of -- sorry, it's a nonsense question.

BY MR. HASFORD:

Q Let me ask it a different way.

A Yeah.

Q Is a chloro group attached to a benzene ring freely water-soluble?

DR. MALIK: Incomplete hypothetical.

THE WITNESS: Yeah, as I say, again, you can't say any group is water-soluble. The compound, the molecule

can be water-soluble. If you're asking me does the chloro group attach to a benzene ring make the benzene ring compound more water-soluble, then I can answer that question. Is that what you mean?

BY MR. HASFORD:

Q Let me ask it that way.

If a chloro group is attached to the benzene ring, does that make the compound more water-soluble or less water-soluble?

MR. MARGOLIS: Objection, vague. Incomplete hypothetical.

THE WITNESS: It's a question that doesn't probably have a general answer because it probably would be -- it would probably depend on what else is attached to the molecule. And actually, for the case of -- for the case of just benzene and chloro benzene, I can take a stab at that. Both of those compounds would be very water-insoluble.

And -- however, if you measured their distribution coefficient between water and octanol, I'm not really sure what the

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answer would be there, but it might be that the chloro would have some effect on the distribution coefficient that would make it appear to be less water-soluble than benzene.

BY MR. HASFORD:

Q Generally speaking, does the addition of a chloro group to a phenyl ring make the compound less water-soluble?

MR. MARGOLIS: Objection, vague. Incomplete hypothetical. Asked and answered.

BY MR. HASFORD:

Q You may answer.

A Yeah, generally speaking, chemists would not look at that and say, "Oh, yeah chlorine will make" -- yeah, it's not considered something that would make a really big difference, a big enough that I would catalogue that as, you know, something noticeable.

Q How does a chloro group differ from a bromo group?

MR. MARGOLIS: Objection, lacks foundation. Vague. Incomplete

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hypothetical.

THE WITNESS: It has a different number of protons, neutrons, electrons and a different molecular -- atomic radius.

BY MR. HASFORD:

Q How do the physical and chemical properties of a chloro group differ from the physical and chemical properties of a bromo group?

MR. MARGOLIS: Objection, lacks foundation. Vague. Incomplete hypothetical.

BY MR. HASFORD:

Q You may answer.

A Sorry. How do the chemical and physical properties of bromine and chlorine, when attached as a substituent, differ? Did you say chemical and physical?

Q Correct.

MR. MARGOLIS: Same objections.

THE WITNESS: There's a lot of answers to that. I'm going to assume you mean attached to a benzene ring. And, you know, they would -- the bromobenzene

compound would have a, you know, let's see. What properties?

I wish you would ask a little bit more focused question. I mean, I could give a lecture about the difference between bromine and chlorine as an aromatic substituent. The density would be different. Probably the dipole moment would be different. I'm not sure about the -- certainly the C log P that is the measure of the distribution coefficient would not be the same. I'm not quite sure how they would differ. I think the bromobenzene compound would be a bit more lipophilic. What else can I say? You know, the effect of the substituents on the NMR spectrum would be different.

So there would be a lot of differences. But they wouldn't be huge differences. They would be -- because they're both halogens. They're both chemically rather inert, although to the extent they are reactive, the bromo compound would be more reactive.

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BY MR. HASFORD:

Q Why would a bromo substituted aromatic compound be more reactive than a chloro substituted aromatic compound?

MR. MARGOLIS: Objection, vague. Incomplete hypothetical.

BY MR. HASFORD:

Q You may answer.

A Well, because bromine is a better leaving group in chemical reactions, so under extreme base conditions, you would be able to eliminate HPR from bromobenzene, forming an intermediate called benzine. And this would be a reaction that would be more facile with a bromobenzene than with chlorobenzene, for example.

MR. MARGOLIS: Justin, we've been running about an hour. Is now a good time for a break?

MR. HASFORD: Give me about five more minutes, if you would, and we'll be at a good stopping point.

MR. MARGOLIS: Sure.

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BY MR. HASFORD:

Q How do the physical and chemical properties of a compound having a bromo-substituted phenyl ring differ from the physical and chemical properties of a compound having a chloro-substituted phenyl ring?

MR. MARGOLIS: Objection. Lacks foundation. Vague. Incomplete hypothetical.

DR. MALIK: Calls for a narrative.

BY MR. HASFORD:

Q You may answer.

A Well, it would depend on the nature of the reaction. As I just illustrated in the last answer, if you use very strong basic conditions, you would be able to, in some cases, eliminate a bromine along with an adjacent hydrogen. A hydrogen on an adjacent carbon more easily than you would with chlorine. That would be one thing.

If you were carrying out an electrophilic reaction on the aromatic ring that had a chlorine or a bromine, the reaction -- the different halogens could cause different

reactivity rates of benzene ring at positions -- not the position where the halogens are attached but other positions different. And in that case, you would expect the chlorine to have a more deactivating effect than the bromine. So it really depends on what the reaction is.

Q Why do the physical and chemical properties of a compound with a chloro-substituted phenyl ring differ from the physical and chemical properties of a compound with a bromo-substituted phenyl ring?

MR. MARGOLIS: Objection. Lacks foundation, vague. Incomplete hypothetical.

BY MR. HASFORD:

Q You may answer.

A Well, generally speaking, the chemical and physical -- I think I've answered this before in another context -- generally speaking the chemical and physical properties of organic compounds are related to the exact structure, and since bromo and chloro aromatic compounds have different structures, they would be expected to have different and physical properties.

Q Have you ever created

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three-dimensional --

MR. MARGOLIS: Were you finished with your answer?

THE WITNESS: Yeah. I could go on all day because -- but, you know, it's just because they have different numbers of nuclear particles and different numbers of electrons, so that will cause the molecules to interact differently with external reagents.

Q Have you ever created three-dimensional structures using molecular mechanics to represent the global minimum energy structure of molecules in a gas phase?

A Yes, certainly.

Q Can creating three-dimensional structures using molecular mechanics to represent the global minimum energy structure of molecules be useful to show the structural differences between molecules?

MR. MARGOLIS: Objection, vague.

THE WITNESS: Yeah. That's what -- generally what you're using them for.

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MR. HASFORD: Okay. We can take a break now.

MR. McCLUTCHY: Going off the record. The time is 11:16. This ends Disc 1.

(Whereupon there was a brief recess.)

MR. McCLUTCHY: We are back on the record. The time is 11:30. This is Disc No. 2.

MR. HASFORD: Counsel, we'll stipulate that the objections that you make, Dan, for on behalf of Lupin will also apply to Innopharma?

DR. MALIK: Likewise, all the objections that I make --

MR. HASFORD: Then the two of you don't have to object, exactly.

MR. MARGOLIS: Thank you.

MR. HASFORD: I'm handing the court reporter what I ask to be marked as Heathcock Exhibit 4.

For the record, Heathcock Exhibit 4 is a copy of U.S. Patent No. 8,129,431.

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(Heathcock Exhibit 4 was marked.)

BY MR. HASFORD:

Q Did you review U.S. Patent No. 8,129,431 in connection with your opinions in this case?

A Yes.

Q If I refer to U.S. Patent No. 8,129,431, as the '431 patent, will you understand what I mean?

A Yes.

Q You can put that aside for a moment when we look at it again shortly.

MR. HASFORD: I'm handing the court reporter what I ask to be marked as Heathcock Exhibit 5.

For the record, Heathcock Exhibit 5 is a copy of U.S. Patent No. 8,669,290.

(Heathcock Exhibit 5 was marked.)

BY MR. HASFORD:

Q Did you review U.S. Patent No. 8,669,290 in connection with your opinions in this case?

A Yes, I did.

Q If I refer to U.S. Patent No.

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8,669,290 as the '290 patent, will you understand what I mean?

A Yes.

Q You can put that aside.

MR. HASFORD: I'm handing the court reporter what I would ask be marked as Heathcock Exhibit 6.

For the record, Heathcock Exhibit 6 is a copy of U.S. Patent No. 8,754,131.

(Heathcock Exhibit 6 was marked.)

BY MR. HASFORD:

Q Did you review U.S. Patent No. 8,754,131 in connection with your opinions in this case?

A Yes.

Q If I refer to U.S. Patent No. 8,754,131 as the '131 patent, will you understand what I mean?

A Yes.

Q You can put that aside for the moment.

MR. HASFORD: I'm handing the court reporter what I would ask be marked as Heathcock Exhibit 7.

For the record, Heathcock Exhibit

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7 is a copy of U.S. Patent No. 8,871,813.

(Heathcock Exhibit 7 was marked.)

BY MR. HASFORD:

Q Did you review U.S. Patent No. 8,871,813 in connection with your opinions in this case?

A Yes, I did.

Q If I refer to U.S. Patent No. 8,871,813 as the '813 patent, will you understand what I mean?

A Yes.

Q You can put that aside for the moment.

MR. HASFORD: I'm handing the court reporter what I would ask to be marked as Heathcock Exhibit-8.

For the record, Heathcock Exhibit 8 is a copy of U.S. Patent No. 8,927,606.

(Heathcock Exhibit 8 was marked.)

BY MR. HASFORD:

Q Did you review U.S. Patent No. 8,927,606 in connection with your declaration in this case? Sorry. Let me strike that and try again.

Did you review U.S. Patent No.

8,927,606 in connection with your opinions in this case?

A Yes, I did.

Q If I refer to U.S. Patent No. 8,927,606 as the '606 patent, will you understand what I mean?

A Yes.

Q If I refer to the '431, '290, '131, '813 and '606 patents collectively as the patents in suit, will you understand what I mean?

A Yes.

Q Did you review the claims of the patents in suit in connection with your opinions in this case?

MR. MARGOLIS: Objection, vague.

THE WITNESS: Yeah. Yes, I -- yes. Well, I did. I scanned over them. Yeah. They're different.

Q When you say you scanned over them, what do you mean?

A I read them.

Q Turn, if you would, to the claims of each of the patents in suit.

A You want me to open all six?

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Q You may just want to open them all.

A I'm running out of table space is what I'm doing. Fold these over. Okay.

Q Do the claimed formulations of the patents in suit use polysorbates?

MR. MARGOLIS: Objection. Calls for legal conclusion.

BY MR. HASFORD:

Q You may answer.

MR. MARGOLIS: Outside the scope of his report.

THE WITNESS: Yeah, I'm going to have to study that because I don't -- sorry, but I'm just going to have to read all these patents again to see what they've included in each claim.

BY MR. HASFORD:

Q Please.

A All right.

MR. MARGOLIS: And objection, compound.

THE WITNESS: I'm not the one to object, but this is not something I've really been asked to do before. It's

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totally outside the scope of what I was hired for. So I don't think I really have to answer that question.

BY MR. HASFORD:

Q Well, so you have to answer my question, but let me ask it again.

Did you consider whether the claimed formulations of the patents in suit use polysorbates?

A I was not asked to consider that, and I did not.

Q Did you consider whether the claimed formulations of the patents in suit use octoxynols?

MR. MARGOLIS: Objection, vague.

THE WITNESS: Again, I was not asked to look for that, and so whether they include that -- those two surfactants is an option in one of the claims, I don't know.

BY MR. HASFORD:

Q Did you consider whether the claimed formulations of the patents in suit include hypochlorous acid?

A No.

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MR. MARGOLIS: Objection, vague, compound.

THE WITNESS: I did not consider that.

BY MR. HASFORD:

Q Did you consider whether the claimed formulations of the patents in suit include hydroxyl radicals?

MR. MARGOLIS: Objection, vague, compound.

THE WITNESS: No, that would not be a component of any formulation.

BY MR. HASFORD:

Q Did you consider whether the claimed formulations of the patents in suit include partially reduced O2 species?

MR. MARGOLIS: Objection, vague compound.

THE WITNESS: That again is not an ingredient that anyone would ever be able to use.

BY MR. HASFORD:

Q In connection with your opinions in this case, did you address any secondary

considerations of non-obviousness?

MR. MARGOLIS: Objection. Calls for a legal conclusion.

THE WITNESS: I was not asked to give an opinion about secondary considerations.

Q In connection with your opinions in this case, did you assess the full scope of the prior art?

MR. MARGOLIS: Objection, vague. Calls nor a legal conclusion.

THE WITNESS: Yeah, I don't know what you mean by full scope. You'll have to explain that.

BY MR. HASFORD:

Q Well, you've testified earlier that you provided some opinions on certain prior art references; do you remember that?

A Yes.

Q In connection with your opinions in this case, did you address -- strike that, try again.

In connection with your opinions in this case, did you assess the full scope of the

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prior art?

MR. MARGOLIS: Objection, vague, calls for a legal conclusion.

THE WITNESS: I was asked to give opinions about some rather focused chemistry questions that were brought up by Dr. Davies, and I can tell you that I considered sufficient prior art just to support my opinions if I needed prior art. Some of my opinions are based on my knowledge -- my common sense knowledge as a chemistry expert. To the extent that I needed to bolster that with any kind of information from the prior art, I consider it sufficient.

Now, whether there's more that could have been considered also, I can't tell you because I only went as far as I felt I needed to, to document my own opinion.

BY MR. HASFORD:

Q Do you know whether in connection with your opinions in this case, you assessed the full scope of the prior art?

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MR. MARGOLIS: Objection, vague. Calls for legal conclusion. Asked and answered.

BY MR. HASFORD:

Q You may answer.

A Again, I don't know what you mean by "full scope."

Q Do you have an understanding of the full scope of the prior art in connection with these patents?

MR. MARGOLIS: Objection, vague. Calls for a legal conclusion.

THE WITNESS: Again, I don't really know what you mean. I mean, these patents have a lot of prior art. I'm certain that they cite, and I have not reviewed all of that prior art that is cited to support these six patents.

Q Which document or documents did you consider first in connection with your opinions in this case?

MR. MARGOLIS: Objection. Lacks foundation.

THE WITNESS: Probably read

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Dr. Davies' report first, or one of the patents in suit. I'm not really sure which one. But certainly along together.

BY MR. HASFORD:

Q Which document or documents do you consider most important to your opinions in this case?

MR. MARGOLIS: Objection, vague. Lacks foundation.

THE WITNESS: Most important in what way?

BY MR. HASFORD:

Q Most important to your opinions as a whole?

MR. MARGOLIS: Objection, vague. Lacks foundation.

THE WITNESS: Well, I guess because I was asked to comment on opinions that were advanced by Dr. Davies in his original report. That would be the one I considered most important for me because I was responding to things that he wrote that he raised. Points that he raised.

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BY MR. HASFORD:

Q Of the documents that you considered that Dr. Davies cited in his report, which document or documents do you consider most important to your opinions in this case?

MR. MARGOLIS: Objection, vague, lacks foundation.

THE WITNESS: Yeah, I don't know that I could -- I don't know that I have an answer that I would consider any one thing that he cited, unless it was the patent in suit as the most important thing.

BY MR. HASFORD:

Q Which document or documents do you consider least important to your opinions in this case?

MR. MARGOLIS: Objection, vague. Lacks foundation.

THE WITNESS: Yeah, I don't have an answer to that, sorry. I just can't give you an answer to that.

BY MR. HASFORD:

Q How complex are the types of problems encountered in the art of the patents in suit?

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MR. MARGOLIS: Objection. Vague. Lacks foundation.

THE WITNESS: Yeah. Could you focus that just a little bit more, how complex are what kind of problems?

BY MR. HASFORD:

Q Let me repeat it for you.

How complex are the types of problems encountered in the art of the patents in suit?

MR. MARGOLIS: Objection. Lacks foundation. Vague. Compound.

THE WITNESS: That's sufficiently vague that I don't know that I can answer. Look, I was asked to respond to some very specific chemistry issues, which in my opinion, are not very complex. The general art of the subject formulations for using eyedrops is something that I don't hold myself out to be experienced in, and therefore, I can't tell you how complex or simple that might be.

BY MR. HASFORD:

Q Do you have an understanding as to how complex the types of problems encountered in the

art of the patents in suit are?

MR. MARGOLIS: Objection. Vague. Compound. Lacks foundation.

THE WITNESS: To the extent that chemistry and the interaction of chemicals with each other is involved, I believe I have a good understanding of that.

BY MR. HASFORD:

Q Do you have -- sorry, go ahead.

Do you have an understanding as to how complex the types of formulation problems encountered in the art of the patents in suit are?

MR. MARGOLIS: Objection. Vague. Compound. Lacks foundation.

THE WITNESS: Yeah, no. I don't. That's not something I've studied. I don't have a good feel for what problems people who do formulations, specialize in formulations encounter, and how they solve those problems.

BY MR. HASFORD:

Q Take a look back at your responsive report, if you would. It's going to be Heathcock

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Exhibit 1.

A Let me tidy up my stack of patents.

Q Please. Take your time.

A Okay.

Q Let me direct your attention to Page 6. And in particular let me direct your attention to Section 7, entitled "The Person of Ordinary Skill in the Art."

In paragraphs 28 through 31 of your responsive report, you set forth your opinions regarding the person of ordinary skill in the art.

A Yes.

Q Could you please read those paragraphs to yourself and let me know when you're ready.

A Okay.

Q Aside from adopting Dr. Lawrence's definition and disagreeing with Dr. Davies' definition, do you cite anything in support of your proposed definition of a person of ordinary skill in the art of the patents in suit?

MR. MARGOLIS: Objection, to the extent it mischaracterizes the document. And lacks foundation.

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BY MR. HASFORD:

Q You may answer.

A No. I don't cite anything. I've never cited anything when I've given an opinion of my understanding of this case or any other case.

Q In proposing your definition of a person of ordinary skill in the art, did you consider the definitions that any other experts have provided in other cases?

MR. MARGOLIS: Objection, to the extent it mischaracterizes the document. Lacks foundation.

THE WITNESS: No. I was --

MR. MARGOLIS: Vague.

THE WITNESS: All I can answer is I wrote what I wrote. I was told what Dr. Lawrence's definition was, and I was told what Dr. Davies' definition was, and did I agree with them. And my answer is given here in this document.

BY MR. HASFORD:

Q In proposing your definition of a person of ordinary skill in the art, did you

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consider the definitions that any courts have adopted in other cases?

MR. MARGOLIS: Objection. Lacks foundation. Mischaracterizes the document. Vague, calls for a legal conclusion.

BY MR. HASFORD:

Q You may answer.

A Yeah, I didn't -- no, I didn't consult with any court opinions about...

Q In proposing your definition of a person of ordinary skill in the art, did you consider the education level of the inventors of the patents in suit?

MR. MARGOLIS: Objection. Mischaracterizes the document. Lacks foundation.

THE WITNESS: Yeah, I did not. And I do not know what the education levels are of the inventors.

Q In your opinion, would the inventors of the patents in suit be considered persons of ordinary skill in the art?

MR. MARGOLIS: Objection, calls for a legal conclusion. Compound. Lacks

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foundation.

THE WITNESS: Well, yeah, generally from what my -- I don't know about these particular inventors, but in general -- in general, I think most of the named inventors owned patents that I've known about would be considered person of ordinary skill. Not 100 percent of the time, because sometimes lab assistants who make one or two particularly important discoveries are included as inventors, and I might not consider that person a person of ordinary skill. And sometimes the inventors are persons of much more than ordinary skill.

BY MR. HASFORD:

Q Do you know whether these inventors of the patents in suit would be considered persons of ordinary skill in the art?

MR. MARGOLIS: Objection. Calls for a legal conclusion.

THE WITNESS: Yeah, I don't know anything about these inventors actually.

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BY MR. HASFORD:

Q In your opinion, would the patent examiner who allowed the patents in suit be considered a person of ordinary skill in the art?

MR. MARGOLIS: Objection. Calls for a legal conclusion. Lacks foundation. Calls for speculation.

THE WITNESS: I actually don't know much about the backgrounds of patent examiners. I assume that they would have -- they have medicinal chemistry training, but I'm not certain that they do, so I don't really know.

Q In connection with your opinions in this case, did you consider the prosecution histories of the patents in suit?

A No, I don't think I've seen any -- well, wait a minute. I may have -- no, I don't think I've seen any prosecution history, files.

Q Do you know Dr. Steven Davies?

A Yes.

Q Is he a good scientist?

MR. MARGOLIS: Objection, vague.

THE WITNESS: Yes, he's got a good

reputation.

Q Turn, if you would, to Page 7 of your responsive report. Let me direct your attention to Paragraph 32.

A All right.

Q The first sentence states "NSAIDs are a class of active pharmaceutical agents that are primarily used as painkillers and fever reducers;" do you see that?

A Yes.

Q Does the abbreviation "NSAID" stand for non-steroidal anti-inflammatory drug?

A Yes, it does.

Q As of 2003, how many different NSAIDs were known to exist?

A I can't give you an exact number. A dozen or more I'm sure.

Q Take a look at the next sentence. It says "Unlike steroidal anti-inflammatory drugs, NSAIDs inhibit the activity of the cyclooxygenase 1 (cox 1), and cyclooxygenase 2 (cox 2) enzymes by competitively binding to each of these enzymes." Is that a true statement?

A That's a general -- that's a

high-level general statement, yeah. I think there are probably some NSAIDs that bind to one or the other selectively. So the "and" would be a little broad for this.

Q Generally speaking, unlike steroidal anti-inflammatory drugs, do NSAIDs inhibit the activity of the cyclooxygenase 1 and cyclooxygenase 2 enzymes by competitively binding to each of these enzymes?

A Yes, that's right.

Q As of 2003, how many different steroidal anti-inflammatory drugs were known to exist?

MR. MARGOLIS: Objection. Lacks foundation.

THE WITNESS: Yeah, I don't know exactly how many. Well, how many were in use as drugs, I don't know.

BY MR. HASFORD:

Q Did your own research focus on steroidal compounds or non-steroidal compounds?

MR. MARGOLIS: Objection, vague.

THE WITNESS: My own laboratory research?

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BY MR. HASFORD:

Q Correct.

A Both.

Q As of 2003, would there have been any reason why a person of ordinary skill in the art would have used a steroidal compound instead of a non-steroidal compound in developing an eyedrop formulation to treat pain and inflammation?

MR. MARGOLIS: Objection. Vague. Incomplete hypothetical.

THE WITNESS: Yeah, that's something I haven't really looked into, but I believe that the answer is -- well, someone may have considered using steroids as anti-inflammatories in eyedrops. I don't know if someone has or not. I'm not aware of any products that have been brought forth.

BY MR. HASFORD:

Q As of 2003 -- sorry. As of 2003, why would a person of ordinary skill in the art have used a steroidal compound instead of a non-steroidal compound in developing an eyedrop formulation to treat pain and inflammation?

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MR. MARGOLIS: Objection. Lacks foundation. Vague. Outside the scope of his report.

THE WITNESS: Yeah, it's outside the scope of my report. But also outside the scope of my knowledge. I don't really have any -- I haven't really studied that and don't really know. It's not something that I've worked on.

BY MR. HASFORD:

Q Take a look, if you would, at the last sentence in Paragraph 32 of your responsive report. It says "Different NSAIDs primarily differ based on their selectivity for a particular Cox enzyme." Is that a true statement?

A Well, yes.

Q Why do different NSAIDs differ based on their selectivity for a particular cox enzyme?

A What that means is that these two cyclooxygenase enzymes have related but different physical -- biological outcomes, and if one non-steroidal anti-inflammatory inhibits one more than the other, it will, therefore, have more

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effect on the biological properties -- biological outcomes downstream from that enzyme.

And, you know, for example, the difference between -- some of the NSAIDs are corrosive to the gut because they're primarily inhibiting a cyclooxygenase that's there. Others are not so much. That's what this mentions.

Q From a chemical standpoint, why do different NSAIDs differ based on their selectivity for a particular cox enzyme?

MR. MARGOLIS: Objection, lacks foundation.

THE WITNESS: Yeah, enzymes are -- typically have a binding site, which is meant to bind the natural substrate for that enzyme. And if you have a drug that occupies that binding site, it will affect the ability of the enzyme to carry out its normal function.

And since the binding constant for a given enzyme -- binding site is going to be related to the structure of the compound, two different compounds will typically have different inhibitory constants for that

enzyme. And here we're talking about two different enzymes. And still a given compound will have different binding constants for each enzyme.

And if you compare two compounds, then you've got four different binding constants. Two for each molecule. Two for each enzyme. And so that's why different compounds will have -- you know, will differ in the way they influence these two related cyclooxygenations. That's a very high-level explanation. I hope it's sufficient for your purpose.

Q Thank you very much, Doctor.

Look, if you would, at Paragraph 34 on Page 7 of your responsive report.

A Okay.

Q Take a look at the first sentence. It says "Many NSAIDs are carboxylic acids."

A That's right.

Q Do you see that?

A I see that.

Q Are all NSAIDs carboxylic acids?

A No.

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Q How many different NSAIDs are carboxylic acids?

A I can't tell you the exact number, but, you know, a dozen or more.

Q How many different NSAIDs are not carboxylic acids?

A Yeah, I don't know the exact answer to that. Probably more are carboxylic acids than are not. But again, I don't know the exact numbers.

Q Take a look, if you would, at the top of Page 35. Sorry, the top of Page 8 of your responsive report.

A Eight?

Q And just above Paragraph 35.

A Okay.

Q You show the chemical structure of ibuprofen; do you see that?

A Yes.

Q Is ibuprofen an NSAID?

A Yes.

Q Does ibuprofen have one phenyl ring?

A Yes, it does.

Q Does ibuprofen have an isobutyl group?

A Yes, it does.

Q Is ibuprofen a propanoic acid derivative?

A Yes.

Q Does ibuprofen have a bromo group?

A No.

Q Does ibuprofen have a C double bond O group bridging two phenyl rings?

A No.

Q Does ibuprofen have any kind of amine group?

A No.

Q Does ibuprofen have a chiral carbon?

A It has a stereogenic carbon, right.

Q You show the chemical structure of naproxen; do you see that?

A Yes.

Q Is naproxen an NSAID?

A Yes, it is.

Q Does naproxen have a naphthol ring?

A Yes.

Q Does naproxen have a methoxy group?

A Yes.

Q Does naproxen have a bromo group?

A No.

Q Is naproxen a propanoic acid derivative?

A Yes, it is.

Q Did naproxen have a C double bond O group bridging two phenyl rings?

A No.

Q Does naproxen have any kind of amine group?

A No.

Q Does naproxen have a chiral carbon?

A It has a stereogenic carbon. Chiral carbon is a nonsense term. Sorry.

Q Okay. Thank you for correcting me. Does naproxen have a stereogenic carbon?

A Yes.

Q And just so we have a clear record, does ibuprofen have a stereogenic carbon?

A Yes.

Q You show the chemical structure of flurbiprofen; do you see that?

A Yes.

Q And I apologize, Doctor.

Did you misspell flurbiprofen in your

responsive report?

A It looks like I did. It looks like there's an extra R in there. Doesn't it? Isn't it Flubin?

Q I think there might be an extra I?

A Oh, the extra I, yeah. Flurbiprofen, yeah, okay.

Q Is flurbiprofen an NSAID?

A Yes.

Q Does flurbiprofen have a fluoro group?

A Yes, it does.

Q Does flurbiprofen have a bromo group?

A No.

Q Is flurbiprofen a propanoic acid derivative?

A Yes.

Q Does flurbiprofen have a C double bond O group bridging two phenyl rings?

A No.

Q Does flurbiprofen have any kind of amine group?

A No.

Q Does flurbiprofen have a stereogenic carbon?

A Yes.

Q You show the chemical structure of diclofenac; do you see that?

A Yes.

Q Is diclofenac an NSAID?

A Yes.

Q Does diclofenac have two chloro groups?

A Yes.

Q Are the two chloro groups in diclofenac at the 2 and 6 positions of the phenyl ring?

A Yes.

Q Does diclofenac have a bromo group?

A No.

Q Does diclofenac have a secondary amine group?

A Yes.

Q Does diclofenac have a C double bond O group bridging two phenyl rings?

A No.

Q You show the chemical structure of amfenac; do you see that?

A Yes.

Q Is amfenac an NSAID?

A Yes, it is.

Q Is amfenac the active ingredient in any commercially-marketed NSAID?

A No.

Q Is amfenac the active metabolite of nepafenac?

A Yes.

Q Does amfenac have a bromo group?

A No.

Q You show the chemical structure of nepafenac; do you see that?

A Yes.

Q Is nepafenac an NSAID?

A Yes.

Q Does nepafenac have an amide group? A-m-i-d-e, amide.

A No. Oh, yes, I'm sorry. It does.

Q Just to be clear, does nepafenac have an amide group?

A Yes.

Q Does nepafenac have a carboxylic acid group?

A No.

Q Does nepafenac have a bromo group?

A No.

Q You show on the next page of your responsive report the chemical structure of ketorolac; do you see that?

A Yes.

Q Is ketorolac an NSAID?

A Yes.

Q Does ketorolac have a pyrrolizine group? P-y-r-r-o-l-i-z-i-n-e.

A Yeah, there's a pyrrolizine ring.

Q Does ketorolac have a tertiary amine group?

A Yes. Amine group would technically be considered a tertiary amine.

Q Does ketorolac have a bromo group?

A No.

Q Take a look at the previous page. You show the chemical structure for bromfenac.

A Yes.

Q Is bromfenac an NSAID?

A Yes.

Q Does bromfenac have two phenyl rings?

A Yes.

Q Does bromfenac have a C double bond O group bridging two phenyl rings?

A Yes, it does.

Q Does bromfenac have a naphthol ring?

A No.

Q Does bromfenac have a pyrrolizine group?

A No, it does not.

Q Does bromfenac have an isobutyl group?

A No.

Q Does bromfenac have a methoxy group?

A No.

Q Does bromfenac have an amide group?

A No.

Q Does bromfenac have a carboxylic acid group?

A Yes, it does.

Q Is bromfenac a propanoic acid derivative?

A No.

Q Does bromfenac have a bromo group?

A Yes.

Q Is the bromo group in bromfenac at the 4 position of the phenyl ring?

A Of one of the phenyl rings, yes.

Q Does bromfenac have a fluoro group?

A No.

Q Does bromfenac have a chloro group?

A No.

Q Does bromfenac have a primary amine group?

A Yes.

Q Does bromfenac have a stereogenic carbon?

A No.

Q Is amfenac the active metabolite of bromfenac?

A No.

Q Do you have an understanding of the physical and chemical properties of bromfenac?

MR. MARGOLIS: Objection. Vague.

THE WITNESS: That is kind of vague. I do -- I don't -- well, I don't know that I can even answer that. I don't, sitting here today, remember the melting point or the solubility or any of the properties. I think I would understand any

of these properties if they were shown me, but what do you mean by do I have an understanding of the physical properties?

BY MR. HASFORD:

Q With what physical or chemical properties of bromfenac are you familiar?

MR. MARGOLIS: Objection, vague.

THE WITNESS: I am familiar from looking at its structure -- I know what kinds of reactivity it will have from looking at its structure. I do not have any quantitative knowledge in my mind of, for example, the rates of it reactions with various other reagents. Or I don't know its melting point. I don't remember its solubility. And so I don't know what you mean by do I understand it. I mean, you've got to show me some data and ask me if I understand that, and you haven't done that.

BY MR. HASFORD:

Q Did you review any of that data in connection with your opinions in this case?

A I think I looked up the -- no. I may have looked up -- I think I looked up the pKa

table. And that's probably the only physical property that I tried to track down.

Q Did you try to track down data on any of the chemical properties of bromfenac in connection with your opinions in this case?

A No.

Q What are some of the different physical and chemical properties that different NSAIDs possess?

MR. MARGOLIS: Objection. Lacks foundation. Asked and answered.

MR. HASFORD: You may answer.

MR. MARGOLIS: Vague.

THE WITNESS: Sorry. They would have -- the ones that we've -- the acids that we've reviewed here would have different rates of esterification for example. You're asking very vague questions, so I'm trying to think of answers that are sufficiently responsive to satisfy him. But there could be dozens of different answers to that question.

So these acids can all form esters with alcohols like ethanol. And they would

differ in their rates of esterification. They would all have acidity constants that would be similar but not exact. So they would have pKa's that would be somewhere around the 4-1/2 range, but plus or minus. They would have solubilities that would be different. Some of the ones that have other functionality, for example, amfenac or bromfenac would be able to react as bases to form salts with the amine. With acids like hydrochloric acid, for example. Or they would be able to engage in amide-forming reactions because of those functionalities. So, yeah, those would all be differences that they could have.

Q Why do different NSAIDs having different chemical structures have different solubilities?

MR. MARGOLIS: Objection, vague. Compound.

THE WITNESS: That's because -- it's a general property of any compounds, solubility is going to be related to its structure, and, for example, if you took any

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pair of these compounds that I've drawn on Page 8 of my report, and compared their distribution coefficient, their log D, the distribution coefficient between water and oil, you would find that they have different distribution coefficients. For example naproxen has more hydrophobic part. And so it's probably got a somewhat -- somewhat more lipophilic than ibuprofen.

BY MR. HASFORD:

Q Why do different NSAIDs with different chemical structures have different pKa's?

MR. MARGOLIS: Objection. Lacks foundation. Vague. Compound.

THE WITNESS: That's going to be generally because of the presence of -- the electronic distribution elsewhere in the molecule. The product of an acid forming -- of an acid losing a proton. The anionic, a-n-i-o-n-i-c, product has a negative charge and therefore if the molecule has a dipole moment that such that the positive end of the dipole is near the carboxylic ion, that would facilitate forming the carboxylic ion.

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That would be one example. But there are different molecules, and so they'll have slightly different abilities to accommodate to make sure to produce when ionization occurs.

BY MR. HASFORD:

Q Why do different NSAIDs with different chemicals structures have different rates of forming esters?

MR. MARGOLIS: Objection. Vague. Compound.

THE WITNESS: That would be because primarily because of the electronics of the molecule. Also the stearics. For example, a compound like ibuprofen, probably undergoes esterification reaction slower than a compound like, say, diclofenac because there's not a carbon branch next to the carboxy group.

BY MR. HASFORD:

Q Why do different NSAIDs with different chemical structures have different rates of forming amides?

MR. MARGOLIS: Objection, vague.

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Compound. Lacks foundation.

THE WITNESS: That would be a similar answer. It's a different chemical structure. The rate of reaction of forming an amide requires -- has certain -- well, when you form an amide, that's typically a multi-step process where you first activate the acid by converting the OH group into something which is a better leaving group. And then that is treated with an amine to make the amide. And, for example, naproxen or ibuprofen, which have a carboxy group that has a branch next to it would typically form an amide somewhat slower than, say, diclofenac, which doesn't have a stearically-hindering substituent.

BY MR. HASFORD:

Q How would a person of ordinary skill in the art go about formulating new aqueous liquid preparations of NSAIDs?

MR. MARGOLIS: Objection. Vague. Outside the scope of his report.

THE WITNESS: Yeah, that's not something that I have any particular

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experience with in making such formulations. And it's not something I've been asked to study for this report. So I don't really have an answer to that.

BY MR. HASFORD:

Q Why would a person of ordinary skill in the art want to formulate a new aqueous liquid preparation of an NSAID?

MR. MARGOLIS: Objection, lacks foundation. Outside the scope of his report. Vague. Incomplete hypothetical.

THE WITNESS: Well, generally, yeah, generally you're making -- if you are making any kind of a product of this sort, I would assume it's to sell it to make money. I mean, you're formulating something that's going to be useful to someone. And, though I suppose your motivation would be to make a product that's safe and efficacious so that you can -- that you can profit by marketing it.

BY MR. HASFORD:

Q Is there a limit to the number of different possible ways to formulate aqueous

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liquid preparations of NSAIDs?

MR. MARGOLIS: Objection. Vague. Incomplete hypothetical. Outside the scope of his report.

THE WITNESS: I don't know -- I don't know if there is a limit or not. I would -- I just don't know. I mean, the answer is probably no, there's not a limit, but I don't really know.

BY MR. HASFORD:

Q How would a person of ordinary skill in the art go about characterizing the physical and chemical properties of aqueous liquid preparations of NSAIDs?

MR. MARGOLIS: Objection. Vague. Incomplete hypothetical.

THE WITNESS: It's not something that I studied so I don't have -- I don't really know.

BY MR. HASFORD:

Q Do you have an understanding of the pharmacokinetic properties of bromfenac?

A No, I haven't studied that.

Q Do you have an understanding of the

pharmacodynamic properties of bromfenac?

A No, I haven't studied that either.

Q Do you have an understanding of the toxicological properties of bromfenac?

A No, again, it's something I haven't looked at.

Q Do you know the oil and water partition coefficient of bromfenac?

MR. MARGOLIS: Objection. Vague.

THE WITNESS: I have not looked it up or measured it. No, I don't know.

BY MR. HASFORD:

Q Take a look, if you would, at Paragraph 36 of your responsive report. It's on Page 9.

A Okay. Right.

Q In the second sentence, you state "For example, ocufen, with the active ingredient flurbiprofen, was approved in 1986 for inhibition of miosis during cataract surgery;" do you see that?

A Yes.

Q Does ocufen contain bromfenac?

A No, it contains flurbiprofen.

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Q Was ocufen approved for treatment of pain and inflammation following cataract surgery?

MR. MARGOLIS: Objection, lacks foundation.

THE WITNESS: Yeah, I don't know the answer to that.

BY MR. HASFORD:

Q The next sentence, you state "Voltaren ophthalmic solution, with the active ingredient diclofenac, was approved in 1991 for minimizing postoperative inflammation after cataract surgery;" do you see that?

A Yes.

Q Does Voltaren contain bromfenac?

A No. It contains diclofenac as the NSAID.

Q Was Voltaren approved for treatment of pain following cataract surgery?

MR. MARGOLIS: Objection, lacks foundation.

THE WITNESS: Yeah, I believe that's its main purpose.

BY MR. HASFORD:

Q You state --

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A As it's stated here, postoperative inflammation, which would be pain.

BY MR. HASFORD:

Q Do you understand postoperative inflammation to be the same thing as postoperative pain?

MR. MARGOLIS: Objection, pain.

THE WITNESS: Yeah, I've had cataract surgery. I don't know which one I've used, but it's painful.

BY MR. HASFORD:

Q Okay. The next sentence states "Acular with ketorolac tromethamine, as the active ingredient, was approved in 1992;" do you see that?

A Yes.

Q Does Acular contain bromfenac?

A No, it contains ketorolac.

Q Was Acular approved for treatment of pain and inflammation following cataract surgery?

MR. MARGOLIS: Objection. Lacks foundation.

THE WITNESS: Yeah, I don't know exactly what it was approved for in 1992.

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Probably, but I don't really know the answer sitting here.

BY MR. HASFORD:

Q Before 2003, was Acular also formulated in a preservative-free version called Acular PF, which does not contain benzalkonium chloride?

MR. MARGOLIS: Objection, lacks foundation.

THE WITNESS: Yeah, I don't know the answer to that. I don't know.

BY MR. HASFORD:

Q Would formulation of an NSAID without benzalkonium chloride avoid what you have called the interaction complexation or precipitation problem?

MR. MARGOLIS: Objection. Vague. Incomplete hypothetical.

THE WITNESS: Well, only insofar as the problem is caused by association of anions with the BAC. If the BAC is there -- it's not there, it wouldn't -- but there may be something else that's added to take its place that would have a similar problem.

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BY MR. HASFORD:

Q Let me ask it this way.

Would formulation of an NSAID without any preservative, such as benzalkonium chloride, avoid what you have called the interaction complexation or precipitation problem?

MR. MARGOLIS: Objection. Vague. Incomplete hypothetical. Outside the scope of his report.

BY MR. HASFORD:

Q You may answer.

A Well, to the extent -- the problem I've been asked to give opinions about specifically has to do with the formation of turbidity or solids separating from solution that involved the BAC. If the BAC is not there, then that problem can't -- that particular focus problem obviously can't exist. Other problems might exist, but that one can't.

Q Take a look, if you would, at the next sentence. It states "In 2000, bromfenac sodium was used in Japan under the name Bronuck; do you see that?

A Yes.

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Q Are you aware that sales of a product outside the United States before 2003 do not constitute prior art to the patents in suit?

MR. MARGOLIS: Objection, calls for a legal conclusion.

THE WITNESS: That's been explained to me, yes.

BY MR. HASFORD:

Q Take a look, if you would, at Paragraph 40. And in the first sentence, you state "When the surfactant concentration exceeds a certain value known as the critical micelle concentration or CMC, the surfactant molecule spontaneously forms into micelles, spherical bundles of surfactant molecules arranged in such a way that the hydrophilic head groups are on the outside of the sphere in contact with the aqueous environment, and the hydrophobic tails are clustered together inside the sphere."

Is that a true statement?

A Yes. This is generally a true statement with regard to -- yeah. I mean, that's a true statement, I think.

Q And the next statement says "The CMC

is a unique characteristic of each surfactant."

Is that a true statement?

A Yes, that's right.

Q Why is the CMC a unique characteristic of each surfactant?

A Okay. The -- these molecules -- these surfactant molecules, as I said previously, are amphiphilic, which means that they have a hydrophobic part and a hydrophilic part. And when they're in solution, the hydrophilic part is perfectly happy being surrounded by water. The hydrophobic part wants to not be in water. And so the hydrophobic parts of these amphiphilic molecules will tend to crowd together so that they can be touching each other. And they'll also be touching other molecules, other hydrophilic molecules that might be in solution. And so a surfactant -- it's a surfactant because of this property.

For example, if you wash your clothes and you put in a soap, the soap is a surfactant, and the soap molecules will gather up the oily stuff from your dirty shirts, and because they have this water-soluble tail, they'll make that

oily stuff go into water. And they may make it -- if you have enough of the soap, you'll get these actual micelles, where they're actually associating with each other so much that they can't -- no more can come to the party. And so they just form a ball. And there's no more room for any more to be -- and that's -- this is the way -- this is one of the ways that surfactants act to remove oily substances from water to make oily substances be soluble so that they can be removed from your clothes, for example, and your dirty dishes.

Now, you don't have to have micelles for surfactants to work. Surfactant molecules can just surround -- you know, a few surfactant molecules can surround some oily drop and make it be water-soluble, but the CMC is a unique characteristic because when you -- you know, the different molecules have different links, for example. And there will be some different number of molecules that are enough to form a spherical bundle like I've shown here.

Q Take a look, if you would, at Paragraph 41 of your responsive report.

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A Okay.

Q Let me direct your attention to the first sentence. It states "Surfactants are sorted into four classes based on the characteristics of their head groups;" do you see that?

A Yes.

Q What are the four classes of surfactants?

A Well, let's see. You can have -- you can have molecules where the hydrophilic part is a negatively charged thing, like a carboxylate or sulphonate. You can actually -- and then there's a hydrophobic end. You can have other amphiphilic molecules where the hydrophilic end is non-ionic like, you know, for example, like the surfactants that we're talking about in these formulations, where it's a polyether with lots of oxygens in a chain ending with an OH group.

And then you can have -- you can have other polar head groups that are positively charged. These can be surfactants. And I forget what the fourth class is, but --

Q The classes you just described, were

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those non-ionic, cationic and anionics?

A Those would be three, yeah.

Q And you don't remember what the fourth category is?

A Yeah.

Q As of 2003, how many non-ionic surfactants were known to exist?

MR. MARGOLIS: Objection, vague.

THE WITNESS: Yeah, I don't know how many. I really don't know. You know, "to exist" is a broad question. I think you mean were in use or something of that sort, because there would be -- there would be many surfactants known to exist that weren't marketed by someone for a purpose.

BY MR. HASFORD:

Q As of 2003, how many cationic surfactants were known no exist?

A I don't know the answer to that either.

Q As of 2003, how many anion surfactants were known to exist?

A I don't have the answer to that.

Q Take a look, if you would, at the

third sentence in that paragraph, and read that to yourself and let me know when you're ready.

A Okay.

Q What differences in three-dimensional structures do different non-ionic surfactants possess?

MR. MARGOLIS: Objection, vague, incomplete hypothetical. Lacks foundation. Compound.

THE WITNESS: Any two molecules differ from each other in their composition because they have different -- well, they may have different formulas, but they -- if they're different, there's some difference in their chemical structure. It could be a difference in formula. Could be a difference in their chemistry. And that difference will cause them to have a different three-dimensional shape. So, you know.

BY MR. HASFORD:

Q What --

A Two molecules are generally different because they have different structures.

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Q What differences in chemical compositions do different non-ionic surfactants possess?

MR. MARGOLIS: Objection, vague compound.

THE WITNESS: Well, I mean, yes, I just answered that. They have different chemical compositions because, for example, they have different formulas. That's a chemical composition.

BY MR. HASFORD:

Q You state in Paragraph 41 of your responsive report that tyloxapol is a non-ionic surfactant; do you see that?

A Yes.

Q What does it mean that tyloxapol is a non-ionic surfactant?

A Well, tyloxapol is interesting because it's got a hydrophobic end. It's got this octylphenol, which is the hydrophobic end, the same piece that's in octoxynol. And then it's got this long chain of the polyethoxy chain, which is the water-loving, or the hydrophilic part.

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But it's got seven of these octylphenol groups joined together so they're like a picket fence. They're like holding hands with each other. And so the hydrophobic part of tyloxapol is somewhat like a sheet. And then extending out from the sheet are a lot of water-loving strings. And that makes it a very different kind of a surfactant in that it's got this nice big hydrophobic sheet that can wrap around. So it doesn't really even need to form a micelle to wrap around something hydrophobic and make it -- make that something be water-soluble. It's got a nice big hydrophobic surface.

So it's like a -- it's like one of these other surfactants that's already started its life toward being a micelle, by joining a number together.

Q When you testified that tyloxapol is a different kind of surfactant, different from what?

MR. MARGOLIS: Objection. Mischaracterizes his testimony.

THE WITNESS: Well, it would have -- you know, I've got to say that I'm

not -- I have no practical experience experimentally with this, but I would expect that tyloxapol would be able to remove, you know -- to remove -- it would make particularly good soap because it would be able to remove oily substances or to dissolve oily substances in water without having to form a micelle. That is, it could -- because it's already got a number of these surfactant molecules essentially joined together. So it's different from, for example, a polysorb, or the octoxynols pieces that went together to make up the tyloxapol.

BY MR. HASFORD:

Q Do you have an understanding of the physical and chemical properties of tyloxapol?

MR. MARGOLIS: Objection, vague. Compound.

THE WITNESS: Well, I just gave you some testimony that would be somewhat responsive that I don't know -- I don't know, sitting here, any quantitative data such as solubilities, and I don't even

remember the CMC for tyloxapol, although I've looked it up.

But so -- I think I do understand something about its properties, yes.

BY MR. HASFORD:

Q Have you ever accurately predicted the physical and chemical properties of a non-ionic surfactant based on the physical and chemical properties of a different non-ionic surfactant with a different chemical structure?

MR. MARGOLIS: Objection. Vague. Asked and answered.

THE WITNESS: Well, yeah. There are a lot of elements. I just gave you a prediction in my previous answer that tyloxapol would be better in some applications than surfactants like, let's say, the octoxynols monomeric piece from which tyloxapol is made, you know.

So I made a prediction about how, you know, just from looking at the structures and my understanding of the principles of molecular interaction.

Now, you added in your question

have I ever accurately predict -- well, I don't know how accurate that prediction is. I'm confident that that prediction is valid, but accurate is a -- kind of implies a quantitativeness that I don't know about.

BY MR. HASFORD:

Q How would a person of ordinary skill in the art know whether they have accurately predicted the physical and chemical properties of a non-ionic surfactant based on the physical and chemical properties of a different non-ionic surfactant with a different chemical structure?

MR. MARGOLIS: Objection.

Incomplete hypothetical. Vague.

BY MR. HASFORD:

Q You may answer.

A You set up a simple experiment and carry it out. And I've done experiments with surfactants. It's not difficult. You know, you can -- you just carry out experiments.

Q Have you ever determined the membrane active effects of tyloxapol?

MR. MARGOLIS: Objection, vague.

THE WITNESS: No, I haven't done

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any experiments with tyloxapol.

BY MR. HASFORD:

Q Are you familiar with the various equilibrium phases of tyloxapol in aqueous liquid preparations?

MR. MARGOLIS: Objection, vague.

THE WITNESS: No. Excuse me.

BY MR. HASFORD:

Q Take a look, if you would again, at Paragraph 41 of your responsive report.

A Okay.

Q You state in Paragraph 41 of your responsive report that tyloxapol -- sorry. Let me strike that and start again.

You state in Paragraph 41 of your responsive report that polysorbate 80 is a non-ionic surfactant; do you see that?

A Yes.

Q As of 2003, how many different polysorbates were known to exist?

MR. MARGOLIS: Objection, vague. Lacks foundation.

THE WITNESS: Yeah, I don't know the answer to that. It's -- you know, all

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of these compounds like polysorbate 80 and octoxynol 40 are not specific compounds in any event. They're mixtures of compounds with approximately 80 or 40 of the units that are being numbered.

But there's some distribution of -- it's a mixture of compounds around that average. So, you know, even polysorbate 80 itself is probably a mixture of 12 or 15 different polysorbates with 72, 73, so forth. So I don't know the answer to how many there were.

BY MR. HASFORD:

Q You also mention octoxynol; do you see that?

A Yes.

Q As of 2003, how many different octoxynols were known to exist?

MR. MARGOLIS: Objection, vague. Lacks foundation.

THE WITNESS: Yeah, I don't know the answer to that either. Again, same sort of thing. Octoxynol is a compound that contains a -- any given product is a mixture

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of things averaging about that size, and, you know, known to exist, is different than how many were marketed. And I don't even know that. But certainly more would have been known to exist than were marketed.

BY MR. HASFORD:

Q Take a look, if you would, again, in Paragraph 41. Read that and let me know when you're ready.

A The whole paragraph?

Q Actually, just read the last two sentences.

A Okay.

Q Would the use of polysorbates in an aqueous liquid preparation of an NSAID with benzalkonium chloride avoid what you have called the interaction complexation or precipitation problem?

MR. MARGOLIS: Objection. Incomplete hypothetical. Vague.

THE WITNESS: Yeah, I don't -- I don't have a general answer to that question. I would say you would have to test it and see.

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BY MR. HASFORD:

Q Would the use of octoxynols in aqueous liquid preparation of an NSAID with benzalkonium chloride avoid what you have called the interaction complexation or precipitation problem?

MR. MARGOLIS: Objection. Incomplete hypothetical. Vague.

THE WITNESS: Yeah, I think not generally. Again, you would have to look at each individual case to be sure, but I think -- I'm pretty sure I recall reviewing a table of data in which there was -- in which one or maybe both of these two that you've just questioned me about were used in a product that still did show some problems.

BY MR. HASFORD:

Q Would you have to do testing to determine that?

MR. MARGOLIS: Objection, vague. Incomplete hypothetical.

THE WITNESS: Yeah. A simple testing would be.

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BY MR. HASFORD:

Q Take a look, if you would, at Footnote 2 in your responsive report.

A Uh-huh. Okay.

Q It states "Other non-ionic surfactants listed for ophthalmic solutions include the following. Nonoxynol, N-o-n-o-x-y-n-o-l. Poloxamer 188, P-o-l-o-x-a-m-e-r. Polyoxyethylene. Polyoxypropylene 1,800. Polyoxyl 35 castor oil. And polyoxyl 40 monostearate. Do you see that?

A Oh, yes, I see it now.

Q Would the use of non-oxynol in an aqueous liquid preparation of an NSAID with benzalkonium chloride avoid what you have called the interaction complexation or precipitation problem?

MR. MARGOLIS: Objection, vague. Incomplete hypothetical.

THE WITNESS: I don't know.

BY MR. HASFORD:

Q Would the use of poloxamer 188 in an aqueous liquid preparation of an NSAID with benzalkonium chloride avoid what you have called

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the interaction complexation or precipitation problem?

MR. MARGOLIS: Objection, vague. Incomplete hypothetical.

THE WITNESS: I don't know. Can I just stipulate that I don't know the other three as well?

BY MR. HASFORD:

Q That's fine.

MR. MARGOLIS: Are we getting close to a good time for a break? We've been pushing for well over an hour at this point.

MR. HASFORD: You know what? We probably are, actually.

MR. McCLUTCHY: You want to go off? Okay. Going off the record. The time is 12:38. This ends Disc No. 2.

(Whereupon there was a lunch recess.)

MR. McCLUTCHY: We are back on the record. The time is 1:36. This is Disc No. 3.

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BY MR. HASFORD:

Q Good afternoon, Doctor.

A Good afternoon.

Q Would you please turn in your responsive report to Paragraph 46. That's going to be on Page 13.

A Okay.

Q And let me direct your attention to the first sentence. Read that for me and let me know when you're ready. You can read it to yourself.

A Paragraph 46?

Q Yes, Paragraph 46. Let me know when you're ready.

A Okay.

Q You identify Eudragit RL?

A Yes, I do.

Q Are Eudragit RL and benzalkonium chloride different chemical compounds?

A Yes.

MR. MARGOLIS: Objection, vague.

THE WITNESS: They're different. They related in that they both have a quarternary ammonium unit or structure.

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BY MR. HASFORD:

Q Just to be clear, are Eudragit RL and benzalkonium chloride different chemical compounds?

MR. MARGOLIS: Objection, vague. Asked and answered.

THE WITNESS: Neither -- they're different, but neither is a chemical compound. Both are mixtures of chemical compounds.

BY MR. HASFORD:

Q Thank you for clarifying.

Does Eudragit RL have three methyl groups attached to a nitrogen atom?

A Yes, it does.

Q Does benzalkonium chloride have three methyl groups attached to a nitrogen atom?

A It has two.

Q Take a look, if you would, at Footnote 5?

A Yes.

Q In Footnote 5, you cite a reference by Khalil, et al; do you see that?

A Yes.

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MR. HASFORD: I'm handing the court reporter what I would ask to be marked as Heathcock Exhibit 9.

For the record, Heathcock Exhibit 9 is a copy of the Khalil reference.

(Heathcock Exhibit 9 was marked.)

BY MR. HASFORD:

Q Could you please confirm, Doctor, is Heathcock Exhibit 9 a copy of the Khalil reference that you cite in Footnote 5 of your rebuttal report?

A Yes, it is.

Q If I refer to Heathcock Exhibit 9 as the Khalil reference, will you understand what I mean?

A Yes.

Q Take a look, if you would, at the "Conclusions" portion of the Khalil reference on Page 426. This page bears Bates No. Lupin 0069339. Do you see that?

A Yes.

Q Take a look at the second sentence in the "Conclusion" section of the Khalil reference, and please read that to yourself and let me know

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when you're ready.

A Yes.

Q Does the Khalil reference state that the interaction between Eudragit and diclofenac was dependent on temperature, ionic strength, and the nature of the additives?

A Yes, it does.

Q Take a look, if you would, at the last two sentences of the conclusion. Read those two yourself and let me know when you're ready.

A Okay.

Q Does the Khalil reference deal with ophthalmic formulations?

MR. MARGOLIS: Objection, vague.

THE WITNESS: No, it doesn't.

BY MR. HASFORD:

Q Does the Khalil reference teach the use of bromfenac?

MR. MARGOLIS: Objection, vague.

THE WITNESS: No, it doesn't.

Q Does the Khalil reference teach the use of tyloxapol?

MR. MARGOLIS: Objection, vague.

THE WITNESS: No. It's got

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nothing to do with that.

Q Does the Khalil reference teach the use of benzalkonium chloride?

MR. MARGOLIS: Objection, vague.

THE WITNESS: No, it doesn't have anything to do with that either.

BY MR. HASFORD:

Q What solution does the Khalil reference teach to overcome what you have called the interaction complexation or precipitation problem?

MR. MARGOLIS: Objection, vague. Lacks foundation.

THE WITNESS: It's not cited for that purpose. It's cited for simply the purpose of showing that an NSAID carboxylate salt, in this case, diclofenac salt, can associate through a polar attraction with an ammonium ion, which is the trimethylammonium ion depicted in the ERL. It's depicted -- it's cited as a reference to support my opinion that the association between BAC, which is also an ammonium ion, and NSAID carboxylates has an important polar

component such as is demonstrated here.

Q Does the Khalil reference teach any solution to overcome what you have called the interaction complexation or precipitation problem?

MR. MARGOLIS: Objection, vague. Mischaracterizes the testimony.

THE WITNESS: Yeah, I didn't propose that it teaches any solution to any problem. That's not the purpose.

BY MR. HASFORD:

Q You can put that document aside.

Let me direct your attention to Paragraph 48 of your responsive report. You cite ERPM Patent 0,360,984; do you see that?

A Yes, I do.

MR. HASFORD: I'm handing the court reporter what I ask to be marked as Heathcock Exhibit 10.

For the record, Heathcock Exhibit 10 is a copy of European Patent No. 0,306,984.

(Heathcock Exhibit 10 was marked.)

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BY MR. HASFORD:

Q If I refer to Heathcock Exhibit 10 as EP-984 or the Fu reference, will you understand what I mean?

A Fu, yes.

Q Or EP-984?

A Okay, yes.

Q Does the Fu reference teach the use of bromfenac?

MR. MARGOLIS: Objection, vague.

THE WITNESS: No. This is not -- this one was -- wait just a minute while I refresh my memory on which patent this is.

Okay. So this is not -- this is not one that has the bromfenac, right.

Q Does the Fu teach the reference of the use tyloxapol?

MR. MARGOLIS: Objection, vague.

THE WITNESS: No. Tyloxapol is not, to my knowledge, mentioned anywhere in this patent.

Q Does the Fu reference teach overcoming chemical degradation?

MR. MARGOLIS: Objection. Vague.

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THE WITNESS: Yeah, I'll have to -- I have to review the patent more to answer that because --

BY MR. HASFORD:

Q Please, take your time.

A -- you know, my focus of studying the patent before -- so what was the question you want the answer to now?

Q Does the Fu reference teach overcoming chemical degradation?

A Overcoming chemical?

MR. MARGOLIS: Objection, vague.

THE WITNESS: Yes, I think -- I think generally I can say yes because it does teach the use of preservatives, and that's what the preservative is for, is to avoid or to overcome degradations of various sorts, so...

Q Do the preparations disclosed in the Fu reference have any chemical stability problems?

MR. MARGOLIS: Objection, vague. Calls for speculation. Compound.

THE WITNESS: Now, so the question

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was, do the formulations that are -- what was the question again?

BY MR. HASFORD:

Q I'll ask it again.

Do the preparations disclosed in the Fu reference have any chemical stability problems?

MR. MARGOLIS: Same objections.

THE WITNESS: I haven't really studied that, so I don't -- you know, I don't know.

BY MR. HASFORD:

Q Please look at the examples of the Fu reference.

A Okay.

Q Do all ten examples of the Fu reference use octoxynol 40?

MR. MARGOLIS: Objection, vague. Compound.

THE WITNESS: I can look at the first five and see that octoxynol 40 is mentioned in all of them. I'm going to have to examine the last ten because these are describing -- if you want an answer to

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those, these are describing trials with, according to the foregoing examples.

Yeah, I'm going to say I can answer that easily for the first five. Even the first six because the sixth example talks about using the formulations of the foregoing paragraphs.

Example 7, 8, 9 and 10, I'm not seeing which preparations were used in those -- these appear to be clinical tests. And I'm not seeing, for example, if perhaps they were using some of the formulations that didn't contain Octoxynol. Once, for example, in Example 5. So that's the best I can do.

BY MR. HASFORD:

Q Do any of the ten examples of the Fu reference use octoxynol 9?

MR. MARGOLIS: Objection, vague.

THE WITNESS: I don't see that, so I would say no.

BY MR. HASFORD:

Q Do octoxynol 40 and octoxynol 9 have the same chemical structure?

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A No. They're different because they have a different number of the repeating ethoxy groups.

MR. HASFORD: I'm handing the court reporter what I would ask to be marked as Heathcock Exhibit 11.

For the record, Heathcock Exhibit 11 is a copy of U.S. Patent No. 5,558,876.

(Heathcock Exhibit 11 was marked.)

BY MR. HASFORD:

Q You cite U.S. Patent No. 5,558,876 in your responsive report; correct?

A Yes, I do.

Q If I refer to Exhibit 11, which is U.S. Patent No. 5,558,876 as the Desai '876 patent, will you understand what I mean?

A Yes.

Q Does the Desai '876 patent teach the use of tyloxapol?

MR. MARGOLIS: Objection, vague.

THE WITNESS: No, tyloxapol is not mentioned in this patent.

BY MR. HASFORD:

Q What solution does the Desai '876

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patent provide to what you have called the interaction, complexation or precipitation problem?

MR. MARGOLIS: Objection, lacks foundation. Mischaracterizes his testimony.

THE WITNESS: Yeah, I haven't studied it for that purpose. I cited this as an example of one of the prior art patents that disclose that there was a problem forming insoluble complexes with the -- with BAC and NSAIDs.

Q Do you know what solution the Desai '876 patent application provides to what you have called the interaction, complexation or precipitation problem?

MR. MARGOLIS: Objection. Lacks foundation. Mischaracterizes his testimony. Vague.

THE WITNESS: I haven't studied the patent for that purpose. So I don't know.

BY MR. HASFORD:

Q The approach that the Desai '876 patent took is different from the approach that

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the inventors of the patents in suit took when formulating the claimed aqueous liquid preparations of those patents; correct?

MR. MARGOLIS: Objection. Vague. Lacks foundation.

THE WITNESS: I haven't really studied the patent for that purpose. It wasn't asked -- I wasn't asked to give an opinion about that, and I don't have an opinion about that.

BY MR. HASFORD:

Q Do the formulations disclosed in the Desai '876 patent have any stability problems?

MR. MARGOLIS: Objection, lacks foundation. Vague.

THE WITNESS: Again, it's outside the scope of what I was asked to study, so I don't have an answer to that question.

BY MR. HASFORD:

Q You may put that document aside.

Take a look, if you would, at Paragraph 50 in your responsive report. It's on Page 15.

A Okay.

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Q 4in Paragraph 50 of your responsive report, you cite the published PCT application designated WO 1994/015597 A1; do you see that?

A Yes.

MR. HASFORD: I'm handing the court reporter what I would ask to be marked as Heathcock Exhibit 12.

For the record, Heathcock Exhibit 12 is a copy of the published PCT application with international publication number WO 94/15597.

(Heathcock Exhibit 12 was marked.)

BY MR. HASFORD:

Q If I refer to Heathcock Exhibit 12 as WO '597 or the Wong reference, will you understand what I mean?

A Yeah, Wong, yes. Okay. Yes.

Q And you cite Heathcock Exhibit 12, the Wong reference, in connection with your opinions in this case; correct?

A Yes.

Q Does the Wong reference teach the use of bromfenac?

MR. MARGOLIS: Objection, vague.

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THE WITNESS: No, it does not use bromfenac.

BY MR. HASFORD:

Q Does the Wong reference teach the use of tyloxapol?

MR. MARGOLIS: Objection, vague.

THE WITNESS: No, it does not.

BY MR. HASFORD:

Q Do you know what solution the Wong reference provides to what you have called the interaction, complexation or precipitation problem?

MR. MARGOLIS: Okay, lacks foundation. Mischaracterizes his testimony.

THE WITNESS: Well, I quoted this paper -- this patent application for, again, the purpose of laying a background for the fact that BAC does create a problem and with many of the anionic NSAIDs. That was in the background part that I actually reproduced in my report here.

I haven't -- I don't really recall that I studied the rest of the patent to see what particular solution they had proposed

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for that, but it appears that they have studied replacing the BAC with a different antimicrobial substance.

BY MR. HASFORD:

Q The approach that the Wong reference took is different from the approach that the inventors of the patents in suit took when formulating the claimed aqueous liquid preparations of those patent; correct?

MR. MARGOLIS: Objection, vague, mischaracterizes the document.

THE WITNESS: Yes.

BY MR. HASFORD:

Q The Wong patent -- sorry. Strike that. Try again.

Does the Wong patent teach overcoming degradation?

MR. MARGOLIS: Objection, vague.

THE WITNESS: I haven't studied that for chemical degradation. I think any of these patents that are using -- that are making -- that are teaching a way to prepare an ophthalmic solution do include an antimicrobial agent, and since that involves

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a certain amount of degradation, it's chemical -- a chemical reaction, they all teach that. So this one, to that extent, does teach that.

BY MR. HASFORD:

Q You may put this document aside.

You also cite in Paragraph 50 of your responsive report, U.S. Patent No. 5,504,113; do you see that?

A Yes.

MR. HASFORD: I'm handing the court reporter what I'll ask to be marked as Heathcock Exhibit 13.

For the record, Heathcock Exhibit 13 is a copy of U.S. Patent No. 5,504,113.

(Heathcock Exhibit 13 was marked.)

BY MR. HASFORD:

Q If I refer to Heathcock Exhibit 13 as the '113 patent or the Lucero patent, will you understand what I mean?

A Yes.

Q Does the Lucero patent teach the use of bromfenac?

MR. MARGOLIS: Objection, vague.

C. Heathcock, Ph.D.

THE WITNESS: No. Bromfenac is not included in the various formulations that are taught by this patent.

BY MR. HASFORD:

Q Does the Lucero patent teach the use of tyloxapol?

MR. MARGOLIS: Objection, vague.

THE WITNESS: Apparently not. I don't see tyloxapol mentioned in this patent.

BY MR. HASFORD:

Q Take a look, if you would, at Column 5 of the Lucero patent, and let me direct your attention to Claim 1.

A All right.

Q Tell me when you're there.

A Yeah, I see it.

Q Claim 1 of the Lucero patent reads "A formulation comprising a drug interactive with benzalkonium chloride, benzalkonium chloride active as a preservative, and L-arginine, a-r-g-i-n-i-n-e, present in an amount sufficient to interfere with the interaction between the drug and benzalkonium chloride in order to

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maintain the preservative activity of benzalkonium chloride;" do you see that?

A Yes, I see that. You read that correctly.

Q Does the Lucero patent teach overcoming incompatibility with benzalkonium chloride in ophthalmic formulations by using L-arginine?

MR. MARGOLIS: Objection, vague. Lacks foundation.

THE WITNESS: Yeah. So state the question again? I'm trying to get my arms around this one.

Q Certainly. Does the Lucero repeat patent teach overcoming incompatibility with benzalkonium chloride in ophthalmic formulations by using L-arginine?

MR. MARGOLIS: Same objections.

THE WITNESS: Yeah, this claim does -- which is very broad and general, does seem to -- does seem to name arginine acting as an agent to interfere with an interaction of unspecified nature between benzalkonium chloride and any drug.

C. Heathcock, Ph.D.

BY MR. HASFORD:

Q The approach that the Lucero patent took is different from the approach that the inventors of the patents in suit took when formulating the claimed aqueous liquid preparations of those patents correct?

MR. MARGOLIS: Objection, vague, lacks foundation.

THE WITNESS: Well, yeah. You know, it's not clear to me that they were dealing with the same problem, but certainly arginine is -- yeah, is not used in the inventor's products. So it's different.

BY MR. HASFORD:

Q Does the Lucero patent teach overcoming chemical degradation?

MR. MARGOLIS: Objection, vague.

THE WITNESS: Well, yeah, I don't know -- you know, the -- this patent describes that a certain compound bufrolin is a classy example of an anionic drug that forms an insoluble complex with benzalkonium chloride. So this is something that we're quite familiar with.

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Whether you would call that a chemical degradation, I don't -- I wouldn't call it a chemical degradation, although it does certainly remove the benzalkonium chloride from the formulation. And, therefore, it's the same as if you degraded it. So you have degraded since its ability to function as a preservative by removing it in the form of this insoluble complex. So to that extent, if the arginine interferes with that, it does -- it does interfere with chemical degradation.

BY MR. HASFORD:

Q You may put this document aside.

Turn, if you would, to the next page in your responsive report. Its Page 16. Let me direct your attention up to toward the top of the page, you cite U.S. patent No. 6,265,444; do you see that?

A Yes.

MR. HASFORD: For the record, I'm handing the court reporter a copy of U.S. Patent No. 6,265,444 that I would ask to be marked as Heathcock Exhibit 14.

C. Heathcock, Ph.D.

(Heathcock Exhibit 14 was marked.)

BY MR. HASFORD:

Q If I refer to Exhibit 14, Heathcock Exhibit 14 as the '444 patent or the Bowman patent, will you understand what I mean?

A Yes.

Q Does the Bowman patent teach the use of bromfenac?

MR. MARGOLIS: Objection, vague.

THE WITNESS: Doesn't seem to. Diclofenac, cuprofen and flurbiprofen. I don't think bromfenac is mentioned in this patent.

BY MR. HASFORD:

Q Does the Bowman patent teach the use of tyloxapol?

MR. MARGOLIS: Objection, vague.

THE WITNESS: No, not to my knowledge.

BY MR. HASFORD:

Q Please turn, if you would, to Column 8 in the Bowman patent.

A Okay.

Q Let me direct your attention to Lines

47 through 61.

A Forty-seven through 51, "Wherein q, r, s, and t are each independently an integer," is that what you mean? "Q, r, s and t are 0 or 1"?

Q Sorry. It's actually going to be Column 7, Lines 47 through 61. I apologize. It's going to be the paragraph starting with "Composition of the present invention."

A Okay.

Q Could you read that paragraph to yourself and please let me know when you're ready.

A Okay. I've read it.

Q Does the Bowman patent teach that Diclofenac and benzalkonium chloride were compatible together in an aqueous liquid preparation for ophthalmic use?

MR. MARGOLIS: Objection, vague, compound.

THE WITNESS: Yes. They state that they were together compatible and they were quite surprised that they were compatible. And they advanced an explanation for why they were compatible.

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Q Did the aqueous liquid preparations of the Bowman patent have any interaction, complexation or precipitation problem?

MR. MARGOLIS: Objection, vague. Compounds.

THE WITNESS: Apparently not. They don't state that explicitly in this paragraph, but I think a person of ordinary skill would assume that that was the reason they were saying it was unexpectedly compatible. That would be because it did not show turbidity or precipitate.

BY MR. HASFORD:

Q Does the Bowman patent provide any data showing that the aqueous liquid preparations of the Bowman patent have any interaction, complexation or precipitation problem?

MR. MARGOLIS: Objection, vague, compound.

THE WITNESS: Well, data would be something like a measurement of turbidity, and I don't see it, a table of such data. Or I don't see any data cited.

Q The approach that the Bowman patent

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took is different from the approach that the inventors of the patents in suit took when formulating the claimed aqueous liquid preparations of those patents; correct?

MR. MARGOLIS: Objection, vague. Lacks foundation.

THE WITNESS: Yes.

BY MR. HASFORD:

Q Does the --

A They have -- they've included -- they've included this, what they call the divalent cations in their preparation.

Q Does the Bowman patent teach overcoming chemical degradation?

MR. MARGOLIS: Objection, vague.

THE WITNESS: Well, again, to the extent that you consider overcoming the formation of the insoluble salt, the chemical degradation, they do teach that. I don't see anything in the patent that addresses other kinds of chemical degradation, oxidation, for example.

BY MR. HASFORD:

Q You can put this document aside.

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Let me direct your attention to Paragraph 52 in your rebuttal report. It's on Page 16 and it carries over to Page 17. Read, if you would, to yourself the last sentence in that paragraph and let me know when you're ready.

A Yes. Okay.

Q Is it your opinion that diclofenac, ketorolac, flurbiprofen and pranlukast differ from each other in much the same way that bromfenac differs from these compounds?

A Yeah. What I meant by that, maybe that's not clear. They differ from -- if you took any pair of these compounds and pointed out differences, you would be able to identify the same kind of structural differences that Dr. Davies identified when he compared bromfenac with each one of these individually.

Q Is pranlukast an NSAID?

A No.

Q Does pranlukast have a secondary amine?

A Let me -- I have to go back and look at the structure.

Q You might consider looking at Page 21

of your rebuttal report.

A Okay. Yeah. No.

Q Does pranlukast have an oxo group?

A Well, yes, it does.

Q And just so we're clear on the previous question, does pranlukast have a secondary amine?

A No, there's nothing in here we would call a secondary amine. It has an amide and it has the tetrazole ring structure, but a secondary amine would be, for example, like the one in bromfenac, which is shown to the right of that structure we're looking at, which is an NH2 group. Except it would have another R group. The NH groups in the tetrazole are not considered a secondary amine because that's part of the aromatic tetrazole.

Q Does pranlukast have a tetrazole group?

A Yes.

Q Does pranlukast have a chromenyl group?

A A what?

Q C-h-r-o-m-e-n-y-l group?

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A Well, it has -- it has -- the bicyclic ring structure is -- would be, without anything attached to it, would be -- can be called chromene.

Q Does pranlukast have a phenylbutoxy group?

A Yes, it does.

Q Does pranlukast have a bromo group?

A No, it does not.

Q Does pranlukast have a C double bond O group bridging two phenyl rings?

A No, it does not.

Q Take a look, if you would, at Paragraph 53 of your rebuttal report. It's at the top of Page 17. You cite Exhibit 2098 in IPR 2015-00903; do you see that?

A Yes.

MR. HASFORD: I'm handing the court reporter what I would ask to be marked as Heathcock Exhibit 15.

For the record, Heathcock Exhibit 15 is a copy of Exhibit 2098 from IPR 2015-00903.

(Heathcock Exhibit 15 was marked.)

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BY MR. HASFORD:

Q Is Exhibit -- is Heathcock Exhibit 15 in fact a copy of Exhibit 2098 in IPR 2015-00903?

A Yes.

Q And you have relied on Exhibit -- Heathcock Exhibit 15 in connection with your opinions in this case; correct?

A To one very small part of this I have, yes.

Q Is Heathcock Exhibit 15 an internal Senju document?

MR. MARGOLIS: Objection, lacks foundation.

THE WITNESS: It appears to be. I think it was submitted in an IPR proceeding which is cited here. And so, therefore, it became public. I'm not sure if that makes it still an internal document by definition.

Q Does it appear that it was generated from Senju?

A Yeah. It does appear that it's their reports, yeah.

Q Are you aware that it is improper to rely on a patent owner's internal document when

making an argument that a patent would have been obvious?

MR. MARGOLIS: Objection, calls for a legal conclusion. Vague.

THE WITNESS: Yes. I think my purpose of not relying on this information that a person of ordinary skill would know, but relying on this as a matter of fact to demonstrate that a person of ordinary skill would carry out a test to find something out.

Q You can put that document aside.

Take a look, if you would, at Paragraph 54 in your rebuttal report. You cite the Remington reference; do you see that?

A Yes.

MR. HASFORD: I'm handing the court reporter what I would ask to be marked as Heathcock Exhibit-16.

For the record, Heathcock Exhibit 16 is a portion of Remington, "The Science and Practice of Pharmacy," bearing Bates numbers Lupin 0069360 through Lupin 0069365.

(Heathcock Exhibit 16 was marked.)

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BY MR. HASFORD:

Q If I refer to Heathcock Exhibit 16 as the Remington reference, will you understand what I mean?

A Yes.

Q Does the Remington reference teach the use of bromfenac?

MR. MARGOLIS: Objection, vague.

THE WITNESS: Well, no, it's not really about bromfenac or about NSAIDs in general.

BY MR. HASFORD:

Q Does the Remington reference teach the use of tyloxapol?

MR. MARGOLIS: Objection, vague.

THE WITNESS: No, it's not about surfactants. The part that's been given me is not about surfactants either.

BY MR. HASFORD:

Q You may put that aside.

Take a look, if you would, now, at Paragraph 57 in your rebuttal report. The first sentence states "Dr. Davies notes that bromfenac is a primary amine, diclofenac is a secondary

amine, ketorolac is a tertiary amine, and flurbiprofen has no amino group and suggests that these and other differences in their chemical structures result in different basicities, different hydrogen bonding abilities and therefore differences in lipophilicity and solubility."

You note in the next sentence of your responsive report that "This is true;" do you see that?

A Yes.

Q How does the fact that bromfenac --

MR. MARGOLIS: Objection, mischaracterizes the document.

BY MR. HASFORD:

Q How does the fact that bromfenac is a primary amine, diclofenac is a secondary amine, ketorolac is a tertiary amine, and flurbiprofen has no amino group result in different basicities, different hydrogen bonding abilities, and, therefore, differences in lipophilicity and solubility among these compounds?

MR. MARGOLIS: Objection, lacks foundation. Compound. Vague.

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THE WITNESS: Well, as I've testified several times in preceding questions, different chemicals, compounds have different structures. And these structures result in their having different properties, both physical, such as melting point and solubility, and chemical reactivities with other reagents. And since these compounds all have different structures, they all have different chemical properties because of their different structures.

BY MR. HASFORD:

Q Take a look, if you would, at Paragraph 58 of your rebuttal report. I'll direct your attention to the first sentence. It's at the top of Page 19. Tell me when you're there.

A Okay.

Q It states "Indeed, the solubility of the complex/salt formed between an NSAID and BAC will depend not only on the nature of the NSAID anion but also on the nature of the cation." Is that a true statement?

A Yes, I think that's a true statement. You know, the cation -- the cation in these examples that we're talking about is always this BAC, which is -- you can think of it as a big ball of grease that has a little positive pimple or indentation in one side. And it's actually not just one entity because part of it's got the chain hanging out. And that chain can be anywhere from 8 to 18 long.

So it's -- but all of them are big greasy balls with this little indentation where there's an N plus. And that's the cation for all these salts.

And the anion for these salts that we're talking about is a relatively smaller piece that's got a -- they all have the same CO2 minus that gets attracted to that positive indentation in the big BAC, but attached to each of those anions is a surface also. And all of those surfaces are different. But -- so all these salts will have slightly different properties. But they'll be dominated by the common feature. And the common feature is this big hydrophobic BAC part.

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So, yes, there will be different properties, but the properties will be buffered by the presence of this common feature. This big bulky salt.

Q Take a look, if you would, at Paragraph 59 of your rebuttal report.

A Okay.

Q You cite U.S. Patent No. 5,597,560. Do you see that?

A Yes.

MR. HASFORD: I am handing the court reporter what I would ask to be marked as Heathcock Exhibit 17.

For the record, Heathcock Exhibit 17 is a copy of U.S. Patent No. 5,597,560.

(Heathcock Exhibit 17 was marked.)

BY MR. HASFORD:

Q If I refer to Heathcock Exhibit 17 as the '560 patent or the Bergamini patent, will you understand what I mean?

A Yes.

Q Does the Bergamini patent teach the use of bromfenac?

MR. MARGOLIS: Objection, vague.

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THE WITNESS: No, it does not deal with bromfenac.

Q Does the Bergamini teach the use of any specific formulation involving tyloxapol?

MR. MARGOLIS: Objection, vague.

THE WITNESS: I don't -- yeah, I think the answer is they were using different -- they seem to be using polysorbate 80 in their the preparations.

BY MR. HASFORD:

Q You may --

A Not tyloxapol.

Q You may put this document aside.

In Paragraph 59 of your responsive report, you cite a reference by Kirkman, et al; do you see that?

A Yes.

MR. HASFORD: I'm handing the court reporter what I would ask be marked as Heathcock Exhibit 18.

For the record, Heathcock Exhibit 18 is a reference entitled "Isolation and Identification of Bromfenac Glucoside from Rat Bile," by Kirkman, et al.

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(Heathcock Exhibit 18 marked.)

BY MR. HASFORD:

Q If I refer to Heathcock Exhibit 18 as the Kirkman reference, will you understand what I mean?

A Yes.

Q Would you have relied on the Kirkman reference in connection with your opinions in this case?

A Yes.

Q Does the Kirkman reference teach the use of tyloxapol?

MR. MARGOLIS: Objection, vague.

THE WITNESS: No, this is not a formulation reference at all. This is an identification of a metabolite.

BY MR. HASFORD:

Q Does the Kirkman reference teach the use of benzalkonium chloride?

MR. MARGOLIS: Objection, vague.

THE WITNESS: No. Again, that's not the subject of this kind of publication.

BY MR. HASFORD:

Q Does the Kirkman reference teach any

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ophthalmic formulation?

MR. MARGOLIS: Objection, vague.

THE WITNESS: No, it's not cited for that purpose. It's a publication about another topic.

BY MR. HASFORD:

Q You may put the Kirkman reference aside.

In Paragraph 59 of your responsive report, you also cite a reference by Hunter, et al; do you see that?

A Yes.

MR. HASFORD: I'm handing the court reporter what I would ask to be marked as Heathcock Exhibit 19.

For the record, Heathcock Exhibit 19 is a document entitled, "Bromfenac Duract Associated Hepatic Failure Requiring Liver Transplantation," by Hunter, et al.

(Heathcock Exhibit 19 was marked.)

BY MR. HASFORD:

Q If I refer to Heathcock Exhibit 19 as the Hunter reference, will you understand what I mean?

A Yes.

Q You are relying on Hunter reference in connection with your opinions in this case; correct?

A Yes, for very focused aspect of my opinion, right.

Q Does the Hunter reference teach the use of tyloxapol?

MR. MARGOLIS: Objection, vague.

THE WITNESS: No. This is -- it's not a formulation paper, so it won't have any surfactant or any antimicrobial. It is simply -- it's a medical case report.

BY MR. HASFORD:

Q Does the Hunter reference teach the use of benzalkonium chloride?

THE WITNESS: No --

MR. MARGOLIS: Objection, vague.

THE WITNESS: No. No. It would be -- there would be no reason for it to. This reference is cited simply to support my statement that this class of acidic NSAIDs, N-S-A-I-D-s, is commonly considered as a group that has similar properties.

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BY MR. HASFORD:

Q Just to be clear, does the Hunter reference teach the use of benzalkonium chloride?

MR. MARGOLIS: Objection, vague. Asked and answered.

THE WITNESS: Have I quit beating my wife?

BY MR. HASFORD:

Q I just want a clear record, Doctor.

A No, it does not teach that.

Q Thank you. Does the Hunter reference teach any ophthalmic formulation?

A No.

MR. MARGOLIS: Objection, vague.

Q Does the Hunter reference teach that bromfenac was associated with hepatic failure requiring liver transplantation?

A Yes. That's the title, in fact, of the paper.

Q You may put that aside.

Take a look, if you would, at the top of Page 20 of your responsive report. Still in Paragraph 59. You cite U.S. Patent No. 6,274,592. Do you see that?

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A Yes.

MR. HASFORD: I'm handing the court reporter what I would ask be marked as Heathcock Exhibit 20.

For the record, Heathcock Exhibit 20 is a copy of U.S. Patent No. 6,274,592.

(Heathcock Exhibit 20 was marked.)

BY MR. HASFORD:

Q If I refer to Patent No. 6,274,592 as the '592 patent, will you understand what I mean?

A Yes.

Q Does the '592 patent teach the use of tyloxapol?

MR. MARGOLIS: Objection, vague.

THE WITNESS: Let's see. No. It doesn't. It does not involve tyloxapol.

BY MR. HASFORD:

Q Turn, if you would, to Column 13, and let me direct your attention to the eight example formulations in the '592 patent.

Do all of the eight formulations in the '592 patent -- strike that and try again.

Do all of the eight example formulations in the '592 patent contain

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pranoprofen as their active ingredient?

A Yes.

Q Do any of the eight example formulations in the '592 patent contain bromfenac?

A No.

Q You can put the '592 patent aside.

MR. HASFORD: Is this a good time for a break?

MR. MARGOLIS: Sure.

MR. McCLUTCHY: Going off the record. The time is 2:33. This ends Disc No. 3.

(Whereupon there was a brief recess.)

MR. McCLUTCHY: We are back on the record. The time is 2:52. This is Disc No. 4.

BY MR. HASFORD:

Q Doctor, if you would, please turn to Paragraph 60 of your responsive report.

A Okay.

Q And let me direct your attention to the third sentence. It begins "While

Dr. Davies."

A Yes.

Q Could you read that to yourself and let me know when you're ready.

A Yes.

Q You note that Dr. Davies is correct that bromfenac's structure is more closely related to that of amfenac than to that of diclofenac; do you see that?

A Yes.

Q Why is bromfenac's structure more close of amfenac than that of diclofenac?

A Well, because it differs from amfenac in only the -- having the bromine at the para position at one of the benzene rings, whereas diclofenac -- different from diclofenac in other ways that are -- well, it differs more from diclofenac because that second benzene ring is attached in a different way. It's attached to the nitrogen atom of the first ring rather than through a carbonyl, bridge -- through a carbonyl bridge to the first ring.

MR. HASFORD: C-a-r-b-o-n-y-l.

THE WITNESS: Chemists think in

pictures, and I'm visualizing these pictures and trying to describe them in words for you.

Q How else does bromfenac differ from diclofenac in structure?

MR. MARGOLIS: Objection, lacks foundation.

THE WITNESS: Well, I think I just described it. I mean, in the case of -- they're both the same in having the acetic acid side chain. They're the same in having the first benzene ring that has an amino group attached to the number 2 carbon. They differ in the ways I've already described. They both have a second benzene ring, in the case of bromfenac, that's attached to the first ring by way of a carbonyl bridge. In the case of diclofenac, the second benzene ring, which has two chlorines attached to it is attached to the amino nitrogen at the 2 position of the first ring.

BY MR. HASFORD:

Q How do bromfenac and diclofenac differ in halogenation?

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MR. MARGOLIS: Objection, lacks foundation.

THE WITNESS: Bromfenac has a bromo group on one of its rings. Diclofenac has two chlorine groups on one of its rings.

BY MR. HASFORD:

Q Are those halogen groups in different positions on bromfenac and diclofenac?

A Yes. In bromfenac, they are -- the halogen is at the -- well, different position relative to what? If you say -- if you say that the chlorine and the bromine are at the number 1 position of their respective rings, then -- well, yeah, they're different positions because it's a hard question to answer. I'm trying to think how to give it an honest answer.

In the case of bromfenac, there's only one bromine and it's at one position on the ring, which is four carbons removed from a carbonyl group. Diclofenac doesn't have a carbonyl group, so I can't really compare them directly. But it has two chlorines. And one of the chlorines is at the 2 position relative to amino group, which is bromfenac.

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So is that enough -- they're different thank you. But it's hard to say how they differ.

MR. HASFORD: Let's go off the record, please.

MR. McCLUTCHY: Going off the record. The time is 2:56.

(Whereupon, there was some technical difficulty.)

MR. McCLUTCHY: We are back on the record. The time is 2:57.

THE WITNESS: Yeah, I'm still struggling to try to know how to answer that question. They differ. Telling you how they differ in words is pretty difficult.

BY MR. HASFORD:

Q Turn, if you would, to Paragraph 64 of your responsive report. It starts on Page 21 and then continues on to Page 22.

A Okay.

Q Let me direct your attention to the first full sentence at the top of Page 22. It begins "While I agree."

A The sentence that begins "Dr. Davies offers the opinion"? That one?

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Q Are you in Paragraph 64? Okay, so that's the first sentence. I'm directing you to the next sentence that begins "While"?

A "While I agree." Okay.

Q So could you read that to yourself and let me know when you're ready.

Why do you agree that a person of ordinary skill in the art could not have known with certainty that bromfenac would form a precipitate with benzalkonium chloride?

MR. MARGOLIS: Objection, to the extent it mischaracterizes the document.

Q You may answer.

A Well, because the statements that I quoted from Dr. Davies was that without carrying out a test, you would not have been able to know with certainty whether -- to have predicted whether the bromfenac cation would form the precipitate.

I agree that if you had not -- if there had not been a test, if someone hadn't reported that it forms a precipitate, you would have had a good idea that it might based on analogy to other similar situations, but to

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confirm that that strong suspicion was correct, you would definitely have to carry out the experiment. It's a simple experiment, but you' nevertheless have to do it.

Q What would have needed to be done to determine whether bromfenac would form a precipitate with benzalkonium chloride?

MR. MARGOLIS: Objection, vague. Incomplete hypothetical.

THE WITNESS: It would be a pretty simple experiment where you would simply measure out known quantities of the benzalkonium chloride and the sodium salt of bromfenac, for example, and mix these quantities together with a certain amount of solvent and observe whether there was turbidity or cloudiness or not.

BY MR. HASFORD:

Q What testing would needed to have been done -- strike that. Try again.

What testing would have needed to be done to determine whether bromfenac would form a precipitate with benzalkonium chloride?

MR. MARGOLIS: Objection, vague

and incomplete hypothetical. Asked and answered.

THE WITNESS: Yeah, that was really the previous answer, was that -- answer to that question. You want me to repeat it?

BY MR. HASFORD:

Q Yes, please.

A So what you would have to do is measure out known quantities of sodium bromfenate -- bromfenac and benzalkonium chloride, and then mix these together with a certain amount of water. And then make some sort of measurement of whether the resulting mixture you made was homogeneous or whether it had some kind of turbidity. You would use some kind of -- turbid -- it's a hard word to say, but it's a device that lets you measure the turbidity of a suspension. Turbinometer I believe it's called. Yeah, that's it.

Q Take a look, if you would, at Paragraph 65 --

A Okay.

Q -- in response to number 4. And about

two-thirds of the way down that paragraph, there's a sentence that begins "Dr. Davies' claim"?

A Yes.

Q Could you please read that to yourself and let me know when you're ready.

A Okay.

Q What does it mean that bromfenac is freely water-soluble?

MR. MARGOLIS: Objection. Vague.

THE WITNESS: Well, that's a pretty -- that is a pretty vague statement. I mean, I think to a chemist if you say something is freely water-soluble, you would understand that you're being told that solubility is not a limitation to something.

And so, of course, depending on what your intended use was, the actual experimental solubility could be 5 grams per liter or 50 grams per liter, but if you only needed to have a real dilute solution for your purpose, 5 grams per liter could be said to be freely water-soluble, so it's a vague statement that really needs to be

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evaluated in context of -- in the context that it's used.

BY MR. HASFORD:

Q You note in your responsive report that bromfenac is freely water-soluble; you see that?

A Well, yes, seems to be -- seems to be quite water-soluble.

Q And what is your basis for noting that bromfenac is freely water-soluble? Actually, let me strike that and try again.

Why is it your understanding that bromfenac is freely water-soluble?

MR. MARGOLIS: Objection, vague.

THE WITNESS: Well, I looked up the aqueous solubility of bromfenac and saw that -- oh, I forget the number now, but it was quite a high number, 50 grams per -- something like that. It was -- it seemed to be very water-soluble.

Q Take a look, if you would, at Paragraph 66 of your responsive report.

A Okay.

Q Read that paragraph to yourself,

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please, and let me know when you're ready.

A Okay.

Q Did you review any document showing that Mr. Sawa actually conducted any test to determine whether bromfenac, in fact, forms an insoluble complex with benzalkonium chloride?

MR. MARGOLIS: Objection, vague.

THE WITNESS: I don't remember right now. I saw a page from Mr. Sawa's report in which he states that it does form a cloudy solution. And to me that means he carried out a test and observed that it formed a cloudy suspension.

Q Did you actually review any document showing that Mr. Sawa actually conducted a test to determine whether bromfenac, in fact, forms an insoluble complex with benzalkonium chloride?

MR. MARGOLIS: Objection, vague. Asked and answered.

THE WITNESS: I'm going to have to refresh my memory as to what's on this -- this is in this big fat document.

BY MR. HASFORD:

Q Please do.

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A And refresh my memory as to what exactly -- Page 4 of Appendix A. Well, yeah, he refers to his notebook, and I don't recall that I looked at the actual notebook, but he says he prepared and tested the stability and formulations. And I don't recall that I looked at the actual notebook page that -- where he recorded the results of those experiments.

Q You can put this document aside.

Take a look, if you would, at Paragraph 67 --

A Okay.

Q -- of your responsive report. You cite U.S. Patent No. 5,603,929; do you see that?

A Uh-huh, yes, I do.

MR. HASFORD: I'm handing the court reporter what I would ask to be marked as Heathcock Exhibit 21.

For the record, Heathcock Exhibit 21 is a copy of U.S. Patent No. 5,603,929.

(Heathcock Exhibit 21 was marked.)

BY MR. HASFORD:

Q If I refer to Heathcock Exhibit 21 as the Desai '929 patent, will you understand what I

mean?

A Yes.

Q Does the Desai '929 patent teach the use of tyloxapol in any specific example formulation?

MR. MARGOLIS: Objection, vague.

THE WITNESS: No. This one does not use tyloxapol.

BY MR. HASFORD:

Q What solution does the Desai '929 patent provide to what you have called the interaction, complexation or precipitation problem?

MR. MARGOLIS: Objection. Lacks foundation. Mischaracterizes his testimony. Vague.

THE WITNESS: Yeah, they have used the technique of adding boric acid to preserve -- to enhance the storage time of their formulations.

BY MR. HASFORD:

Q Take a look at Example 1, if you would. It's on Column 4.

A All right.

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Q The formulation of Example 1 of the Desai '929 patent contains polyquad; do you see that?

A Yes.

Q Is polyquad different from benzalkonium chloride?

A Yes, it's a polymeric material somewhat like the one that we talked about earlier before lunch, in which there are quarternary ammonium ions strung out along the backbone of the polymer.

Q The approach that the Desai '929 patent took is different from the approach that the inventors of the patents in suit took when formulating the claimed aqueous liquid preparations of those patents; correct?

A Yes.

MR. MARGOLIS: Objection, vague. Lacks foundation.

THE WITNESS: Yes, that's correct.

BY MR. HASFORD:

Q Did the formulations disclosed in the Desai '929 patent have any stability problems?

MR. MARGOLIS: Objection, vague,

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lacks foundation.

THE WITNESS: Not that you can see from the patent. Whether they turned up as they began to use them on a large scale, I don't know.

BY MR. HASFORD:

Q You may put that document aside.

Take a look back, if you would, at Paragraph 67 in your responsive report on Page 23.

A Okay.

Q And the third sentence begins "Because the two compounds;" do you see that?

A Yes, I do.

Q Read that sentence to yourself and let me know when you're ready.

A Okay. I've got it.

Q It is your opinion that tyloxapol and polysorbate 80 do not significantly differ in the chemical and physical characteristics that determine how they function as surfactants in formulations, correct?

MR. MARGOLIS: Objection, vague. Mischaracterizes the document.

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THE WITNESS: Well, yeah. They certainly differ. I don't -- they're both surfactants. They're both amphiphilic molecules. They have the property -- so they're -- I don't consider them to be significantly different in those two descriptors.

They do differ in certain ways, certainly. They -- tyloxapol, as I've already described, has a feature of being somewhat three-dimensional. And it has seven of these amphiphilic molecules strung together, whereas polysorbate 80 is a single long amphiphilic chain.

And so tyloxapol has the ability to function as a single molecule as a solubilizing agent better than polysorbate 80 does. But they both are surfactants. In this case, I think it's clear why tyloxapol would work better than polysorbate 80, but they both would work to some degree.

Q Is it your opinion that tyloxapol and polysorbate 80 do significantly differ in the chemical and physical characteristics that

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determine how they function as surfactants in formulations?

MR. MARGOLIS: Objection, vague.

THE WITNESS: No. I think -- you know, this is a kind of a qualitative statement. To the extent that they're both surfactants, they can both associate with hydrophobic substances and help to solubilize those substances. They both can form this three-dimensional micelle structure. I would consider -- they don't significantly differ. If one of them couldn't form a micelle, for example, or -- then I would say that would be a significant difference. But, yeah, so I'll stick with saying they don't significantly differ, but they will have different properties.

BY MR. HASFORD:

Q Just to be clear, you wrote in your report that tyloxapol and polysorbate 80 do not significantly differ in the chemical and physical characteristics that determine how they function as surfactants in formulations; correct?

A I wrote that; that's right.

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Q Okay. Take a look, if you would, at the Paragraph 68 in your rebuttal report. Let me direct your attention to the second sentence that begins "Although non-ionic" at the bottom of Page 23.

A Third sentence, okay.

Q Sorry, third sentence. Please read that and let me know when you're ready.

A All right. Got it.

Q Why is it your opinion that non-ionic surfactants all differ somewhat in their chemical compositions in their three-dimensional structures?

MR. MARGOLIS: Objection. Mischaracterizes the document.

THE WITNESS: So the question was why do I say they may differ somewhat in their chemical structure?

BY MR. HASFORD:

Q Yeah. Why is it your opinion that non-ionic surfactants all differ in their chemical compositions in three-dimensional structures?

MR. MARGOLIS: Same objection.

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THE WITNESS: Well, because they're different molecules. Again, as I've said repeatedly, some are single chains of amphiphilic substances, and tyloxapol is an assembly of those chains, and so it has, rather than an amphiphilic end, it has an amphiphilic edge and it has a hydrophobic edge.

BY MR. HASFORD:

Q Take a look now at Paragraph 69 in your responsive report.

A All right.

Q And let me direct your attention to the third sentence. Read that to yourself and let me know when you're ready.

A Okay.

Q I'd like to break this down a bit with you starting at the end and working backward, if that's okay.

Given the disclosures in the prior art and the presence of polysorbate 80 in prior formulations containing bromfenac and benzalkonium chloride, why would a person of ordinary skill in the art have wanted to

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substitute octoxynol 40 for polysorbate 80 in these formulations?

MR. MARGOLIS: Objection, lacks foundation.

THE WITNESS: Well, you know, there was this -- there was this -- it's just an experiment. There was a problem. There was a problem with these -- with these complexes or these salt ion pairs separating from solution causing cloudy mixtures and turbid mixtures, and although that problem had not been identified with bromfenac, because it's enough like the other NSAIDs, I think a person would be concerned that it could be occurring or it could occur over time. And it would be a simple enough thing to do to substitute some of these other surfactants, especially tyloxapol and feel that you would have a better chance that this turbidity problem would not appear.

BY MR. HASFORD:

Q Given the disclosures in the prior art and the presence of polysorbate 80 in prior formulations containing bromfenac and

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benzalkonium chloride, why would a person of ordinary skill in the art have wanted to substitute octoxynol 9 for polysorbate 80 in those formulations?

MR. MARGOLIS: Objection. Lacks foundation. Incomplete hypothetical.

THE WITNESS: Well, again, because it was -- it's a different surfactant that has the potential to be -- to have a better outcome in preventing this turbidity problem.

BY MR. HASFORD:

Q Given the disclosures in the prior art and the presence of polysorbate 80 in prior formulations containing bromfenac and benzalkonium chloride, why would a person of ordinary skill in the art have wanted to substitute octoxynol 40 for polysorbate 80 in those formulations?

MR. MARGOLIS: Objection, lacks foundation. Incomplete hypothetical.

BY MR. HASFORD:

Q You may answer.

A Yeah. I think the same basic answer.

I mean, trying these different -- you know, you've got these different alternatives. Formulations are pretty simple. You've got bromfenac and BAC or diclofenac and BAC. You've got all these three -- these three pieces, and making various combinations of these three pieces with -- you know, using these three surfactants, which seem to be in -- these four surfactants, which seem to be in pretty widespread use would have been a simple thing. It's routine experimentation.

I think especially with the case of tyloxapol, you have -- you would have a better idea that this is going to stabilize your ion pair against separating from solution than any of the others, but even the octoxynol 9 and 40 had -- had been successful in other cases.

Q Let me -- I want to direct your attention specifically to octoxynol 40.

Given the disclosures in the prior art and the presence of polysorbate 80 in prior formulations containing bromfenac and benzalkonium chloride, why would a person of ordinary skill in the art have wanted to

substitute octoxynol 40 for polysorbate 80 in those formulations?

MR. MARGOLIS: Objection. Lacks foundation. Incomplete hypothetical. Vague. Asked and answered.

MR. HASFORD: You may answer.

A Well, I think I've kind of answered that. Octoxynol 40 had been used successfully in other formulations, and it would be a simple matter to experiment with it and try it out in this one.

BY MR. HASFORD:

Q Take a look, if you would, at the next sentence in Paragraph 69 of your rebuttal report. It's actually the last sentence in the paragraph.

It says "Indeed, given the prior art disclosures that non-ionic surfactants could resolve the NSAID BAC complexation issue, CEG 493 at 231 to 35, a person of ordinary skill in the art would be motivated to seek out and utilize other non-ionic surfactants in the formulation."

Given --

A Yeah, yeah.

Q Given the prior art disclosures, what

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other non-ionic surfactants would a person of ordinary skill in the art have been motivated to use in a formulation containing bromfenac and benzalkonium chloride?

MR. MARGOLIS: Objection. Vague. Outside the scope of his report.

MR. HASFORD: You may answer.

THE WITNESS: Well, I think that I have indicated that you would probably focus first on the surfactants of this class that were already approved by the FDA for use in ophthalmic preparations, and there weren't very many, so you would be probably motivated to begin with those compounds -- with those surfactants.

BY MR. HASFORD:

Q I want to focus in on what are the other non-ionic surfactants you're referring to. So given the prior art --

A I think that would be tyloxapol and octoxynol 40.

Q Okay. Were you referring to any others?

A No. I believe those were the only two

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that I found on the FDA list of approved surfactants for ophthalmic formulations.

Q Take a look, if you would, at Paragraph 70. Let me direct your attention to the third sentence. It starts "As an initial matter."

A Yes, okay.

Q Read that to yourself and let me know when you're ready.

A Okay.

Q What are some of the structural differences between polysorbate 80 and tyloxapol?

A Well, polysorbate 80 is a single long amphiphilic chain structure. Tyloxapol is assembly in which seven chain amphiphilic molecules have been linked together by methylene bridges. That's the main structural difference. The monomeric pieces are different as well. The hydrophobic part of polysorbate 80 is different structurally from the hydrophobic part of the tyloxapol monomer. And likewise, the hydrophilic chains are not the same, but so those are the ways they differ.

Q Take a look, if you would, at the

bottom sentence on Page 24 in Paragraph 70.

A Uh-huh.

Q It starts "Although a person of ordinary skill in the art."

A Okay.

Q Could you read that to yourself and let me know when you're ready.

A All right.

Q Why would a person of ordinary skill in the art not expect polysorbate 80 and tyloxapol to behave in the same way in a given formulation containing bromfenac or otherwise?

MR. MARGOLIS: Objection, to the extent it mischaracterizes the document.

BY MR. HASFORD:

Q You may answer.

A Yeah. So I think it's correct that in the same general way that they would both be expected to have a solubilizing effect on hydrophobic substances. I think a person of ordinary skill looking at the two structures and the nature of the hydrophobic substance that needs to be solubilized would actually come to the conclusion that tyloxapol -- although it

might work in generally the same way would actually work better because it has a sort of hydrophobic sheet. Whereas polysorbate is just a long amphiphilic rope. But they would both function roughly in the same general mechanistic way, although, you see, tyloxapol could associate -- just one molecule of tyloxapol could associate with one BAC ion pair. And do some good making it soluble, where it might take seven molecules of the polysorb to do the same thing.

Q Take a look, if you would, at Paragraph 71 and let me direct your attention to the third sentence.

A Okay.

Q Read that sentence to yourself and let me know when you're ready.

A All right. I've got it.

Q In what respects do the polar head groups of polysorbate 80 and tyloxapol differ?

A I read the wrong sentence.

Q Okay. Yeah. It's Paragraph 71.

A Okay. Let's see.

Q So let me ask the question again just so it's clear.

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In what respects do the polar head groups of polysorbate 80 and tyloxapol differ?

A Well, they're both hydrophilic. They both have carbons and oxygens. But if you look at the -- at them at the structural level, you'll see that they're made of monomeric units that are not the same. And of course polysorbate 80, hydrophilic group head is longer.

Q Take a look, if you would, at Paragraph 73, and let me direct your attention to the first sentence. Read that to yourself, please and let me know when you're ready.

A I've read it.

Q What important structural interactions occur when surfactant molecules assemble into micelles?

MR. MARGOLIS: Objection, vague.

THE WITNESS: When an assembly of surfactant molecules form a micelle structure, they pack together in such a way that they make a kind of a ball. And if you look at the surface of the ball, you'll find all the hydrophilic parts of those molecules at the surface, and then if you would cut

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into the ball, hypothetically cut into the ball and look inside, all the hydrophobic parts would be inside the ball.

So imagine that the micelle is like a tennis ball, and the fuzzy part of the tennis ball outside is all the head groups. In this case, in these cases, it's kind of a real fuzzy tennis ball because it's got long chains sticking out from the surface, and then inside is all this oil. It's the hydrocarbon parts of the surfactants. And of course, these two different -- I think you're asking me how do two different surfactants -- well, you only asked me how they pack together. So I think I answered your question.

Q What molecular changes occur when a micelle has incorporated a solute?

MR. MARGOLIS: Objection, lacks foundation.

THE WITNESS: Well, the purpose of this paragraph was to show that a calculation of what shape a surfactant would have in the gas phase is very -- is not

really going to give you any information about what shape it has when it's in this micelle structure, right, because in the micelle, let's say you calculate -- say Dr. Davies calculates the structure of, you know, polysorbate or octoxynol, and it's a long stick sticking out, you know, with little bumps on it, which are the H's.

But when a bunch of these things clump together, it's not a bunch of long sticks anymore. A bunch of long sticks don't fit.

So then it's got to coil up in some totally different way. And he rightfully responded in his little sort of reply report that you can't calculate that way. I agree, you can't calculate that way. So you can't know really how two different surfactants are going to fit together in a micelle from how they look in the gas phase. That's all I meant.

And of course when you -- if the micelle absorbs something that's hydrophobic like, let's say the benzalkonium salt with a

bromfenac anion, if it absorbs that little hydrophobic unit, then all those chains are going to be different because they're not going to be avoiding each other or nestling up to each other. They're going to be wrapped around the ball in some way.

So the point is, you know, just giving the picture of what it looks like in the gas phase is not very useful. It doesn't really -- yeah, it might know that polysorbate and tyloxapol, they have this shape. But when you pack together, they might look a lot more alike.

BY MR. HASFORD:

Q What molecular changes occur when a micelle is incorporated in a solute?

A I think I just answered that. I don't want to give that speech again.

Q No, I'm looking for just a general answer from you. Let me ask it again.

What -- generally speaking, what molecular changes occur when a micelle is incorporated in a solute?

MR. MARGOLIS: Objection, vague

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and asked and answered.

THE WITNESS: When a micelle incorporates a solute, the nature of the packing of the hydrophobic parts inside will change. It might also cause the micelle to loosen its structure so that additional surfactant molecules can now fit in.

BY MR. HASFORD:

Q Do the molecular changes that occur when a micelle has incorporated a solute depend on the nature of the micelle?

MR. MARGOLIS: Objection, vague.

DR. MALIK: Incomplete hypothetical.

THE WITNESS: I'm sure they do.

MR. MARGOLIS: Incomplete hypothetical.

Q Do the molecular changes that occur when a micelle has incorporated a solute depend on the nature of the solute?

MR. MARGOLIS: Objection, vague. Compound.

DR. MALIK: Incomplete hypothetical.

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BY MR. HASFORD:

Q You may answer.

A I'm sure they would, yes.

Q Take a look, if you would, at Paragraph 74 in your rebuttal report. And you cite the Schott reference in that paragraph; do you see that?

A Yes.

MR. HASFORD: I'm handing the court reporter what I would ask to be marked as Heathcock Exhibit 22.

For the record, Heathcock Exhibit 22 is a document entitled "Comparing the Surface Chemical Properties and the Effect of Salts on the Cloud Point of a Conventional Non-ionic Surfactant, octoxynol 9 (Triton X 100) and of its oligomer, tyloxapol, triton," and -- I'll tell you what. Let's just -- I'll make it easier for you. For the record, Heathcock Exhibit 22 is a copy of the Schott reference.

(Heathcock Exhibit 22 was marked.)

BY MR. HASFORD:

Q If I refer to Heathcock Exhibit 22 as

the Schott reference, will you understand what I mean?

A Yes, certainly.

Q You were relying on the Schott reference in connection with your opinions in this case; correct.

A Yes.

Q Please look at the introduction section of the Schott reference on the first page.

A Okay.

Q And let me direct your attention to the first sentence of the second paragraph.

A Okay.

Q It's states "Tyloxapol is essentially an oligomer of octoxynol 9;" do you see that?

A Yes.

Q Based on the Schott reference, would a person of ordinary skill in the art understand that tyloxapol is an exact oligomer of octoxynol 9?

MR. MARGOLIS: Objection, vague. Calls for speculation.

THE WITNESS: Oligomer is a term

that is used in polymer chemistry to refer to -- essentially an incomplete polymer. Tyloxapol is an incomplete copolymer.

So in my opinion, tyloxapol is correctly called an oligomer of octoxynol 9. You probably should say an oligomer of octoxynol 9 and formaldehyde. But, yeah, it's a term that does not have a precise definition that I'm aware of written down somewhere.

BY MR. HASFORD:

Q To be clear, is it your opinion that tyloxapol is a copolymer, not a polymer exclusively of octoxynol 9?

MR. MARGOLIS: Objection.

THE WITNESS: Yes, that's correct. Tyloxapol is a short copolymer of octoxynol 9 and formaldehyde.

BY MR. HASFORD:

Q Take a look, if you would, at the experimental section of the Schott reference. It's on the first page.

A The first page, okay. Okay.

Q Under the "Chemical Structure for

Octoxynol 9," the Schott reference states "The molecular weight of octoxynol 9 is approximately equal to 625;" do you see that?

A Yes.

Q Please turn the page. Under the "Chemical Structure for Tyloxapol," the Schott reference states that "The molecular weight of tyloxapol is 4,500;" do you see that?

A Yes.

Q Let me direct your attention to the "Chemical Structure for Tyloxapol."

Does tyloxapol contain a CH2 methylene bridge adjacent -- let me strike that and try again.

Does tyloxapol contain a CH2 methylene bridge attached to the adjacent phenyl rings?

A Tyloxapol contains six CH2 groups that bridge phenyl rings.

Q Take a look back, if you would, at the chemical structure for octoxynol 9.

A Okay.

Q Does octoxynol 9 contain a CH2 methylene bridge attached to the phenyl ring?

A No. This is a monomeric substance

that does not have any CH2 joined to other molecules.

Q You can put that document aside.

Take a look, if you would, at Paragraph 77 of your responsive report.

A Okay.

Q On Page 27. Let me direct your attention to the bottom of the page to the statement beginning "However, these surfactants."

A Uh-huh.

Q Read that to yourself and let me know when you're ready.

A Okay.

Q Why is it your opinion that tyloxapol, octoxynol 9, octoxynol 40 and polysorbate 80 differ considerably in molecular weight?

MR. MARGOLIS: Objection, vague.

THE WITNESS: Well, it's not an opinion. It's a fact. I mean, you look them up and they range from -- I think you showed me two of them. 625 to 4,500. I forget where polysorb -- I forget where the other one is. Yeah.

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BY MR. HASFORD:

Q Take a look, if you would, at the next sentence. It starts "Tyloxapol's CMC."

A Uh-huh.

Q Read that to yourself, and let me know when you're ready.

A Okay.

Q Even when expressed in grams per liter, is the CMC of Octoxynol 9 between two to four times greater than the CMC of tyloxapol?

MR. MARGOLIS: Objection. Vague.

THE WITNESS: I didn't understand the question.

BY MR. HASFORD:

Q Let me ask it again.

Even when expressed in grams per liter, is the CMC of octoxynol 9 between two to four times that -- strike that.

Even when expressed in grams per liter, is the CMC of octoxynol 9 between two to four times that of tyloxapol?

MR. MARGOLIS: Objection, vague.

THE WITNESS: Okay, yes.

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BY MR. HASFORD:

Q Even when expressed in grams per liter, is the CMC of tyloxapol three to six times that of polysorbate 80?

MR. MARGOLIS: Objection, vague.

THE WITNESS: Yeah, that seems to be correct.

Q Did you calculate the CMC of octoxynol 40 in grams per liter?

A I did, but I don't remember what it is.

Q Take a look, if you would, at Paragraph 78 in your responsive report.

A Okay.

Q In Paragraph 78, you cite U.S. Patent No. 5,474,760; do you see that?

A Yes.

MR. HASFORD: I'm handing the court reporter what I would ask to be marked as Heathcock Exhibit 23.

For the record, Heathcock Exhibit 23 is a copy of U.S. Patent No. 5,474,760.

(Heathcock Exhibit 23 was marked.)

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BY MR. HASFORD:

Q If I refer to Heathcock Exhibit 23 as the '760 patent or the Ghio patent, will you understand what I mean?

A Yes.

Q Does the Ghio patent teach bromfenac?

MR. MARGOLIS: Objection, vague.

THE WITNESS: No, bromfenac is not involved in this.

BY MR. HASFORD:

Q Does the Ghio patent teach any non-steroidal anti-inflammatory drug?

MR. MARGOLIS: Objection, vague.

THE WITNESS: No, it's not about NSAIDs.

BY MR. HASFORD:

Q Does the Ghio patent teach benzalkonium chloride?

MR. MARGOLIS: Objection, vague.

THE WITNESS: No, it's not -- does not.

BY MR. HASFORD:

Q Does the Ghio patent teach any ophthalmic formulations?

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MR. MARGOLIS: Objection, vague.

THE WITNESS: No, it's not about ophthalmic formulations.

BY MR. HASFORD:

Q The approach that the Ghio patent took is different from the approach that the inventors of the patents in suit took when formulating the claimed aqueous liquid preparations of those patents; correct?

MR. MARGOLIS: Objection, lacks foundation. Vague.

THE WITNESS: This is a hard question to answer because it's kind of like apples and oranges. You know, these are different kinds of -- these are products that are intended for totally different kinds of applications. And so --

BY MR. HASFORD:

Q Take a look, if you would, at Column 2 of the Ghio patent. Let me direct your attention to lines 38 through 41.

A Uh-huh.

Q Read that sentence beginning "As can be explained below," and let me know when you're

ready.

A Okay. I've read it.

Q Does the Ghio patent describe how alkyl aryl polyether alcohol polymers are useful as anti-oxidants in blocking oxidant reactions and biologic injury from partially reduced O2 species?

MR. MARGOLIS: Objection, vague.

THE WITNESS: Yeah, that's what it says.

BY MR. HASFORD:

Q Are partially reduced O2 species different from O2 itself?

A Well, yes, but when O2 oxidizes something, it produces products which are then partially reduced O2 species, so...

Q How are partially reduced O2 species different from O2 itself?

A Well, they're more reactive typically because they -- they are typically things that have an OO single bond. Often they're a free radical. An OH dot or an OOH dot. So those would all be examples of partially reduced oxygen.

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And partially reduced oxygen -- it's not in the air we breathe, but if the oxygen begins to oxidize something, then the products of that reaction would be partially reduced O2 species.

Q Chemically, how do partially reduced O2 species differ from O2 itself?

MR. MARGOLIS: Objection, lacks foundation. Vague.

THE WITNESS: Well, oxygen is a molecule that has a certain stability associated with it, so it's not reactive -- well, you just asked for a 90-minute lecture.

BY MR. HASFORD:

Q You can give me the short version. Let me ask it again just so it's clear.

Chemically, how do partially reduced O2 species differ from O2 itself?

THE WITNESS: Well, okay, so I've already described --

MR. MARGOLIS: Objection, lacks foundation. Vague. Asked and answered.

THE WITNESS: Okay. I've already

told you that the term "partially reduced O2 species" is a blanket term that can describe a number of different products when oxygen begins to be reactive with something. And, for example, when oxygen -- when oxygen -- if oxygen takes a hydrogen from a certain position, then that position could become a free radical. It would be like an R dot. And the oxygen would then have the hydrogen and its electron, so it would be HOO dot.

Now, that's a partially reduced oxygen species. And it's like you've cocked a gun. It's now more reactive than oxygen itself because it doesn't want to stay around that way with that free electron. So it's going to find something to react with pretty fast. So it's different chemically, and it's got generally higher reactivity than the oxygen molecule from which it originated as.

BY MR. HASFORD:

Q Structurally, how do partially reduced O2 species differ from O2 itself?

MR. MARGOLIS: Objection, vague,

lacks foundation.

BY MR. HASFORD:

Q You may answer.

A Do I have to answer?

MR. MARGOLIS: Asked and answered. Thank you.

THE WITNESS: Well, it differs structurally in that it has a single bond between the two oxygen rather than a double bond. It has -- generally many of the partially reduced oxygen species have a single electron, whereas oxygen itself has electron pairs. But there can be partially reduced oxygen species that don't have a free radical, like hydrogen peroxide, H2O2 is a partially reduced oxygen. And so they can differ in a number of different ways depending on exactly what partially reduced oxygen entity it is.

BY MR. HASFORD:

Q You may put this document aside.

You also cite U.S. Patent No. 6,165,445; do you see that?

A Yes.

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MR. HASFORD: I'm handing the court reporter what I would ask to be marked as Heathcock Exhibit 24.

For the record, Heathcock Exhibit 24 is a copy of U.S. Patent No. 6,165,445.

(Heathcock Exhibit 24 was marked.)

BY MR. HASFORD:

Q If I refer to U.S. Patent No. 6,165,445 as the '445 patent or the Kennedy patent, will you understand what I mean?

A Yes, right.

Q Does the Kennedy patent teach bromfenac?

MR. MARGOLIS: Objection, vague.

THE WITNESS: No. Bromfenac is not in this patent.

Q Does the Kennedy patent teach any NSAID?

MR. MARGOLIS: Objection, vague.

THE WITNESS: No.

BY MR. HASFORD:

Q Does the Kennedy patent teach benzalkonium chloride?

MR. MARGOLIS: Objection, vague.

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THE WITNESS: No, it doesn't.

BY MR. HASFORD:

Q Does the Kennedy patent disclose any ophthalmic formulations?

A No, it does not.

Q The approach that the Kennedy patent took is different from the approach that the inventors of the patents in suit took when formulating the claimed aqueous liquid preparations of those patents; correct?

MR. MARGOLIS: Objection, lacks foundation. Vague.

THE WITNESS: Yeah. Again, it's certainly different because these are totally different kinds of products. So...

BY MR. HASFORD:

Q Take a look, if you would, at Column 7. Let me direct your attention to Lines 52 through 54.

A Okay.

Q The Kennedy patent states that "It was a further object of the Kennedy patent's invention to provide a method to inhibit oxidant chemical reactions caused by partially reduced O2

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species;" correct?

A Yes, I see that.

Q You can put that document aside.

MR. HASFORD: And let's take a break.

MR. McCLUTCHY: Going off the record. The time is 3:48 p.m.

(Whereupon there was a brief recess.)

MR. McCLUTCHY: We are back on the record. The time is 4:01.

BY MR. HASFORD:

Q Doctor, please look back again at Paragraph 78 of your responsive report.

A Okay.

Q You rely on the Ghio reference that is entitled "Tyloxapol Inhibits NF Kappa B and Cytokine Release Scavenges HOCL and Reduces Viscosity of Cystic Fibrosis Sputum;" do you see that?

A Yes.

MR. HASFORD: For the record, I am handing the court reporter what I would ask be marked as Heathcock Exhibit 25.

C. Heathcock, Ph.D.

For the record, Heathcock Exhibit 25 is a copy of the Ghio reference. It bears Bates numbers Lupin 0069301 through Lupin 0069306.

(Heathcock Exhibit 25 was marked.)

BY MR. HASFORD:

Q You are relying on the Ghio reference, Heathcock Exhibit 25, in connection with your opinions in this case; correct?

A Yeah. This is another reference that documented the antioxidant properties of tyloxapol.

Q Does the Ghio reference teach bromfenac?

MR. MARGOLIS: Objection, vague.

THE WITNESS: No, there's nothing about bromfenac in this article.

BY MR. HASFORD:

Q Does the Ghio reference teach any NSAID?

MR. MARGOLIS: Objection, vague.

THE WITNESS: No, there's nothing about NSAIDs in this article.

C. Heathcock, Ph.D.

BY MR. HASFORD:

Q Does the Ghio reference teach using benzalkonium chloride?

MR. MARGOLIS: Objection, vague.

THE WITNESS: No, that would not be in included in the scope of this article.

BY MR. HASFORD:

Q Does the Ghio reference disclose any ophthalmic formulations?

A No, it's not about that kind of product.

BY MR. HASFORD:

Q The approach that the Ghio reference took is different from the approach that the inventors of the patents in suit took when formulating the claimed aqueous liquid preparations of those patents; correct?

MR. MARGOLIS: Objection, lacks foundation. Vague.

THE WITNESS: Yeah. I didn't quite understand. This is not a patent. This is not -- I'm not sure how you compare the approaches. This is an article which isn't about really the same -- it's not a

patent. It's about manufacturing a product.

BY MR. HASFORD:

Q Take a look, if you would, at the first page. In particular, the abstract at the top of that page.

A Okay.

Q It's at the top of the page bearing Bates No. Lupin 0069301.

A Yeah.

Q Could you please read the abstract to yourself and let me know when you're ready.

A Okay.

Q Let me direct your attention to the second sentence in the -- sorry, the third sentence of the abstract, beginning "Tyloxapol inhibits;" do you see that?

A Uh-huh.

Q The Ghio reference discloses the study -- strike that. Try again.

The Ghio reference discloses the use of tyloxapol in biological systems to inhibit activation of a transcription factor nuclear factor kappa B; correct?

MR. MARGOLIS: Objection, vague.

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THE WITNESS: Yes. So what they -- what this study reports is that -- is the use of tyloxapol as a -- as an antioxidant for a product that could be used that has -- that has the unintended side effect when oxidations take place of activating a certain undesirable biological factor, the one that you named, which I won't read again.

BY MR. HASFORD:

Q Just to be clear, the Ghio reference studies the use of tyloxapol in biological systems to inhibit activation of a transcription factor nuclear factor kappa B; correct?

A I'm just not sure. I have to look carefully. I'm not sure if they actually carried out, you know, the degree to which they carried out actual -- hold on just a minute. So these were laboratory experiments. But they were -- I think it's fair to say that they were doing biological tests, yes.

Q Take a look again at the abstract.

A Okay.

Q And let me direct your attention to

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the sentence "We have previously shown;" do you see that?

A The one that begins "We have previously shown;" that one?

Q Yes.

A Yeah, okay.

Q The Ghio reference discloses tyloxapol's ability to serve as an antioxidant for hydroxyl radicals, correct?

A Yeah. In the abstract, he's reciting that he had previously shown that it is an antioxidant for hydroxyl radicals.

Q The Ghio reference discloses tyloxapol's ability to serve as an antioxidant for hypochlorous acid; correct?

A To scavage hypochloric acid; right.

Q You can put that document aside.

Are biological data very important to a medicinal chemist?

MR. MARGOLIS: Objection, vague. Incomplete hypothetical.

THE WITNESS: Yeah. Generally speaking, yes, because your purpose in medicinal chemistry is -- well, if you're

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developing drugs, which is what you're most familiar with, your purpose is to develop a drug that has potency, selectivity and efficacious for some intended purpose. So you've got to measure that by doing biological tests.

Q Do biological data include cytotoxicity data?

A Yes, that's something that you can measure and is often measured, especially in the intermediate to late stages of a drug development project.

Q Would cytotoxicity be an unwanted side effect for any kind of drug?

MR. MARGOLIS: Objection, vague. Incomplete hypothetical.

THE WITNESS: Not if it's an anticancer drug, for example, or if it's an antiviral and you're trying to kill virus particles, you know, so cytotoxicity as a byproduct -- as a byproduct of a drug that has some intended beneficial property is undesirable.

Q Would cytotoxicity be an unwanted side

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effect for an ophthalmic drug?

MR. MARGOLIS: Objection, vague. Incomplete hypothetical.

THE WITNESS: Yes, I would say yes.

BY MR. HASFORD:

Q Okay. Does in vitro potency drive medicinal chemistry discovery at the first stage?

MR. MARGOLIS: Objection, vague. Calls for speculation. Incomplete hypothetical.

THE WITNESS: Yeah. Often the first stage of drug development is to carry out some kind of an in vitro test, and you're looking for potency. And often selectivity along with potency because you may or may not have two tests that you're, you know, for two related systems. But potency is usually the first thing you're looking for in drug development.

BY MR. HASFORD:

Q Take a look back, if you would, at Heathcock Exhibit 3. It's the court's opinion in OSI Pharmaceuticals v. Mylan.

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A It's in the stack somewhere. This one here?

Q Yes. Turn, if you would, to Page 15 of Heathcock Exhibit 3.

A Okay.

Q Let me direct your attention to the left-hand column, the top paragraph. It's a carryover from Paragraph 39 from the previous page. And about toward the end of that paragraph, do you see the sentence that begins "Heathcock agreed"?

A Toward the end. Yeah, okay.

Q Are you the Dr. Heathcock who agreed that in vitro potency is what drives medicinal chemistry discovery at the first stage?

MR. MARGOLIS: Objection, vague.

THE WITNESS: That would be me. I don't remember the context at all. And this is -- yeah, I don't remember the context. I must have been asked that question, and I must have said yes.

BY MR. HASFORD:

Q Do you still agree that in vitro potency is what drives medicinal chemistry

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discovery at the first stage?

MR. MARGOLIS: Objection, asked and answered. Vague.

THE WITNESS: Yeah --

MR. MARGOLIS: Incomplete hypothetical.

THE WITNESS: Sorry. Sorry. I just told you that in the previous answer. I said that's the first thing you almost always do, is carry out in vitro tests, and you're looking for potency in your first steps toward the new drug.

BY MR. HASFORD:

Q You may put that document aside.

What did you do to prepare for your deposition today?

A I came to New York on Wednesday night, and I spent yesterday meeting with these two gentlemen to go over the report. And --

MR. MARGOLIS: I just caution you not to reveal what we talked about.

THE WITNESS: I won't tell you what we talked about, but we went over the report and reviewed many of these documents.

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BY MR. HASFORD:

Q Did you review all of these documents?

DR. MALIK: Let's not talk about what specific documents.

THE WITNESS: Yeah, okay. Should I answer that question or not?

DR. MALIK: No.

MR. MARGOLIS: Calls for privileged information. I instruct you not to answer.

BY MR. HASFORD:

Q When -- are you going to follow Mr. Margolis' instruction and not answer the question?

A Yes.

Q Okay. When you say you met with these two gentlemen, are you referring to Mr. Margolis and Dr. Malik?

A Yes.

DR. MALIK: Dr. Margolis.

MR. HASFORD: Oh, sorry, Doctor. I am sorry.

MR. MARGOLIS: That's okay. I won't take it too hard.

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MR. HASFORD: I actually legitimately did not know.

THE WITNESS: Doctor and Doctor.

MR. HASFORD: Doctor and Doctor. I apologize. Dr. Margolis and Dr. Malik.

I don't have anything further at this point.

DR. MALIK: Let me and Dan step outside for one minute.

MR. MARGOLIS: You want to go off the record?

MR. McCLUTCHY: Going off the record. The time is 4:15.

(Whereupon there was a brief recess.)

MR. McCLUTCHY: We are back on the record. The time is 4:17.

MR. MARGOLIS: Yeah, Lupin doesn't have any questions.

DR. MALIK: Innopharma doesn't have any questions either.

MR. HASFORD: Thank you for your time, Doctor.

THE WITNESS: You're welcome.

C. Heathcock, Ph.D.

MR. McCLUTCHY: Going off the record. The time is 4:17. This ends Disc 4.

* * *

CLAYTON HEATHCOCK, Ph.D.

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OF _____, 2016.

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C. Heathcock, Ph.D.

INDEX TO TESTIMONY

EXAMINATION OF

* * *

E X H I B I T S

(Exhibits continued.)

C. Heathcock, Ph.D.

(Exhibits continued.)

E X H I B I T S

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(Exhibits were retained by reporter.)

* * *

C. Heathcock, Ph.D.

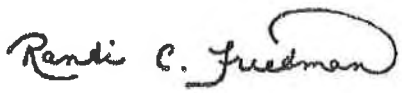
C E R T I F I C A T I O N

I, Randi Friedman, Registered Professional Reporter and Notary Public of the State of New York, do hereby certify:

THAT, the witness whose testimony is herein before set forth, was duly sworn by me, and THAT, the within transcript is a true record of the testimony given by said witness.

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

IN WITNESS WHEREOF, I have hereunto set my hand this day, February 23, 2016.



Randi Friedman, RPR

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ERRATA SHEET
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ASSIGNMENT NO. NJ2238541
CASE NAME: Senju Pharmaceutical Co., Ltd v. Lupin Limited And Lupin Pharmaceuticals
DATE OF DEPOSITION: 2/19/2016
WITNESS' NAME: Clayton Heathcock

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Clayton Heathcock

(Notary not required in California)
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_____, 2016

To: Daniel Margolis, Esq.

Case Name: Senju Pharmaceutical Co., Ltd v. Lupin Limited
And Lupin Pharmaceuticals

Veritext Reference Number: 2238541

Witness: Clayton Heathcock Deposition Date: 2/19/2016

Dear Sir/Madam:

Enclosed please find a deposition transcript. Please have the witness review the transcript and note any changes or corrections on the included errata sheet, indicating the page, line number, change, and the reason for the change. Have the witness' signature at the bottom of the sheet notarized except in California where they are signing under penalty of perjury and forward the errata sheet back to us at the address shown above.

If the jurat is not returned within thirty days of your receipt of this letter, the reading and signing will be deemed waived.

Sincerely,

Production Department

Encl.

cc: Justin Hasford, Esq.
Jitendra Malik, Ph.D.

f

Federal Rules of Civil Procedure

Rule 30

(e) Review By the Witness; Changes.

(1) Review; Statement of Changes. On request by the deponent or a party before the deposition is completed, the deponent must be allowed 30 days after being notified by the officer that the transcript or recording is available in which:

(A) to review the transcript or recording; and

(B) if there are changes in form or substance, to sign a statement listing the changes and the reasons for making them.

(2) Changes Indicated in the Officer's Certificate. The officer must note in the certificate prescribed by Rule 30(f)(1) whether a review was requested and, if so, must attach any changes the deponent makes during the 30-day period.

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