

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, :

-----x

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

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C. Heathcock, Ph.D.

APPEARANCES:

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, LLP
Attorneys for Plaintiffs
901 New York Avenue, NW
Washington, D.C. 20001

BY: JUSTIN J. HASFORD, ESQ.

GOODWIN PROCTER, LLP
Attorneys for Defendants, Lupin
620 Eighth Avenue
New York, New York 10018

BY: DANIEL P. MARGOLIS, Ph.D.

ALSTON & BIRD, LLP
Attorneys for Defendants, Innopharma
4721 Emperor Boulevard, Suite 400
Durham, North Carolina 27703

BY: JITENDRA MALIK, Ph.D.

* * *

ALSO PRESENT:

Dan McClutchy - Videographer
Terrence Kim

1 C. Heathcock, Ph.D.

2 MR. McCLUTCHY: Good morning. We
3 are now on the record. Please note that the
4 microphones are sensitive and can pick up
5 whispering and private conversations.

6 Please turn off all cellphones or place them
7 away from the microphones, as they can
8 interfere with the deposition audio.

9 Recording will continue until all parties
10 agree to go off the record. My name is --

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

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

15 (Whereupon there was a beverage
16 spill.)

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

25 The caption of this case is Senju

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C. Heathcock, Ph.D.
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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C. Heathcock, Ph.D.

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.

1 C. Heathcock, Ph.D.

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

6 A Yes.

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

9 A No.

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

16 (Heathcock Exhibit 1 was marked.)

17 BY MR. HASFORD:

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

20 A Yes, it is.

21 Q Please turn to Page 29.

22 A Yes.

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

25 A Yes, it does.

1 C. Heathcock, Ph.D.

2 Q Who prepared your responsive report
3 for this case?

4 A I did.

5 MR. MARGOLIS: Objection, form.

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

9 BY MR. HASFORD:

10 Q How did the attorneys help you prepare
11 this report?

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

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

25 They then took my -- my ideas.

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C. Heathcock, Ph.D.

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.

1 C. Heathcock, Ph.D.

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

8 Do you see that?

9 A Yes.

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

12 A Yes.

13 MR. MARGOLIS: Objection, vague.

14 BY MR. HASFORD:

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

18 MR. MARGOLIS: Objection, vague.

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

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

1 C. Heathcock, Ph.D.

2 MR. MARGOLIS: Objection, vague.

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

14 BY MR. HASFORD:

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

18 MR. MARGOLIS: Objection, vague.

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

21 BY MR. HASFORD:

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

1 C. Heathcock, Ph.D.

2 MR. MARGOLIS: Objection, vague.

3 Calls for legal conclusion.

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

8 BY MR. HASFORD:

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

11 A Yes, it is.

12 Q Does your curriculum vitae list your
13 relevant professional experience?

14 MR. MARGOLIS: Objection, vague.

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

22 BY MR. HASFORD:

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

1 C. Heathcock, Ph.D.

2 MR. MARGOLIS: Objection, vague.

3 Calls for a legal conclusion.

4 BY MR. HASFORD:

5 Q You may answer.

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

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

12 A Yes.

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

15 A Okay.

16 Q Are you there?

17 A Yes.

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

21 A Right.

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

25 A Yes.

1 C. Heathcock, Ph.D.

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

5 A Yes.

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

9 A Yes, there is.

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

13 A No.

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

18 A Yes, I do.

19 Q Do your research interests include
20 drug discovery?

21 A No.

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

25 MR. MARGOLIS: Objection. Vague.

1 C. Heathcock, Ph.D.

2 THE WITNESS: Yes. That's
3 correct.

4 BY MR. HASFORD:

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

10 A Yes, it does.

11 Q Did you publish your last paper in
12 2008?

13 A Yes, I did.

14 Q How many years ago is that?

15 A That would be eight years ago.

16 Q Have you published only one paper
17 since 2004?

18 A Yes.

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

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

23 Q Please do.

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

1 C. Heathcock, Ph.D.

2 project.

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

6 A Yes.

7 Q Have you ever published any papers
8 involving bromfenac?

9 MR. MARGOLIS: Objection, vague.

10 THE WITNESS: No.

11 BY MR. HASFORD:

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

15 A No.

16 MR. MARGOLIS: Objection, vague.

17 BY MR. HASFORD:

18 Q Have you ever published any papers
19 involving tyloxapol?

20 MR. MARGOLIS: Objection, vague.

21 THE WITNESS: No.

22 BY MR. HASFORD:

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

25 MR. MARGOLIS: Objection, vague.

1 C. Heathcock, Ph.D.

2 THE WITNESS: Yes.

3 BY MR. HASFORD:

4 Q Have you ever published any papers
5 involving benzalkonium chloride?

6 MR. MARGOLIS: Objection, vague.

7 THE WITNESS: No, I have not.

8 BY MR. HASFORD:

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

12 A Yes.

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

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

21 A Yes.

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

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

1 C. Heathcock, Ph.D.

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

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

7 A Yeah. Deposition and/or trial, yes.

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

12 A Yes, that's correct.

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

15 MR. MARGOLIS: Objection.

16 THE WITNESS: I have not testified
17 to that.

18 MR. MARGOLIS: Calls for a legal
19 conclusion.

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

23 BY MR. HASFORD:

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

1 C. Heathcock, Ph.D.

2 and non-obvious?

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

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

8 BY MR. HASFORD:

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

12 MR. MARGOLIS: Objection, vague.

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

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

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

1 C. Heathcock, Ph.D.

2 2010, 9:30 a.m., U.S. District Court for the
3 District of Delaware.

4 (Heathcock Exhibit 2 was marked.)

5 BY MR. HASFORD:

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

10 A Okay.

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

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

17 A Yes.

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

21 A Yes.

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

1 C. Heathcock, Ph.D.

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

6 And you answered: "That's correct."
7 That was your sworn testimony;
8 correct?

9 A Yes, that's right, yeah.

10 Q You can put this document aside for
11 now.

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

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

17 A No.

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

21 MR. MARGOLIS: Objection, vague.

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

1 C. Heathcock, Ph.D.

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

10 BY MR. HASFORD:

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

14 A No.

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

18 MR. MARGOLIS: Objection, vague.

19 THE WITNESS: Not that I can
20 recall.

21 BY MR. HASFORD:

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

25 A No, not that I can recall.

1 C. Heathcock, Ph.D.

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

4 A No.

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

8 MR. MARGOLIS: Objection. Vague.

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

15 BY MR. HASFORD:

16 Q Do you remember which NSAIDs you were
17 referring to?

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

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

24 MR. MARGOLIS: Objection, form.

25 THE WITNESS: Because they were --

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C. Heathcock, Ph.D.

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.

1 C. Heathcock, Ph.D.

2 BY MR. HASFORD:

3 Q Are you an expert in pharmaceutical
4 formulation?

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

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

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

15 A No.

16 MR. MARGOLIS: Objection, vague.

17 Q Are you an expert in the field of
18 pharmacy?

19 MR. MARGOLIS: Objection, vague.

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

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

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

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C. Heathcock, Ph.D.

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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C. Heathcock, Ph.D.

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?

1 C. Heathcock, Ph.D.

2 MR. MARGOLIS: Objection, vague.

3 Calls for a legal conclusion.

4 THE WITNESS: No.

5 BY MR. HASFORD:

6 Q Are you an expert in ophthalmology?

7 MR. MARGOLIS: Objection, vague.

8 Calls for a legal conclusion.

9 THE WITNESS: No, I'm not.

10 BY MR. HASFORD:

11 Q Are you an expert in any field of
12 medicine?

13 MR. MARGOLIS: Objection, vague.

14 Calls for a legal conclusion.

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

18 Q Have you ever prescribed medication to
19 a patient?

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

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

24 MR. MARGOLIS: Objection, vague.

25 THE WITNESS: No, I have not.

1 C. Heathcock, Ph.D.

2 BY MR. HASFORD:

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

5 MR. MARGOLIS: Objection, vague.

6 THE WITNESS: No, I have not.

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

9 A No.

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

13 MR. MARGOLIS: Objection, vague.

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

19 BY MR. HASFORD:

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

23 A Same answer.

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

1 C. Heathcock, Ph.D.

2 MR. MARGOLIS: Objection, vague.

3 THE WITNESS: No, I have not.

4 BY MR. HASFORD:

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

7 A No, I have not.

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

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

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

18 BY MR. HASFORD:

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

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

23 THE WITNESS: Only under the same
24 sort of circumstances.

25

1 C. Heathcock, Ph.D.

2 BY MR. HASFORD:

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

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

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

13 BY MR. HASFORD:

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

16 MR. MARGOLIS: Objection, vague.
17 Lacks foundation.

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

21 BY MR. HASFORD:

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

24 A No.

25 Q Have you ever conducted any research

1 C. Heathcock, Ph.D.

2 on any non-steroidal anti-inflammatory drug
3 product?

4 A I don't think so.

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

7 A No.

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

11 A I don't think so, no.

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

14 A No.

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

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

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

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C. Heathcock, Ph.D.

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

1 C. Heathcock, Ph.D.

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

14 BY MR. HASFORD:

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

20 A Okay.

21 Q Let me direct your attention on Page
22 222 to Lines 12 -- sorry, Lines 9 through 13.

23 A Yes.

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

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C. Heathcock, Ph.D.

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.

1 C. Heathcock, Ph.D.

2 pharmacopoeia criteria for antimicrobial
3 effectiveness?

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

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

8 BY MR. HASFORD:

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

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

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

17 BY MR. HASFORD:

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

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

22 THE WITNESS: No, I'm not.

23 BY MR. HASFORD:

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

1 C. Heathcock, Ph.D.

2 MR. MARGOLIS: Objection, vague.

3 Calls for legal conclusion.

4 THE WITNESS: No.

5 BY MR. HASFORD:

6 Q Are you an expert in patent law?

7 MR. MARGOLIS: Objection, vague.

8 Calls for a legal conclusion.

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

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

21 BY MR. HASFORD:

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

24 MR. MARGOLIS: Objection, vague.

25 THE WITNESS: What do I know about

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C. Heathcock, Ph.D.

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

1 C. Heathcock, Ph.D.

2 involving any non-ionic surfactant?

3 A No.

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

6 A No.

7 Q Are you an expert in FDA regulatory
8 law?

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

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

14 BY MR. HASFORD:

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

18 A No.

19 MR. MARGOLIS: Objection, vague.

20 BY MR. HASFORD:

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

24 MR. MARGOLIS: Objection, vague.

25 THE WITNESS: Let me think about

1 C. Heathcock, Ph.D.

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

13 So that's a complicated answer.

14 But, yes, I have provided opinions about
15 anti-inflammatory drugs.

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

18 MR. MARGOLIS: Objection,
19 mischaracterizes his testimony. Lacks
20 foundation.

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

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C. Heathcock, Ph.D.

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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C. Heathcock, Ph.D.

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.

1 C. Heathcock, Ph.D.

2 BY MR. HASFORD:

3 Q Have you ever formulated any product
4 containing benzalkonium chloride?

5 MR. MARGOLIS: Objection, vague.

6 THE WITNESS: No.

7 BY MR. HASFORD:

8 Q Have you ever formulated any marketed
9 drug product?

10 MR. MARGOLIS: Objection, vague.

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

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

16 MR. MARGOLIS: Objection, vague.

17 THE WITNESS: No.

18 BY MR. HASFORD:

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

22 MR. MARGOLIS: Objection, vague.

23 THE WITNESS: That's correct, no.

24 BY MR. HASFORD:

25 Q Have you ever authored or edited any

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C. Heathcock, Ph.D.

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.

1 C. Heathcock, Ph.D.

2 Q Have you ever consulted for the
3 National Formulary?

4 A No, I have not.

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

8 A No, I have not.

9 Q Have you ever consulted for the FDA?

10 A For the FDA? No.

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

13 MR. MARGOLIS: Objection, vague.

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

16 BY MR. HASFORD:

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

20 MR. MARGOLIS: Objection, vague.

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

1 C. Heathcock, Ph.D.

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

4 BY MR. HASFORD:

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

8 A Yeah, I'll say no.

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

11 BY MR. HASFORD:

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

14 MR. MARGOLIS: Objection, vague.

15 THE WITNESS: No.

16 BY MR. HASFORD:

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

19 MR. MARGOLIS: Objection, vague.

20 THE WITNESS: That's right, no.

21 BY MR. HASFORD:

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

25 A No.

1 C. Heathcock, Ph.D.

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

6 A No.

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

10 A No.

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

14 A No.

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

18 A No.

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

22 MR. MARGOLIS: Objection, vague.

23 THE WITNESS: No.

24 BY MR. HASFORD:

25 Q Have you ever published a book chapter

1 C. Heathcock, Ph.D.
2 dealing with the use of any non-steroidal
3 anti-inflammatory drug in a pharmaceutical
4 formulation?

5 MR. MARGOLIS: Objection, vague.

6 THE WITNESS: No.

7 BY MR. HASFORD:

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

11 MR. MARGOLIS: Objection, vague.

12 THE WITNESS: No.

13 BY MR. HASFORD:

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

17 MR. MARGOLIS: Objection, vague.

18 THE WITNESS: No.

19 BY MR. HASFORD:

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

23 MR. MARGOLIS: Objection, vague.

24 THE WITNESS: No.

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1 C. Heathcock, Ph.D.

2 BY MR. HASFORD:

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

6 MR. MARGOLIS: Objection, vague.

7 THE WITNESS: No.

8 BY MR. HASFORD:

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

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

14 THE WITNESS: Could you say the
15 question again?

16 BY MR. HASFORD:

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

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

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

1 C. Heathcock, Ph.D.
2 melting points. Boiling points.
3 Solubilities. Densities. Refractive
4 indices. They can have -- different colors.
5 I think that all of the common ones that
6 we've talked about are colors. But that's a
7 physical property. They can have --
8 depending on their functional groups, they
9 can have different chemical reactivity.
10 Even if they have the same functional
11 groups, the chemical -- the rates of
12 chemical reactions could be -- could be
13 different, either slightly different or in
14 some cases largely different. How far would
15 you like me to go? Is that enough?

16 BY MR. HASFORD:

17 Q Please. Continue.

18 A That's probably enough to give you.

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

22 MR. MARGOLIS: Objection. Vague.
23 Compound.

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

1 C. Heathcock, Ph.D.

2 because they're different entities. And the
3 physical and chemical properties of a
4 molecule are related to the chemical
5 structure. And generally, if two things
6 have a different chemical structure, they
7 have different chemical and physical
8 properties.

9 BY MR. HASFORD:

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

16 MR. MARGOLIS: Objection, vague.

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

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

1 C. Heathcock, Ph.D.
2 predict what that change will do to the
3 properties. And with some confidence
4 because we have a lot of experience. So if
5 you make a small change in structure, you
6 would expect a small change in properties
7 and so forth. So the accuracy of that
8 prediction is going to be depending on how
9 big the change is.

10 BY MR. HASFORD:

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

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

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

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

25 MR. MARGOLIS: Objection. Vague.

1 C. Heathcock, Ph.D.

2 Compound. Lacks foundation.

3 BY MR. HASFORD:

4 Q You may answer.

5 A Yeah, it would be a similar answer.

6 They would have different -- you know, they would
7 have different melting points. Different
8 solubilities. In the case of surfactants, they
9 have this property of -- because they're
10 amphiphilic and they have a hydrophobic section
11 and a hydrophilic section, they have this
12 property of forming aggregates both with each
13 other and with other molecules in solution. They
14 can even form aggregates to a sufficient size
15 that they form what we call micelles, which is a
16 particular kind of structure. But they can also
17 form complexes without forming micelles with
18 other substances in solution and therefore alter
19 the properties of that other substance.

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

1 C. Heathcock, Ph.D.

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

4 MR. MARGOLIS: Objection, vague.
5 Compound.

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

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

15 MR. MARGOLIS: Objection, vague.

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

19 BY MR. HASFORD:

20 Q What is pKa?

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

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C. Heathcock, Ph.D.

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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C. Heathcock, Ph.D.

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

1 C. Heathcock, Ph.D.

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

4 A Okay.

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

8 A Yeah.

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

12 A Right.

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

16 A Yes.

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

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

22 BY MR. HASFORD:

23 Q Oh, please do.

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

1 C. Heathcock, Ph.D.

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

4 A Oh, non-polar and lipophilic.

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

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

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

1 C. Heathcock, Ph.D.
2 lipophilic substituent. And it's non-polar
3 because it doesn't cause the compound to have a
4 charge. Yeah. Is that enough?

5 Q Yes. Thank you.
6 Is a chloro group freely
7 water-soluble?

8 MR. MARGOLIS: Objection, vague.

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

16 BY MR. HASFORD:

17 Q Let me ask it a different way.

18 A Yeah.

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

21 DR. MALIK: Incomplete
22 hypothetical.

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

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C. Heathcock, Ph.D.

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

1 C. Heathcock, Ph.D.

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

7 BY MR. HASFORD:

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

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

14 BY MR. HASFORD:

15 Q You may answer.

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

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

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

1 C. Heathcock, Ph.D.

2 hypothetical.

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

6 BY MR. HASFORD:

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

11 MR. MARGOLIS: Objection, lacks
12 foundation. Vague. Incomplete
13 hypothetical.

14 BY MR. HASFORD:

15 Q You may answer.

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

20 Q Correct.

21 MR. MARGOLIS: Same objections.

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

1 C. Heathcock, Ph.D.

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

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

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

1 C. Heathcock, Ph.D.

2 BY MR. HASFORD:

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

6 MR. MARGOLIS: Objection, vague.
7 Incomplete hypothetical.

8 BY MR. HASFORD:

9 Q You may answer.

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

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

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

24 MR. MARGOLIS: Sure.

25

1 C. Heathcock, Ph.D.

2 BY MR. HASFORD:

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

8 MR. MARGOLIS: Objection. Lacks
9 foundation. Vague. Incomplete
10 hypothetical.

11 DR. MALIK: Calls for a narrative.

12 BY MR. HASFORD:

13 Q You may answer.

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

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

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

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

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

15 BY MR. HASFORD:

16 Q You may answer.

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

25 Q Have you ever created

1 C. Heathcock, Ph.D.

2 three-dimensional --

3 MR. MARGOLIS: Were you finished
4 with your answer?

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

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

16 A Yes, certainly.

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

22 MR. MARGOLIS: Objection, vague.

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

1 C. Heathcock, Ph.D.

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

4 MR. McCLUTCHY: Going off the
5 record. The time is 11:16. This ends Disc
6 1.

7 (Whereupon there was a brief
8 recess.)

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

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

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

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

20 MR. MARGOLIS: Thank you.

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

24 For the record, Heathcock Exhibit
25 4 is a copy of U.S. Patent No. 8,129,431.

1 C. Heathcock, Ph.D.

2 (Heathcock Exhibit 4 was marked.)

3 BY MR. HASFORD:

4 Q Did you review U.S. Patent No.
5 8,129,431 in connection with your opinions in
6 this case?

7 A Yes.

8 Q If I refer to U.S. Patent No.
9 8,129,431, as the '431 patent, will you
10 understand what I mean?

11 A Yes.

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

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

17 For the record, Heathcock Exhibit
18 5 is a copy of U.S. Patent No. 8,669,290.

19 (Heathcock Exhibit 5 was marked.)

20 BY MR. HASFORD:

21 Q Did you review U.S. Patent No.
22 8,669,290 in connection with your opinions in
23 this case?

24 A Yes, I did.

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

1 C. Heathcock, Ph.D.

2 8,669,290 as the '290 patent, will you understand
3 what I mean?

4 A Yes.

5 Q You can put that aside.

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

9 For the record, Heathcock Exhibit
10 6 is a copy of U.S. Patent No. 8,754,131.

11 (Heathcock Exhibit 6 was marked.)

12 BY MR. HASFORD:

13 Q Did you review U.S. Patent No.
14 8,754,131 in connection with your opinions in
15 this case?

16 A Yes.

17 Q If I refer to U.S. Patent No.
18 8,754,131 as the '131 patent, will you understand
19 what I mean?

20 A Yes.

21 Q You can put that aside for the moment.

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

25 For the record, Heathcock Exhibit

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C. Heathcock, Ph.D.

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.

1 C. Heathcock, Ph.D.

2 8,927,606 in connection with your opinions in
3 this case?

4 A Yes, I did.

5 Q If I refer to U.S. Patent No.
6 8,927,606 as the '606 patent, will you understand
7 what I mean?

8 A Yes.

9 Q If I refer to the '431, '290, '131,
10 '813 and '606 patents collectively as the patents
11 in suit, will you understand what I mean?

12 A Yes.

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

16 MR. MARGOLIS: Objection, vague.

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

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

22 A I read them.

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

25 A You want me to open all six?

1 C. Heathcock, Ph.D.

2 Q You may just want to open them all.

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

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

7 MR. MARGOLIS: Objection. Calls
8 for legal conclusion.

9 BY MR. HASFORD:

10 Q You may answer.

11 MR. MARGOLIS: Outside the scope
12 of his report.

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

18 BY MR. HASFORD:

19 Q Please.

20 A All right.

21 MR. MARGOLIS: And objection,
22 compound.

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

1 C. Heathcock, Ph.D.

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

5 BY MR. HASFORD:

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

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

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

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

16 MR. MARGOLIS: Objection, vague.

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

21 BY MR. HASFORD:

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

25 A No.

1 C. Heathcock, Ph.D.

2 MR. MARGOLIS: Objection, vague,
3 compound.

4 THE WITNESS: I did not consider
5 that.

6 BY MR. HASFORD:

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

10 MR. MARGOLIS: Objection, vague,
11 compound.

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

14 BY MR. HASFORD:

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

18 MR. MARGOLIS: Objection, vague
19 compound.

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

23 BY MR. HASFORD:

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

1 C. Heathcock, Ph.D.

2 considerations of non-obviousness?

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

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

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

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

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

16 BY MR. HASFORD:

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

20 A Yes.

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

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

1 C. Heathcock, Ph.D.

2 prior art?

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

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

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

22 BY MR. HASFORD:

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

1 C. Heathcock, Ph.D.

2 MR. MARGOLIS: Objection, vague.

3 Calls for legal conclusion. Asked and
4 answered.

5 BY MR. HASFORD:

6 Q You may answer.

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

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

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

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

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

23 MR. MARGOLIS: Objection. Lacks
24 foundation.

25 THE WITNESS: Probably read

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C. Heathcock, Ph.D.

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.

1 C. Heathcock, Ph.D.

2 BY MR. HASFORD:

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

7 MR. MARGOLIS: Objection, vague,
8 lacks foundation.

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

14 BY MR. HASFORD:

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

18 MR. MARGOLIS: Objection, vague.
19 Lacks foundation.

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

23 BY MR. HASFORD:

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

1 C. Heathcock, Ph.D.

2 MR. MARGOLIS: Objection. Vague.
3 Lacks foundation.

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

7 BY MR. HASFORD:

8 Q Let me repeat it for you.

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

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

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

23 BY MR. HASFORD:

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

1 C. Heathcock, Ph.D.

2 art of the patents in suit are?

3 MR. MARGOLIS: Objection. Vague.

4 Compound. Lacks foundation.

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

9 BY MR. HASFORD:

10 Q Do you have -- sorry, go ahead.

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

15 MR. MARGOLIS: Objection. Vague.

16 Compound. Lacks foundation.

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

23 BY MR. HASFORD:

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

1 C. Heathcock, Ph.D.

2 Exhibit 1.

3 A Let me tidy up my stack of patents.

4 Q Please. Take your time.

5 A Okay.

6 Q Let me direct your attention to Page

7 6. And in particular let me direct your

8 attention to Section 7, entitled "The Person of

9 Ordinary Skill in the Art."

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

14 A Yes.

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

17 A Okay.

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

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

1 C. Heathcock, Ph.D.

2 BY MR. HASFORD:

3 Q You may answer.

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

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

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

15 THE WITNESS: No. I was --

16 MR. MARGOLIS: Vague.

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

23 BY MR. HASFORD:

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

1 C. Heathcock, Ph.D.
2 consider the definitions that any courts have
3 adopted in other cases?

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

7 BY MR. HASFORD:

8 Q You may answer.

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

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

15 MR. MARGOLIS: Objection.
16 Mischaracterizes the document. Lacks
17 foundation.

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

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

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

1 C. Heathcock, Ph.D.

2 foundation.

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

17 BY MR. HASFORD:

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

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

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

25

1 C. Heathcock, Ph.D.

2 BY MR. HASFORD:

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

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

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

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

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

21 Q Do you know Dr. Steven Davies?

22 A Yes.

23 Q Is he a good scientist?

24 MR. MARGOLIS: Objection, vague.

25 THE WITNESS: Yes, he's got a good

1 C. Heathcock, Ph.D.

2 reputation.

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

6 A All right.

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

11 A Yes.

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

14 A Yes, it does.

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

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

19 Q Take a look at the next sentence. It
20 says "Unlike steroidal anti-inflammatory drugs,
21 NSAIDs inhibit the activity of the cyclooxygenase
22 1 (cox 1), and cyclooxygenase 2 (cox 2) enzymes
23 by competitively binding to each of these
24 enzymes." Is that a true statement?

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

1 C. Heathcock, Ph.D.

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

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

11 A Yes, that's right.

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

15 MR. MARGOLIS: Objection. Lacks
16 foundation.

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

20 BY MR. HASFORD:

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

23 MR. MARGOLIS: Objection, vague.

24 THE WITNESS: My own laboratory
25 research?

1 C. Heathcock, Ph.D.

2 BY MR. HASFORD:

3 Q Correct.

4 A Both.

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

10 MR. MARGOLIS: Objection. Vague.
11 Incomplete hypothetical.

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

20 BY MR. HASFORD:

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

1 C. Heathcock, Ph.D.

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

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

11 BY MR. HASFORD:

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

18 A Well, yes.

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

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

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C. Heathcock, Ph.D.

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

1 C. Heathcock, Ph.D.

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

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

15 Q Thank you very much, Doctor.

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

18 A Okay.

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

21 A That's right.

22 Q Do you see that?

23 A I see that.

24 Q Are all NSAIDs carboxylic acids?

25 A No.

1 C. Heathcock, Ph.D.

2 Q How many different NSAIDs are
3 carboxylic acids?

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

6 Q How many different NSAIDs are not
7 carboxylic acids?

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

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

15 A Eight?

16 Q And just above Paragraph 35.

17 A Okay.

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

20 A Yes.

21 Q Is ibuprofen an NSAID?

22 A Yes.

23 Q Does ibuprofen have one phenyl ring?

24 A Yes, it does.

25 Q Does ibuprofen have an isobutyl group?

1 C. Heathcock, Ph.D.

2 A Yes, it does.

3 Q Is ibuprofen a propanoic acid
4 derivative?

5 A Yes.

6 Q Does ibuprofen have a bromo group?

7 A No.

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

10 A No.

11 Q Does ibuprofen have any kind of amine
12 group?

13 A No.

14 Q Does ibuprofen have a chiral carbon?

15 A It has a stereogenic carbon, right.

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

18 A Yes.

19 Q Is naproxen an NSAID?

20 A Yes, it is.

21 Q Does naproxen have a naphthol ring?

22 A Yes.

23 Q Does naproxen have a methoxy group?

24 A Yes.

25 Q Does naproxen have a bromo group?

1 C. Heathcock, Ph.D.

2 A No.

3 Q Is naproxen a propanoic acid
4 derivative?

5 A Yes, it is.

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

8 A No.

9 Q Does naproxen have any kind of amine
10 group?

11 A No.

12 Q Does naproxen have a chiral carbon?

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

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

17 A Yes.

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

20 A Yes.

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

23 A Yes.

24 Q And I apologize, Doctor.

25 Did you misspell flurbiprofen in your

1 C. Heathcock, Ph.D.

2 responsive report?

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

6 Q I think there might be an extra I?

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

9 Q Is flurbiprofen an NSAID?

10 A Yes.

11 Q Does flurbiprofen have a fluoro group?

12 A Yes, it does.

13 Q Does flurbiprofen have a bromo group?

14 A No.

15 Q Is flurbiprofen a propanoic acid
16 derivative?

17 A Yes.

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

20 A No.

21 Q Does flurbiprofen have any kind of
22 amine group?

23 A No.

24 Q Does flurbiprofen have a stereogenic
25 carbon?

1 C. Heathcock, Ph.D.

2 A Yes.

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

5 A Yes.

6 Q Is diclofenac an NSAID?

7 A Yes.

8 Q Does diclofenac have two chloro
9 groups?

10 A Yes.

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

14 A Yes.

15 Q Does diclofenac have a bromo group?

16 A No.

17 Q Does diclofenac have a secondary amine
18 group?

19 A Yes.

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

22 A No.

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

25 A Yes.

1 C. Heathcock, Ph.D.

2 Q Is amfenac an NSAID?

3 A Yes, it is.

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

6 A No.

7 Q Is amfenac the active metabolite of
8 nepafenac?

9 A Yes.

10 Q Does amfenac have a bromo group?

11 A No.

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

14 A Yes.

15 Q Is nepafenac an NSAID?

16 A Yes.

17 Q Does nepafenac have an amide group?

18 A-m-i-d-e, amide.

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

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

22 A Yes.

23 Q Does nepafenac have a carboxylic acid
24 group?

25 A No.

1 C. Heathcock, Ph.D.

2 Q Does nepafenac have a bromo group?

3 A No.

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

7 A Yes.

8 Q Is ketorolac an NSAID?

9 A Yes.

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

12 A Yeah, there's a pyrrolizine ring.

13 Q Does ketorolac have a tertiary amine
14 group?

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

17 Q Does ketorolac have a bromo group?

18 A No.

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

21 A Yes.

22 Q Is bromfenac an NSAID?

23 A Yes.

24 Q Does bromfenac have two phenyl rings?

25 A Yes.

1 C. Heathcock, Ph.D.

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

4 A Yes, it does.

5 Q Does bromfenac have a naphthol ring?

6 A No.

7 Q Does bromfenac have a pyrrolizine
8 group?

9 A No, it does not.

10 Q Does bromfenac have an isobutyl group?

11 A No.

12 Q Does bromfenac have a methoxy group?

13 A No.

14 Q Does bromfenac have an amide group?

15 A No.

16 Q Does bromfenac have a carboxylic acid
17 group?

18 A Yes, it does.

19 Q Is bromfenac a propanoic acid
20 derivative?

21 A No.

22 Q Does bromfenac have a bromo group?

23 A Yes.

24 Q Is the bromo group in bromfenac at the
25 4 position of the phenyl ring?

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C. Heathcock, Ph.D.

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

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C. Heathcock, Ph.D.

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 its 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

1 C. Heathcock, Ph.D.

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

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

7 A No.

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

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

13 MR. HASFORD: You may answer.

14 MR. MARGOLIS: Vague.

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

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

1 C. Heathcock, Ph.D.

2 differ in their rates of esterification.

3 They would all have acidity constants that

4 would be similar but not exact. So they

5 would have pKa's that would be somewhere

6 around the 4-1/2 range, but plus or minus.

7 They would have solubilities that would be

8 different. Some of the ones that have other

9 functionality, for example, amfenac or

10 bromfenac would be able to react as bases to

11 form salts with the amine. With acids like

12 hydrochloric acid, for example. Or they

13 would be able to engage in amide-forming

14 reactions because of those functionalities.

15 So, yeah, those would all be differences

16 that they could have.

17 Q Why do different NSAIDs having
18 different chemical structures have different
19 solubilities?

20 MR. MARGOLIS: Objection, vague.

21 Compound.

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

1 C. Heathcock, Ph.D.

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

11 BY MR. HASFORD:

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

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

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

1 C. Heathcock, Ph.D.

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

7 BY MR. HASFORD:

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

11 MR. MARGOLIS: Objection. Vague.
12 Compound.

13 THE WITNESS: That would be
14 because primarily because of the electronics
15 of the molecule. Also the sterics. For
16 example, a compound like ibuprofen, probably
17 undergoes esterification reaction slower
18 than a compound like, say, diclofenac
19 because there's not a carbon branch next to
20 the carboxy group.

21 BY MR. HASFORD:

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

25 MR. MARGOLIS: Objection, vague.

1 C. Heathcock, Ph.D.

2 Compound. Lacks foundation.

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

18 BY MR. HASFORD:

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

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

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

1 C. Heathcock, Ph.D.
2 experience with in making such formulations.
3 And it's not something I've been asked to
4 study for this report. So I don't really
5 have an answer to that.

6 BY MR. HASFORD:

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

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

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

23 BY MR. HASFORD:

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

1 C. Heathcock, Ph.D.

2 liquid preparations of NSAIDs?

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

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

11 BY MR. HASFORD:

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

16 MR. MARGOLIS: Objection. Vague.
17 Incomplete hypothetical.

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

21 BY MR. HASFORD:

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

24 A No, I haven't studied that.

25 Q Do you have an understanding of the

1 C. Heathcock, Ph.D.

2 pharmacodynamic properties of bromfenac?

3 A No, I haven't studied that either.

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

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

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

10 MR. MARGOLIS: Objection. Vague.

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

13 BY MR. HASFORD:

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

17 A Okay. Right.

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

23 A Yes.

24 Q Does ocufen contain bromfenac?

25 A No, it contains flurbiprofen.

1 C. Heathcock, Ph.D.

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

4 MR. MARGOLIS: Objection, lacks
5 foundation.

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

8 BY MR. HASFORD:

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

14 A Yes.

15 Q Does Voltaren contain bromfenac?

16 A No. It contains diclofenac as the
17 NSAID.

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

20 MR. MARGOLIS: Objection, lacks
21 foundation.

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

24 BY MR. HASFORD:

25 Q You state --

1 C. Heathcock, Ph.D.

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

4 BY MR. HASFORD:

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

8 MR. MARGOLIS: Objection, pain.

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

12 BY MR. HASFORD:

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

17 A Yes.

18 Q Does Acular contain bromfenac?

19 A No, it contains ketorolac.

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

22 MR. MARGOLIS: Objection. Lacks
23 foundation.

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

1 C. Heathcock, Ph.D.

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

4 BY MR. HASFORD:

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

9 MR. MARGOLIS: Objection, lacks
10 foundation.

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

13 BY MR. HASFORD:

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

18 MR. MARGOLIS: Objection. Vague.
19 Incomplete hypothetical.

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

1 C. Heathcock, Ph.D.

2 BY MR. HASFORD:

3 Q Let me ask it this way.

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

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

11 BY MR. HASFORD:

12 Q You may answer.

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

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

25 A Yes.

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C. Heathcock, Ph.D.

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

1 C. Heathcock, Ph.D.

2 is a unique characteristic of each surfactant."

3 Is that a true statement?

4 A Yes, that's right.

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

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

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

1 C. Heathcock, Ph.D.

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

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

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

1 C. Heathcock, Ph.D.

2 A Okay.

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

8 A Yes.

9 Q What are the four classes of
10 surfactants?

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

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

25 Q The classes you just described, were

1 C. Heathcock, Ph.D.

2 those non-ionic, cationic and anionics?

3 A Those would be three, yeah.

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

6 A Yeah.

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

9 MR. MARGOLIS: Objection, vague.

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

17 BY MR. HASFORD:

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

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

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

24 A I don't have the answer to that.

25 Q Take a look, if you would, at the

1 C. Heathcock, Ph.D.

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

4 A Okay.

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

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

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

22 BY MR. HASFORD:

23 Q What --

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

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C. Heathcock, Ph.D.

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.

1 C. Heathcock, Ph.D.

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

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

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

22 MR. MARGOLIS: Objection.

23 Mischaracterizes his testimony.

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

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C. Heathcock, Ph.D.

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

1 C. Heathcock, Ph.D.

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

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

6 BY MR. HASFORD:

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

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

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

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

25 Now, you added in your question

1 C. Heathcock, Ph.D.

2 have I ever accurately predict -- well, I
3 don't know how accurate that prediction is.
4 I'm confident that that prediction is valid,
5 but accurate is a -- kind of implies a
6 quantitateness that I don't know about.

7 BY MR. HASFORD:

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

14 MR. MARGOLIS: Objection.

15 Incomplete hypothetical. Vague.

16 BY MR. HASFORD:

17 Q You may answer.

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

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

24 MR. MARGOLIS: Objection, vague.

25 THE WITNESS: No, I haven't done

1 C. Heathcock, Ph.D.

2 any experiments with tyloxapol.

3 BY MR. HASFORD:

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

7 MR. MARGOLIS: Objection, vague.

8 THE WITNESS: No. Excuse me.

9 BY MR. HASFORD:

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

12 A Okay.

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

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

19 A Yes.

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

22 MR. MARGOLIS: Objection, vague.
23 Lacks foundation.

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

1 C. Heathcock, Ph.D.

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

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

14 BY MR. HASFORD:

15 Q You also mention octoxynol; do you see
16 that?

17 A Yes.

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

20 MR. MARGOLIS: Objection, vague.
21 Lacks foundation.

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

1 C. Heathcock, Ph.D.

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

7 BY MR. HASFORD:

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

11 A The whole paragraph?

12 Q Actually, just read the last two
13 sentences.

14 A Okay.

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

20 MR. MARGOLIS: Objection.

21 Incomplete hypothetical. Vague.

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

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C. Heathcock, Ph.D.

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.

1 C. Heathcock, Ph.D.

2 BY MR. HASFORD:

3 Q Take a look, if you would, at Footnote
4 2 in your responsive report.

5 A Uh-huh. Okay.

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

13 A Oh, yes, I see it now.

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

19 MR. MARGOLIS: Objection, vague.

20 Incomplete hypothetical.

21 THE WITNESS: I don't know.

22 BY MR. HASFORD:

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

1 C. Heathcock, Ph.D.
2 the interaction complexation or precipitation
3 problem?

4 MR. MARGOLIS: Objection, vague.
5 Incomplete hypothetical.

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

9 BY MR. HASFORD:

10 Q That's fine.

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

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

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

20 (Whereupon there was a lunch
21 recess.)

22 MR. McCLUTCHY: We are back on the
23 record. The time is 1:36. This is Disc No.
24 3.

25

1 C. Heathcock, Ph.D.

2 BY MR. HASFORD:

3 Q Good afternoon, Doctor.

4 A Good afternoon.

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

8 A Okay.

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

13 A Paragraph 46?

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

16 A Okay.

17 Q You identify Eudragit RL?

18 A Yes, I do.

19 Q Are Eudragit RL and benzalkonium
20 chloride different chemical compounds?

21 A Yes.

22 MR. MARGOLIS: Objection, vague.

23 THE WITNESS: They're different.

24 They related in that they both have a
25 quarternary ammonium unit or structure.

1 C. Heathcock, Ph.D.

2 BY MR. HASFORD:

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

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

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

12 BY MR. HASFORD:

13 Q Thank you for clarifying.

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

16 A Yes, it does.

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

19 A It has two.

20 Q Take a look, if you would, at Footnote
21 5?

22 A Yes.

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

25 A Yes.

1 C. Heathcock, Ph.D.

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

5 For the record, Heathcock Exhibit
6 9 is a copy of the Khalil reference.

7 (Heathcock Exhibit 9 was marked.)

8 BY MR. HASFORD:

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

13 A Yes, it is.

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

17 A Yes.

18 Q Take a look, if you would, at the
19 "Conclusions" portion of the Khalil reference on
20 Page 426. This page bears Bates No. Lupin
21 0069339. Do you see that?

22 A Yes.

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

1 C. Heathcock, Ph.D.

2 when you're ready.

3 A Yes.

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

8 A Yes, it does.

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

12 A Okay.

13 Q Does the Khalil reference deal with
14 ophthalmic formulations?

15 MR. MARGOLIS: Objection, vague.

16 THE WITNESS: No, it doesn't.

17 BY MR. HASFORD:

18 Q Does the Khalil reference teach the
19 use of bromfenac?

20 MR. MARGOLIS: Objection, vague.

21 THE WITNESS: No, it doesn't.

22 Q Does the Khalil reference teach the
23 use of tyloxapol?

24 MR. MARGOLIS: Objection, vague.

25 THE WITNESS: No. It's got

1 C. Heathcock, Ph.D.

2 nothing to do with that.

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

5 MR. MARGOLIS: Objection, vague.

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

8 BY MR. HASFORD:

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

13 MR. MARGOLIS: Objection, vague.
14 Lacks foundation.

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

1 C. Heathcock, Ph.D.

2 component such as is demonstrated here.

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

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

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

12 BY MR. HASFORD:

13 Q You can put that document aside.

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

17 A Yes, I do.

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

21 For the record, Heathcock Exhibit
22 10 is a copy of European Patent No.
23 0,306,984.

24 (Heathcock Exhibit 10 was marked.)

25

1 C. Heathcock, Ph.D.

2 BY MR. HASFORD:

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

6 A Fu, yes.

7 Q Or EP-984?

8 A Okay, yes.

9 Q Does the Fu reference teach the use of
10 bromfenac?

11 MR. MARGOLIS: Objection, vague.

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

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

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

19 MR. MARGOLIS: Objection, vague.

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

23 Q Does the Fu reference teach overcoming
24 chemical degradation?

25 MR. MARGOLIS: Objection. Vague.

1 C. Heathcock, Ph.D.

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

5 BY MR. HASFORD:

6 Q Please, take your time.

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

10 Q Does the Fu reference teach overcoming
11 chemical degradation?

12 A Overcoming chemical?

13 MR. MARGOLIS: Objection, vague.

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

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

23 MR. MARGOLIS: Objection, vague.

24 Calls for speculation. Compound.

25 THE WITNESS: Now, so the question

1 C. Heathcock, Ph.D.

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

4 BY MR. HASFORD:

5 Q I'll ask it again.

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

9 MR. MARGOLIS: Same objections.

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

13 BY MR. HASFORD:

14 Q Please look at the examples of the Fu
15 reference.

16 A Okay.

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

19 MR. MARGOLIS: Objection, vague.
20 Compound.

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

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C. Heathcock, Ph.D.

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?

1 C. Heathcock, Ph.D.

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

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

8 For the record, Heathcock Exhibit
9 11 is a copy of U.S. Patent No. 5,558,876.
10 (Heathcock Exhibit 11 was marked.)

11 BY MR. HASFORD:

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

14 A Yes, I do.

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

18 A Yes.

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

21 MR. MARGOLIS: Objection, vague.

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

24 BY MR. HASFORD:

25 Q What solution does the Desai '876

1 C. Heathcock, Ph.D.
2 patent provide to what you have called the
3 interaction, complexation or precipitation
4 problem?

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

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

13 Q Do you know what solution the Desai
14 '876 patent application provides to what you have
15 called the interaction, complexation or
16 precipitation problem?

17 MR. MARGOLIS: Objection. Lacks
18 foundation. Mischaracterizes his testimony.
19 Vague.

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

23 BY MR. HASFORD:

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

1 C. Heathcock, Ph.D.
2 the inventors of the patents in suit took when
3 formulating the claimed aqueous liquid
4 preparations of those patents; correct?

5 MR. MARGOLIS: Objection. Vague.
6 Lacks foundation.

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

12 BY MR. HASFORD:

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

15 MR. MARGOLIS: Objection, lacks
16 foundation. Vague.

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

20 BY MR. HASFORD:

21 Q You may put that document aside.
22 Take a look, if you would, at
23 Paragraph 50 in your responsive report. It's on
24 Page 15.

25 A Okay.

1 C. Heathcock, Ph.D.

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

5 A Yes.

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

9 For the record, Heathcock Exhibit
10 12 is a copy of the published PCT
11 application with international publication
12 number WO 94/15597.

13 (Heathcock Exhibit 12 was marked.)

14 BY MR. HASFORD:

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

18 A Yeah, Wong, yes. Okay. Yes.

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

22 A Yes.

23 Q Does the Wong reference teach the use
24 of bromfenac?

25 MR. MARGOLIS: Objection, vague.

1 C. Heathcock, Ph.D.

2 THE WITNESS: No, it does not use
3 bromfenac.

4 BY MR. HASFORD:

5 Q Does the Wong reference teach the use
6 of tyloxapol?

7 MR. MARGOLIS: Objection, vague.

8 THE WITNESS: No, it does not.

9 BY MR. HASFORD:

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

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

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

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

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C. Heathcock, Ph.D.

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

1 C. Heathcock, Ph.D.
2 a certain amount of degradation, it's
3 chemical -- a chemical reaction, they all
4 teach that. So this one, to that extent,
5 does teach that.

6 BY MR. HASFORD:

7 Q You may put this document aside.
8 You also cite in Paragraph 50 of your
9 responsive report, U.S. Patent No. 5,504,113; do
10 you see that?

11 A Yes.

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

15 For the record, Heathcock Exhibit
16 13 is a copy of U.S. Patent No. 5,504,113.
17 (Heathcock Exhibit 13 was marked.)

18 BY MR. HASFORD:

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

22 A Yes.

23 Q Does the Lucero patent teach the use
24 of bromfenac?

25 MR. MARGOLIS: Objection, vague.

1 C. Heathcock, Ph.D.

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

5 BY MR. HASFORD:

6 Q Does the Lucero patent teach the use
7 of tyloxapol?

8 MR. MARGOLIS: Objection, vague.

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

12 BY MR. HASFORD:

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

16 A All right.

17 Q Tell me when you're there.

18 A Yeah, I see it.

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

1 C. Heathcock, Ph.D.

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

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

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

10 MR. MARGOLIS: Objection, vague.
11 Lacks foundation.

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

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

19 MR. MARGOLIS: Same objections.

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

1 C. Heathcock, Ph.D.

2 BY MR. HASFORD:

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

8 MR. MARGOLIS: Objection, vague,
9 lacks foundation.

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

15 BY MR. HASFORD:

16 Q Does the Lucero patent teach
17 overcoming chemical degradation?

18 MR. MARGOLIS: Objection, vague.

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

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C. Heathcock, Ph.D.

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.

1 C. Heathcock, Ph.D.

2 (Heathcock Exhibit 14 was marked.)

3 BY MR. HASFORD:

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

7 A Yes.

8 Q Does the Bowman patent teach the use
9 of bromfenac?

10 MR. MARGOLIS: Objection, vague.

11 THE WITNESS: Doesn't seem to.

12 Diclofenac, cuprofen and flurbiprofen. I
13 don't think bromfenac is mentioned in this
14 patent.

15 BY MR. HASFORD:

16 Q Does the Bowman patent teach the use
17 of tyloxapol?

18 MR. MARGOLIS: Objection, vague.

19 THE WITNESS: No, not to my
20 knowledge.

21 BY MR. HASFORD:

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

24 A Okay.

25 Q Let me direct your attention to Lines

1 C. Heathcock, Ph.D.

2 47 through 61.

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

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

10 A Okay.

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

14 A Okay. I've read it.

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

19 MR. MARGOLIS: Objection, vague,
20 compound.

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

1 C. Heathcock, Ph.D.

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

5 MR. MARGOLIS: Objection, vague.
6 Compounds.

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

14 BY MR. HASFORD:

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

19 MR. MARGOLIS: Objection, vague,
20 compound.

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

25 Q The approach that the Bowman patent

1 C. Heathcock, Ph.D.
2 took is different from the approach that the
3 inventors of the patents in suit took when
4 formulating the claimed aqueous liquid
5 preparations of those patents; correct?

6 MR. MARGOLIS: Objection, vague.
7 Lacks foundation.

8 THE WITNESS: Yes.

9 BY MR. HASFORD:

10 Q Does the --

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

14 Q Does the Bowman patent teach
15 overcoming chemical degradation?

16 MR. MARGOLIS: Objection, vague.

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

24 BY MR. HASFORD:

25 Q You can put this document aside.

1 C. Heathcock, Ph.D.

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

7 A Yes. Okay.

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

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

19 Q Is pranlukast an NSAID?

20 A No.

21 Q Does pranlukast have a secondary
22 amine?

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

25 Q You might consider looking at Page 21

1 C. Heathcock, Ph.D.

2 of your rebuttal report.

3 A Okay. Yeah. No.

4 Q Does pranlukast have an oxo group?

5 A Well, yes, it does.

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

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

19 Q Does pranlukast have a tetrazole
20 group?

21 A Yes.

22 Q Does pranlukast have a chromenyl
23 group?

24 A A what?

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

1 C. Heathcock, Ph.D.

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

6 Q Does pranlukast have a phenylbutoxy
7 group?

8 A Yes, it does.

9 Q Does pranlukast have a bromo group?

10 A No, it does not.

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

13 A No, it does not.

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

18 A Yes.

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

22 For the record, Heathcock Exhibit
23 15 is a copy of Exhibit 2098 from IPR
24 2015-00903.

25 (Heathcock Exhibit 15 was marked.)

1 C. Heathcock, Ph.D.

2 BY MR. HASFORD:

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

5 A Yes.

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

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

11 Q Is Heathcock Exhibit 15 an internal
12 Senju document?

13 MR. MARGOLIS: Objection, lacks
14 foundation.

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

20 Q Does it appear that it was generated
21 from Senju?

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

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

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C. Heathcock, Ph.D.

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.)

1 C. Heathcock, Ph.D.

2 BY MR. HASFORD:

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

6 A Yes.

7 Q Does the Remington reference teach the
8 use of bromfenac?

9 MR. MARGOLIS: Objection, vague.

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

13 BY MR. HASFORD:

14 Q Does the Remington reference teach the
15 use of tyloxapol?

16 MR. MARGOLIS: Objection, vague.

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

20 BY MR. HASFORD:

21 Q You may put that aside.

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

1 C. Heathcock, Ph.D.

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

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

12 A Yes.

13 Q How does the fact that bromfenac --

14 MR. MARGOLIS: Objection,
15 mischaracterizes the document.

16 BY MR. HASFORD:

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

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

1 C. Heathcock, Ph.D.

2 THE WITNESS: Well, as I've
3 testified several times in preceding
4 questions, different chemicals, compounds
5 have different structures. And these
6 structures result in their having different
7 properties, both physical, such as melting
8 point and solubility, and chemical
9 reactivities with other reagents. And since
10 these compounds all have different
11 structures, they all have different chemical
12 properties because of their different
13 structures.

14 BY MR. HASFORD:

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

20 A Okay.

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

1 C. Heathcock, Ph.D.

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

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

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

1 C. Heathcock, Ph.D.

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

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

8 A Okay.

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

11 A Yes.

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

15 For the record, Heathcock Exhibit
16 17 is a copy of U.S. Patent No. 5,597,560.

17 (Heathcock Exhibit 17 was marked.)

18 BY MR. HASFORD:

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

22 A Yes.

23 Q Does the Bergamini patent teach the
24 use of bromfenac?

25 MR. MARGOLIS: Objection, vague.

1 C. Heathcock, Ph.D.

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

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

6 MR. MARGOLIS: Objection, vague.

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

11 BY MR. HASFORD:

12 Q You may --

13 A Not tyloxapol.

14 Q You may put this document aside.

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

18 A Yes.

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

22 For the record, Heathcock Exhibit
23 18 is a reference entitled "Isolation and
24 Identification of Bromfenac Glucoside from
25 Rat Bile," by Kirkman, et al.

1 C. Heathcock, Ph.D.

2 (Heathcock Exhibit 18 marked.)

3 BY MR. HASFORD:

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

7 A Yes.

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

11 A Yes.

12 Q Does the Kirkman reference teach the
13 use of tyloxapol?

14 MR. MARGOLIS: Objection, vague.

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

18 BY MR. HASFORD:

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

21 MR. MARGOLIS: Objection, vague.

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

24 BY MR. HASFORD:

25 Q Does the Kirkman reference teach any

1 C. Heathcock, Ph.D.

2 ophthalmic formulation?

3 MR. MARGOLIS: Objection, vague.

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

7 BY MR. HASFORD:

8 Q You may put the Kirkman reference
9 aside.

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

13 A Yes.

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

17 For the record, Heathcock Exhibit
18 19 is a document entitled, "Bromfenac Duract
19 Associated Hepatic Failure Requiring Liver
20 Transplantation," by Hunter, et al.

21 (Heathcock Exhibit 19 was marked.)

22 BY MR. HASFORD:

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

1 C. Heathcock, Ph.D.

2 A Yes.

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

6 A Yes, for very focused aspect of my
7 opinion, right.

8 Q Does the Hunter reference teach the
9 use of tyloxapol?

10 MR. MARGOLIS: Objection, vague.

11 THE WITNESS: No. This is -- it's
12 not a formulation paper, so it won't have
13 any surfactant or any antimicrobial. It is
14 simply -- it's a medical case report.

15 BY MR. HASFORD:

16 Q Does the Hunter reference teach the
17 use of benzalkonium chloride?

18 THE WITNESS: No --

19 MR. MARGOLIS: Objection, vague.

20 THE WITNESS: No. No. It would
21 be -- there would be no reason for it to.
22 This reference is cited simply to support my
23 statement that this class of acidic NSAIDs,
24 N-S-A-I-D-s, is commonly considered as a
25 group that has similar properties.

1 C. Heathcock, Ph.D.

2 BY MR. HASFORD:

3 Q Just to be clear, does the Hunter
4 reference teach the use of benzalkonium chloride?

5 MR. MARGOLIS: Objection, vague.

6 Asked and answered.

7 THE WITNESS: Have I quit beating
8 my wife?

9 BY MR. HASFORD:

10 Q I just want a clear record, Doctor.

11 A No, it does not teach that.

12 Q Thank you. Does the Hunter reference
13 teach any ophthalmic formulation?

14 A No.

15 MR. MARGOLIS: Objection, vague.

16 Q Does the Hunter reference teach that
17 bromfenac was associated with hepatic failure
18 requiring liver transplantation?

19 A Yes. That's the title, in fact, of
20 the paper.

21 Q You may put that aside.

22 Take a look, if you would, at the top
23 of Page 20 of your responsive report. Still in
24 Paragraph 59. You cite U.S. Patent No.
25 6,274,592. Do you see that?

1 C. Heathcock, Ph.D.

2 A Yes.

3 MR. HASFORD: I'm handing the
4 court reporter what I would ask be marked as
5 Heathcock Exhibit 20.

6 For the record, Heathcock Exhibit
7 20 is a copy of U.S. Patent No. 6,274,592.

8 (Heathcock Exhibit 20 was marked.)

9 BY MR. HASFORD:

10 Q If I refer to Patent No. 6,274,592 as
11 the '592 patent, will you understand what I mean?

12 A Yes.

13 Q Does the '592 patent teach the use of
14 tyloxapol?

15 MR. MARGOLIS: Objection, vague.

16 THE WITNESS: Let's see. No. It
17 doesn't. It does not involve tyloxapol.

18 BY MR. HASFORD:

19 Q Turn, if you would, to Column 13, and
20 let me direct your attention to the eight example
21 formulations in the '592 patent.

22 Do all of the eight formulations in
23 the '592 patent -- strike that and try again.

24 Do all of the eight example
25 formulations in the '592 patent contain

1 C. Heathcock, Ph.D.

2 pranopfen as their active ingredient?

3 A Yes.

4 Q Do any of the eight example
5 formulations in the '592 patent contain
6 bromfenac?

7 A No.

8 Q You can put the '592 patent aside.

9 MR. HASFORD: Is this a good time
10 for a break?

11 MR. MARGOLIS: Sure.

12 MR. McCLUTCHY: Going off the
13 record. The time is 2:33. This ends Disc
14 No. 3.

15 (Whereupon there was a brief
16 recess.)

17 MR. McCLUTCHY: We are back on the
18 record. The time is 2:52. This is Disc No.
19 4.

20 BY MR. HASFORD:

21 Q Doctor, if you would, please turn to
22 Paragraph 60 of your responsive report.

23 A Okay.

24 Q And let me direct your attention to
25 the third sentence. It begins "While

1 C. Heathcock, Ph.D.

2 Dr. Davies."

3 A Yes.

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

6 A Yes.

7 Q You note that Dr. Davies is correct
8 that bromfenac's structure is more closely
9 related to that of amfenac than to that of
10 diclofenac; do you see that?

11 A Yes.

12 Q Why is bromfenac's structure more
13 close of amfenac than that of diclofenac?

14 A Well, because it differs from amfenac
15 in only the -- having the bromine at the para
16 position at one of the benzene rings, whereas
17 diclofenac -- different from diclofenac in other
18 ways that are -- well, it differs more from
19 diclofenac because that second benzene ring is
20 attached in a different way. It's attached to
21 the nitrogen atom of the first ring rather than
22 through a carbonyl, bridge -- through a carbonyl
23 bridge to the first ring.

24 MR. HASFORD: C-a-r-b-o-n-y-l.

25 THE WITNESS: Chemists think in

1 C. Heathcock, Ph.D.

2 pictures, and I'm visualizing these pictures
3 and trying to describe them in words for
4 you.

5 Q How else does bromfenac differ from
6 diclofenac in structure?

7 MR. MARGOLIS: Objection, lacks
8 foundation.

9 THE WITNESS: Well, I think I just
10 described it. I mean, in the case of --
11 they're both the same in having the acetic
12 acid side chain. They're the same in having
13 the first benzene ring that has an amino
14 group attached to the number 2 carbon. They
15 differ in the ways I've already described.
16 They both have a second benzene ring, in the
17 case of bromfenac, that's attached to the
18 first ring by way of a carbonyl bridge. In
19 the case of diclofenac, the second benzene
20 ring, which has two chlorines attached to it
21 is attached to the amino nitrogen at the 2
22 position of the first ring.

23 BY MR. HASFORD:

24 Q How do bromfenac and diclofenac differ
25 in halogenation?

1 C. Heathcock, Ph.D.

2 MR. MARGOLIS: Objection, lacks
3 foundation.

4 THE WITNESS: Bromfenac has a
5 bromo group on one of its rings. Diclofenac
6 has two chlorine groups on one of its rings.

7 BY MR. HASFORD:

8 Q Are those halogen groups in different
9 positions on bromfenac and diclofenac?

10 A Yes. In bromfenac, they are -- the
11 halogen is at the -- well, different position
12 relative to what? If you say -- if you say that
13 the chlorine and the bromine are at the number 1
14 position of their respective rings, then -- well,
15 yeah, they're different positions because it's a
16 hard question to answer. I'm trying to think how
17 to give it an honest answer.

18 In the case of bromfenac, there's only
19 one bromine and it's at one position on the ring,
20 which is four carbons removed from a carbonyl
21 group. Diclofenac doesn't have a carbonyl group,
22 so I can't really compare them directly. But it
23 has two chlorines. And one of the chlorines is
24 at the 2 position relative to amino group, which
25 is bromfenac.

1 C. Heathcock, Ph.D.

2 So is that enough -- they're different
3 thank you. But it's hard to say how they differ.

4 MR. HASFORD: Let's go off the
5 record, please.

6 MR. McCLUTCHY: Going off the
7 record. The time is 2:56.

8 (Whereupon, there was some
9 technical difficulty.)

10 MR. McCLUTCHY: We are back on the
11 record. The time is 2:57.

12 THE WITNESS: Yeah, I'm still
13 struggling to try to know how to answer that
14 question. They differ. Telling you how
15 they differ in words is pretty difficult.

16 BY MR. HASFORD:

17 Q Turn, if you would, to Paragraph 64 of
18 your responsive report. It starts on Page 21 and
19 then continues on to Page 22.

20 A Okay.

21 Q Let me direct your attention to the
22 first full sentence at the top of Page 22. It
23 begins "While I agree."

24 A The sentence that begins "Dr. Davies
25 offers the opinion"? That one?

1 C. Heathcock, Ph.D.

2 Q Are you in Paragraph 64? Okay, so
3 that's the first sentence. I'm directing you to
4 the next sentence that begins "While"?

5 A "While I agree." Okay.

6 Q So could you read that to yourself and
7 let me know when you're ready.

8 Why do you agree that a person of
9 ordinary skill in the art could not have known
10 with certainty that bromfenac would form a
11 precipitate with benzalkonium chloride?

12 MR. MARGOLIS: Objection, to the
13 extent it mischaracterizes the document.

14 Q You may answer.

15 A Well, because the statements that I
16 quoted from Dr. Davies was that without carrying
17 out a test, you would not have been able to know
18 with certainty whether -- to have predicted
19 whether the bromfenac cation would form the
20 precipitate.

21 I agree that if you had not -- if
22 there had not been a test, if someone hadn't
23 reported that it forms a precipitate, you would
24 have had a good idea that it might based on
25 analogy to other similar situations, but to

1 C. Heathcock, Ph.D.
2 confirm that that strong suspicion was correct,
3 you would definitely have to carry out the
4 experiment. It's a simple experiment, but you'
5 nevertheless have to do it.

6 Q What would have needed to be done to
7 determine whether bromfenac would form a
8 precipitate with benzalkonium chloride?

9 MR. MARGOLIS: Objection, vague.
10 Incomplete hypothetical.

11 THE WITNESS: It would be a pretty
12 simple experiment where you would simply
13 measure out known quantities of the
14 benzalkonium chloride and the sodium salt of
15 bromfenac, for example, and mix these
16 quantities together with a certain amount of
17 solvent and observe whether there was
18 turbidity or cloudiness or not.

19 BY MR. HASFORD:

20 Q What testing would needed to have been
21 done -- strike that. Try again.

22 What testing would have needed to be
23 done to determine whether bromfenac would form a
24 precipitate with benzalkonium chloride?

25 MR. MARGOLIS: Objection, vague

1 C. Heathcock, Ph.D.

2 and incomplete hypothetical. Asked and
3 answered.

4 THE WITNESS: Yeah, that was
5 really the previous answer, was that --
6 answer to that question. You want me to
7 repeat it?

8 BY MR. HASFORD:

9 Q Yes, please.

10 A So what you would have to do is
11 measure out known quantities of sodium
12 bromfenate -- bromfenac and benzalkonium
13 chloride, and then mix these together with a
14 certain amount of water. And then make some sort
15 of measurement of whether the resulting mixture
16 you made was homogeneous or whether it had some
17 kind of turbidity. You would use some kind of --
18 turbid -- it's a hard word to say, but it's a
19 device that lets you measure the turbidity of a
20 suspension. Turbinometer I believe it's called.
21 Yeah, that's it.

22 Q Take a look, if you would, at
23 Paragraph 65 --

24 A Okay.

25 Q -- in response to number 4. And about

1 C. Heathcock, Ph.D.

2 two-thirds of the way down that paragraph,
3 there's a sentence that begins "Dr. Davies'
4 claim"?

5 A Yes.

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

8 A Okay.

9 Q What does it mean that bromfenac is
10 freely water-soluble?

11 MR. MARGOLIS: Objection. Vague.

12 THE WITNESS: Well, that's a
13 pretty -- that is a pretty vague statement.
14 I mean, I think to a chemist if you say
15 something is freely water-soluble, you would
16 understand that you're being told that
17 solubility is not a limitation to something.

18 And so, of course, depending on
19 what your intended use was, the actual
20 experimental solubility could be 5 grams per
21 liter or 50 grams per liter, but if you only
22 needed to have a real dilute solution for
23 your purpose, 5 grams per liter could be
24 said to be freely water-soluble, so it's a
25 vague statement that really needs to be

1 C. Heathcock, Ph.D.

2 evaluated in context of -- in the context
3 that it's used.

4 BY MR. HASFORD:

5 Q You note in your responsive report
6 that bromfenac is freely water-soluble; you see
7 that?

8 A Well, yes, seems to be -- seems to be
9 quite water-soluble.

10 Q And what is your basis for noting that
11 bromfenac is freely water-soluble? Actually, let
12 me strike that and try again.

13 Why is it your understanding that
14 bromfenac is freely water-soluble?

15 MR. MARGOLIS: Objection, vague.

16 THE WITNESS: Well, I looked up
17 the aqueous solubility of bromfenac and saw
18 that -- oh, I forget the number now, but it
19 was quite a high number, 50 grams per --
20 something like that. It was -- it seemed to
21 be very water-soluble.

22 Q Take a look, if you would, at
23 Paragraph 66 of your responsive report.

24 A Okay.

25 Q Read that paragraph to yourself,

1 C. Heathcock, Ph.D.

2 please, and let me know when you're ready.

3 A Okay.

4 Q Did you review any document showing
5 that Mr. Sawa actually conducted any test to
6 determine whether bromfenac, in fact, forms an
7 insoluble complex with benzalkonium chloride?

8 MR. MARGOLIS: Objection, vague.

9 THE WITNESS: I don't remember
10 right now. I saw a page from Mr. Sawa's
11 report in which he states that it does form
12 a cloudy solution. And to me that means he
13 carried out a test and observed that it
14 formed a cloudy suspension.

15 Q Did you actually review any document
16 showing that Mr. Sawa actually conducted a test
17 to determine whether bromfenac, in fact, forms an
18 insoluble complex with benzalkonium chloride?

19 MR. MARGOLIS: Objection, vague.

20 Asked and answered.

21 THE WITNESS: I'm going to have to
22 refresh my memory as to what's on this --
23 this is in this big fat document.

24 BY MR. HASFORD:

25 Q Please do.

1 C. Heathcock, Ph.D.

2 A And refresh my memory as to what
3 exactly -- Page 4 of Appendix A. Well, yeah, he
4 refers to his notebook, and I don't recall that I
5 looked at the actual notebook, but he says he
6 prepared and tested the stability and
7 formulations. And I don't recall that I looked
8 at the actual notebook page that -- where he
9 recorded the results of those experiments.

10 Q You can put this document aside.

11 Take a look, if you would, at
12 Paragraph 67 --

13 A Okay.

14 Q -- of your responsive report. You
15 cite U.S. Patent No. 5,603,929; do you see that?

16 A Uh-huh, yes, I do.

17 MR. HASFORD: I'm handing the
18 court reporter what I would ask to be marked
19 as Heathcock Exhibit 21.

20 For the record, Heathcock Exhibit
21 21 is a copy of U.S. Patent No. 5,603,929.

22 (Heathcock Exhibit 21 was marked.)

23 BY MR. HASFORD:

24 Q If I refer to Heathcock Exhibit 21 as
25 the Desai '929 patent, will you understand what I

1 C. Heathcock, Ph.D.

2 mean?

3 A Yes.

4 Q Does the Desai '929 patent teach the
5 use of tyloxapol in any specific example
6 formulation?

7 MR. MARGOLIS: Objection, vague.

8 THE WITNESS: No. This one does
9 not use tyloxapol.

10 BY MR. HASFORD:

11 Q What solution does the Desai '929
12 patent provide to what you have called the
13 interaction, complexation or precipitation
14 problem?

15 MR. MARGOLIS: Objection. Lacks
16 foundation. Mischaracterizes his testimony.
17 Vague.

18 THE WITNESS: Yeah, they have used
19 the technique of adding boric acid to
20 preserve -- to enhance the storage time of
21 their formulations.

22 BY MR. HASFORD:

23 Q Take a look at Example 1, if you
24 would. It's on Column 4.

25 A All right.

1 C. Heathcock, Ph.D.

2 Q The formulation of Example 1 of the
3 Desai '929 patent contains polyquad; do you see
4 that?

5 A Yes.

6 Q Is polyquad different from
7 benzalkonium chloride?

8 A Yes, it's a polymeric material
9 somewhat like the one that we talked about
10 earlier before lunch, in which there are
11 quarternary ammonium ions strung out along the
12 backbone of the polymer.

13 Q The approach that the Desai '929
14 patent took is different from the approach that
15 the inventors of the patents in suit took when
16 formulating the claimed aqueous liquid
17 preparations of those patents; correct?

18 A Yes.

19 MR. MARGOLIS: Objection, vague.
20 Lacks foundation.

21 THE WITNESS: Yes, that's correct.

22 BY MR. HASFORD:

23 Q Did the formulations disclosed in the
24 Desai '929 patent have any stability problems?

25 MR. MARGOLIS: Objection, vague,

1 C. Heathcock, Ph.D.

2 lacks foundation.

3 THE WITNESS: Not that you can see
4 from the patent. Whether they turned up as
5 they began to use them on a large scale, I
6 don't know.

7 BY MR. HASFORD:

8 Q You may put that document aside.

9 Take a look back, if you would, at
10 Paragraph 67 in your responsive report on Page
11 23.

12 A Okay.

13 Q And the third sentence begins "Because
14 the two compounds;" do you see that?

15 A Yes, I do.

16 Q Read that sentence to yourself and let
17 me know when you're ready.

18 A Okay. I've got it.

19 Q It is your opinion that tyloxapol and
20 polysorbate 80 do not significantly differ in the
21 chemical and physical characteristics that
22 determine how they function as surfactants in
23 formulations, correct?

24 MR. MARGOLIS: Objection, vague.

25 Mischaracterizes the document.

1 C. Heathcock, Ph.D.

2 THE WITNESS: Well, yeah. They
3 certainly differ. I don't -- they're both
4 surfactants. They're both amphiphilic
5 molecules. They have the property -- so
6 they're -- I don't consider them to be
7 significantly different in those two
8 descriptors.

9 They do differ in certain ways,
10 certainly. They -- tyloxapol, as I've
11 already described, has a feature of being
12 somewhat three-dimensional. And it has
13 seven of these amphiphilic molecules strung
14 together, whereas polysorbate 80 is a single
15 long amphiphilic chain.

16 And so tyloxapol has the ability
17 to function as a single molecule as a
18 solubilizing agent better than polysorbate
19 80 does. But they both are surfactants. In
20 this case, I think it's clear why tyloxapol
21 would work better than polysorbate 80, but
22 they both would work to some degree.

23 Q Is it your opinion that tyloxapol and
24 polysorbate 80 do significantly differ in the
25 chemical and physical characteristics that

1 C. Heathcock, Ph.D.

2 determine how they function as surfactants in
3 formulations?

4 MR. MARGOLIS: Objection, vague.

5 THE WITNESS: No. I think -- you
6 know, this is a kind of a qualitative
7 statement. To the extent that they're both
8 surfactants, they can both associate with
9 hydrophobic substances and help to
10 solubilize those substances. They both can
11 form this three-dimensional micelle
12 structure. I would consider -- they don't
13 significantly differ. If one of them
14 couldn't form a micelle, for example, or --
15 then I would say that would be a significant
16 difference. But, yeah, so I'll stick with
17 saying they don't significantly differ, but
18 they will have different properties.

19 BY MR. HASFORD:

20 Q Just to be clear, you wrote in your
21 report that tyloxapol and polysorbate 80 do not
22 significantly differ in the chemical and physical
23 characteristics that determine how they function
24 as surfactants in formulations; correct?

25 A I wrote that; that's right.

1 C. Heathcock, Ph.D.

2 Q Okay. Take a look, if you would, at
3 the Paragraph 68 in your rebuttal report. Let me
4 direct your attention to the second sentence that
5 begins "Although non-ionic" at the bottom of Page
6 23.

7 A Third sentence, okay.

8 Q Sorry, third sentence. Please read
9 that and let me know when you're ready.

10 A All right. Got it.

11 Q Why is it your opinion that non-ionic
12 surfactants all differ somewhat in their chemical
13 compositions in their three-dimensional
14 structures?

15 MR. MARGOLIS: Objection.

16 Mischaracterizes the document.

17 THE WITNESS: So the question was
18 why do I say they may differ somewhat in
19 their chemical structure?

20 BY MR. HASFORD:

21 Q Yeah. Why is it your opinion that
22 non-ionic surfactants all differ in their
23 chemical compositions in three-dimensional
24 structures?

25 MR. MARGOLIS: Same objection.

1 C. Heathcock, Ph.D.

2 THE WITNESS: Well, because
3 they're different molecules. Again, as I've
4 said repeatedly, some are single chains of
5 amphiphilic substances, and tyloxapol is an
6 assembly of those chains, and so it has,
7 rather than an amphiphilic end, it has an
8 amphiphilic edge and it has a hydrophobic
9 edge.

10 BY MR. HASFORD:

11 Q Take a look now at Paragraph 69 in
12 your responsive report.

13 A All right.

14 Q And let me direct your attention to
15 the third sentence. Read that to yourself and
16 let me know when you're ready.

17 A Okay.

18 Q I'd like to break this down a bit with
19 you starting at the end and working backward, if
20 that's okay.

21 Given the disclosures in the prior art
22 and the presence of polysorbate 80 in prior
23 formulations containing bromfenac and
24 benzalkonium chloride, why would a person of
25 ordinary skill in the art have wanted to

1 C. Heathcock, Ph.D.
2 substitute octoxynol 40 for polysorbate 80 in
3 these formulations?

4 MR. MARGOLIS: Objection, lacks
5 foundation.

6 THE WITNESS: Well, you know,
7 there was this -- there was this -- it's
8 just an experiment. There was a problem.
9 There was a problem with these -- with these
10 complexes or these salt ion pairs separating
11 from solution causing cloudy mixtures and
12 turbid mixtures, and although that problem
13 had not been identified with bromfenac,
14 because it's enough like the other NSAIDs, I
15 think a person would be concerned that it
16 could be occurring or it could occur over
17 time. And it would be a simple enough thing
18 to do to substitute some of these other
19 surfactants, especially tyloxapol and feel
20 that you would have a better chance that
21 this turbidity problem would not appear.

22 BY MR. HASFORD:

23 Q Given the disclosures in the prior art
24 and the presence of polysorbate 80 in prior
25 formulations containing bromfenac and

1 C. Heathcock, Ph.D.
2 benzalkonium chloride, why would a person of
3 ordinary skill in the art have wanted to
4 substitute octoxynol 9 for polysorbate 80 in
5 those formulations?

6 MR. MARGOLIS: Objection. Lacks
7 foundation. Incomplete hypothetical.

8 THE WITNESS: Well, again, because
9 it was -- it's a different surfactant that
10 has the potential to be -- to have a better
11 outcome in preventing this turbidity
12 problem.

13 BY MR. HASFORD:

14 Q Given the disclosures in the prior art
15 and the presence of polysorbate 80 in prior
16 formulations containing bromfenac and
17 benzalkonium chloride, why would a person of
18 ordinary skill in the art have wanted to
19 substitute octoxynol 40 for polysorbate 80 in
20 those formulations?

21 MR. MARGOLIS: Objection, lacks
22 foundation. Incomplete hypothetical.

23 BY MR. HASFORD:

24 Q You may answer.

25 A Yeah. I think the same basic answer.

1 C. Heathcock, Ph.D.

2 I mean, trying these different -- you know,
3 you've got these different alternatives.
4 Formulations are pretty simple. You've got
5 bromfenac and BAC or diclofenac and BAC. You've
6 got all these three -- these three pieces, and
7 making various combinations of these three pieces
8 with -- you know, using these three surfactants,
9 which seem to be in -- these four surfactants,
10 which seem to be in pretty widespread use would
11 have been a simple thing. It's routine
12 experimentation.

13 I think especially with the case of
14 tyloxapol, you have -- you would have a better
15 idea that this is going to stabilize your ion
16 pair against separating from solution than any of
17 the others, but even the octoxynol 9 and 40
18 had -- had been successful in other cases.

19 Q Let me -- I want to direct your
20 attention specifically to octoxynol 40.

21 Given the disclosures in the prior art
22 and the presence of polysorbate 80 in prior
23 formulations containing bromfenac and
24 benzalkonium chloride, why would a person of
25 ordinary skill in the art have wanted to

1 C. Heathcock, Ph.D.

2 substitute octoxynol 40 for polysorbate 80 in
3 those formulations?

4 MR. MARGOLIS: Objection. Lacks
5 foundation. Incomplete hypothetical.
6 Vague. Asked and answered.

7 MR. HASFORD: You may answer.

8 A Well, I think I've kind of answered
9 that. Octoxynol 40 had been used successfully in
10 other formulations, and it would be a simple
11 matter to experiment with it and try it out in
12 this one.

13 BY MR. HASFORD:

14 Q Take a look, if you would, at the next
15 sentence in Paragraph 69 of your rebuttal report.
16 It's actually the last sentence in the paragraph.

17 It says "Indeed, given the prior art
18 disclosures that non-ionic surfactants could
19 resolve the NSAID BAC complexation issue, CEG 493
20 at 231 to 35, a person of ordinary skill in the
21 art would be motivated to seek out and utilize
22 other non-ionic surfactants in the formulation."

23 Given --

24 A Yeah, yeah.

25 Q Given the prior art disclosures, what

1 C. Heathcock, Ph.D.

2 other non-ionic surfactants would a person of
3 ordinary skill in the art have been motivated to
4 use in a formulation containing bromfenac and
5 benzalkonium chloride?

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

8 MR. HASFORD: You may answer.

9 THE WITNESS: Well, I think that I
10 have indicated that you would probably focus
11 first on the surfactants of this class that
12 were already approved by the FDA for use in
13 ophthalmic preparations, and there weren't
14 very many, so you would be probably
15 motivated to begin with those compounds --
16 with those surfactants.

17 BY MR. HASFORD:

18 Q I want to focus in on what are the
19 other non-ionic surfactants you're referring to.
20 So given the prior art --

21 A I think that would be tyloxapol and
22 octoxynol 40.

23 Q Okay. Were you referring to any
24 others?

25 A No. I believe those were the only two

1 C. Heathcock, Ph.D.

2 that I found on the FDA list of approved
3 surfactants for ophthalmic formulations.

4 Q Take a look, if you would, at
5 Paragraph 70. Let me direct your attention to
6 the third sentence. It starts "As an initial
7 matter."

8 A Yes, okay.

9 Q Read that to yourself and let me know
10 when you're ready.

11 A Okay.

12 Q What are some of the structural
13 differences between polysorbate 80 and tyloxapol?

14 A Well, polysorbate 80 is a single long
15 amphiphilic chain structure. Tyloxapol is
16 assembly in which seven chain amphiphilic
17 molecules have been linked together by methylene
18 bridges. That's the main structural difference.
19 The monomeric pieces are different as well. The
20 hydrophobic part of polysorbate 80 is different
21 structurally from the hydrophobic part of the
22 tyloxapol monomer. And likewise, the hydrophilic
23 chains are not the same, but so those are the
24 ways they differ.

25 Q Take a look, if you would, at the

1 C. Heathcock, Ph.D.

2 bottom sentence on Page 24 in Paragraph 70.

3 A Uh-huh.

4 Q It starts "Although a person of
5 ordinary skill in the art."

6 A Okay.

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

9 A All right.

10 Q Why would a person of ordinary skill
11 in the art not expect polysorbate 80 and
12 tyloxapol to behave in the same way in a given
13 formulation containing bromfenac or otherwise?

14 MR. MARGOLIS: Objection, to the
15 extent it mischaracterizes the document.

16 BY MR. HASFORD:

17 Q You may answer.

18 A Yeah. So I think it's correct that in
19 the same general way that they would both be
20 expected to have a solubilizing effect on
21 hydrophobic substances. I think a person of
22 ordinary skill looking at the two structures and
23 the nature of the hydrophobic substance that
24 needs to be solubilized would actually come to
25 the conclusion that tyloxapol -- although it

1 C. Heathcock, Ph.D.

2 might work in generally the same way would
3 actually work better because it has a sort of
4 hydrophobic sheet. Whereas polysorbate is just a
5 long amphiphilic rope. But they would both
6 function roughly in the same general mechanistic
7 way, although, you see, tyloxapol could
8 associate -- just one molecule of tyloxapol could
9 associate with one BAC ion pair. And do some
10 good making it soluble, where it might take seven
11 molecules of the polysorb to do the same thing.

12 Q Take a look, if you would, at
13 Paragraph 71 and let me direct your attention to
14 the third sentence.

15 A Okay.

16 Q Read that sentence to yourself and let
17 me know when you're ready.

18 A All right. I've got it.

19 Q In what respects do the polar head
20 groups of polysorbate 80 and tyloxapol differ?

21 A I read the wrong sentence.

22 Q Okay. Yeah. It's Paragraph 71.

23 A Okay. Let's see.

24 Q So let me ask the question again just
25 so it's clear.

1 C. Heathcock, Ph.D.

2 In what respects do the polar head
3 groups of polysorbate 80 and tyloxapol differ?

4 A Well, they're both hydrophilic. They
5 both have carbons and oxygens. But if you look
6 at the -- at them at the structural level, you'll
7 see that they're made of monomeric units that are
8 not the same. And of course polysorbate 80,
9 hydrophilic group head is longer.

10 Q Take a look, if you would, at
11 Paragraph 73, and let me direct your attention to
12 the first sentence. Read that to yourself,
13 please and let me know when you're ready.

14 A I've read it.

15 Q What important structural interactions
16 occur when surfactant molecules assemble into
17 micelles?

18 MR. MARGOLIS: Objection, vague.

19 THE WITNESS: When an assembly of
20 surfactant molecules form a micelle
21 structure, they pack together in such a way
22 that they make a kind of a ball. And if you
23 look at the surface of the ball, you'll find
24 all the hydrophilic parts of those molecules
25 at the surface, and then if you would cut

1 C. Heathcock, Ph.D.

2 into the ball, hypothetically cut into the
3 ball and look inside, all the hydrophobic
4 parts would be inside the ball.

5 So imagine that the micelle is
6 like a tennis ball, and the fuzzy part of
7 the tennis ball outside is all the head
8 groups. In this case, in these cases, it's
9 kind of a real fuzzy tennis ball because
10 it's got long chains sticking out from the
11 surface, and then inside is all this oil.
12 It's the hydrocarbon parts of the
13 surfactants. And of course, these two
14 different -- I think you're asking me how do
15 two different surfactants -- well, you only
16 asked me how they pack together. So I think
17 I answered your question.

18 Q What molecular changes occur when a
19 micelle has incorporated a solute?

20 MR. MARGOLIS: Objection, lacks
21 foundation.

22 THE WITNESS: Well, the purpose of
23 this paragraph was to show that a
24 calculation of what shape a surfactant would
25 have in the gas phase is very -- is not

1 C. Heathcock, Ph.D.

2 really going to give you any information
3 about what shape it has when it's in this
4 micelle structure, right, because in the
5 micelle, let's say you calculate -- say
6 Dr. Davies calculates the structure of, you
7 know, polysorbate or octoxynol, and it's a
8 long stick sticking out, you know, with
9 little bumps on it, which are the H's.

10 But when a bunch of these things
11 clump together, it's not a bunch of long
12 sticks anymore. A bunch of long sticks
13 don't fit.

14 So then it's got to coil up in
15 some totally different way. And he
16 rightfully responded in his little sort of
17 reply report that you can't calculate that
18 way. I agree, you can't calculate that way.
19 So you can't know really how two different
20 surfactants are going to fit together in a
21 micelle from how they look in the gas phase.
22 That's all I meant.

23 And of course when you -- if the
24 micelle absorbs something that's hydrophobic
25 like, let's say the benzalkonium salt with a

1 C. Heathcock, Ph.D.

2 bromfenac anion, if it absorbs that little
3 hydrophobic unit, then all those chains are
4 going to be different because they're not
5 going to be avoiding each other or nestling
6 up to each other. They're going to be
7 wrapped around the ball in some way.

8 So the point is, you know, just
9 giving the picture of what it looks like in
10 the gas phase is not very useful. It
11 doesn't really -- yeah, it might know that
12 polysorbate and tyloxapol, they have this
13 shape. But when you pack together, they
14 might look a lot more alike.

15 BY MR. HASFORD:

16 Q What molecular changes occur when a
17 micelle is incorporated in a solute?

18 A I think I just answered that. I don't
19 want to give that speech again.

20 Q No, I'm looking for just a general
21 answer from you. Let me ask it again.

22 What -- generally speaking, what
23 molecular changes occur when a micelle is
24 incorporated in a solute?

25 MR. MARGOLIS: Objection, vague

1 C. Heathcock, Ph.D.

2 and asked and answered.

3 THE WITNESS: When a micelle
4 incorporates a solute, the nature of the
5 packing of the hydrophobic parts inside will
6 change. It might also cause the micelle to
7 loosen its structure so that additional
8 surfactant molecules can now fit in.

9 BY MR. HASFORD:

10 Q Do the molecular changes that occur
11 when a micelle has incorporated a solute depend
12 on the nature of the micelle?

13 MR. MARGOLIS: Objection, vague.

14 DR. MALIK: Incomplete
15 hypothetical.

16 THE WITNESS: I'm sure they do.

17 MR. MARGOLIS: Incomplete
18 hypothetical.

19 Q Do the molecular changes that occur
20 when a micelle has incorporated a solute depend
21 on the nature of the solute?

22 MR. MARGOLIS: Objection, vague.
23 Compound.

24 DR. MALIK: Incomplete
25 hypothetical.

1 C. Heathcock, Ph.D.

2 BY MR. HASFORD:

3 Q You may answer.

4 A I'm sure they would, yes.

5 Q Take a look, if you would, at
6 Paragraph 74 in your rebuttal report. And you
7 cite the Schott reference in that paragraph; do
8 you see that?

9 A Yes.

10 MR. HASFORD: I'm handing the
11 court reporter what I would ask to be marked
12 as Heathcock Exhibit 22.

13 For the record, Heathcock Exhibit
14 22 is a document entitled "Comparing the
15 Surface Chemical Properties and the Effect
16 of Salts on the Cloud Point of a
17 Conventional Non-ionic Surfactant, octoxynol
18 9 (Triton X 100) and of its oligomer,
19 tyloxapol, triton," and -- I'll tell you
20 what. Let's just -- I'll make it easier for
21 you. For the record, Heathcock Exhibit 22
22 is a copy of the Schott reference.

23 (Heathcock Exhibit 22 was marked.)

24 BY MR. HASFORD:

25 Q If I refer to Heathcock Exhibit 22 as

1 C. Heathcock, Ph.D.

2 the Schott reference, will you understand what I
3 mean?

4 A Yes, certainly.

5 Q You were relying on the Schott
6 reference in connection with your opinions in
7 this case; correct.

8 A Yes.

9 Q Please look at the introduction
10 section of the Schott reference on the first
11 page.

12 A Okay.

13 Q And let me direct your attention to
14 the first sentence of the second paragraph.

15 A Okay.

16 Q It's states "Tyloxapol is essentially
17 an oligomer of octoxynol 9;" do you see that?

18 A Yes.

19 Q Based on the Schott reference, would a
20 person of ordinary skill in the art understand
21 that tyloxapol is an exact oligomer of octoxynol
22 9?

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

25 THE WITNESS: Oligomer is a term

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C. Heathcock, Ph.D.

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

1 C. Heathcock, Ph.D.

2 Octoxynol 9," the Schott reference states "The
3 molecular weight of octoxynol 9 is approximately
4 equal to 625;" do you see that?

5 A Yes.

6 Q Please turn the page. Under the
7 "Chemical Structure for Tyloxapol," the Schott
8 reference states that "The molecular weight of
9 tyloxapol is 4,500;" do you see that?

10 A Yes.

11 Q Let me direct your attention to the
12 "Chemical Structure for Tyloxapol."

13 Does tyloxapol contain a CH₂ methylene
14 bridge adjacent -- let me strike that and try
15 again.

16 Does tyloxapol contain a CH₂ methylene
17 bridge attached to the adjacent phenyl rings?

18 A Tyloxapol contains six CH₂ groups that
19 bridge phenyl rings.

20 Q Take a look back, if you would, at the
21 chemical structure for octoxynol 9.

22 A Okay.

23 Q Does octoxynol 9 contain a CH₂
24 methylene bridge attached to the phenyl ring?

25 A No. This is a monomeric substance

1 C. Heathcock, Ph.D.

2 that does not have any CH₂ joined to other
3 molecules.

4 Q You can put that document aside.

5 Take a look, if you would, at
6 Paragraph 77 of your responsive report.

7 A Okay.

8 Q On Page 27. Let me direct your
9 attention to the bottom of the page to the
10 statement beginning "However, these surfactants."

11 A Uh-huh.

12 Q Read that to yourself and let me know
13 when you're ready.

14 A Okay.

15 Q Why is it your opinion that tyloxapol,
16 octoxynol 9, octoxynol 40 and polysorbate 80
17 differ considerably in molecular weight?

18 MR. MARGOLIS: Objection, vague.

19 THE WITNESS: Well, it's not an
20 opinion. It's a fact. I mean, you look
21 them up and they range from -- I think you
22 showed me two of them. 625 to 4,500. I
23 forget where polysorb -- I forget where the
24 other one is. Yeah.

25

1 C. Heathcock, Ph.D.

2 BY MR. HASFORD:

3 Q Take a look, if you would, at the next
4 sentence. It starts "Tyloxapol's CMC."

5 A Uh-huh.

6 Q Read that to yourself, and let me know
7 when you're ready.

8 A Okay.

9 Q Even when expressed in grams per
10 liter, is the CMC of Octoxynol 9 between two to
11 four times greater than the CMC of tyloxapol?

12 MR. MARGOLIS: Objection. Vague.

13 THE WITNESS: I didn't understand
14 the question.

15 BY MR. HASFORD:

16 Q Let me ask it again.

17 Even when expressed in grams per
18 liter, is the CMC of octoxynol 9 between two to
19 four times that -- strike that.

20 Even when expressed in grams per
21 liter, is the CMC of octoxynol 9 between two to
22 four times that of tyloxapol?

23 MR. MARGOLIS: Objection, vague.

24 THE WITNESS: Okay, yes.

25

1 C. Heathcock, Ph.D.

2 BY MR. HASFORD:

3 Q Even when expressed in grams per
4 liter, is the CMC of tyloxapol three to six times
5 that of polysorbate 80?

6 MR. MARGOLIS: Objection, vague.

7 THE WITNESS: Yeah, that seems to
8 be correct.

9 Q Did you calculate the CMC of octoxynol
10 40 in grams per liter?

11 A I did, but I don't remember what it
12 is.

13 Q Take a look, if you would, at
14 Paragraph 78 in your responsive report.

15 A Okay.

16 Q In Paragraph 78, you cite U.S. Patent
17 No. 5,474,760; do you see that?

18 A Yes.

19 MR. HASFORD: I'm handing the
20 court reporter what I would ask to be marked
21 as Heathcock Exhibit 23.

22 For the record, Heathcock Exhibit
23 23 is a copy of U.S. Patent No. 5,474,760.

24 (Heathcock Exhibit 23 was marked.)

25

1 C. Heathcock, Ph.D.

2 BY MR. HASFORD:

3 Q If I refer to Heathcock Exhibit 23 as
4 the '760 patent or the Ghio patent, will you
5 understand what I mean?

6 A Yes.

7 Q Does the Ghio patent teach bromfenac?

8 MR. MARGOLIS: Objection, vague.

9 THE WITNESS: No, bromfenac is not
10 involved in this.

11 BY MR. HASFORD:

12 Q Does the Ghio patent teach any
13 non-steroidal anti-inflammatory drug?

14 MR. MARGOLIS: Objection, vague.

15 THE WITNESS: No, it's not about
16 NSAIDs.

17 BY MR. HASFORD:

18 Q Does the Ghio patent teach
19 benzalkonium chloride?

20 MR. MARGOLIS: Objection, vague.

21 THE WITNESS: No, it's not -- does
22 not.

23 BY MR. HASFORD:

24 Q Does the Ghio patent teach any
25 ophthalmic formulations?

1 C. Heathcock, Ph.D.

2 MR. MARGOLIS: Objection, vague.

3 THE WITNESS: No, it's not about
4 ophthalmic formulations.

5 BY MR. HASFORD:

6 Q The approach that the Ghio patent took
7 is different from the approach that the inventors
8 of the patents in suit took when formulating the
9 claimed aqueous liquid preparations of those
10 patents; correct?

11 MR. MARGOLIS: Objection, lacks
12 foundation. Vague.

13 THE WITNESS: This is a hard
14 question to answer because it's kind of like
15 apples and oranges. You know, these are
16 different kinds of -- these are products
17 that are intended for totally different
18 kinds of applications. And so --

19 BY MR. HASFORD:

20 Q Take a look, if you would, at Column 2
21 of the Ghio patent. Let me direct your attention
22 to lines 38 through 41.

23 A Uh-huh.

24 Q Read that sentence beginning "As can
25 be explained below," and let me know when you're

1 C. Heathcock, Ph.D.

2 ready.

3 A Okay. I've read it.

4 Q Does the Ghio patent describe how
5 alkyl aryl polyether alcohol polymers are useful
6 as anti-oxidants in blocking oxidant reactions
7 and biologic injury from partially reduced O2
8 species?

9 MR. MARGOLIS: Objection, vague.

10 THE WITNESS: Yeah, that's what it
11 says.

12 BY MR. HASFORD:

13 Q Are partially reduced O2 species
14 different from O2 itself?

15 A Well, yes, but when O2 oxidizes
16 something, it produces products which are then
17 partially reduced O2 species, so...

18 Q How are partially reduced O2 species
19 different from O2 itself?

20 A Well, they're more reactive typically
21 because they -- they are typically things that
22 have an OO single bond. Often they're a free
23 radical. An OH dot or an OOH dot. So those
24 would all be examples of partially reduced
25 oxygen.

1 C. Heathcock, Ph.D.

2 And partially reduced oxygen -- it's
3 not in the air we breathe, but if the oxygen
4 begins to oxidize something, then the products of
5 that reaction would be partially reduced O2
6 species.

7 Q Chemically, how do partially reduced
8 O2 species differ from O2 itself?

9 MR. MARGOLIS: Objection, lacks
10 foundation. Vague.

11 THE WITNESS: Well, oxygen is a
12 molecule that has a certain stability
13 associated with it, so it's not reactive --
14 well, you just asked for a 90-minute
15 lecture.

16 BY MR. HASFORD:

17 Q You can give me the short version.
18 Let me ask it again just so it's clear.

19 Chemically, how do partially reduced
20 O2 species differ from O2 itself?

21 THE WITNESS: Well, okay, so I've
22 already described --

23 MR. MARGOLIS: Objection, lacks
24 foundation. Vague. Asked and answered.

25 THE WITNESS: Okay. I've already

1 C. Heathcock, Ph.D.

2 told you that the term "partially reduced O₂
3 species" is a blanket term that can describe
4 a number of different products when oxygen
5 begins to be reactive with something. And,
6 for example, when oxygen -- when oxygen --
7 if oxygen takes a hydrogen from a certain
8 position, then that position could become a
9 free radical. It would be like an R dot.
10 And the oxygen would then have the hydrogen
11 and its electron, so it would be HOO dot.

12 Now, that's a partially reduced
13 oxygen species. And it's like you've cocked
14 a gun. It's now more reactive than oxygen
15 itself because it doesn't want to stay
16 around that way with that free electron. So
17 it's going to find something to react with
18 pretty fast. So it's different chemically,
19 and it's got generally higher reactivity
20 than the oxygen molecule from which it
21 originated as.

22 BY MR. HASFORD:

23 Q Structurally, how do partially reduced
24 O₂ species differ from O₂ itself?

25 MR. MARGOLIS: Objection, vague,

1 C. Heathcock, Ph.D.

2 lacks foundation.

3 BY MR. HASFORD:

4 Q You may answer.

5 A Do I have to answer?

6 MR. MARGOLIS: Asked and answered.

7 Thank you.

8 THE WITNESS: Well, it differs
9 structurally in that it has a single bond
10 between the two oxygen rather than a double
11 bond. It has -- generally many of the
12 partially reduced oxygen species have a
13 single electron, whereas oxygen itself has
14 electron pairs. But there can be partially
15 reduced oxygen species that don't have a
16 free radical, like hydrogen peroxide, H₂O₂
17 is a partially reduced oxygen. And so they
18 can differ in a number of different ways
19 depending on exactly what partially reduced
20 oxygen entity it is.

21 BY MR. HASFORD:

22 Q You may put this document aside.

23 You also cite U.S. Patent No.

24 6,165,445; do you see that?

25 A Yes.

1 C. Heathcock, Ph.D.

2 MR. HASFORD: I'm handing the
3 court reporter what I would ask to be marked
4 as Heathcock Exhibit 24.

5 For the record, Heathcock Exhibit
6 24 is a copy of U.S. Patent No. 6,165,445.

7 (Heathcock Exhibit 24 was marked.)

8 BY MR. HASFORD:

9 Q If I refer to U.S. Patent No.
10 6,165,445 as the '445 patent or the Kennedy
11 patent, will you understand what I mean?

12 A Yes, right.

13 Q Does the Kennedy patent teach
14 bromfenac?

15 MR. MARGOLIS: Objection, vague.

16 THE WITNESS: No. Bromfenac is
17 not in this patent.

18 Q Does the Kennedy patent teach any
19 NSAID?

20 MR. MARGOLIS: Objection, vague.

21 THE WITNESS: No.

22 BY MR. HASFORD:

23 Q Does the Kennedy patent teach
24 benzalkonium chloride?

25 MR. MARGOLIS: Objection, vague.

1 C. Heathcock, Ph.D.

2 THE WITNESS: No, it doesn't.

3 BY MR. HASFORD:

4 Q Does the Kennedy patent disclose any
5 ophthalmic formulations?

6 A No, it does not.

7 Q The approach that the Kennedy patent
8 took is different from the approach that the
9 inventors of the patents in suit took when
10 formulating the claimed aqueous liquid
11 preparations of those patents; correct?

12 MR. MARGOLIS: Objection, lacks
13 foundation. Vague.

14 THE WITNESS: Yeah. Again, it's
15 certainly different because these are
16 totally different kinds of products. So...

17 BY MR. HASFORD:

18 Q Take a look, if you would, at Column
19 7. Let me direct your attention to Lines 52
20 through 54.

21 A Okay.

22 Q The Kennedy patent states that "It was
23 a further object of the Kennedy patent's
24 invention to provide a method to inhibit oxidant
25 chemical reactions caused by partially reduced O₂

1 C. Heathcock, Ph.D.

2 species;" correct?

3 A Yes, I see that.

4 Q You can put that document aside.

5 MR. HASFORD: And let's take a
6 break.

7 MR. McCLUTCHY: Going off the
8 record. The time is 3:48 p.m.

9 (Whereupon there was a brief
10 recess.)

11 MR. McCLUTCHY: We are back on the
12 record. The time is 4:01.

13 BY MR. HASFORD:

14 Q Doctor, please look back again at
15 Paragraph 78 of your responsive report.

16 A Okay.

17 Q You rely on the Ghio reference that is
18 entitled "Tyloxapol Inhibits NF Kappa B and
19 Cytokine Release Scavenges HOCL and Reduces
20 Viscosity of Cystic Fibrosis Sputum;" do you see
21 that?

22 A Yes.

23 MR. HASFORD: For the record, I am
24 handing the court reporter what I would ask
25 be marked as Heathcock Exhibit 25.

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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.

1 C. Heathcock, Ph.D.

2 BY MR. HASFORD:

3 Q Does the Ghio reference teach using
4 benzalkonium chloride?

5 MR. MARGOLIS: Objection, vague.

6 THE WITNESS: No, that would not
7 be included in the scope of this article.

8 BY MR. HASFORD:

9 Q Does the Ghio reference disclose any
10 ophthalmic formulations?

11 A No, it's not about that kind of
12 product.

13 BY MR. HASFORD:

14 Q The approach that the Ghio reference
15 took is different from the approach that the
16 inventors of the patents in suit took when
17 formulating the claimed aqueous liquid
18 preparations of those patents; correct?

19 MR. MARGOLIS: Objection, lacks
20 foundation. Vague.

21 THE WITNESS: Yeah. I didn't
22 quite understand. This is not a patent.
23 This is not -- I'm not sure how you compare
24 the approaches. This is an article which
25 isn't about really the same -- it's not a

1 C. Heathcock, Ph.D.

2 patent. It's about manufacturing a product.

3 BY MR. HASFORD:

4 Q Take a look, if you would, at the
5 first page. In particular, the abstract at the
6 top of that page.

7 A Okay.

8 Q It's at the top of the page bearing
9 Bates No. Lupin 0069301.

10 A Yeah.

11 Q Could you please read the abstract to
12 yourself and let me know when you're ready.

13 A Okay.

14 Q Let me direct your attention to the
15 second sentence in the -- sorry, the third
16 sentence of the abstract, beginning "Tyloxapol
17 inhibits;" do you see that?

18 A Uh-huh.

19 Q The Ghio reference discloses the
20 study -- strike that. Try again.

21 The Ghio reference discloses the use
22 of tyloxapol in biological systems to inhibit
23 activation of a transcription factor nuclear
24 factor kappa B; correct?

25 MR. MARGOLIS: Objection, vague.

1 C. Heathcock, Ph.D.

2 THE WITNESS: Yes. So what
3 they -- what this study reports is that --
4 is the use of tyloxapol as a -- as an
5 antioxidant for a product that could be used
6 that has -- that has the unintended side
7 effect when oxidations take place of
8 activating a certain undesirable biological
9 factor, the one that you named, which I
10 won't read again.

11 BY MR. HASFORD:

12 Q Just to be clear, the Ghio reference
13 studies the use of tyloxapol in biological
14 systems to inhibit activation of a transcription
15 factor nuclear factor kappa B; correct?

16 A I'm just not sure. I have to look
17 carefully. I'm not sure if they actually carried
18 out, you know, the degree to which they carried
19 out actual -- hold on just a minute. So these
20 were laboratory experiments. But they were -- I
21 think it's fair to say that they were doing
22 biological tests, yes.

23 Q Take a look again at the abstract.

24 A Okay.

25 Q And let me direct your attention to

1 C. Heathcock, Ph.D.

2 the sentence "We have previously shown;" do you
3 see that?

4 A The one that begins "We have
5 previously shown;" that one?

6 Q Yes.

7 A Yeah, okay.

8 Q The Ghio reference discloses
9 tyloxapol's ability to serve as an antioxidant
10 for hydroxyl radicals, correct?

11 A Yeah. In the abstract, he's reciting
12 that he had previously shown that it is an
13 antioxidant for hydroxyl radicals.

14 Q The Ghio reference discloses
15 tyloxapol's ability to serve as an antioxidant
16 for hypochlorous acid; correct?

17 A To scavenge hypochloric acid; right.

18 Q You can put that document aside.

19 Are biological data very important to
20 a medicinal chemist?

21 MR. MARGOLIS: Objection, vague.
22 Incomplete hypothetical.

23 THE WITNESS: Yeah. Generally
24 speaking, yes, because your purpose in
25 medicinal chemistry is -- well, if you're

1 C. Heathcock, Ph.D.

2 developing drugs, which is what you're most
3 familiar with, your purpose is to develop a
4 drug that has potency, selectivity and
5 efficacious for some intended purpose. So
6 you've got to measure that by doing
7 biological tests.

8 Q Do biological data include
9 cytotoxicity data?

10 A Yes, that's something that you can
11 measure and is often measured, especially in the
12 intermediate to late stages of a drug development
13 project.

14 Q Would cytotoxicity be an unwanted side
15 effect for any kind of drug?

16 MR. MARGOLIS: Objection, vague.
17 Incomplete hypothetical.

18 THE WITNESS: Not if it's an
19 anticancer drug, for example, or if it's an
20 antiviral and you're trying to kill virus
21 particles, you know, so cytotoxicity as a
22 byproduct -- as a byproduct of a drug that
23 has some intended beneficial property is
24 undesirable.

25 Q Would cytotoxicity be an unwanted side

1 C. Heathcock, Ph.D.

2 effect for an ophthalmic drug?

3 MR. MARGOLIS: Objection, vague.

4 Incomplete hypothetical.

5 THE WITNESS: Yes, I would say

6 yes.

7 BY MR. HASFORD:

8 Q Okay. Does in vitro potency drive
9 medicinal chemistry discovery at the first stage?

10 MR. MARGOLIS: Objection, vague.

11 Calls for speculation. Incomplete

12 hypothetical.

13 THE WITNESS: Yeah. Often the
14 first stage of drug development is to carry
15 out some kind of an in vitro test, and
16 you're looking for potency. And often
17 selectivity along with potency because you
18 may or may not have two tests that you're,
19 you know, for two related systems. But
20 potency is usually the first thing you're
21 looking for in drug development.

22 BY MR. HASFORD:

23 Q Take a look back, if you would, at
24 Heathcock Exhibit 3. It's the court's opinion in
25 OSI Pharmaceuticals v. Mylan.

1 C. Heathcock, Ph.D.

2 A It's in the stack somewhere. This one
3 here?

4 Q Yes. Turn, if you would, to Page 15
5 of Heathcock Exhibit 3.

6 A Okay.

7 Q Let me direct your attention to the
8 left-hand column, the top paragraph. It's a
9 carryover from Paragraph 39 from the previous
10 page. And about toward the end of that
11 paragraph, do you see the sentence that begins
12 "Heathcock agreed"?

13 A Toward the end. Yeah, okay.

14 Q Are you the Dr. Heathcock who agreed
15 that in vitro potency is what drives medicinal
16 chemistry discovery at the first stage?

17 MR. MARGOLIS: Objection, vague.

18 THE WITNESS: That would be me. I
19 don't remember the context at all. And this
20 is -- yeah, I don't remember the context. I
21 must have been asked that question, and I
22 must have said yes.

23 BY MR. HASFORD:

24 Q Do you still agree that in vitro
25 potency is what drives medicinal chemistry

1 C. Heathcock, Ph.D.

2 discovery at the first stage?

3 MR. MARGOLIS: Objection, asked
4 and answered. Vague.

5 THE WITNESS: Yeah --

6 MR. MARGOLIS: Incomplete
7 hypothetical.

8 THE WITNESS: Sorry. Sorry. I
9 just told you that in the previous answer.
10 I said that's the first thing you almost
11 always do, is carry out in vitro tests, and
12 you're looking for potency in your first
13 steps toward the new drug.

14 BY MR. HASFORD:

15 Q You may put that document aside.
16 What did you do to prepare for your
17 deposition today?

18 A I came to New York on Wednesday night,
19 and I spent yesterday meeting with these two
20 gentlemen to go over the report. And --

21 MR. MARGOLIS: I just caution you
22 not to reveal what we talked about.

23 THE WITNESS: I won't tell you
24 what we talked about, but we went over the
25 report and reviewed many of these documents.

1 C. Heathcock, Ph.D.

2 BY MR. HASFORD:

3 Q Did you review all of these documents?

4 DR. MALIK: Let's not talk about
5 what specific documents.

6 THE WITNESS: Yeah, okay. Should
7 I answer that question or not?

8 DR. MALIK: No.

9 MR. MARGOLIS: Calls for
10 privileged information. I instruct you not
11 to answer.

12 BY MR. HASFORD:

13 Q When -- are you going to follow
14 Mr. Margolis' instruction and not answer the
15 question?

16 A Yes.

17 Q Okay. When you say you met with these
18 two gentlemen, are you referring to Mr. Margolis
19 and Dr. Malik?

20 A Yes.

21 DR. MALIK: Dr. Margolis.

22 MR. HASFORD: Oh, sorry, Doctor.
23 I am sorry.

24 MR. MARGOLIS: That's okay. I
25 won't take it too hard.

1 C. Heathcock, Ph.D.

2 MR. HASFORD: I actually
3 legitimately did not know.

4 THE WITNESS: Doctor and Doctor.

5 MR. HASFORD: Doctor and Doctor.
6 I apologize. Dr. Margolis and Dr. Malik.

7 I don't have anything further at
8 this point.

9 DR. MALIK: Let me and Dan step
10 outside for one minute.

11 MR. MARGOLIS: You want to go off
12 the record?

13 MR. McCLUTCHY: Going off the
14 record. The time is 4:15.

15 (Whereupon there was a brief
16 recess.)

17 MR. McCLUTCHY: We are back on the
18 record. The time is 4:17.

19 MR. MARGOLIS: Yeah, Lupin doesn't
20 have any questions.

21 DR. MALIK: Innopharma doesn't
22 have any questions either.

23 MR. HASFORD: Thank you for your
24 time, Doctor.

25 THE WITNESS: You're welcome.

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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.
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C. Heathcock, Ph.D.
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C. Heathcock, Ph.D.

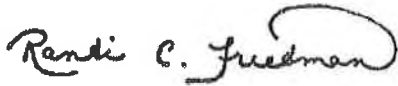
C E R T I F I C A T I O N

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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_____, 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.

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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.

DISCLAIMER: THE FOREGOING FEDERAL PROCEDURE RULES ARE PROVIDED FOR INFORMATIONAL PURPOSES ONLY. THE ABOVE RULES ARE CURRENT AS OF SEPTEMBER 1, 2014. PLEASE REFER TO THE APPLICABLE FEDERAL RULES OF CIVIL PROCEDURE FOR UP-TO-DATE INFORMATION.