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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

MEDA PHARMACEUTICALS, INC.,)
and CIPLA, LTD.,)

))
 Plaintiffs,)

) Civil Action No.
vs.) 1:15-cv-785

)
APOTEX, INC.,)

)
 Defendant.)

)

Videotaped deposition of DR. ROBERT SCHLEIMER,
taken in the above-captioned cause, at
Winston & Strawn, 35 West Wacker Drive,
Chicago, Illinois, before Rachel F. Gard, CSR,
RPR, CLR, CRR, commencing at the hour of
9:04 a.m. on Thursday, September 29, 2016.

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15 ALSO PRESENT:

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1 THE VIDEOGRAPHER: This is Tape No. 1 to the
2 videotaped deposition of Robert Schleimer being
3 taken on September 29th, 2016, at 9:04 a.m., in the
4 matter of Meda Pharmaceuticals, Incorporated, et
5 al., versus Apotex, Incorporated, et al. Case
6 number is 14-1453-LPS.

7 My name is Marvin Oltman, the legal
8 videographer. The court reporter is Rachel Gard.
9 We are located at 35 West Wacker Drive, Suite 4800,
10 in Chicago, Illinois.

11 Will counsel please introduce themselves
12 and the parties they represent, beginning with the
13 party noticing this proceeding.

14 MS. EVERETT: I'm Uma Everett from Sterne,
15 Kessler, Goldstein & Fox on behalf of plaintiffs.
16 With me today is Josh Miller, also of Sterne
17 Kessler, and Matthew Holley from Meda
18 Pharmaceuticals.

19 MR. WARNER: Kevin Warner from Winston & Strawn
20 on behalf of Apotex and the witness.

21 THE VIDEOGRAPHER: Will the court reporter
22 please swear in the witness.

1 (Witness sworn.)

2 WHEREUPON:

3 DR. ROBERT SCHLEIMER,
4 called as a witness herein, having been first duly
5 sworn, was examined and testified as follows:

6 EXAMINATION

7 BY MS. EVERETT:

8 Q. Good morning, Dr. Schleimer.

9 A. Good morning.

10 Q. Can you please state your full name.

11 A. Robert Paul Schleimer.

12 Q. What is your work address?

13 A. 240 East Huron is where my office is
14 located.

15 Q. And that's at Northwestern University?

16 A. That's correct.

17 Q. Have you ever been deposed before?

18 A. I have.

19 Q. What was the nature of the case where you
20 were deposed?

21 A. It was a patent interference case.

22 Q. So it was in front of the Patent Office?

1 A. In a situation such as this.

2 Q. Yes. Have you been deposed in any other
3 cases?

4 A. I've testified in a case in court, but it
5 wasn't a medical case.

6 Q. What was the nature of the case where you
7 testified in court?

8 A. It had to do with a traffic accident that
9 injured my mother.

10 Q. In the patent interference, were you an
11 inventor on one of the patents at issue?

12 A. No.

13 Q. Did you testify as an expert?

14 A. I did.

15 Q. Do you recall the parties involved in the
16 patent interference?

17 A. The primary companies were Dynavax and
18 Coley Pharmaceutical Companies.

19 Q. Who were you retained by?

20 A. Dynavax.

21 Q. What was the nature of the opinion that
22 you gave in that case?

1 A. Well, it was a complicated case. But it
2 was -- in essence, it was about the use of a series
3 of molecules as adjuvants in vaccines.

4 Q. So before we go any further, it's a good
5 time to stop and go over just the general outline or
6 guidelines for a deposition. I'm sure your counsel
7 has gone through them with you.

8 Today I'll ask a series of questions, and
9 you'll give a series of answers. The court reporter
10 is taking down what we say. So I ask you allow me
11 to finish my question, and I will allow you to
12 finish your answer and, so that way, the court
13 reporter can take down a clean record rather than us
14 speaking over one another.

15 If you need a break at any time, please
16 ask for a break and we'll endeavor to get you one.
17 I'll just ask that you not take a break while a
18 question is pending.

19 And if you have a question about or any
20 issue about my question, please ask or ask me to
21 clarify or rephrase and I will do so. If you answer
22 my question, I will assume that you understood it.

1 Is that fair?

2 A. Yes.

3 Q. Okay. Great.

4 (Schleimer Exhibit Number 1 marked
5 for identification.)

6 (Schleimer Exhibit Number 2 marked
7 for identification.)

8 (Schleimer Exhibit Number 3 marked
9 for identification.)

10 BY MS. EVERETT:

11 Q. I have given to the court reporter to be
12 marked your expert reports in this case. The
13 reporter that is marked as Schleimer Exhibit 1,
14 Expert Report of Robert P. Schleimer, which I
15 believe is your opening report.

16 Schleimer Exhibit 2 is Expert Rebuttal
17 Report of Robert P. Schleimer, Ph.D., which is your
18 second-round report.

19 And marked as Schleimer Exhibit 3 is
20 Expert Reply Report of Robert P. Schleimer, Ph.D.,
21 which I believe is your third-round report.

22 So please take a minute, if you need to --

1 I see you flipping through -- just to re-familiarize
2 yourself with your report.

3 A. I just wanted to make sure they are what
4 you say they are, and they appear to be so.

5 Q. Okay. Terrific. So I'm just going to
6 take them one by one. So we're going to go through
7 Exhibit 1, your opening report.

8 A. Okay.

9 Q. Can you just -- You prepared this report;
10 is that correct?

11 A. Yes. I prepared it with the attorneys and
12 Winston & Strawn together.

13 Q. But you reviewed it for accuracy; is that
14 correct?

15 A. Yes.

16 Q. And you made sure it was accurate and true
17 to the best of your ability?

18 A. Yes.

19 Q. And you signed that report?

20 A. Yes.

21 Q. Are there any modifications you wish to
22 make with Schleimer 1?

1 A. No.

2 Q. Okay. Now, looking at Schleimer 2, you
3 prepared this report?

4 A. Yes.

5 Q. And you reviewed it to make sure it was
6 accurate --

7 A. Yes.

8 Q. -- to the best of your ability?
9 You signed this report?

10 A. I did.

11 Q. Are there any changes or modifications you
12 wish to make to this report?

13 A. No.

14 Q. Okay. And then finally Schleimer 3, you
15 prepared this report?

16 A. I did.

17 Q. And you reviewed it to make sure it was
18 accurate, to the best of your ability?

19 A. Yes.

20 Q. And you signed this report?

21 A. I have.

22 Q. Are there any modifications you wish to

1 make to Schleimer 3?

2 A. No.

3 Q. Okay. So Schleimers 1, 2, and 3 contain
4 the sum of your opinions in this case; is that
5 correct?

6 A. The sum of my opinions that are written
7 down in the reports, yes.

8 Q. Are there opinions you are -- have in this
9 case that you have not written that you plan to
10 offer?

11 A. No. But I assume as we discuss these
12 reports, lots of things may come up.

13 Q. But you -- Sitting here today, what is
14 disclosed in Schleimer 1, 2, and 3 is the sum of
15 your opinion?

16 A. It's what I wish to disclose, yes.

17 Q. And if -- I'm going to have you turn to
18 Schleimer 1. In the last set of pages, there's your
19 Materials Considered list, Exhibit B. I'm going to
20 have you turn to that.

21 A. Is that after my CV?

22 Q. It is, yes. It is the end, I believe.

1 A. Okay.

2 Q. Did you prepare this Materials Considered
3 list?

4 A. I didn't build the file, if that's what you
5 mean. But these are all materials that are
6 discussed or referenced in the document.

7 Q. So you reviewed the materials considered
8 list?

9 A. I reviewed the materials that are on the
10 list, yes.

11 Q. Okay. But you didn't review the list
12 itself?

13 A. I'm sure I went through it and didn't see
14 anything out of order.

15 Q. Are there any materials that you
16 considered in preparation of Schleimer 1 that are
17 not either listed in Exhibit B or cited within the
18 report?

19 A. Well, when we were discussing the concepts
20 of it, there were a lot of papers that I thought
21 might be relevant. But they didn't make it to the
22 final cut.

1 Q. Did you consider them in your opinion?

2 A. Well, my opinion is based on the totality
3 of my learnings over the last 35 or 40 years, so I
4 considered the totality of my learnings.

5 Q. Sure. But to the extent you intend to --
6 strike that.

7 So but to the extent you considered or
8 relied upon a written material for your opinion,
9 have you included it either in the text of
10 Schleimer 1 or in Exhibit B?

11 A. Yes.

12 Q. Okay. Great. You can put that to the
13 side.

14 A. Okay.

15 Q. Now we're going to do the same for
16 Schleimer 2.

17 A. The same is true for 2 and 3.

18 Q. Okay. Just wanted to have you -- give you
19 a chance to go through them.

20 A. Okay.

21 Q. At the end of your report, there is a
22 Materials Considered list for your rebuttal report.

1 Do you see that?

2 A. Yes.

3 Q. And does this Materials Considered list
4 include all of the materials you considered in
5 forming the opinions in Schleimer 2?

6 A. In the document, yes.

7 Q. So any material you considered or relied
8 upon for your rebuttal expert report is either cited
9 in your expert rebuttal report or is listed in your
10 materials considered list; is that correct?

11 A. Yes, with the same caveats we went through
12 with No. 1.

13 Q. Right. But to the extent you intend to
14 rely on documentary support --

15 A. Yes, correct.

16 Q. -- it's either in your report or in your
17 Materials Considered listed.

18 A. Yes.

19 Q. Okay. I'm going to have you put that to
20 the side and go to Schleimer 3.

21 And the same set of questions. Please, if
22 you can go towards your Materials Considered list,

1 does this Materials Considered list include all the
2 material you considered in forming -- strike that.

3 Does this Materials Considered list
4 include all the written material you considered in
5 forming your opinions that are disclosed in
6 Schleimer 3?

7 A. Yes.

8 Q. And if you intend to rely on any written
9 document, documentation for your opinions in
10 Schleimer 3, it's either in the text of your report
11 or in the Materials Considered list; is that
12 correct?

13 A. Yes.

14 Q. Okay. Now I'm going to have you turn
15 to -- back to Schleimer 1. I believe your CV is in
16 there.

17 A. Yes.

18 Q. In the middle middle. And I understand
19 this is the CV you submitted with your opening
20 report?

21 A. Yes.

22 Q. Have there been any changes since you

1 submitted this CV?

2 A. I'm sure there have. I publish a lot of
3 papers, and this is months ago. This is May.

4 Q. Do you recall what papers you've published
5 since May?

6 A. I could probably list some of them.

7 Q. Okay.

8 A. I publish about 10 or 20 papers a year.
9 I've given a lot of lectures since then as well. So
10 those are not listed here, but I'm not sure that
11 they tangibly alter the relevance of the CV.

12 Q. What publications do you recall publishing
13 since preparing this CV?

14 A. Well, there's several publications on the
15 pathogenesis of chronic rhinosinusitis. We can do a
16 PubMed search and check against the dates. I can't
17 tell you exactly which ones were published after
18 May 12th and which ones weren't.

19 Q. Okay. So you recall some publications on
20 pathogenesis of chronic rhinosinusitis?

21 A. Yeah.

22 Q. Are there any other publications that you

1 recall?

2 A. Well, that's the main thing that we study.
3 There may be -- Well, there's a paper on epithelial
4 activation by CRAC channels, which was published in
5 Scientific Reports. I'm sure that one just come
6 out. The problem some of them come out e-published
7 before they're officially published. So again, I
8 can't tell you exactly which officially appeared in
9 the literature after May 12th, but I'm sure there's
10 several.

11 Q. Okay. You said you may have given some
12 lectures since May 12th as well?

13 A. Yes.

14 Q. Do you recall what those lectures -- the
15 topics of those lectures?

16 A. Can I look at my calendar?

17 Q. Sure.

18 MR. WARNER: Just -- I guess that's fine.

19 BY THE WITNESS:

20 A. I can tell you what lectures I gave since
21 May 12th. Well, actually this is probably not up to
22 date as of May 12th, but ... I spoke at the European

1 Academy of Allergy in Vienna where I gave two talks
2 in June.

3 Q. What were the -- strike that.

4 What was the topic of those talks?

5 A. One was on the role of loss of epithelial
6 barrier in allergic diseases. And the other was on
7 the pathogenesis of chronic rhinosinusitis. The
8 summer is usually slower, but I think that may -- I
9 also served as an advisor to the Atopic Disease
10 Research Network in September. That's a National
11 Institutes of Health-sponsored network. Gave a
12 presentation there. In terms of lectures, that's
13 it.

14 Q. Okay. So have -- do you recall whether --
15 strike that.

16 Do you recall whether any of your papers
17 or lectures related to the treatment of allergic
18 rhinitis since preparing your CV?

19 A. I would say not, they don't. Allergic
20 rhinitis, which I've studied greatly, is not
21 something I've published on in the last 5 months.

22 Q. Have you either published papers or

1 presented lectures on azelastine?

2 A. I'm not sure if azelastine showed its face
3 in one of my papers over the years. But I've not
4 studied azelastine per se as the main topic of one
5 of my studies.

6 Q. And now you're speaking about ever? Are
7 you speaking about ever or since May 12th?

8 A. Since May 12th.

9 Q. Okay. Have you studied azelastine before
10 May 12th, outside the context of this litigation?

11 MR. WARNER: Objection to the form of the
12 question. It's vague as to "studied."

13 THE WITNESS: I should answer?

14 MR. WARNER: Yeah. If you understand, you can
15 answer.

16 BY THE WITNESS:

17 A. Sure, I'm very aware of azelastine. It's
18 one of the more important antihistamines. It's
19 topically very effective, potent, and it has an
20 interesting and unusual action. So I've studied it
21 over the years.

22 Q. Have you published any papers on

1 azelastine or given any lectures?

2 A. I'm not sure. It's possible that it's
3 shown up in some of the studies that we did earlier.

4 Q. Since preparing your CV, have you
5 published any papers or given any lectures on
6 antihistamines?

7 A. No.

8 Q. Since preparing your CV, have you
9 published any papers or given any lectures on
10 fluticasone?

11 A. Not -- no, not since the CV was prepared.

12 Q. Have you published any papers or given any
13 lectures on corticosteroids since your CV was
14 prepared?

15 A. I don't believe I discussed steroids in
16 either of those two lectures that I mentioned, so
17 no.

18 Q. Okay. And since preparing your CV, have
19 you given any lectures or prepared any papers on
20 Dymista?

21 A. No.

22 Q. Okay. What is your current position,

1 Dr. Schleimer?

2 A. I'm the Roy and Elaine Patterson professor
3 and chief of allergy/immunology at the Northwestern
4 University School of Medicine.

5 Q. Are those two positions or one position?

6 A. It's one position. I'm the chief of
7 allergy/immunology. But the Roy and Elaine
8 Patterson professor is an endowed chair.

9 Q. And what does it mean to have an endowed
10 chair or ...

11 A. An endowed chair is -- it's an endowment.
12 Usually it's a bequeath made at one point or
13 another. Often they grow to be quite large. And a
14 certain amount of money spins off every year,
15 depending how it's invested. 3 to 5 percent of the
16 assets of the chair come to the endowed professor to
17 use for their research or salary or whatever. I
18 mean, they also have honorary -- honorific value in
19 academy to have an endowed chair. They're not
20 common.

21 Q. What are your responsibilities for the
22 chief of allergy/immunology?

1 A. I'm responsible for the direction and
2 running, growth, maintenance of the division of
3 allergy/immunology, which includes over 20 faculty
4 members, both clinicians and scientists, as well as
5 clinician scientists and total employees probably
6 between 90 and 100.

7 We run the -- one of the largest clinical
8 academic allergy practices in the country, so I'm
9 responsible for that as well. And our research
10 funding, if one totals NIH and philanthropic gifts,
11 is probably also one of the two or three largest in
12 the country.

13 Q. Do you have -- strike that.

14 Do you currently teach any courses?

15 A. I do. We offer an immunology course every
16 year and -- which I teach. And I'm invited to teach
17 in other courses throughout the course of time. We
18 have a lot of other courses like journal club
19 manuscript review, and I often teach there
20 presenting current manuscripts and dissecting the
21 data and giving my views of the relevance of the
22 work, et cetera.

1 Q. You don't have a medical degree; is that
2 correct?

3 A. That's correct.

4 Q. Is it fair to say you have not diagnosed
5 or treated patients?

6 A. It's fair to say I've not treated patients,
7 but I've been involved in diagnosis for decades. My
8 colleagues at Johns Hopkins and Northwestern come to
9 me with challenging cases all the time for my
10 insight, my opinions, my questions. I've attended
11 the clinical conferences at Johns Hopkins for the
12 25 years I was there, the allergy rounds. And I'm
13 aware of the treatment approaches to allergic
14 diseases, a variety of allergic diseases.

15 As a pharmacologist, that's one of my
16 interests, I'm also particularly interested in drug
17 treatments, although there are other treatment
18 modalities that are used for allergic diseases in
19 general.

20 So I'm not allowed by law to treat
21 patients, but I often help my colleagues treat their
22 patients by making suggestions for either diagnostic

1 tests that should be ordered and/or therapies that
2 might help them with difficult patients. They
3 generally don't consult me with garden-variety
4 allergic diseases.

5 Q. And so you said you provide consultation
6 to your physician colleagues on treating patients;
7 is that a fair summary?

8 A. I have.

9 Q. But ultimately, it's the physician who
10 makes the decision on how to go treat a patient?

11 A. Yes, of course.

12 Q. Have you ever prescribed medication to a
13 patient?

14 A. No.

15 Q. Have you ever formulated a pharmaceutical
16 drug product?

17 A. Yes. Actually, I've been involved in some
18 of that. Years ago we did some studies, testing a
19 compound called glycyrrhetnic acid. And we got
20 approval, got an IND, obtained the compound from
21 Japan, and we did a study on it.

22 And I've been involved in other studies

1 over the years that have involved the development of
2 new drugs, including a startup company that I'm a
3 founder of and patentholder that now has three
4 clinical trials. I did not personally formulate,
5 but I've been involved in the process.

6 Q. When you say you've been involved in the
7 process of formulation, what role have you taken?

8 A. Well, in the study with glycyrrhetic acid,
9 we did the study in my lab and the lab of one of my
10 colleagues.

11 Q. And when you say study, do you mean the
12 clinical trial study? Or what study are you
13 referring to?

14 A. It was a small single-site evaluation of a
15 hypothesis that we had at the time where we gave
16 drug to a small number of people, including
17 ourselves.

18 Q. So you were involved in determining the
19 efficacy of the drug; is that accurate?

20 A. No, I wouldn't say that's the case. We
21 were testing a hypothesis that this drug would alter
22 levels of glucocorticoid metabolites in the nose.

1 So it was just looking at biomarkers. It was not an
2 efficacy trial.

3 Q. So earlier, a few minutes ago I think you
4 said you weren't personally involved in formulation
5 but you have been involved. So have you been
6 involved as a formulator might select the excipients
7 and the variations in the excipients and active
8 ingredients?

9 A. No, not really.

10 Q. Okay.

11 A. Not in a complex preparation.

12 Q. Have you been involved in it in any
13 preparation?

14 A. The one I was telling you about.

15 Q. Okay. So did you select the active --
16 inactive ingredients in that case?

17 A. Yes, but they were minimal. It was mostly
18 a buffered saline preparation adjusted for pH.

19 Q. Is that the only example where you've
20 selected excipients for a formulation?

21 A. Yes. Where I personally in my lab, yes,
22 that's the only example.

1 Q. Earlier you explained how your physician
2 colleagues consult with you when deciding what
3 treatment approach to take with a patient. Is that
4 an accurate assessment?

5 A. Yes, especially with difficult patients.

6 Q. With difficult patients. In that course
7 of that, did you review the patient records? Do
8 you ...

9 A. Typically they tell me what they think I
10 need to know of the records. I don't look at charts
11 generally, no.

12 Q. Okay. Have you been consulted in
13 treatment of allergic rhinitis?

14 A. By pharmaceutical companies, yes, for
15 years.

16 Q. Okay. In -- when you were discussing
17 treatment -- strike that.

18 When you were discussing consultation with
19 your physician colleagues --

20 A. Yes.

21 Q. -- have they consulted you in treating
22 patients with allergic rhinitis?

1 A. I'm sure they have, but typically not. I
2 don't think that particularly difficult cases arise
3 with the same frequency as other diseases.

4 Q. Do you ever recall consulting with your
5 physician colleagues on the use of azelastine and
6 fluticasone for patients with allergic rhinitis?

7 A. Consulting with my colleagues as opposed to
8 consulting with pharmaceutical companies?

9 Q. Yes.

10 A. No, I don't have specific recollections of
11 consulting with them over azelastine and
12 fluticasone.

13 Q. Do you have any specific recollections,
14 again outside of this lawsuit, of any physician
15 colleagues discussing the treatment of allergic
16 rhinitis -- strike that.

17 Outside of this lawsuit, do you have any
18 recollections of discussing with fellow physicians
19 the treatment of allergic rhinitis using azelastine
20 and fluticasone?

21 A. Yeah, these drugs were discussed a lot in
22 the '90s, 2000, and subsequently. I was more likely

1 to discuss fluticasone than azelastine just because
2 I'm recognized as an expert in glucocorticoid
3 action, and I'm more interested in the
4 glucocorticoids. But all of the major drugs that
5 are used in the armamentarium of allergists are ones
6 that I've participated in numerous discussion at
7 allergy rounds over the years.

8 Q. Again, outside of litigation, do you
9 recall discussions of physicians using azelastine
10 together with fluticasone to treat patients with
11 allergic rhinitis?

12 A. I don't have any specific recollection
13 where I can remember one person talking about using
14 the two at the same time, so I'll have to say no.

15 Q. Okay. Earlier you made a distinction of
16 that you've consulted with pharmaceutical
17 companies --

18 A. Yes.

19 Q. -- on treatments for allergic rhinitis?

20 A. Yes.

21 Q. And with those companies, did you discuss
22 the use of azelastine?

1 A. Possibly. But pharmaceutical countries --
2 companies generally invited me to talk about
3 glucocorticoids because that's my area of greatest
4 expertise. And I was -- I've been involved in
5 everything from clinical trial design to basic
6 molecular biology and discovery of new compounds in
7 the glucocorticoid area.

8 Now, some of those companies were also
9 interested in topical antihistamines. I'm sure it
10 came up, but that's -- that was less likely to --
11 well, probably was never the central topic.
12 Although certainly I remember going to meetings
13 about other antihistamines like loratadine and
14 desloratadine and many others at international
15 consulting.

16 Q. What role would you take -- strike that.

17 So as you consulted with the
18 pharmaceutical companies, what is your typical role?
19 What did they ask you to do?

20 MR. WARNER: Objection. Form. Vague as to
21 "typical." Go ahead, you can answer, if you know.

22 BY THE WITNESS:

1 A. It's an interesting question. As you
2 probably figured, I'm not the typical chief of a
3 clinical division since I don't hold an M.D. My
4 research interests have always been clinical,
5 though, and my work often involves patients.

6 As a result, the leadership at Northwestern
7 thought I could manage running a clinical division,
8 and they wanted -- they invited me to build the
9 division, a research portfolio, both in the clinical
10 and the laboratory domain.

11 As a result, I was -- I am considered by a
12 dozen, two dozen pharmaceutical companies as
13 somebody that can provide advice on the range from
14 very basic molecular discovery to very clinical,
15 clinical trials designs, and even postmarketing
16 studies and marketing strategy sometimes.

17 So what that means is that I've been
18 invited to a range of meetings from basic discovery,
19 which may be if it involves mammals will be in mice,
20 but usually it's in vitro and high throughput
21 screens of drugs to designing clinical trials for
22 Phase I, II, and III or afterwards.

1 So there is no typical expertise that
2 companies are looking for from me. Each meeting has
3 its own nature. I was at a meeting 2 days ago where
4 they haven't done any studies in humans yet and they
5 want to know, well, what should be our first study
6 in humans? Should we go after this disease or this
7 disease or this disease? And they were providing us
8 with information on the cellular molecular
9 mechanisms of action of the drug. Complex answer,
10 I'm sorry, but ...

11 Q. No, it's a very helpful answer.

12 In those interactions, have -- strike
13 that.

14 In those interactions, have you ever
15 appeared before FDA on behalf of a pharmaceutical
16 company?

17 A. Over the phone, I have been on
18 presentations to FDA. I've been on FDA mock
19 advisory panels. I've never been on an FDA panel,
20 but -- I have been involved in such things.

21 Q. So you said you were involved in a
22 presentation to FDA over the phone?

1 A. Yeah. I was consulting with a company
2 that's interested in chronic rhinosinusitis and
3 developed a drug-containing stent to treat the
4 disease and presenting it to the FDA to get approval
5 for one of their studies, and I was one of the
6 experts on the phone. I didn't make the trip
7 because I had conflicts.

8 Q. Have you appeared before FDA on behalf of
9 a pharmaceutical company in any other context?

10 A. No.

11 Q. Was this a one-time phone call, or were
12 there multiple?

13 A. I think there were two calls.

14 Q. Two calls, okay.

15 A. Right.

16 Q. You said you were part of a mock advisory
17 panel. What is that?

18 A. Yes. Well, I've done that more than once.
19 Companies, before they make their big presentation
20 to the FDA, will, especially if it's a big drug
21 likely to have a big market, they'll impanel a
22 group, sometimes 20 or 30 experts. And they'll give

1 their presentation they plan to give to the FDA in
2 front of these experts whose charge is to critically
3 evaluate the portfolio that they're presenting, as
4 if they were an FDA panel. And I think they see
5 benefit in it because it provides them practice for
6 their actual presentation.

7 Q. And can you think of any other
8 circumstance in which you appeared before FDA?

9 A. No.

10 Q. Okay. So from your opening report and
11 your statements, I understand you've consulted with
12 a number of pharmaceutical companies. That's
13 correct?

14 A. Yes.

15 Q. Have you ever published a paper with a
16 person who was employed at a pharmaceutical company
17 at the time?

18 A. Yes.

19 Q. Why did you decide to do that?

20 A. The one that I first thought of is one
21 where we wrote a review about steroid actions, and
22 so I co-wrote it with them. Actually turned out to

1 be a highly cited review.

2 Q. Was the pharmaceutical company involved in
3 any way in the research underlying the paper?

4 A. It was a review, so it didn't tout the
5 project -- a product. It was a review of the whole
6 field. I have avoided getting involved in
7 product-centric marketing targeting publications.

8 Q. How do you determine what areas you will
9 focus your research on?

10 A. How much time do you have? That's an
11 interesting question.

12 I would say, for the most part, I follow my
13 nose, which you can see is substantial. I let the
14 data drive the hypotheses that I generate, and so
15 new data can bring us into completely new areas of
16 research. Over the years, I've studied eight or ten
17 different inflammatory cells, for example. Many
18 people will focus on one and spend their whole
19 career on it. But if I have to study a different
20 cell type because the biology and the data tell me
21 that cell type is the one of interest, I'll do it.

22 So generally I study what I'm interested

1 in; and I try to pick things that I can get funded,
2 of course. Sometimes I'm interested in arcane
3 things and I'll do it on the side because you can't
4 get funded to study arcane things until they become
5 important. But many a case has there been where
6 something seemed odd and unusual turned into
7 something important.

8 Q. So is it fair to say certain criteria that
9 go into determining your research are importance and
10 funding; is that ...

11 A. So as I said, the biology and the science
12 of it is the primary driver. But if I see four or
13 five interesting things and we have limited
14 resources in terms of people, money to go after
15 them, if two are equally interesting but one will be
16 very easy to get funded and another will be
17 difficult to get funded, that might influence the
18 choice.

19 But if there's funding for something that's
20 not interesting, I generally avoid it. That's a
21 luxury.

22 Q. It's a good position to be in.

1 And in many of your publications on your
2 research, you've published with a number of
3 co-authors; is that correct?

4 A. Yes.

5 Q. And how do you determine who you will
6 publish with?

7 A. I'm surprised he's not objecting. That
8 question can be interpreted many different ways.

9 Q. Okay. Let me try it again.

10 MR. WARNER: I'm going to object that that
11 question is vague.

12 THE WITNESS: Sorry, Kevin.

13 MR. WARNER: That's all right.

14 BY MS. EVERETT:

15 Q. Is -- You've published with a number of
16 co-authors?

17 A. Yes.

18 Q. On many of your papers?

19 A. Yes.

20 Q. Is it fair to say that you've published
21 with people who you have -- who have participated in
22 your research?

1 A. Yes. Authors, authors need to have
2 contributed one way or another to a manuscript to be
3 authors.

4 Q. And is it fair to say you have each -- you
5 respect the scientific integrity of the paper, the
6 research you are publishing on?

7 A. Yes, the integrity of the work is
8 essential. And I do everything I can to be sure
9 that the data are correct, at the very least.
10 Sometimes our interpretations are speculative, and
11 we take chances on that. But we label it as
12 speculation. But the integrity of the data is first
13 and foremost.

14 Q. Would it be fair to say you try to publish
15 with people who you consider to be good scientists?

16 A. Yes.

17 Q. Earlier we were just talking about how you
18 determine what you research. Do you consider
19 scholarly impact of your research?

20 A. And again, that's an interesting question.
21 I try to focus on important questions. And if one
22 approaches an important question and gets a

1 meaningful answer, then that has scholarly impact.

2 Q. Okay.

3 A. But if one approaches an important question
4 and one's hypothesis was wrong, sometimes that can
5 have great scholarly impact. Other times, it's,
6 okay, one more thing that doesn't explain this
7 phenomenon. So I always try to focus on important
8 questions that, intellectually speaking, serve an
9 unmet need.

10 Q. Okay. When you are working either at
11 Northwestern or with your pharmaceutical -- strike
12 that.

13 Just you focusing, you've been consulted
14 on potential treatments for allergic rhinitis; is
15 that correct?

16 A. Yes.

17 Q. And you, when you are looking for a
18 certain treatment for a condition, you wouldn't
19 limit yourself to treatments that are just FDA
20 approved; is that right?

21 MR. WARNER: Object to the form of the question
22 as vague as to time and other things involved.

1 MS. EVERETT: I can ask a better question.

2 BY MS. EVERETT:

3 Q. So if you were looking to develop a better
4 treatment for a particular condition, you wouldn't
5 limit yourself to only FDA-approved treatments,
6 would you?

7 MR. WARNER: Objection. Form of the question.
8 It's an incomplete hypothetical.

9 BY THE WITNESS:

10 A. One of my greatest interests is drug
11 development. And almost by its nature, at least at
12 the level I'm interested in, that means looking at
13 entirely new treatments, entirely new approaches to
14 diseases. That would describe the drugs in our
15 startup company that I mentioned. That would
16 describe many of the drugs that I'm asked to consult
17 on with pharmaceutical companies because they're
18 usually trying to find completely different, new,
19 novel ways to approach disease that are not well
20 managed by the existing drugs.

21 I don't know if that's what you're looking
22 for.

1 Q. That was very helpful. Thank you.

2 Would you limit your search for a better
3 treatment -- strike that.

4 You wouldn't limit your search for a
5 better treatment to compounds that were available
6 only in the U.S., would you?

7 MR. WARNER: Objection to the form of the
8 question. Incomplete hypothetical.

9 BY THE WITNESS:

10 A. I have no idea what that question means,
11 I'm sorry.

12 Q. So if a product was used in Europe but not
13 yet used in the U.S., would you consider the product
14 that was used in Europe?

15 MR. WARNER: Same objections.

16 BY THE WITNESS:

17 A. I'm more interested in compounds and their
18 molecular, cellular, and physiological mechanisms.
19 Who owns them and where they're synthesized or where
20 they're prescribed is of secondary relevance. So
21 no, I wouldn't limit myself. As I said, I let -- I
22 follow the biological questions and I -- if I need a

1 compound that does something, I'll find the
2 compound. It doesn't matter, you know, if it comes
3 from Europe or somewhere else.

4 But again, I usually work with experimental
5 preclinical compounds. I should say I often work.

6 Q. Understood. Would you -- When you are
7 working with these compounds, would you consider
8 whether it was possible to develop them in a
9 different dosage form? So, for example, if
10 something was in a tablet, would you -- and you
11 wanted a nasal spray, would it be prohibitive?
12 Would you not look at the tablet because it's a
13 tablet?

14 MR. WARNER: Objection to the form of the
15 question. It's an incomplete hypothetical.

16 BY THE WITNESS:

17 A. Again, I focus on the compounds. For
18 instance, if you have an antihistamine in tablet and
19 you have it in a spray or suspension or liquid, I
20 would be mostly interested in the compound and in
21 its pharmacology and biology.

22 Q. So you're saying you would not be

1 dissuaded from considering a compound that currently
2 exists only in solid dosage form, even if you're
3 potentially considering using it in a different
4 dosage form?

5 A. Well, in the example of antihistamines,
6 which I'm sure we're going to talk a lot about, it's
7 been known for decades that they have a number of
8 pharmaceutical properties that are completely
9 distinct from their ability to block the H1
10 receptor. Those pharmaceutical properties are
11 interesting not only scientifically but clinically
12 because some of the actions that they include
13 inhibition of inflammatory responses that we know
14 are important in disease.

15 And that knowledge was very important in
16 the development of intranasal antihistamines such as
17 azelastine because it meant because of the topical
18 application, that you could achieve local
19 concentrations of the drug that far exceeded the
20 concentrations you would have in the nose if you
21 took a tablet and reach concentrations that started
22 to turn off these other inflammatory responses that

1 are not affected either at all or as well by a
2 tablet.

3 So with that knowledge, with the knowledge
4 that topical application of a drug can have superior
5 pharmacological effects to oral application, I would
6 not be dissuaded at all. In fact, I lived through
7 this whole phenomenon in the steroid field. When
8 steroids were -- when glucocorticoids were
9 discovered, they very rapidly were appreciated to be
10 lifesaving drugs. People were literally dying of
11 asthma and rheumatoid arthritis and a number of
12 other serious diseases, and these drugs saved their
13 lives. It was an amazing period. In fact, the
14 discoverer, Hench, who discovered these drugs, won a
15 Nobel Prize within years, just a few years, because
16 it was revolutionary.

17 But then after that period of time, it
18 became appreciated that they have really bad side
19 effects. If you take too much prednisone, you start
20 to have bone fractures, your skin gets thin, you get
21 cataracts, all sorts of problems. And then the
22 pharmaceutical industry discovered in the '70s and

1 '80s, the early parts of my career, that they could
2 develop topically active potent corticosteroids that
3 had a high affinity for the same receptor, that were
4 lipophilic so they stayed in the nose for a long
5 period of time that were not absorbed systemically
6 so they did not cause the systemic side effects of
7 the drug, and they had fantastic local action
8 against allergic rhinitis and against asthma, et
9 cetera.

10 So there was a huge movement in the field
11 away from oral corticosteroids to topical
12 corticosteroids because they were much, much safer.
13 With the benefit of that field, the antihistamine
14 field, pursued the same logic. In other words,
15 people discovered actually going way back to the
16 '60s and '70s, they discovered more later in the
17 '80s, they discovered these really interesting
18 anti-inflammatory effects of antihistamines, a
19 number of them, including azelastine, and were
20 motivated therefore to try to give them topically
21 locally in the nose to avoid -- not only to avoid
22 systemic side effects but also to benefit from these

1 anti-inflammatory effects, which were not readily
2 achievable with oral medication because they were
3 too sedating. They had other side effects that
4 precluded getting to high enough concentrations.

5 Q. Okay. So if I understood you, then you
6 are agreeing --

7 A. I would not be dissuaded.

8 Q. You would not be dissuaded.

9 Prior to this litigation, were you
10 familiar with the ARIA guidelines?

11 A. Yes. Yeah, I'm aware of the guidelines.
12 They're guidelines for most diseases. Some are
13 European, some are American. I was aware of ARIA.

14 Q. Strike that. In your practice, did you
15 consult with ARIA for any reason, ARIA guidelines?

16 A. As you know, I don't treat patients. So I
17 don't pay as close attention to guidelines since I
18 don't need to use the stepwise approaches that they
19 recommend. But I've always been interested in
20 guidelines because, again, as a pharmacologist, the
21 guidelines are the consensus of the clinical experts
22 in the field as to what is the best way to approach

1 the management of these various diseases. So the
2 guidelines are of interest to me.

3 Q. Did you need to -- strike that.

4 Are you aware of the Dykewicz guidelines
5 prior to this litigation?

6 A. Yes, I was aware of them. But as I said, I
7 don't read them or use any of the guidelines because
8 I don't, on a regular basis, because I don't treat
9 patients. But I have an intellectual interest in
10 them and was aware of them. In fact, Mark Dykewicz
11 I really know quite well. He's a graduate of our
12 program.

13 Q. Did you consult them in any way when
14 physicians called upon you to assist in treatment of
15 the more difficult patients?

16 A. No, because my colleagues at Johns Hopkins
17 and Northwestern are very well aware of the
18 guidelines. They were coming to me for problem
19 cases where they followed the guidelines, and it
20 wasn't getting them where they wanted to be.

21 Q. And you're aware that the relevant --
22 strike that.

1 So you've given a lot of opinions on this
2 case about whether or not these patents-in-suit are
3 obvious. Is that correct?

4 A. Yes.

5 Q. And you understand that that should be
6 measured as of June 2002?

7 A. I do.

8 Q. And you understand that should be assessed
9 from the vantage point of a person of ordinary
10 skill?

11 A. Yes.

12 Q. As of 2002, were physicians using
13 anticholinergics to treat allergic rhinitis?

14 A. I'm trying to think of approved
15 anticholinergics. I don't think it was a
16 particularly popular class of drugs. It's a class
17 that's been around for centuries starting with
18 atropine. And they have value because they dry
19 secretions. Often they dry them too much. I
20 believe there was an approved one that was used, but
21 I don't think they were ever very popular. They're
22 more popular in asthma and chronic obstructive

1 pulmonary diseases.

2 Q. Okay. But they were known and used as of
3 June 2002?

4 A. I believe so.

5 Q. Do you have experience with use of
6 anticholinergics?

7 A. Well, I'm trained as a pharmacologist, and
8 I understand that the autonomic nervous system, at
9 the end of the nerve terminals, uses acetylcholine
10 to induce all sorts of responses: salivation,
11 lacrimation, urination, defecation. It controls a
12 lot of those autonomic functions, as they're called.
13 And that's mediated by acetylcholine release by the
14 nerves.

15 And a cholinergic receptor in the end
16 organ, whether it's smooth muscle or a gland or what
17 have you, atropine and its descendants,
18 anticholinergic drugs, block that transmission and
19 prevent those things I just mentioned, salivation
20 being one. But rhinorrhea is related to salivation,
21 and it is inhibited to some extent by cholinergic
22 drugs. But they're not going to block some of the

1 other things that we're interested in, allergic
2 rhinitis, like the itching and sneezing and
3 congestion for the most part.

4 So I'm aware of those drugs, but I don't
5 think they've ever become very popular.

6 Q. They treat runny nose; is that correct?

7 A. I believe so, yes.

8 Q. Have you -- And just to clarify, when I
9 said did you have experience, have you ever studied
10 a particular anticholinergic?

11 A. Well, I've been involved in studies where
12 atropine was used. But generally I don't think I've
13 got many publications that have used
14 anticholinergics.

15 Q. And there -- strike that.

16 As of June 2002, leukotriene receptor
17 antagonists were used to treat allergic rhinitis; is
18 that correct?

19 A. Yes.

20 Q. And as of that time, leukotriene receptor
21 antagonists had been shown to treat congestion; is
22 that correct?

1 A. Yeah, so the issue with leukotriene
2 antagonists is that they only block one pathway,
3 which is the leukotriene pathway. And the
4 leukotriene pathway has some involvement in
5 bronchospasm in asthma and has some involvement in
6 regulating vascular tone in the nose.

7 But the problem is when the inflammatory
8 cells such as the mast cells degranulate, they do
9 make leukotrienes, but they release lots of
10 histamine. And histamine is probably the most
11 important mediator of itchiness and sneezing and
12 vascular responses in the nose.

13 So the leukotriene antagonists are
14 generally perceived as being fairly weak drugs.
15 They're reasonably popular because they're oral and
16 they're pretty safe. So doctors like them, patients
17 like them, they take benefit of the placebo effect.
18 But they're not very effective drugs in either in
19 the lungs or in the nose.

20 So if I were trying to think of what to
21 combine with a steroid to take benefit of the
22 complementary actions of a drug that would block the

1 immediate phase, I would be much more likely to look
2 at antihistamines that had the ability to shut off
3 the other pathways, including the leukotriene
4 pathway, by the way. So azelastine inhibits the
5 release of leukotrienes, along with blocking the
6 action of histamine. That would be, mechanistically
7 speaking, something that my person of skill in the
8 art would be aware of and interested in and would be
9 a basis by which they deemed that the azelastine or
10 topical antihistamine was superior to a leukotriene
11 inhibitor.

12 Q. Dr. Schleimer, my question was, as of that
13 time, June 2002, leukotriene receptor antagonists
14 had been shown to be efficacious in congestion; is
15 that correct?

16 MR. WARNER: Objection. Asked and answered.

17 BY THE WITNESS:

18 A. I believe that's correct. I have not
19 reviewed the leukotriene rhinitis literature for
20 this case. But as I've already said, they're not
21 believed to be particularly effective drugs, and
22 they're not that popular, other than the fact that

1 they're oral and fairly safe. So I don't know if
2 that's a better answer, but I believe that there are
3 probably studies to which you're referring to that
4 show that leukotrienes can -- antagonists can block
5 congestion somewhat.

6 Q. Have you studied any particular
7 leukotriene receptor agonist -- strike that.

8 Have you studied any particular
9 leukotriene receptor antagonist?

10 A. I'm not sure. If you did a PubMed search
11 of montelukast and my name, you could answer that
12 question. It's possible that montelukast, which
13 is -- I think it's still the most widely selling
14 CYSLT1 or leukotriene 1 receptor antagonist. It may
15 be that some of the studies I did in collaboration
16 with one of my colleagues at Johns Hopkins used it
17 in a study, but I'm not sure. But it's not been a
18 major focus of my work. I've been interested in
19 leukotrienes and published, I'd say, fairly
20 extensively on leukotrienes.

21 MR. WARNER: Let's take a break, whenever
22 you're ready.

1 MS. EVERETT: Now's a good spot.

2 THE VIDEOGRAPHER: We are now going off the
3 record at 10:08 a.m.

4 (A short break was taken.)

5 THE VIDEOGRAPHER: We are now going back on the
6 record at the beginning of media No. 2. The time is
7 10:26 a.m.

8 BY MS. EVERETT:

9 Q. Welcome back.

10 A. Thank you.

11 Q. In the last session, you mentioned chronic
12 rhinosinusitis?

13 A. Yes.

14 Q. What is a chronic rhinosinusitis?

15 A. It's a disease of the nose and sinuses.
16 It's very similar to allergic rhinitis in the nose,
17 actually, in many ways. But it also affects the
18 sinuses. And there can either be a great deal of
19 swelling or filling of the sinuses. The sinuses can
20 fill with fluid.

21 In some cases, nasal polyps grow from the
22 sinuses and they occupy the nasal cavity. It's

1 very -- as I said, it's very similar to allergic
2 rhinitis in some ways. But it's different in the
3 sense if it's driven by antigens, the antigens are
4 not well known, whereas with allergic rhinitis,
5 usually skin testing can determine the antigens that
6 drive disease, be it grass pollen or tree pollen or
7 cat dander or house dust mite. But with chronic
8 rhinosinusitis, we don't even know for sure that
9 it's an antigen-driven disease.

10 Q. Before the break we were discussing
11 certain pharmaceuticals that were available as of --
12 before June 2002. Do you recall that?

13 A. Yes.

14 Q. Okay. And isn't it true that
15 decongestants were available as of June 2002 and
16 earlier for allergic rhinitis?

17 A. Yes.

18 Q. And they were useful in treating
19 congestion; is that correct?

20 A. Yes. There were some drugs. One that
21 comes to mind is Afrin, which is an alpha adrenergic
22 agonist, and those drugs can constrict blood

1 vessels. One of the big problems with decongestants
2 is either some of them are not that effective but
3 Afrin is addictive. Not in the traditional sense of
4 drugs of abuse; but if people use that decongestant
5 and then they stop, they get terrible congestion, so
6 bad rebound congestion that they continue to use the
7 drug.

8 There certainly are decongestants. But the
9 same thing applies to that, that I said with the
10 leukotriene antagonists, which is that, compared to
11 topical antihistamines, which would not only block
12 the action of histamine but also prevent the release
13 of histamine, prevent the release of leukotrienes,
14 prevent the release of other mediators, some of
15 which are contributing to congestion, the
16 decongestants have a narrower range of action. They
17 wouldn't be expected to prevent sneezing, itching,
18 some of the other symptoms as well.

19 So if I were considering what among the
20 panoply of possibilities to include with a topical
21 steroid, decongestants would not be my first choice.
22 Also, it's important to remember that the steroids

1 themselves are probably the best drugs in blocking
2 congestion, so they would be overlapping in a
3 combination. And I'm not even sure they would have
4 additional benefits when combined.

5 Q. If two drugs had overlapping -- and when
6 you say overlapping, do you mean overlapping
7 mechanisms of action?

8 A. No, but overlapping targets. They both
9 target congestion.

10 Q. So if drugs had overlapping targets, would
11 that dissuade you from combining them?

12 A. Well, no, as long as they also had
13 non-overlapping targets, which in the case of a
14 topic antihistamine or azelastine, in particular,
15 and a topical steroid or fluticasone, in particular,
16 they have quite complementary action. The steroid
17 has almost no effect on the immediate sneezing,
18 itching, response to antigen exposure, whereas the
19 antihistamine, especially topical, knocks those
20 things flat.

21 So on the other hand, the later congestion
22 and prolonged inflammation phase is not as well

1 inhibited by the antihistamines but the steroids are
2 particularly good in blocking that.

3 To give you an example, I was thinking of a
4 typical allergic person, say a woman named Laurie,
5 who is allergic to cats and -- but she avoids cats,
6 doesn't have them in her home, doesn't have them in
7 her work so she's asymptomatic. But once a month
8 she goes to visit her Aunt Flo, and Flo has three
9 cats and loves them. But Laurie loves Flo, so
10 Laurie goes to visit Aunt Flo, spends a whole
11 afternoon with her once a month.

12 As soon as she walks in the door, her nose
13 starts itching. She starts sneezing her head off.
14 She's blowing into Kleenex like she's at a funeral,
15 and that makes the visit uncomfortable. So this
16 particular patient, their doctor or they themselves
17 may realize that a dose of antihistamine, oral or
18 topical, before visiting Aunt Flo would prevent that
19 immediate sneeze and itch and rhinorrhea and makes
20 the visit much more comfortable.

21 The problem is that what she would also
22 experience after a whole afternoon at Aunt Flo's

1 house, she would go home and she would have
2 congestion and couldn't breathe through her nose.
3 And that would last for a day or two. And the
4 antihistamine is not particularly good against that
5 delayed and prolonged effect, whereas she would
6 probably have been prescribed by her doctor topical
7 steroid. And the topical steroid, even a single
8 dose before visiting her aunt, would prevent that
9 late response.

10 So this model of an allergic response has
11 been modeled in the laboratory. We did this for
12 years. In fact, investigators have done this for a
13 century, where you take an allergic person who is
14 asymptomatic because they've been avoiding their
15 allergen but they're sensitized. You expose them to
16 the antigen intentionally, either injecting it in
17 the skin or putting it in the nose or the eyes,
18 having them inhale it, depends on which disease
19 you're interested in. And what happens, it's dose
20 dependent, but at higher doses of the antigen, you
21 get an immediate response. And that's when the mast
22 cells that have IGE antibodies against the antigen

1 release histamine, release leukotrienes, and they
2 cause that sneezing and itching and rhinorrhea in
3 the nose.

4 But then what happens is, over the course
5 of the next many hours, inflammatory white blood
6 cells start coming in from the blood. And they have
7 their own mediators, and they cause their own mess,
8 lots of inflammation. They cause the blood vessels
9 to dilate also causing the congestion.

10 What we call those responses when we use on
11 experimental subject is the early phase and acute
12 phase and the late phase because the symptoms peak
13 and then they resolve after an hour or two. But
14 they peak again at 4 to 10 hours, and they can stay
15 up for a day.

16 If you give an antihistamine before this
17 challenge in the laboratory, it blocks that early
18 phase but it doesn't block the late phase. If you
19 give the steroid, it blocks the late phase but
20 doesn't block the early phase. And that is one of
21 the important pieces of information that my person
22 of skill in the art would have known because there's

1 a huge literature describing this. And that would
2 have led one to conclude that there's great
3 complementarity of these two classes of drugs. In
4 fact, these two classes of drugs have been used
5 together for a very long time because of it.

6 And my theoretical Laurie may have taken a
7 loratadine before she went to visit her Aunt Flo,
8 but she may have also taken a spray of Flonase
9 before she visited Flo. And just those single
10 treatments before a single exposure would have been
11 enough to block the acute phase because the
12 antihistamine and the late phase because of the
13 topical steroid.

14 And the topical antihistamines are just
15 much better at that than the oral antihistamines for
16 the reasons I explained before. You can get higher
17 concentrations. They start to inhibit the
18 inflammatory mechanisms, and so that's part of the
19 essence of why it's my opinion that it was obvious
20 to combine an antihistamine, particularly
21 azelastine, that blocks the acute-phase response or
22 early-phase response and a topical steroid,

1 particularly fluticasone, which blocks the late
2 phase response.

3 Q. Okay. Dr. Schleimer, I know you're very
4 eager to get your full opinion out, and I will ask
5 you questions that go through your opinion. But if
6 you could just answer the questions that I'm asking,
7 I think this will go a little bit easier.

8 So when you said "target," initially you
9 said target, did you mean symptom?

10 A. So the word "target," I suppose, has
11 multiple uses. Sometimes it can refer to molecular
12 target. And other times it can refer to a
13 symptomatic target. In that case, by antihistamines
14 targeting the early phase, I meant they block that
15 early phase, they inhibit that early phase of
16 response very well, whereas the steroids do not
17 block that early phase well at all, unless they're
18 given for a very prolonged period of time, they
19 start to.

20 Q. Okay. My question is on the definition of
21 the word "target."

22 A. I gave you an example.

1 Q. So when you used the word "target," were
2 you referring to symptomatic, targeting a certain
3 set of symptoms?

4 MR. WARNER: And one second. You can make
5 sure -- you can answer that, but also make sure to
6 finish your previous question if you weren't done.
7 I don't know if she cut you off or if you weren't
8 done or not.

9 BY THE WITNESS:

10 A. I think I was actually cutting her off, and
11 I apologize.

12 So as I said, the word "target" has many
13 uses. In that particular case, if I recall how I
14 was using it, I was referring to a drug targeting a
15 physiologic response. And in that case, the early
16 phase is one physiologic response and the late phase
17 is another different physiologic response. And I
18 was making the point that the antihistamine, the
19 topical antihistamine, especially targets or
20 inhibits that early phase but not the late phase,
21 whereas the steroid inhibits or targets the late
22 phase but not the early phase. And that's one of

1 the great sources of complementarity of these two
2 classes of drugs and these two drugs in particular
3 that made them so appealing and obvious to
4 combining.

5 Q. Is congestion the same thing as
6 inflammation, or is it a different symptom?

7 A. Congestion is one of the symptoms of
8 inflammation. But inflammation takes many forms,
9 and congestion is just one of them.

10 Q. As of June 2002, mast cell stabilizers
11 were known and available for treatment of allergic
12 rhinitis; is that correct?

13 A. Yes.

14 Q. And these mast cell stabilizers were used
15 prophylactically; is that correct?

16 A. I believe so.

17 Q. Have you studied any mast cell
18 stabilizers?

19 A. Yeah. Yes. Sorry. Yes, I have. It's not
20 been a major area of my interest, partly because
21 those drugs are really not very effective and, in
22 fact, I don't even know if they're -- they have much

1 of a market at all now. Disodium cromoglycate is
2 one example; and then there was a followup drug
3 which was mostly developed, in my opinion, because
4 the patent on Cromolyn was expiring. It was
5 actually a worse drug. It was called nedocromil.
6 I'm not sure I studied the latter, but I did some
7 experiments with Cromolyn and it's just not a very
8 effective drug. I have to say even though it's
9 referred to as a mast cell stabilizer, it's not at
10 all clear and the literature at that time made it
11 clear that mast cell stabilization was probably not
12 the main mechanism of action of that drug.

13 Q. So you're saying Cromolyn was not useful
14 in the treatment of allergic rhinitis?

15 A. I'm saying -- no, it had a market and it
16 was prescribed for a while, but it was not very
17 effective and it probably did not work by
18 stabilizing mast cells entirely or at all. In fact,
19 I don't know if people ever figured out exactly how
20 it works.

21 But the main point in the context of the
22 patents-in-suit is that that drug would have been a

1 very poor choice for a combination because of its
2 relative -- relatively weak activity compared to
3 topical antihistamine and azelastine in particular.

4 Q. As of June 2002, there were dozens of
5 antihistamines that were available, correct?

6 A. It depends on what you mean by "available."
7 I think there were maybe a half dozen that were on
8 the market of oral antihistamines. But if we're
9 talking about intranasal application, there were two
10 that I'm aware of, azelastine and levocabastine,
11 that were available. So two topical antihistamines
12 and I don't know the exact number, perhaps half a
13 dozen or so, oral ones. Some of them were in the
14 process of falling out of favor. Other ones were
15 newer ones but ...

16 Q. And antihistamines provide relief of
17 congestion; is that correct?

18 A. They can provide some, but they're not --
19 that is not the physiologic endpoint of allergic
20 rhinitis that they're most effective against.
21 They're more effective against the sneezing and
22 itching and things that are primarily driven by

1 histamine because when you talk about oral
2 antihistamines, as I mentioned, their main mechanism
3 of action is to block the H1 receptor.

4 Q. And have you researched any antihistamines
5 outside of this case?

6 A. I have.

7 Q. Which ones?

8 A. We did some experiments with desloratadine
9 actually, which are somewhat relevant to this case.
10 Desloratadine is an active metabolite of the
11 antihistamine loratadine. It turns out that when
12 loratadine is given to a patient, it's converted to
13 desloratadine. And desloratadine is actually the
14 active form of the drug; so the loratadine itself is
15 not causing the beneficial effects, but its
16 metabolite is.

17 So when Schering was about to lose the
18 patent on loratadine, they pursued this, whether
19 they could use desloratadine as a separate compound,
20 and I believe they were successful. And they asked
21 us to do some experiments on some of the
22 anti-inflammatory effects of the antihistamines that

1 are distinct from those mediated by blocking the H1
2 receptor.

3 And we did a series of experiments and
4 discovered a number of important effects that
5 desloratadine inhibited leukotriene release and I
6 believe histamine release and some other mediators.
7 And they were excited about the data and actually
8 wrote a patent, and I'm on a patent with
9 desloratadine, which they licensed from John
10 Hopkins.

11 I know I was involved in other studies of
12 antihistamine effects on basophils. Human basophils
13 are circulating cells that are similar to tissue
14 mast cells.

15 But again, antihistamines as a class of
16 drugs, I'm very interested in as a pharmacologist
17 and followed very closely because it's one of the
18 major beneficial classes in our diseases. But I
19 didn't do as much bench research on them as
20 steroids.

21 Q. And did you find that desloratadine did
22 have the anti-inflammatory effects separate from the

1 histamine inhibitors?

2 A. Yes, we did. And as I mentioned, Schering
3 he helped us write a patent, which was granted, and
4 they licensed it from Johns Hopkins. And that's
5 illustrative of the antihistamine effects that I'm
6 talking about, but one can only take benefit of with
7 topical application of with most of these drugs
8 because the drug concentration required to inhibit
9 the inflammatory cell responses is higher than the
10 oral doses of a tolerated range can lead to in the
11 nose, so you would have to put it in the nose at
12 higher concentrations.

13 Q. Is desloratadine topical?

14 A. I don't believe it's been developed as a
15 topical antihistamine, but I could be wrong.

16 Q. So it was developed as an oral?

17 A. Well, yes, it was. And I don't know if
18 they ever did in vivo experiments in humans to see
19 if oral desloratadine could give you high enough
20 concentrations to inhibit inflammation locally of
21 the sort that we studied. I would be a little
22 surprised because the concentrations were high

1 enough that they were hard to achieve by oral
2 delivery.

3 I think that azelastine and levocabastine
4 in the class of antihistamines that had
5 non-H1-mediated effects were superior to most of the
6 others, and that probably includes desloratadine.
7 But I'm not -- I haven't done experiments nor have I
8 seen specific data, so ...

9 Q. So the experiments you did an
10 desloratadine, they were in vitro?

11 A. Yes.

12 Q. And they were on the solid dosage form?

13 A. No, because in vitro studies, you have to
14 dissolve the drug. The drug is dissolved into the
15 buffers or media that we use.

16 Q. How -- What form is the drug before it was
17 dissolved?

18 A. Well, I don't recall. But usually I insist
19 on a chemical-grade preparation of drug, so it's not
20 a formulation. It's pure drug. And then we
21 dissolve it in the buffers that we use, so it's not
22 a clinically relevant preparation in any sense of

1 the term. It's not either. It's drug. It's pure
2 drug.

3 Q. And you found in your in vitro experiments
4 that it did have these anti-inflammatory properties?

5 A. Yes.

6 Q. Earlier you made a distinction between in
7 vitro and in vivo studies. Is that because in vitro
8 studies do not necessary represent what you might
9 find from in vivo studies?

10 A. Well, it's well known by investigators that
11 in vitro studies can be very useful and perfectly
12 reflect what happens in vivo. But on occasion, they
13 give different results than what happens in vivo.
14 So one has to usually follow the process from in
15 vitro to in vivo if it's involved in drug
16 development.

17 But in vitro models are very powerful tools
18 in drug discovery and understanding the actions of
19 pharmacologically active compounds on cells of
20 interest.

21 Q. But one would still have to do in vivo
22 studies to confirm your in vitro findings, correct?

1 A. Yes, yes.

2 Q. Given your research on desloratadine,
3 would you expect it to work on both the early and
4 late phase of allergic rhinitis?

5 A. So I would expect that -- As I mentioned, I
6 don't believe that they developed it topically
7 because I think the concentrations required were
8 still too high. But if it were given topically, I
9 would imagine that it would have a similar
10 pharmacologic profile to other second-generation
11 antihistamines that are given topically, like
12 levocabastine and azelastine, meaning that it would
13 have some anti-inflammatory effects in vivo, but
14 those effects would be inferior to the steroids,
15 which are profound anti-inflammatory drugs. And --
16 but beyond that, I don't think it was pursued. So
17 it's -- you're asking me to speculate, and even
18 though I was advised not to speculate, I did.

19 Q. As of June 2002, there were seven
20 different intranasal corticosteroids; is that
21 correct?

22 MR. WARNER: Can you say it again? Did you say

1 intranasal?

2 MS. EVERETT: Yes.

3 BY THE WITNESS:

4 A. I could probably think of five or six, but
5 I will accept there were seven. Let's -- I'm not
6 sure, but it's close to the number that I'm aware
7 of.

8 Q. In your report, you set forth a definition
9 of person of ordinary skill, correct?

10 A. Yes.

11 Q. I'm going to have you turn to -- if you
12 need to, I believe it's in your opening report.

13 A. Is it Paragraph 26? Oh, wait.

14 Q. It's 12. No, 27.

15 A. 25.

16 MR. WARNER: 27, I think she said.

17 THE WITNESS: Yes.

18 BY MS. EVERETT:

19 Q. You start at 25.

20 A. Yes.

21 Q. I think your actual definition is at 27.

22 A. Okay.

1 Q. Is this still your definition of person of
2 ordinary skill?

3 A. Yes.

4 Q. So in your construction, a person of
5 ordinary skill could be either an M.D. or a Ph.D. or
6 a PharmD; is that correct?

7 A. Yes.

8 Q. And then you go on to say that the person
9 would need at least 3 years of additional experience
10 in the treatment or research for treatments of
11 allergic rhinitis, including with nasally
12 administered steroids and antihistamines; is that
13 correct?

14 A. Yes.

15 Q. Would the M.D. or Ph.D. or PharmD need --
16 would each of them need three additional years of
17 treatment of patients with allergic rhinitis?

18 A. No.

19 Q. So it's fair to say just the M.D. would
20 need to have treatment; is that right?

21 MR. WARNER: Objection. Mischaracterizes the
22 report.

1 BY THE WITNESS:

2 A. Yeah, I think that treating patients is not
3 a necessary requirement for my person of skill in
4 the art. It could be helpful. And most important
5 is the experience in treatment, research,
6 development, that sort of thing and discovery.
7 Let's use the term discovery.

8 Q. Would a person of ordinary skill require
9 research in treatments or development and discovery,
10 as you've just added?

11 A. I would think so, but it's possible -- I
12 mean, I've known a lot of clinician academics that
13 are very knowledgeable in the art and would fit this
14 definition, so I ... I would say not all M.D.s that
15 treated patients for 3 years would be my person of
16 skill in the art. They would have to be an M.D.
17 that follows carefully the literature on mechanisms
18 of action of disease and mechanisms of action of
19 drugs. But, I mean, this is a very short statement
20 here.

21 Q. Yeah, so I'm trying to understand what you
22 meant here in this statement. Do you mean that your

1 person of ordinary skill must have done research for
2 treatments, as you've written in Paragraph 27?

3 A. I'd say that's highly preferable.

4 Q. Is it required?

5 A. Yeah, yeah, I would say so.

6 Q. Okay. So are you modifying your
7 definition to --

8 A. No, I'm not.

9 Q. I see and "or" here.

10 A. Yes, you're right.

11 Q. Are you telling me it's an "and"?

12 A. No, it's not an "and." The "and" is before
13 the "and at least 3 additional years of experience
14 in research." Maybe there should be an "and" there,
15 treatment and research for treatments of. I believe
16 it should be a person with an up-to-date knowledge
17 of the literature on treating allergic rhinitis on
18 pharmacological options on mechanisms of disease.

19 Can I continue with that answer?

20 Q. Just one second. I want to make sure the
21 court reporter is back.

22 Okay. Please go ahead.

1 A. Well, so also not stated here is that a
2 person of skill in the art should understand
3 allergic diseases. So a physician that manages
4 allergic diseases should be board-certified in
5 allergic diseases. And in the process of getting
6 board certification, usually research is part. And
7 it wouldn't bother me if it's clinical research,
8 epidemiological research even. But preferably it
9 would be research that involves building a knowledge
10 base that's relevant to drug discovery, invention,
11 because we're talking about patents and inventions
12 so the person of skill in the art should be one with
13 skill in that art at one level or another.

14 Q. Okay. So I want to make sure I've
15 understood the criteria you are defining as relevant
16 for your person of ordinary skill.

17 So if your person is an M.D., they should
18 be board-certified in allergic diseases; is that
19 correct?

20 A. Uh-huh, yes. With experience in research,
21 which almost always comes with board certification.

22 Q. With experience in research. Anything

1 else?

2 A. Nope.

3 Q. Okay. For your Ph.D. and your PharmD,
4 what factors must -- Let's actually strike that.
5 We'll take it one at a time.

6 For your POSA that's a Ph.D., what
7 additional criteria, if any, must he or she have?

8 MR. WARNER: Objection to the form of the
9 question. Vague. Additional beyond what's said
10 here?

11 BY MS. EVERETT:

12 Q. Beyond --

13 A. You would only strike "treatment" from what
14 I'm saying for the M.D.

15 Q. So for your POSA who's a Ph.D., they
16 should have at least 3 additional years of
17 experience in the research for treatments of
18 allergic rhinitis?

19 A. Yes.

20 Q. Okay. Is there anything else the Ph.D.
21 should have?

22 A. This is a hypothetical. It's vague, but I

1 think that the important point, which I already made
2 to you verbally and I'll make again, is that they
3 should have an understanding of the mechanisms of
4 allergic rhinitis, the mechanisms of drugs, and
5 disease management that would help them to
6 understand the next opportunity for drug
7 development. They certainly shouldn't be ignorant
8 of the medical literature in allergic rhinitis.

9 Q. And what you've just explained, does that
10 count for -- that criteria, does that apply to the
11 Ph.D., the M.D., and the PharmD?

12 A. Yes.

13 Q. Okay. And finally, your PharmD, would he
14 or she also require 3 additional years of experience
15 in the research for treatments of allergic rhinitis?

16 A. Yes.

17 Q. Are there any other criteria that would
18 apply to your PharmD POSA?

19 A. No.

20 Q. So when you applied your opinion, did you
21 use the definition you set forth in Paragraph 27, or
22 the one we've just talked about now?

1 MR. WARNER: Objection to the form of the
2 question and the implication that they're
3 significantly different.

4 BY THE WITNESS:

5 A. Yeah, I don't think they're different.
6 I've elaborated slightly more because this is a
7 short paragraph. As I said, it's a couple sentences
8 and ...

9 Q. Well, in 27 you don't require the M.D. to
10 have experience in research; is that correct?

11 A. Well, as I said the "or" probably should
12 have an "and" on Line 4. The problem is that the
13 Ph.D. can't have experience in treatment. So I
14 think I've made it clear that they need not
15 necessarily have that experience in treatment. So
16 short of putting more sentences, I hope I'm getting
17 my meaning across.

18 Q. Right. I'm just making sure I understand
19 what you use to assess the prior art, the standard
20 you use for the POSA.

21 A. As I've just described it.

22 Q. And that's what we've talked about today?

1 A. Yes.

2 Q. Not explicitly as written in 27?

3 A. That's right. That's right.

4 Q. Okay. It's -- strike that.

5 You've opined on the early phase and the
6 late phase of allergic rhinitis; is that correct?

7 A. Yes.

8 Q. And there are certain symptoms that
9 overlap -- or strike that.

10 There are certain symptoms which are found
11 in both the early and late phase of allergic
12 rhinitis; is that accurate?

13 A. Yes.

14 Q. And those symptoms are inflammation, nasal
15 congestion, and rhinorrhea; is that accurate?

16 A. Yes.

17 Q. Are there any other symptoms that appear
18 in both early and late phase?

19 A. Yes, sneezing can occur in both phases. I
20 suppose itching can as well.

21 Q. I'm going to have you turn -- oh, you're
22 on it. Your first report, Paragraph 94.

1 A. Okay.

2 Q. Paragraph 94 reads: It is with this
3 background in mind that I analyzed the following
4 general question: What would a POSA have done prior
5 to June 2002 in order to create a better treatment
6 for allergic rhinitis than what was already
7 available on the market. Is that correct?

8 A. Yes.

9 Q. How did you determine that this was the
10 question to address?

11 A. Well, I think this is one of the central
12 issues in the case over the patents-in-suit.

13 Q. I'm -- You talked about developing a
14 better treatment as opposed to opining on whether
15 the patents are obvious or not. So that was the
16 question. So I'm curious on why you chose to frame
17 the question this way.

18 MR. WARNER: Objection. Asked and answered.

19 BY THE WITNESS:

20 A. Yeah, I don't know how I can better answer
21 it.

22 Q. Did you come up with this question?

1 A. Working with Elan and Kevin, we came up
2 with this question as an important element of this
3 document.

4 Q. Did you look at the patents to develop
5 this question?

6 A. I looked at the three patents-in-suit as
7 part of the evaluation of the corpus of data that
8 was presented to me for my opinion.

9 Q. So when you reviewed the patents-in-suit,
10 did you -- is this what you thought the patents were
11 trying to address, better treatment for allergic
12 rhinitis than what was available on the market?

13 A. Yes. I mean, the patents were proposing a
14 specific combination, which appeared to me to be an
15 obvious combination. But that's what they had in
16 mind is developing a better treatment.

17 Q. Did you review the claims of the patent?

18 A. I did.

19 Q. Okay.

20 A. All three.

21 Q. Of all three patents, you mean?

22 A. Yes.

1 Q. Okay. Earlier I think you stated that
2 glucocorticosteroids work on the late phase; is that
3 correct?

4 A. Yes.

5 Q. They also work on the early phase; is that
6 correct?

7 A. It's not a simple answer. But to simplify
8 it as much as I can, a single treatment with a
9 glucocorticoid has no effect on the acute phase
10 response/early phase response. And that's also true
11 for oral steroids. A person can be on oral steroids
12 for months and their skin test response, which is
13 the early phase response is unaffected by the oral
14 steroids. That's because they don't inhibit the
15 mast cell responses, something I actually studied in
16 the laboratory.

17 But it turns out that prolonged treatment
18 with higher doses of intranasal or inhaled
19 corticosteroids can have some effect on the early
20 phase response. And they do it by reducing the
21 number of mast cells on the surface of the mucosa.
22 So they don't really inhibit the mast cell response.

1 They reduce the number of mast cells. And in so
2 doing, they can blunt the early phase, but they
3 still are not as effective in blocking that acute
4 response as, say, antihistamines topically. And as
5 I said, they only do so after a longer period of
6 time of exposure.

7 Q. So you distinguish between single
8 treatment and prolonged treatment. When you said
9 single treatment, did you just mean to use the
10 steroid once?

11 A. I was speaking in reference to the
12 experimental setting where one can control all these
13 variables. And yeah, a single dose of topical
14 steroids will block the late phase profoundly and
15 have absolutely no effect on the early phase.

16 If one gives these drugs for a prolonged
17 period, especially a week or 2 weeks or longer,
18 higher doses, the early phase begins to reduce
19 somewhat but it's still there and it's still an
20 issue.

21 Q. And in the treatment of allergic rhinitis,
22 corticosteroids are given over a prolonged period;

1 is that correct?

2 A. That's certainly the way they're
3 prescribed, less so the way they're used by
4 patients. Yes.

5 (Schleimer Exhibit Number 4 marked
6 for identification.)

7 BY MS. EVERETT:

8 Q. Okay. And I'm handing to the court
9 reporter to be marked as Schleimer Exhibit 4,
10 APOTEX_AZFL0132708 through 12. Excuse me, let me
11 correct that. Through 13.

12 And, Dr. Schleimer, please take a minute
13 to look through this article.

14 A. Okay.

15 Q. What is Schleimer Exhibit 4?

16 A. This is a paper published in the New
17 England Journal of Medicine by Ulf Pipkorn, David
18 Proud, Lawrence Lichtensten, Anne Kagey-Sobotka,
19 Philip Norman, and Robert Nacierio, who were my
20 colleagues at Johns Hopkins.

21 Q. And were they your colleagues during the
22 time of this research and publication?

1 A. What's the date? Yes.

2 Q. And this is something you cited in your
3 reports?

4 A. I know we cited a Pipkorn paper. I thought
5 the one we cited was one I was an author on with
6 Ulf, but maybe that's not right. Maybe this is the
7 one we cited. I think maybe Dr. Kaliner cited this.

8 Q. And for your convenience, if you want to
9 go to your opening report Materials Considered --

10 A. Okay.

11 Q. It is --

12 A. Is it this paper?

13 Q. It is, I believe, this paper.

14 A. Okay. Yeah, I see that.

15 Q. Were you involved in this research?

16 A. No. I would have been an author, if I
17 were. But I was aware of it, and I collaborated
18 with Ulf on a similar study around the same period
19 of time.

20 Q. In this study, it appears that the author
21 studied the effect of intranasal glucocorticosteroid
22 on early and late phase; is that correct?

1 A. Yes.

2 Q. And the authors concluded that intranasal
3 glucocorticosteroid actually had an effect on early
4 phase. Is that true?

5 MR. WARNER: Objection to the form of the
6 question. I don't know if you're quoting. Anyway,
7 take the time to read the article.

8 BY THE WITNESS:

9 A. So this is a study with one week's
10 treatment, which in our previous discussion, I would
11 consider a more prolonged treatment, in which
12 there's a partial inhibition of the early phase.

13 Q. I'm going to have you turn to Page 1508.
14 And in the Results section, it says in the
15 concluding sentences in the first full paragraph:
16 Topical flunisolide, unlike systemic prednisone,
17 also reduce the early response. Not only do
18 symptoms and mediators decrease absolutely, but the
19 dose response curves appeared to be shifted
20 approximately tenfold.

21 Do you see that?

22 A. It's the bottom left?

1 Q. Yes. So under Results --

2 A. Yeah, I see. Yes.

3 Q. And here, the authors are discussing the
4 effect of topical flunisolide on the earlier
5 response?

6 A. Yes.

7 Q. And they said not only did symptoms and
8 mediators decrease absolutely, do you see that first
9 part?

10 A. Uh-huh.

11 Q. But the dose response curves appeared to
12 be shifted tenfold?

13 A. Yes.

14 Q. When the authors say not only did symptoms
15 and mediators decrease absolutely, were they
16 referring -- what were they referring to?

17 MR. WARNER: Objection to the form of the
18 question. Calls for speculation. You can read the
19 document, if you need to.

20 BY THE WITNESS:

21 A. I believe they were referring to the
22 symptoms and mediators that are reported in the

1 data.

2 Q. Okay. Earlier you said that this showed
3 that there was a partial effect on the early phase.
4 Why did you say there was a partial effect on the
5 early phase?

6 A. Because the early phase is still there and
7 intact. It requires slightly more antigen. And in
8 any given dose of antigen, it's partially blocked by
9 40 percent or 50 percent, in some cases, or more or
10 less.

11 Q. If you move to the next column, the first
12 full sentence says: The net increase in the amount
13 of histamine released in the entire early response
14 was decreased by 75 percent, less than 0.01, as was
15 the amount of histamine released during the maximal
16 response to the antigen.

17 Do you see that?

18 A. Yes, uh-huh.

19 Q. So histamine is released in the early
20 phase; is that correct?

21 A. Yes.

22 Q. And this is reporting that 75 percent of

1 what was released in the early phase was decreased;
2 is that accurate?

3 A. Yes, but it's important to point out that
4 this is in the nasal lavage fluid. So the nose is
5 washed out with fluid, and the histamine is measured
6 in the fluid that's recovered from the nose. That
7 only reflects the histamine released by the mast
8 cells that are right at the very surface of the
9 mucosa.

10 And as I explained previously, one thing
11 that steroids do after a week or more of treatment
12 is they cause the mast cells to move deeper into the
13 tissue. They're still there. In fact, Ulf Pipkorn
14 is the one who showed this very, very clearly. And
15 he has other papers showing, very similar to this
16 showing that a single dose of steroid has absolutely
17 no affect on the early phase and inhibits the late
18 phase. And he showed that the mast cells, which
19 during the season, an allergic person or after
20 exposure to antigen move up to the surface and the
21 steroids can't prevent that movement of the mast
22 cell.

1 So what I'm saying is the collection of
2 histamine in the fluid only reflects what's released
3 from a portion of the mast cells; and the ones
4 deeper in the tissue may release more or less, but
5 you can't measure it in this protocol.

6 Q. So you have no way of knowing whether
7 there are any histamines that were unreleased but
8 still in the nose from this protocol; is that
9 correct?

10 A. Well, in this study, they didn't collect
11 that. But I believe there are some methods to
12 measure that. It's very difficult because histamine
13 doesn't stick around very long.

14 But if you look at Figure 1, you also see
15 that the late phase reaction in terms of total
16 number of sneezes was completely inhibited, whereas
17 the early phase reaction was inhibited by about half
18 in the sneezing there. And there was similar
19 differential effects with the kinins and the
20 TAME-esterase.

21 Q. Can you say that last sentence again,
22 similar differentials with?

1 A. Right, where the late phase was inhibited
2 more than the early phase, for instance, with the
3 kinins, although there are very little kinins in the
4 late phase. So the TAME-esterase.

5 Q. So you noted earlier that sneezes were
6 reduced by 50 percent in Figure 1?

7 A. Yeah, maybe 55. I don't know. I don't
8 have the precise number.

9 Q. And just to be clear, you're referring to
10 the effect of flunisolide on the total number of
11 sneezes?

12 A. Yes.

13 Q. Okay. So it's fair to say the flunisolide
14 reduces a fair number -- strike that.

15 So are you focusing on sneezes because
16 they're early phase sneezes?

17 A. No. I mention sneezes because it
18 differentiates the inhibitory effect against the
19 late phase versus early phase, even with prolonged
20 steroid. So you see the late phase is inhibited,
21 the sneezing is inhibited by 90 percent. I can't
22 tell exactly, but it looks like 90 percent or more,

1 whereas the early phase is inhibited by 55 percent
2 or whatever the number is.

3 Q. If, as it's shown here, the flunisolide
4 inhibits sneezing in the early phase by 55 percent,
5 that's a significant reduction; isn't that correct?

6 A. It's meaningful.

7 Q. Okay.

8 A. But in the real world, it could mean -- in
9 the real world, it could mean instead of sneezing
10 your head off, you're sneezing half your head off.

11 Q. So you would say then there is still, even
12 with these treatments, there was a call for better
13 treatments at this time?

14 A. Yeah, they're still sneezing ten times on
15 the steroid.

16 Q. And is that your opinion in the '80s, that
17 as of this -- strike that.

18 As of the time of this article, 1987, was
19 it your opinion that there was a need for treatments
20 that provided better symptom relief?

21 A. Yes. I think in the '80s and even now,
22 patients with severe disease still suffer from this

1 disease, even with the available drugs.

2 Q. So when you said the '80s, is it fair to
3 assume you also had the same opinion in the '90s
4 that there was a need for treatments that provided
5 better symptom relief for patients suffering from
6 allergic rhinitis?

7 A. Yes, of course.

8 Q. I'm going to ask again. And in June 2002,
9 was there a need for treatment -- strike that.

10 As of June 2002, was there a need for
11 treatments that provided better symptom relief for
12 patients suffering from allergic rhinitis over what
13 was available then?

14 A. There was.

15 (Schleimer Exhibit Number 5 marked
16 for identification.)

17 BY MS. EVERETT:

18 Q. I'm handing to the court reporter to be
19 marked as Schleimer Exhibit 5, APOTEX_AZFL012232
20 through 56.

21 MR. WARNER: You should wait until she asks you
22 to mark up the document.

1 BY THE WITNESS:

2 A. Oh, I'm sorry.

3 Q. Do you recognize what's been marked as
4 Schleimer Exhibit 5?

5 A. I do.

6 Q. What is it?

7 A. It's a review that I wrote for the
8 Middleton Textbook of Allergy, which is the leading
9 allergy textbook.

10 MR. WARNER: Do you want me to give him my
11 clean one?

12 BY THE WITNESS:

13 A. I'm just helping myself find a passage,
14 but ...

15 MS. EVERETT: I'm fine with that copy.

16 MR. WARNER: I just don't want you later to
17 complain that he marked it improperly or something.

18 MS. EVERETT: I would probably not make that
19 complaint. If it becomes an issue, we can put in a
20 clean version for the exhibit and things.

21 BY THE WITNESS:

22 A. I'm sorry. I didn't know I couldn't have a

1 pen.

2 Q. We like to put a lot of rules on our
3 witnesses.

4 A. I understand. We're a country of rules.
5 That's what makes it great.

6 Q. You are telling me that this was a book
7 chapter that you had written?

8 A. Yes.

9 Q. And it was published, this -- strike that.
10 This particular version was published in
11 1998; is that correct?

12 A. Yeah, I wrote it many times, so this is
13 '98? Yeah, yes, '98.

14 Q. I apologize. I didn't mean to speak over
15 you.

16 A. Yes, it's 1998.

17 Q. And I believe you cite this article in
18 your expert reports?

19 A. Yeah, I don't remember why I cited it, but
20 I believe we did.

21 Q. Okay. So I'm going to have you turn to
22 Page 650.

1 A. Okay.

2 Q. In the second column --

3 A. Okay.

4 Q. -- the paragraph that starts: The
5 question of the mechanism of action?

6 A. Uh-huh. It's the one I wrote on.

7 Q. Yes. And then towards the end of that
8 particular paragraph, you state: Treatment with
9 topical steroids one week or longer inhibits the
10 acute phase response as measured by symptoms in the
11 appearance of mediators, footnote to -- strike
12 that -- excuse me. I'm going to start over.

13 In the paragraph you write: Treatment
14 with topical steroids one week or longer inhibits
15 the acute phase response as measured by symptoms and
16 the appearance of mediators and a footnote to 306.

17 Do you see that?

18 A. Yes.

19 MR. WARNER: I think it's an endnote.

20 MS. EVERETT: Kevin is more accurate. I will
21 accept that. That is an endnote.

22 BY THE WITNESS:

1 A. Right. A reference.

2 Q. And if you see, the endnote refers to the
3 Pipkorn article that we just looked at?

4 A. Yes.

5 Q. As Schleimer 4; is that correct?

6 A. Correct.

7 Q. So here you have described the results of
8 the studies; is that accurate?

9 MR. WARNER: Objection to the form of the
10 question. Vague.

11 BY THE WITNESS:

12 A. Actually, this is topical steroid in that
13 paper. And in the review, you may have found an
14 error. I put oral steroid in this review.

15 Q. You may want to go back and look at
16 Schleimer 4.

17 A. Wait. Does that say 305?

18 Q. 306 is the endnote.

19 A. Are you sure? Oh, I see. The one I
20 referenced. I'm sorry. I looked at what I
21 underlined instead of what you said.

22 Q. Okay. So just to be clear we're on the

1 same spot, I am at the sentence that says:

2 Treatment with topical steroids --

3 A. Yes.

4 Q. -- one week or longer inhibits the acute
5 phase response --

6 A. Yes.

7 Q. -- as referenced by the appearance of
8 symptoms and mediators?

9 A. Yes, we're caught up. My bad.

10 Q. 306 looks at the Pipkorn study --

11 A. Yes.

12 Q. -- that we just looked at?

13 A. That's correct.

14 Q. You, in this chapter, summarized the
15 Pipkorn study; is that fair?

16 A. Well, to the extent that one sentence
17 summarizes it, yes. Ulf would be upset at me to
18 summarize his whole paper with one sentence.

19 Q. I won't tell him.

20 A. Okay.

21 Q. In your summary, you write that the
22 topical steroid inhibited the acute phase response.

1 Is that correct?

2 A. Uh-huh.

3 Q. And by acute phase, did you mean early
4 phase?

5 A. Yes.

6 Q. And you did not qualify how much of the
7 acute or early phase was inhibited; is that
8 accurate?

9 A. That's correct.

10 Q. Okay.

11 A. Can I point out in that same paragraph that
12 I wrote 2-day treatment with oral steroids preceding
13 experimental challenge demonstrates no inhibition of
14 the acute phase response after challenge and nearly
15 complete inhibition of the late phase. And that was
16 reference 305, which is another Pipkorn study. So
17 as I said, the experimental challenge model is a
18 model. And so 2 days of oral steroid treatment
19 selectively inhibited the late phase while having no
20 effect on the early or acute phase.

21 Q. And one day -- or strike that. Excuse me.

22 One week of treatment with topical

1 steroids inhibited both early and late phase. Is
2 that accurate?

3 A. It's accurate, but the early phase was
4 partially inhibited.

5 Q. And in your summary in Schleimer 5, you
6 did not note that it was partially inhibited? You
7 wrote that it inhibits the acute phase response?

8 A. I just used the word inhibition. I didn't
9 qualify it, total, partial, modest. I didn't use
10 any qualifiers.

11 MR. WARNER: Should we try another break? I've
12 got about an hour and 10 minutes, I think.

13 MS. EVERETT: Oh, sure.

14 THE VIDEOGRAPHER: We're now going off the
15 record at 11:36 a.m.

16 (A short break was taken.)

17 THE VIDEOGRAPHER: We are now going back on the
18 record with the beginning of media No. 3. The time
19 is now 11:53 a.m.

20 BY MS. EVERETT:

21 Q. Actually, I am going to have you refer
22 back to Exhibit 5, Dr. Schleimer. Welcome back.

1 A. Thank you.

2 Q. You're welcome.

3 And you -- Exhibit 5, you cited Exhibit 5
4 in your report; is that correct?

5 A. Yes.

6 Q. Okay. Great. Thank you. That's all.

7 A. That's all?

8 Q. That's all.

9 A. Oh, okay.

10 (Schleimer Exhibit Number 6 marked
11 for identification.)

12 BY MS. EVERETT:

13 Q. I am handing to the court reporter to be
14 marked as Schleimer Exhibit 6, Middleton's Allergy
15 Principles and Practices, Volume I, 6th Edition.

16 Do you recognize Schleimer Exhibit 6?

17 A. I do.

18 Q. What is it?

19 A. It's the same chapter but a different
20 edition of Middleton that was published in, looks
21 like, 2003. Is that what it was? Wait. It says
22 copyright 2003. Is that right?

1 Q. Yes, that's what I'm seeing.

2 A. Yeah.

3 Q. So is this the next edition of your
4 chapter on glucocorticosteroids?

5 A. Yeah, I don't think there was an
6 intervening one.

7 Q. And I'm going to have you turn to
8 Page 903.

9 A. 903, okay.

10 Q. And at the top of the page, it continues
11 from the bottom of 902. There's a section nasal --
12 excuse me, strike that. Nasal glucocorticoids in
13 allergic rhinitis, anti-inflammatory effects.

14 A. Yes.

15 Q. And at the bottom of the first paragraph
16 on 903, you write: Nasal GC, which are
17 glucocorticoids, when chronically administered can
18 block the development of both the immediate and late
19 phase allergic responses.

20 Do you see that?

21 A. Yes. Uh-huh.

22 Q. And so in this edition, you've said that

1 they can block the development of the immediate
2 phase. Is that accurate?

3 A. Yes. Block is a word like inhibit that has
4 a range of penetrants of the effect.

5 Q. And in there, you have an endnote to 589.

6 A. Uh-huh. Yes.

7 Q. And the article that you cite by Nelson,
8 Mechanisms of Intranasal Steroids in the Management
9 of Upper Respiratory Allergic Diseases is dated
10 1999; is that right?

11 A. Yes.

12 Q. And you just said say moment ago that
13 "block" can have a number of penetrants. But you
14 did not specify any in your summary?

15 A. That's correct.

16 Q. Thank you. You can put that aside. In
17 your report, you opined that one of the reasons to
18 select -- strike that.

19 In your report, you opine that a person of
20 ordinary skill might have selected fluticasone
21 propionate over other topical steroids due to its
22 potency.

1 Do you recall that?

2 A. Yes.

3 Q. So I'm going to have you turn to
4 Paragraph 66 of your opening report.

5 A. Uh-huh.

6 Q. And here you cite Martin and Stellato?

7 A. Yes.

8 Q. Okay. For the proposition that
9 fluticasone is -- has an increased potency over
10 potentially other steroids; is that fair?

11 A. Yes. Which means that you need smaller
12 microgram quantities of the drug to get the same
13 amount of effect.

14 Q. And would the amounts that you administer
15 vary based on condition that you're treating?

16 MR. WARNER: Objection to the form. Vague.

17 BY MS. EVERETT:

18 Q. Strike that.

19 So, for example, if you were using
20 fluticasone to treat allergic rhinitis and then you
21 were also using it to treat a different condition,
22 could potency in one area be translated into

1 another?

2 A. Generally yes.

3 Q. Are there exceptions?

4 A. If pressed, I'm sure I could find some
5 exceptions where there was some kind of local
6 metabolism of one selectively or what have you. But
7 in general, yes. The most potent ones are -- of the
8 topical steroids are -- most have the same rank or
9 similar rank order of potency in, for instance, the
10 nose as they do in the lungs. But that's a general
11 statement.

12 Q. Would potency vary based on the dosage
13 form? For example, would it vary if one
14 administered it through the nose versus it's
15 inhaled?

16 A. Well, have to be careful not to conflate
17 dose and potency. I mean, potency determines the
18 dose that is half maximally effective or the dose
19 that is maximally effective. The more potent a drug
20 is, the lower the dose for half maximal effect and
21 the lower the dose for maximal effect.

22 Another issue is efficacy. And somewhere

1 in one of these reports, we talked about the
2 difference between potency and efficacy. Efficacy
3 refers to the maximal effect that a similar class of
4 drugs can have. So if you have drugs A, B, C, D,
5 and E, A being the most potent and E being the least
6 potent, you'll get a family of dose response curves
7 where they all have the same maximal effect when
8 they get up to their maximal dose. But the doses
9 required to get that maximal effect or the half
10 maximal effect are lower and lower as you go to the
11 more potent drug.

12 And the paper by Stellato is one in which
13 we compared the potency of, I think, just about all
14 of the topical intranasal or inhaled steroids at the
15 time, using several in vitro systems. And we ranked
16 them. And fluticasone and mometasone -- When I say
17 fluticasone, I mean fluticasone propionate. When I
18 say mometasone, I mean mometasone furoate. But
19 those two were more potent than the others. And the
20 least potent was hydrocortisone, which is our
21 endogenous steroid. Potency and efficacy are
22 different. Potency determines the dose generally.

1 So the more potent a drug, the lower the microgram
2 quantity required.

3 Q. Got it. I think we may have -- you may
4 have misunderstood my question or I misspoke.

5 When I was talking about dosage form, I
6 wasn't talking about the amount given, micrograms
7 given. I was asking, my question is: Is there a
8 difference in potency of a drug if it is
9 administered through the nose versus orally?

10 A. Well, as I discussed with the
11 antihistamines, the same is -- the same would be
12 true with the steroids. If you give a drug orally,
13 only a minute fraction of it will end up in the
14 nose. And even a fraction of it only will end up in
15 the circulation.

16 So in general, drugs are more -- well, the
17 total dose that needs to be administered locally is
18 less than the total dose that needs to be
19 administered systemically at a given site. I don't
20 know if that answers your question.

21 Q. So can you extrapolate potency of a drug
22 when it is given in a different dosage form?

1 MR. WARNER: Objection to the form. Vague.

2 BY THE WITNESS:

3 A. I still, the question makes -- doesn't make
4 sense to me. I'm sorry.

5 Q. Okay. If a drug is potent in an oral
6 form, can you extrapolate whether it would be potent
7 in a nasal form?

8 A. No. I mean, if we're talking about
9 steroids.

10 (Schleimer Exhibit Number 7 marked
11 for identification.)

12 BY MS. EVERETT:

13 Q. I'm handing to the court reporter to be
14 marked as Schleimer Exhibit 7, a document with the
15 Bates APOTEX_AZFL0132133 through 141.

16 A. Okay.

17 Q. Do you recognize what's been marked as
18 Schleimer Exhibit 7?

19 A. Yes.

20 Q. What is it?

21 A. It's a paper by Richard Martin and his
22 group with the Asthma Clinical Research Network.

1 Q. Is this the paper you cited in
2 Paragraph 66 of your report?

3 A. What's the citation number? Yes.

4 Q. Have you worked with any of the authors
5 listed in Martin 2002, which is Schleimer Exhibit 7?

6 A. Could you please define "worked"?

7 Q. Sure. Have you ever conducted any
8 research or published with any of the authors listed
9 in Schleimer Exhibit 7?

10 A. Have I ever published with any of them?
11 Steven Peters, I've published with. We were fellows
12 together at Johns Hopkins. Jim Fish, I believe I
13 have a couple papers with. And I think that's it.

14 Q. Okay. And this appears to be a comparison
15 of inhaled corticosteroids preparations; is that
16 correct?

17 A. Yes.

18 Q. And it's for use in asthma?

19 A. Yes.

20 Q. Is that right? So is it a different form,
21 a different -- strike that.

22 It's a different dosage form to inhale a

1 corticosteroids than to take it nasally?

2 A. Yes. It's a topical application in both
3 cases; but the formulations will be different more
4 often than they're similar, I would think.

5 Q. But there are differences between --

6 A. Yes.

7 MR. WARNER: Let her finish the question.

8 BY THE WITNESS:

9 A. I'm sorry.

10 Q. I'll ask it again.

11 But there are differences between inhaled
12 corticosteroids and corticosteroids taken nasally;
13 is that accurate?

14 MR. WARNER: Objection to the form of the
15 question. It's vague.

16 BY THE WITNESS:

17 A. Talking about formulation differences?

18 Q. Correct.

19 A. Yes. The drugs are identical, but the
20 formulation can differ.

21 Q. Can there be differences in potencies?

22 A. Yes. The point of this paper is there are

1 differences in potency of these drugs. In this
2 case, they're looking at systemic or undesirable
3 effects. Yes, there can be differences in potency.

4 Q. And to be clear, when I say there's
5 difference in potencies between the same drug taken
6 intranasally versus inhaled form?

7 A. I don't think you can make the comparison
8 because you're looking at nasal readouts in one case
9 and lung readouts in the other. So I don't think
10 you can make the comparison. The surface area of
11 the lung is roughly equal to the size of a tennis
12 court. The surface area of the nose is very small.
13 It's less than this napkin. So you just really
14 can't compare from one to the other. But the drugs
15 are compared to each other in one model.

16 Q. So then is it fair to say you can't
17 extrapolate the potency of fluticasone propionate in
18 an inhaled form and the potency of fluticasone
19 propionate in an intranasal form?

20 A. So it has relative potency to the other
21 drugs in any given model. And as I've already
22 answered to your question, that in general, the rank

1 order of potency will be the same from tissue to
2 tissue. So I think that fluticasone is potent.
3 It's among the most potent steroids we have in both
4 the nose and the lungs.

5 Q. So here you made a distinction, and you
6 said there's the same potency from tissue to tissue.
7 Earlier I thought you had said you can't actually
8 make a comparison of an steroid taken in oral form
9 versus an intranasal form; is that right?

10 A. Those are different questions. Now you're
11 talking about systemic delivery with measurement in
12 one tissue. I'm talking about topical delivery to
13 two different tissues but they're both mucosal
14 tissues. And you could extend that to injecting the
15 steroids in skin, which has been done. And the rank
16 order of potency in the skin is similar. It's never
17 identical, but it's similar to the rank order of
18 potency in other locations. And that's the point
19 I'm trying to make.

20 Q. Are you aware of any studies comparing the
21 potency of corticosteroids in -- taken intranasally?

22 MR. WARNER: Can you read that back? I'm

1 sorry. Or just repeat it.

2 (Record read as requested.)

3 BY THE WITNESS:

4 A. I am not aware of a study done in the nose
5 comparable to this where a large number of steroids
6 were compared by one investigative group in the
7 nose. That doesn't mean it doesn't exist, but I'm
8 not aware of a study similar to this. And it's
9 partly why I chose this study.

10 Q. Okay. And it's fair to say that if you
11 knew one that existed, you would have cited that in
12 your report?

13 MR. WARNER: Objection to the form of the
14 question. It's an incomplete hypothetical.

15 BY THE WITNESS:

16 A. If I was aware of one in the nose that
17 looked at a large number of steroids, I would cite
18 it.

19 (Schleimer Exhibit Number 8 marked
20 for identification.)

21 BY MS. EVERETT:

22 Q. I'm handing to the court reporter to be

1 marked as Schleimer Exhibit 8, APOTEX_AZFL0132282
2 through 288.

3 A. Okay.

4 Q. Do you recognize what's been marked as
5 Schleimer Exhibit 8?

6 A. Yes, I do.

7 Q. What is it?

8 A. This is a paper that we wrote in 1999 in
9 which we evaluated most of the available topical
10 glucocorticoids used in the nose or lungs for their
11 potency, the relative potency of inhibiting a
12 variety of cell types, human basophil responses,
13 human eosinophil responses, human epithelial
14 responses. These are three of the cell types
15 integrally involved in allergic responses.

16 The reason this paper was of interest and
17 published in the leading allergy journal and also
18 cited a great deal is that it's one of, if not the
19 most complete comparison of all these drugs. So
20 often studies of these drugs individually are
21 sponsored by the company that own the drugs, and
22 they're not interested in comparing to other drugs.

1 So we did this to some extent probably against the
2 wishes of some of these companies.

3 Q. And this is what -- strike that.

4 You have cited the Stellato article in
5 Paragraph 66 of your report, correct?

6 A. Yes.

7 Q. And Schleimer 8 is an in vitro comparison;
8 is that accurate?

9 A. That's correct, although these responses
10 are thought to be very relevant to what happens in
11 vivo. So eosinophils are cells that come into the
12 late phase and mediate the physiologically phase
13 response. And steroids cause them to die, undergo
14 apoptosis.

15 Epithelial cells, when antigen exposure
16 occurs, are activated and play a role in recruiting
17 the inflammatory cells. So these are cells that are
18 activated during allergic disease and the steroids
19 are thought to work against them.

20 More relevant is that when you spray an
21 intranasal steroid into the nose, the main cell type
22 that is exposed to the drug immediately is the

1 epithelium. So in the nose, the airway epithelial
2 cells are like the skin. They cover the whole nose.
3 So looking at the effects of all these steroids on
4 the epithelial response is very relative to disease.

5 The final thing is human basophils release
6 histamine, and they've been used for 50 years as a
7 very powerful surrogate of the mast cells that are
8 involved in allergic responses. And studies have
9 shown over and over again for many decades that they're a
10 very good indicator of what happens in the mast
11 cells.

12 So again, since these were three of the
13 most relevant cell types, this paper was highly
14 cited and performed a useful function for the field
15 because it directly compared the potency of all
16 these drugs that were receiving widespread clinical
17 use.

18 And as you can see, it showed that
19 fluticasone propionate and mometasone furoate were
20 the two most potent steroids in all three assays.
21 And if you look at Figure 6, when we compared all
22 the drugs in the composite of the three assays, you

1 see fluticasone is the furthest to the left. That
2 means it's the most potent in the balance of these
3 three assays, although in one of the assays,
4 mometasone was slightly more potent than the
5 epithelial cells.

6 So I think that was the main value of this
7 report.

8 Q. And to be clear, my question was, this was
9 an in vitro comparison? I just want to make --

10 A. Yes, this is an in vitro comparison.

11 Q. So you and your fellow co-authors
12 concluded that this data should be combined with
13 data in vivo to -- that -- strike that.

14 I'm going to have you turn to the
15 conclusion in the abstract.

16 A. In the abstract, okay.

17 Q. These data combined with pharmacodynamics
18 of these drugs in vivo may be useful in estimating
19 GC local anti-inflammatory effects?

20 A. Yes.

21 Q. Did I read that correctly?

22 A. Uh-huh.

1 Q. So at the time you published this article,
2 you concluded that your results should still be
3 combined with in vivo results to determine the
4 further usefulness of these drugs and their
5 anti-inflammatory effects; is that correct?

6 A. I think I need to elaborate on that because
7 pharmacodynamics is the field of the study of drug
8 action whereby one looks at the factors that
9 influence the local concentration of a drug. So
10 drugs can be absorbed at different rates from each
11 other. They can be metabolized at different rates
12 from each other. They can stick in the tissue
13 longer or shorter. But we're actually not giving a
14 lot of ground here in terms of in vivo/in vitro
15 differences.

16 What we're saying is if you were able to
17 measure the actual concentration of these drugs
18 that's found in vivo in the clinical situation, the
19 data we have combined with that could be merged to
20 make fairly precise predictions about the relative
21 efficacy. So I'm not saying here that these are
22 just in vitro studies and they're not meaningful or

1 I'm saying that in vivo studies are the only
2 meaningful ones.

3 What I'm saying is these are very
4 meaningful, but they're even more useful if you have
5 means and methods to determine the concentration of
6 the drug at the site that you're interested in. And
7 that's what pharmacodynamics and pharmacokinetics
8 are. They're whole fields of pharmacology.

9 Q. On the same page in the paper, second
10 column, you say midway through: It is not a
11 certainty that all GC will behave similarly either
12 in vitro or in different in vivo cellular systems.

13 Do you see that?

14 A. Uh-huh. Well, I don't. But I accept that
15 I say that. Yes, I see it now, it is not a
16 certainty that all -- yes, uh-huh.

17 Q. So you would still need to take your
18 findings and consider whether the glucocorticoids
19 would behave similarly in vivo; is that what you're
20 saying?

21 A. Yeah, and that's what that pharmacodynamic
22 reference is. If you look at the next sentence:

1 Variation in lipid solubility receptor affinity
2 binding to lung tissue at sites other than the GR,
3 glucocorticoid receptor, and other factors can
4 influence the potency and duration in the lungs in
5 vivo. But we think that the data we present here
6 are still valid structure activity relations, as
7 it's called, which determines the relative potency
8 of these drugs.

9 I even go on to say that because of the
10 presence of the enzyme 11-beta-hydroxysteroid
11 dehydrogenase in epithelial cells, local metabolism
12 may also affect the effectiveness of inhaled or
13 endogenous glucocorticosteroids.

14 Now, we know from other studies that most
15 steroids are not sensitive to that enzyme, but some
16 of them are. Triamcinolone acetylene is an example.
17 This is an enzyme found in the lungs and nose that
18 will degrade that drug, and that makes it less
19 appealing because it shortens its duration of action
20 in the tissue.

21 So based on the potency, a person of skill
22 in the art who wanted to build allergic rhinitis

1 treatment around an intranasal steroid would realize
2 that fluticasone is the most potent and, therefore,
3 would require likely lower quantities of drug in
4 these several assays. And that would be added to
5 all the other factors that I'm sure we'll discuss,
6 like the popularity of the drug, its proven
7 efficacy, its safety, et cetera, which made it,
8 among the topical steroids, the most attractive.

9 Q. I'm going to have you turn back to
10 Figure 6.

11 A. Okay.

12 Q. In that exhibit we're looking at right
13 now.

14 A. Yes.

15 Q. Schleimer 8. You've compared in this
16 chart fluticasone, mometasone, budesonide,
17 triamcinolone, is it beclomethasone?

18 A. Uh-huh.

19 Q. And hydrocortisone?

20 A. Very good, yes. Exactly right.

21 Q. Is there a statistically significant
22 difference between the effect of fluticasone,

1 mometasone, and budesonide on the basophils?

2 A. Oh, my gosh. Let me see. So one asterisk,
3 significant ... You asked about fluticasone,
4 mometasone, and budesonide?

5 Q. I did.

6 A. Pound sign. They're all, all three of them
7 are statistically significantly different from
8 hydrocortisone. So that's the only test we discuss
9 there. So just based on this, without going back to
10 the notebooks, there's no statement here that they
11 are statistically significantly different from each
12 other.

13 Q. Okay. Does formulation of each of these
14 corticosteroids affect their potency?

15 A. Are you talking about intranasal
16 application in this case?

17 Q. Yes.

18 A. I would think that it could, but I'm not
19 aware of studies comparing different formulations.
20 So I have to say I don't know.

21 Q. Okay. This article was published in the
22 Journal of Allergy and Clinical Immunology.

1 A. Yes.

2 Q. And I believe you are an editor of that
3 journal at one time; is that accurate?

4 A. I was an associate editor at one time. I
5 don't remember at this time. But yes, I was an
6 associate editor at one time.

7 Q. Do you recall when you were an associate
8 editor at -- do you have an abbreviation? Do you
9 call it JACI? Or ...

10 A. JACI, yes. Good guess.

11 Q. Do you recall when you were an editor,
12 associate editor at JACI?

13 A. I can't tell you the precise years. I
14 believe it was before this time, but I don't. If
15 it's not in my CV, which it may not be, it seems odd
16 to leave out an editorship, but I'm afraid I'm not
17 very attentive to my CV. Everything that's there is
18 correct, mostly. But there are lots of things that
19 I did that are not here.

20 I don't know if the time overlaps. But if
21 it did overlap, the policy of the journal at that
22 time was that all papers from Johns Hopkins, which

1 is where the associated editors were, would be sent
2 to a managing editor outside of Johns Hopkins who
3 would make all of the assignment of reviewers and
4 all the decisions independent of any influence from
5 the editors at Johns Hopkins.

6 Q. Sorry. I'm just lost in my exhibits for a
7 moment. Just bear with me.

8 MR. WARNER: Are you all right to keep going?
9 Or do you want a break?

10 THE WITNESS: Oh, it's up to you. I'm fine.

11 MS. EVERETT: It's actually up to you. You are
12 the star of the show.

13 THE WITNESS: It's up to me?

14 MR. WARNER: Is this a good time for lunch?

15 MS. EVERETT: Now is as good as any.

16 THE WITNESS: Okay. That's fine.

17 MS. EVERETT: Thank you.

18 THE VIDEOGRAPHER: We are now going off the
19 record at 12:33 p.m.

20 (A lunch break was taken.)

21 THE VIDEOGRAPHER: We are now going back on the
22 record at 1:25 p.m.

1 BY MS. EVERETT:

2 Q. Welcome back.

3 A. Thank you.

4 Q. Before the break, we were talking about
5 your tenure as an associate editor on JACI, I
6 believe?

7 A. Yes.

8 Q. And I'm going to have you turn to your CV.
9 I believe it's in the editorial board section.

10 A. Okay. Where is that section? Sorry.

11 Q. I believe it's Page 3 of your CV.

12 A. Page 3, okay. Ah. Okay.

13 Q. So here it says you are on the editorial
14 board in 1990 to 1996. Is that accurate?

15 A. Hopefully that's what it says. I tend to
16 believe it.

17 Q. Actually, there's two so you're on the
18 editorial board 1990 to 1996, and you were senior
19 associate editor 1993 to 1998?

20 A. Okay. Yes.

21 Q. Did you hold any other positions at JACI?

22 A. No, no formal positions. I reviewed

1 manuscripts. I have for decades.

2 Q. And you continue to review manuscripts for
3 JACI?

4 A. I continue to be invited to. When I have
5 the time, I do.

6 Q. Okay. In your report, Paragraph 11, you
7 characterize JACI as the worldwide leading journal
8 in the field of allergy. Do you see that sentence?

9 A. Yes, it's the allergy journal with the
10 highest impact factor among all allergy journals.

11 Q. Is that what you mean by leading journal
12 in the field of allergy?

13 A. Yes, highest impact.

14 Q. And this journal -- strike that.

15 You go on to state: This journal
16 publishes the best research in the field relevant to
17 the actions of antihistamines, or glucocorticoids, a
18 class of steroids, in allergic disease.

19 Do you see that?

20 A. Yes, I do.

21 Q. Do you continue to believe the journal
22 publishes the best research in the field?

1 A. It's an average obviously. There's a range
2 of quality published by all journals. This is not
3 to say that JACI never publishes bad papers or that
4 other journals don't publish great papers. It's
5 just on average, yes.

6 Q. And do you believe the editors review the
7 publications and review it for scientific accuracy
8 and integrity?

9 A. That's one of their main functions, yes.

10 Q. Have you ever participated in selecting a
11 feature for the editor's choice section of JACI?

12 A. I have had a couple of my papers selected
13 as editor's choice features, and of course I was
14 pleased for that. And when that happened, they
15 asked me to write a paragraph that was the paragraph
16 that appears in the front of the journal. So that's
17 actually how I know that those paragraphs are
18 written by the authors.

19 Q. If the editors at JACI had disagreed with
20 your sentences in the paragraph, would they have
21 edited them?

22 A. One would hope so. Although in cases where

1 I was invited, I don't recall any editorial
2 oversight of the process. I mean, the editor didn't
3 alter any of my statements, so they went in
4 verbatim.

5 Q. Is that potentially because the editors
6 agreed with your statements?

7 A. Yes. One would hope that we've read it,
8 but presumably they had some oversight of it. But I
9 don't know that they did.

10 Q. In your experience with JACI, do you have
11 a reason to doubt their integrity when they select
12 something for the editor's choice?

13 A. No, no, not at all, although I'm sure they
14 select papers for different reasons.

15 Q. Have you been involved in -- strike that.
16 What do you mean by "different reasons"?

17 A. Well, sometimes they may think that a paper
18 is of particular interest because it is important in
19 the basic pathophysiology of a disease or mechanism
20 of the disease.

21 Other times they may pick a paper because
22 they think its of interest to clinicians. So

1 there's a range of things that must go into their
2 selection of editor's choice. And I'm also sure
3 that it depends on what's in that particular volume
4 of the journal. If it's slim pickings, then it may
5 be a lower bar than if it's a volume that has lots
6 of really great papers in it.

7 Q. Were you involved in any editorial
8 selection for -- strike that.

9 You're aware that papers by Warner Carr
10 discussing the clinical trials for Dymista was
11 selected for an editor's choice?

12 A. A paper, the paper, yes.

13 Q. Did you have any involvement in that
14 selection?

15 A. What year was that? That was fairly
16 recently. 2012?

17 Q. I believe it was 2012.

18 A. Yeah. No. I've not served on the
19 editorial board at the JACI since the dates in my
20 CV, the late '90s.

21 Q. So you have no firsthand knowledge of the
22 reasons Dr. Carr's paper was selected in the

1 editor's choice section?

2 A. That's correct.

3 Q. And you have no firsthand knowledge of who
4 drafted the blurb in the editor's choice
5 regarding -- strike that.

6 You have no firsthand knowledge who
7 drafted the summary of Dr. Carr's research in the
8 editor's choice section?

9 A. I have reason to believe from my own
10 experience with my papers that were selected to
11 believe that Dr. Carr and his co-authors wrote it;
12 and the text in that editor's choice blurb, although
13 I've not compared it with a word checker, is very
14 similar to text within the paper. So although I
15 have no firsthand knowledge, it's a pretty good
16 hypothesis that it was written by Dr. Carr and his
17 other authors.

18 Q. But you have no firsthand knowledge if
19 that's true?

20 A. That's what I stated, yes.

21 Q. Okay. Okay. Now I am going to switch
22 topics. And in your report, you spent -- strike

1 that.

2 In your report, you discuss the selection
3 of azelastine as one of the active ingredients in
4 the patents-in-suit. Do you recall that?

5 A. Yes.

6 MR. WARNER: Object to the form of the question
7 to the extent it mischaracterizes the report.

8 BY MS. EVERETT:

9 Q. I'm going to have you turn to your opening
10 report. You're on it. Paragraph 44, let's start at
11 44.

12 A. Okay.

13 Q. And here, you summarize that
14 antihistamines were known to work on the early phase
15 of allergic rhinitis. Is that accurate, this
16 section of your report?

17 A. I state that histamine has long been known
18 to play a role in the early phase.

19 Q. And if you go -- continue, sorry, just the
20 next few paragraphs, you -- strike that.

21 Why don't you take a look at Paragraphs 44
22 through 47.

1 A. Okay. Okay.

2 Q. And in here, you state that antihistamines
3 were known to work on the early phase of allergic
4 rhinitis. Is that accurate?

5 A. Well, I have stated that. But I'm not sure
6 which sentence you're referring to.

7 Q. So we can start Paragraph 46: The first
8 generation of antihistamines were shown to inhibit
9 the early phase of AR but have little or no affect
10 on the late phrase?

11 A. Yes, okay.

12 Q. And it is also true -- strike that.

13 And it's also true, correct, that
14 second-generation antihistamines were known to
15 inhibit the early phase of allergic rhinitis?

16 A. Yes.

17 Q. And is that true for all antihistamines?

18 MR. WARNER: Objection to the form of the
19 question. Vague.

20 BY THE WITNESS:

21 A. As I've mentioned already, some
22 antihistamines, a second generation in particular,

1 but among them with variable potency, have effects
2 beyond the ability to block the H1 receptor. All
3 drugs defined as antihistamines block the action of
4 histamine on either that receptor or one of the
5 other receptors. There's a total of four different
6 receptors, so it's complicated.

7 So if a drug has the name antihistamine, it
8 means it blocks histamine's actions on one of those
9 receptors. In order to inhibit the early phase,
10 especially for an oral antihistamine, it should
11 block the H1 receptor. So drugs that block the H1
12 receptor would all be expected to inhibit the early
13 phase as long as there are no pharmacodynamic issues
14 that lead them not to be found at the site of the
15 exposure.

16 Q. Okay. And as of June 2002, there were a
17 number of antihistamines that were known to block
18 the H1 receptor, such as loratadine and cetirizine,
19 among others; is that correct?

20 A. Yes.

21 Q. You note also in your report that one of
22 the benefits -- or strike that.

1 You note in your report one of the reason,
2 potential reason to work -- strike that.

3 In your report, you note that a potential
4 reason to select azelastine is that it acts faster.
5 Is that accurate?

6 A. You want to tell me where we're referring
7 to?

8 Q. Sure. Could we go to Paragraph 61? And
9 I'm going to take you to a second paragraph when
10 you've finished reading.

11 A. Okay. So we're quoting Berger, who stated
12 something similar to what you said.

13 Q. And -- Okay. Then if you could look at
14 Paragraph 74 of your report.

15 A. Okay. Oh, I'm sorry.

16 Q. Sorry, I was waiting for you. Sorry,
17 sorry.

18 A. Should I --

19 Q. No, I was just waiting for when you were
20 finished. Apologies.

21 So these paragraphs reflect -- strike
22 that.

1 Is it fair to say that these paragraphs
2 reflect your view that one would select azelastine
3 due to its onset of action?

4 A. Well, "these paragraphs" I'm not sure what
5 you're referring to. If you're asking about
6 Paragraph 74, then Lieberman states clearly the
7 mainstay of treatment of chronic allergic rhinitis
8 is the application of topical nasal steroids and/or
9 azelastine. And then we go on to say: Thereby
10 calling out azelastine as an antihistamine that
11 would have been preferred by a person of skill in
12 the art. I think it's self-explanatory.

13 Then the ARIA guidelines, which are also
14 followed around the world, state that topical
15 antihistamines have a rapid onset, less than 15
16 minutes, at low drug dosage, which is important from
17 our earlier discussions because it protects
18 systemically from side effects and it also yields
19 high concentrations that it can be more effectively,
20 but they acted only on the treated organ.

21 So yes. These combined with many other
22 factors, such as azelastine was only one of two

1 intranasal steroids available on the market, had
2 already proven itself to be a popular, effective
3 intranasal antihistamine. It had been shown to be
4 more potent than levocabastine, its other competitor
5 on the market. Those would lead a person of skill
6 in the art who was interested in combining an
7 antihistamine to be desirous of using azelastine.

8 Q. Okay. But for the moment, I just want to
9 stick with this point about the speed in which
10 antihistamines, azelastine and antihistamines, work.

11 A. Yes.

12 Q. It's in a number of spots in your report.
13 I want to make sure we're getting all of them, and
14 we can talk about them. I want to turn to Paragraph
15 78.

16 A. Yes.

17 Q. So here you're saying one of the benefits
18 of using an antihistamine is that it gave patients
19 a -- an immediate -- strike that.

20 I believe here you're saying that when
21 combined with a steroid, the antihistamine, you're
22 arguing gave the patient a sense of immediate

1 relief?

2 A. The sense of immediate relief comes from
3 the antihistamine whether it's combined with the
4 steroid or not.

5 Q. Okay.

6 A. But if a person were desirous of building a
7 combination around a potent and effective
8 anti-inflammatory steroid, this rapid action, which
9 would be contributed by the antihistamine, would be
10 a very, very beneficial feature of the combination.

11 Q. Okay.

12 A. But that's not due to the combination.
13 It's due to the antihistamine, which has
14 intrinsically very rapid effects.

15 Q. The final paragraph for now, of course,
16 83, please.

17 A. Okay. Yes.

18 Q. So in this paragraph, you state: A person
19 of ordinary skill would also still have been
20 motivated to combine an intranasal histamine with an
21 intranasal steroid, knowing that localized
22 application permitted higher concentrations with

1 better, faster, and safer effects. And then you
2 cite the Nielsen reference; is that correct?

3 A. Yes.

4 Q. So your citation here is to Nielsen and
5 the onset of action; is that correct?

6 A. Yes.

7 Q. And what did you mean here by "better
8 effects"?

9 A. Well, that's an important point and one
10 that distinguishes us from the plaintiffs, which is
11 that our person of skill in the art would have been
12 aware of this vast literature on showing that
13 second-generation antihistamines, and certain ones
14 in particular, had some impressive anti-inflammatory
15 effects that had nothing to do with blockade of the
16 histamine receptor. And, in fact, azelastine had
17 been shown to be very effective locally. And there
18 are a number of experiments with various local
19 antihistamines that evaluated local
20 anti-inflammatory effects of these drugs.

21 So the "better" refers to the combination
22 of an intranasal antihistamine such as azelastine

1 compared to an oral one.

2 Q. You didn't cite anything -- strike that.

3 You just said the person of ordinary skill
4 would know about this vast literature demonstrating
5 these benefits.

6 A. Well, it is cited in our documents
7 elsewhere.

8 Q. Okay. So what would you rely on to say
9 that "better" refers to a combination of intranasal
10 antihistamine, such as azelastine, compared to an
11 oral one?

12 A. Well, "better" means that the combination
13 would be superior to the monotherapies and/or
14 superior to a different combination, for example,
15 with an oral antihistamine. "Faster" refers to the
16 contribution of the antihistamine to the
17 combination. And "safer" refers to what we talked
18 about before, which is local application of both
19 drugs is generally safer than systemic application
20 of both drugs, drug classes.

21 Q. Okay. So I just want to be clear, when
22 you say "better," you are referring to the

1 combination of azelastine and fluticasone being
2 better than either alone or a different pairing?

3 A. Yes, a person -- our person of skill in the
4 art would expect that they would be better because
5 of the acute phase versus late phase issue, because
6 of the complementary actions, because of the prior
7 art that was clear from the monotherapies, which had
8 both established themselves as being exceedingly
9 popular drugs but which had slightly different
10 physiologic targets.

11 So the "better" is -- it's not specified
12 which of those things it refers to, but it refers in
13 general to what a person of skill in the art would
14 believe, which is that the combination would be
15 better.

16 Now, the "faster" refers to the combination
17 compared to an -- a glucocorticoid alone.

18 Q. And "safer" refers to topical versus oral?

19 A. Yes, so without parsing the sentence with
20 many more sentences, that's what I meant.

21 (Schleimer Exhibit Number 9 marked
22 for identification.)

1 BY MS. EVERETT:

2 Q. Okay. I'm handing to the court reporter
3 to be marked as Schleimer Exhibit 9, a document
4 bearing the Bates APOTEX_AZFL0060888 through 904.

5 Do you recognize this article?

6 A. Yes.

7 Q. What is it?

8 A. It's a review by Nielsen, Lars Peter
9 Nielsen, Niels Mygind, and Ronald Dahl about
10 intranasal steroids and allergic rhinitis.

11 Q. Have you ever researched or published with
12 these articles?

13 A. I know I've met Niels Mygind and Ronald
14 Dahl, but I don't believe I've ever published with
15 him. Ulf Pipkorn, one of my collaborators, I
16 believe was trained by Niels Mygind. And there's a
17 remote possibility that he's on one of those papers,
18 but I don't think I've ever published with either.
19 It would be easy to tell, but I don't think I have.

20 Q. Is what's marked as Schleimer 9 the
21 reference you have cited in Paragraph 83?

22 A. It doesn't appear to be. It appears to be

1 different.

2 MR. WARNER: He's looking at the --

3 BY THE WITNESS:

4 A. Am I looking at the wrong place?

5 Q. Where are you looking?

6 MR. WARNER: He's looking at the Documents
7 Reviewed.

8 THE WITNESS: I mean, that's Nielsen 2003.

9 MR. WARNER: They're potentially two different
10 concepts.

11 BY MS. EVERETT:

12 Q. Got it. So I'm going to have you go to
13 Paragraph 83. I think you were on --

14 A. Yeah, it says Nielsen 2001, but I don't see
15 it here in this list. There's only one Nielsen.

16 MR. WARNER: It might be you reviewed that one
17 and cited that one.

18 BY THE WITNESS:

19 A. Yeah. Yeah. I read a lot of documents.
20 It was a while back, and I don't remember this one.

21 Q. So in Paragraph 83, you have Nielsen 2001.
22 Do you see that citation?

1 A. Yes.

2 Q. And what I handed you as Schleimer 9,
3 hopefully will also be Nielsen 2001.

4 A. I can't confirm that.

5 Q. If you look at the top right, it's in
6 small print, but it says Drugs 2001.

7 A. Uh-huh. Yeah, it's the right year.

8 Q. Okay.

9 A. But I didn't bring the literature with me,
10 so I don't have the copy of the paper that I read by
11 Nielsen. But I suspect it's the one that we
12 reference in the table here so ... So I apologize
13 for that if they're different. So a review of
14 randomized controlled trials. I believe that's the
15 paper that I read and we were referring to, but the
16 year is different.

17 MR. WARNER: The one you're looking at there
18 might be different. She's asking I think about the
19 particular Paragraph 83 in your report.

20 THE WITNESS: Right.

21 MR. WARNER: I would just suggest you check the
22 page number and quotation there and see if they

1 match up.

2 MS. EVERETT: Right.

3 BY MS. EVERETT:

4 Q. We can do that. Maybe if you go back to
5 your Materials Considered list ...

6 A. 1572. Well, there is a 1572, so the fact
7 that I don't remember is because it's right when we
8 started. Okay. So what's the question? I don't
9 know the source of the discrepancy here, but ...

10 Q. In Paragraph 83, you cite Nielsen 2001 at
11 1565 saying: Azelastine has a, quote, faster onset
12 of action than oral antihistamines and acts within
13 15 to 30 minutes.

14 Do you see that in your report?

15 A. Yeah, I'm looking at the quote here. Okay.
16 And where is it on 1565?

17 Q. Section 1.3 says Topical Antihistamines.

18 A. Okay. I'm sorry. Faster onset of action
19 in oral antihistamines acts within 15 to 30 seconds.
20 Yes, I found it. Sorry to be so slow.

21 Q. No problem.

22 A. Okay.

1 Q. What does onset of action mean?

2 A. Ah. Onset of action refers to the amount
3 of time it takes between administration of a drug
4 and the ability of the investigators or the patients
5 to perceive the beneficial action. And so in this
6 case, it states that time, that 15 to 30 minutes,
7 which would be considered a rapid onset of action.

8 Q. In the sentence it says: They have a
9 faster onset of action than oral antihistamines. Do
10 you see the first half of the sentence?

11 A. Yes.

12 Q. It goes on to state: And act within 15 to
13 30 minutes.

14 A. Uh-huh.

15 Q. Isn't there a distinction between onset of
16 action and acting in 15 to 30 minutes?

17 MR. WARNER: Objection. Argumentative.

18 BY THE WITNESS:

19 A. No. As I defined onset of action, it's the
20 amount of time until there's a perceptible
21 beneficial effect, perceived either by the
22 investigator or the patient.

1 Q. When you say there's a perceptible
2 beneficial effect, what do you mean specifically?

3 A. Well, some endpoints of clinical trials are
4 patient reported outcomes. So if the patient
5 reports that their itchy nose is reduced, you know,
6 a group of patients, so its statistically
7 significant, then that would be an outcome. Or it
8 could be an investigator measured outcome like peak
9 nasal inspiratory flow rate or measurement of
10 inflammatory mediators, so ...

11 Q. Is your definition the same as FDA's
12 definition for onset of action?

13 A. I've never read FDA's, if they have a
14 formal definition of onset of action, so I can't --
15 I hope so. I don't know.

16 Q. So in your view, does the benefit need to
17 reach statistical significance -- strike that.

18 So when you say there is a -- strike that.

19 When you say the time it takes for a
20 patient to perceive the beneficial actions, are you
21 referring to a meaningful reduction in the decrease
22 in symptoms or -- I'll just leave it at that.

1 A. As I mentioned, action can be measured in
2 many different ways. Some are patient-reported
3 outcomes. Some are physician-reported outcomes.
4 And to document an action rigorously, one would want
5 to see data with either of those kinds of outcomes
6 that met the requirements of statistical analysis.
7 So there are lots of anecdotal findings, and they
8 appear in the literature all the time. But you
9 would want to see documentation and statistical
10 evidence for any kind of statement, whether it's
11 onset or potency or you name it.

12 Q. So when you were defining faster onset of
13 action, were you -- did you define it such that the
14 patient had to have a meaningful decrease in their
15 symptoms of allergic rhinitis?

16 MR. WARNER: Objection to the form of the
17 question.

18 BY THE WITNESS:

19 A. Are you distinguishing between meaningful
20 and measurable? I'm sorry.

21 Q. Yes. Is it your view that any benefit
22 that can be measured is onset of action?

1 MR. WARNER: Objection to the form of the
2 question. Incomplete hypothetical.

3 BY THE WITNESS:

4 A. When patient-reported outcomes are
5 measured, they're usually done in four domains. The
6 total nasal symptom score, I'm sure you're familiar
7 with it, it includes nasal itching, sneezing,
8 rhinorrhea, or congestion or stuffiness. And if
9 one -- so one could measure any one of those or a
10 composite of those. But if in a population of
11 subjects treated with a drug you had a significant
12 effect, that would be acceptable data to make the
13 case, at least for that one outcome.

14 As we discussed already, some of these
15 drugs work better against one outcome than another,
16 and antihistamines and particularly the topical ones
17 and azelastine are very good inhibitors of sneezing
18 and itching. They're not as effective against
19 congestion. So one might see onset for one outcome
20 and not another.

21 But another issue here is that there's
22 almost nothing in the literature where people have

1 done 5 minutes, 10 minutes, 15 minutes, 20 minutes,
2 30 minutes, 45 minutes, an hour. And as a scientist
3 you'd like to see rigorous studies like that, but
4 it's just generally not available in the field. So,
5 you know, you rely on the statements of experts that
6 have used and administer any class of drug for their
7 views on this sometimes.

8 Q. Does Nielsen in the sentence that we've
9 been discussing have any citation for his view that
10 azelastine acts within 15 to 30 minutes?

11 A. I don't see a reference for it.

12 Q. Do you have any knowledge of how 15 to
13 30 -- strike that.

14 Do you have any knowledge of how he
15 determined azelastine acts within 15 to 30 minutes?

16 A. How Nielsen himself in this paper? No.
17 But it appears in the ARIA guidelines and in other
18 similar documents, it seems to be common knowledge.

19 (Schleimer Exhibit Number 10
20 marked for identification.)

21 BY MS. EVERETT:

22 Q. Okay. I'm handing to the court reporter

1 to be marked as Schleimer 10, a document with the
2 Bates MEDA_APTX01331418 through 1620.

3 Have you had a chance --

4 A. Yeah, I'm sorry.

5 Q. No problem.

6 A. I'm not going to read it now.

7 Q. I'm sure it's very enticing but ...

8 A. Yes.

9 Q. Are you familiar with what's been marked
10 as Schleimer Exhibit 10?

11 A. Yes. This is the ARIA guidelines chaired
12 by John Bousquet, Paul Cauwenberge, and Nikolai
13 Khaltaev.

14 Q. And these were the ARIA guidelines you
15 were referring to just a moment ago?

16 A. Yeah, I don't see the date on here.
17 Probably.

18 Q. If you go to the front cover ...

19 A. 2001, yeah. Those would be the ones
20 relative to the date.

21 Q. And I'm going to have you turn to Page
22 S230, specifically Section 8234.

1 A. S230. 8, what did you say, 234?

2 Q. Yes, 8 --

3 A. Recommendations?

4 Q. Strike that, excuse me. Section 8234,
5 Recommendations.

6 A. Okay.

7 Q. And under that you'll see it says:
8 Topical H1 antihistamines have a rapid onset of
9 action, less than 15 minutes --

10 A. Okay.

11 Q. -- at low drug dosage, but they act only
12 on the treated organ.

13 A. Yes.

14 Q. Do you see that? Is there any citation
15 for this proposition that antihistamines -- strike
16 that.

17 Is there any citation for the proposition
18 that a topical antihistamine has an onset of action
19 of less than 15 minutes?

20 A. Of less than 15 minutes? Oh, for this
21 statement? There's no reference attached to the
22 statement, if that's what you're asking.

1 Q. That is what I'm asking. Thank you.

2 A. Yes.

3 Q. Are you aware of -- strike that.

4 Do you have any knowledge of how the
5 authors determined that topical antihistamines have
6 a rapid onset of action less than 15 minutes at a
7 low drug dosage?

8 A. For this particular statement, I don't know
9 what they base the statement on, no. But I believe
10 it to be correct.

11 Q. And what do you believe -- strike that.

12 What do you base your belief on?

13 A. Well, as I mentioned, I'm not aware of
14 careful studies in which the drug was administered
15 5, 10, 20, 30 minutes before challenged with
16 antigen. But I am aware of a study which we put in
17 one of these reports, I think it was a rebuttal, by
18 Grief, et al., a very good lab, where they used the
19 challenge with histamine to assess the time of onset
20 of action. And they found by 1 hour total, total
21 blockade of the response to histamine.

22 So this means that the onset, since that

1 was complete inhibition, there's a curve that goes
2 somewhere between zero minutes and 60 minutes, and
3 so that would not be incompatible with either
4 anecdotal or data coming out of clinical studies
5 suggesting that it has a rapid onset of action on
6 the order of 15 minutes.

7 Q. Okay. And we can talk about Grief in a
8 moment. But just to be clear, ARIA does not cite
9 Grief for that proposition; is that accurate?

10 A. That's correct.

11 Q. At the end -- I just want to make sure, at
12 the end of paragraph, there is an endnote, 2088. Do
13 you see that?

14 A. Oh, yeah. For on-demand use?

15 Q. Yes.

16 A. I don't think we found that reference. Oh,
17 2088. 78, okay. Is that Weiler?

18 Q. Yes.

19 A. And Meltzer, okay.

20 Q. And in your review in -- strike that.

21 In forming your opinions of this case, did
22 you review that reference?

1 A. We found that reference in the paragraph
2 that you directed us to, but I don't recall reading
3 this Weiler paper. I may have looked at it briefly.
4 But Meltzer, that's an outstanding group.

5 Q. Okay. So you have no knowledge or
6 opinions one way or the other whether the Weiler
7 article supports that or not? I can't tell given
8 where the endnotes are. So if you --

9 A. Sure. I don't recall reading that paper.
10 I saw that reference, and -- but as I mentioned,
11 I've not seen a single paper that actually studied
12 the kinetics of onset of action over the first hour,
13 which would have to be done to really make any
14 statement about the precise time of onset of action.
15 So I have every reason to believe that the common
16 knowledge of all these leaders in the field, that
17 these drugs work within 15 minutes is correct. And
18 as you said, we're going to talk about Grief, and
19 that supports it as well.

20 MS. EVERETT: Could we take a quick break?

21 MR. WARNER: Sure.

22 THE VIDEOGRAPHER: We are now going off the

1 record at 2:15 p.m.

2 (A short break was taken.)

3 THE VIDEOGRAPHER: We are now going back on the
4 record at 2:30 p.m.

5 (Schleimer Exhibit Number 11
6 marked for identification.)

7 BY MS. EVERETT:

8 Q. The court reporter has marked as Schleimer
9 Exhibit 11, a document bearing the Bates stamp
10 APOTEX_AZFL0031361 through 68.

11 A. Okay.

12 Q. Dr. Schleimer, do you recognize
13 Exhibit 11?

14 A. I do.

15 Q. Is this the Grief article you referenced
16 earlier today?

17 A. Yes, it is.

18 Q. Do you know -- strike that.

19 Have you either researched or published
20 with any of the authors listed?

21 A. I certainly know Carl Person. I don't
22 believe I have published with him, interacted with

1 him a lot, but I don't think I've published with
2 him.

3 Q. The Grief article -- strike that.

4 The patients in the Grief article were
5 healthy patients; is that correct?

6 A. Subjects, yes.

7 Q. And if you look on Page 439, it states:
8 The subject had no history of general allergic or
9 recent nasal disease and no history of recent drug
10 treatment.

11 A. Yes.

12 Q. And this study concerns a histamine
13 challenge; is that correct?

14 A. That's correct.

15 Q. And histamine challenge differs from an
16 allergen challenge?

17 A. Yes, it does, although it can be used as a
18 model of the results of an allergen challenge
19 insofar as the allergen induces effects through
20 histamine.

21 Q. When you say it's a model for -- it can
22 be -- strike that.

1 When you say it can be used as a model for
2 the results of the allergen challenge, were you
3 referring to the symptoms that the patients
4 experience?

5 A. Yes, the administration of a histamine will
6 cause the same physiologic changes when it
7 administered exogenously like this that histamine
8 coming out of mast cells will cause when it's
9 released endogenously with an antigen.

10 Q. In a histamine challenge, would patients
11 be given more histamine than would be released in an
12 allergen challenge?

13 A. That's hard to say because the same
14 pharmacodynamic issues we were talking about before,
15 but dose response curves with histamine would be
16 done as they were in this paper to titrate the
17 amount of histamine so it gave you a relevant,
18 reliable and useful response.

19 Q. And you cite this paper for the
20 proposition -- strike this.

21 Earlier today you said this paper
22 supported your view that azelastine acts -- has an

1 onset of action within 15 minutes; is that accurate?

2 A. I said that it was consistent with an onset
3 of 15 minutes based on the fact that by one hour,
4 there was complete inhibition of the response.

5 Q. And when you say by one hour there's
6 complete inhibition of the response, are you looking
7 at the tables on Page 441?

8 A. Well, I was actually looking at the figure,
9 Panel B, where you can see at 40 micrograms,
10 40 micrograms, the response was completely inhibited
11 by both antihistamines and which means that the
12 entire onset curve, kinetic of onset, took place in
13 less than an hour, and these curves usually take
14 time. So that was, as I said, was consistent with
15 an onset that might be measurable within 15 minutes,
16 15 to 30 as it's stated in other documents.

17 In fact, I would be surprised if it was
18 measurable -- sorry. Strike that. I would be
19 surprised if it wasn't obvious that early based on
20 the entire response being inhibited by one hour of
21 pretreatment.

22 Q. So you reference these onset curves and

1 kinetic onset of action curves. Is that accurate?

2 A. Reference them where? In my testimony just
3 now?

4 Q. Yes.

5 A. I'm discussing curves that are not apparent
6 here because the entire onset from partial
7 inhibition to total inhibition took place within an
8 hour. It was completely finished by an hour, which
9 means we don't know exactly when it started. But it
10 would be, in my view, consistent with the common
11 knowledge from John Bousquet and from Nielsen and
12 from the other authors which states that
13 cetirizine -- sorry, that azelastine has an onset 15
14 to 30 minutes.

15 Q. In Figure B, which you're looking at, the
16 onset -- strike that.

17 At hour 1, you stated that the cetirizine
18 also reduced all the histamine; is that accurate?

19 A. Yes.

20 Q. So does cetirizine have an onset of action
21 at 15 to 30 minutes?

22 A. Well, it would be consistent with that as

1 well, it having a rapid onset if the entire effect
2 took place by one hour in this model.

3 Q. Is cetirizine known for having a rapid
4 onset of action?

5 MR. WARNER: Objection to the form of the
6 question. Vague as to dosage form.

7 BY THE WITNESS:

8 A. I'm not aware of studies on the precise
9 curve of the onset of action of cetirizine, I'm
10 sorry.

11 Q. So in this study, there appeared to be no
12 difference in the onset of action between the oral
13 cetirizine and the intranasal azelastine; is that
14 correct?

15 A. That's correct, even though one would
16 expect the topical drug to work much more quickly
17 than the oral drug.

18 Q. You stated earlier that you thought the
19 studies consistent with, I think you called it the
20 common knowledge from Bouskay and others that
21 azelastine acted within 15 minutes; is that
22 accurate?

1 A. Yes.

2 Q. And do you have any other basis to suggest
3 where this knowledge came from?

4 A. Well, I never had a chance to see that
5 Weiler and Meltzer paper. I'm aware of the paper,
6 but I haven't seen it. So that would be the first
7 place I would look to see if there's more
8 information in a peer-reviewed paper. But I'm
9 sorry, I don't -- haven't seen that paper.

10 Q. Okay.

11 A. But it was referenced in ARIA, so maybe
12 there's something there.

13 Q. I'm going to turn you to Page 442, the
14 discussion section, the second column.

15 A. Okay.

16 Q. The first full paragraph, second sentence,
17 it says: Cetirizine appeared at least as potent as
18 azelastine with somewhat superior inhibition at 6
19 and 9 hours after treatment.

20 A. Okay.

21 Q. Do you see that?

22 A. Uh-huh.

1 Q. Based on these results, do you agree with
2 that?

3 A. Well, I don't think so. Can we go back?
4 Let me see the study design. So the azelastine was
5 given as a spray. And the cetirizine was taken as a
6 tablet, so it's really not possible to compare them.

7 The other thing is as we've read earlier,
8 the duration of effect for the intranasal form is
9 short enough that twice a day is the preferred
10 dosing frequency, whereas the oral would have --
11 would be expected to have a longer duration. Final
12 issue is that the term potency is not relevant or
13 even comparable for two drugs delivered in different
14 ways. So in that sentence, I do not agree with the
15 statement.

16 Q. The last sentence of that paragraph
17 states: The present findings suggest that around
18 the clock antiexudative -- how do you say --

19 A. Where are we talking about, which
20 paragraph?

21 Q. The same paragraph, last sentence.

22 A. Antiexudative -- exudative -- it's a hard

1 work.

2 Q. Okay.

3 A. It refers to a blockade of an exudate.
4 That's something that exudes from the tissue. They
5 were measuring alpha II macroglobulin, which is a
6 marker, leaks the fluid into the nose. So
7 exudative, it's not a word people use very much.

8 Q. In that sentence, it states: The present
9 findings suggest that around-the-clock antiexudative
10 effects require administration twice daily of either
11 topical antihistamine or oral cetirizine.

12 Do you see that?

13 A. I do.

14 Q. So that's contrary to what you just said
15 about the dosage of cetirizine being once a day?

16 A. Not necessarily. We don't know in this
17 study what the time course, the duration of the
18 presence of the drug in the nose for either form of
19 delivery. It's not measured. Not even sure where
20 the kinetic data are. Oh, I see. It's difficult to
21 compare the two when they're delivered by different
22 routes.

1 Q. Okay. In the paragraph we talked about
2 earlier -- Oh, sorry.

3 A. Which paragraph.

4 Q. I'm on your opening report.

5 A. Oh, are we done with this?

6 Q. We're done with that one.

7 A. Okay. Good grief. Sorry.

8 Q. A little humor.

9 A. Which paragraph?

10 Q. 61.

11 A. 61. Okay.

12 Q. And we talked about this earlier. You
13 contrasted antihistamines' onset of action in
14 comparison to corticosteroids' onset of action, and
15 you cited Berger.

16 A. Okay.

17 Q. Do you recall that?

18 A. Okay. In this paragraph?

19 Q. Yes.

20 A. Yes, I can see it.

21 (Schleimer Exhibit Number 12
22 marked for identification.)

1 BY MS. EVERETT:

2 Q. I am going to hand to the court reporter
3 to be marked as Exhibit 12, a document bearing the
4 Bates APOTEX_AZFL0059666 through 672.

5 MR. WARNER: What number?

6 MS. EVERETT: 12.

7 BY THE WITNESS:

8 A. Okay.

9 Q. And is this the Berger article you cited
10 in Paragraph 61?

11 A. I believe so.

12 Q. Here, Dr. Berger and his colleagues --
13 strike that.

14 I'm going to have you actually refer just
15 to the title page again.

16 A. Okay.

17 Q. Have you ever researched or published with
18 any of these authors?

19 A. I certainly know Drs. Berger and Lieberman,
20 but I do not believe I've published with either.
21 The reason I pause about these things is some papers
22 have a lot of authors, and I have a fair number of

1 papers so ... but I don't believe I've published
2 with either.

3 Q. Then I'm going to have you now turn back
4 to where you were on Page 536, so you can see the
5 full context of your quote that you put in
6 Paragraph 61.

7 A. Okay. Which column is it on?

8 Q. First one.

9 A. Okay.

10 Q. And here it says: Onset and duration of
11 action assessments show that azelastine nasal spray
12 improved baseline symptom scores within 1 to 3
13 hours.

14 A. Okay.

15 Q. While other studies suggest that
16 improvements may be evident in less than 30 minutes
17 in some patients?

18 A. What's the number of that reference? Is
19 that an 18? I can't read it.

20 Q. I think it might be a 13.

21 A. 13? Oh, Weiler and Meltzer. There you go.
22 Apparently that paper shows onset 15 to 30 minutes,

1 since that's the second citation we found to it.

2 Q. So here, Dr. Berger appears to be
3 suggesting that in some cases, onset of action is
4 1 to 3 hours. Is that accurate?

5 A. No, I don't believe that is. I think he
6 says that some study, which I guess he's referring
7 to, the onset is within 1 to 3 hours. But what
8 needs to be asked is whether the study that that
9 refers to had any measurements at less than one
10 hour.

11 So all you can do is use the earliest time
12 point and set that. And if there's already
13 efficacy, you can say within that to whatever the
14 latest time point that you saw a clear onset. So I
15 don't think that in any way eliminates the
16 possibility that the onset was 15 to 30 minutes in
17 whatever study he's referring to there. He actually
18 lists several trials, but rather may reflect the
19 protocol of the studies that they didn't collect
20 data at less than one hour. That's something that
21 we would have to actually go through those trials
22 and look to see if it's the case. But I don't think

1 you can make a firm conclusion that it doesn't work
2 until one hour based on that document.

3 Q. Did you review any of the underlying
4 studies when forming your opinion?

5 A. Well, so which ones is he referencing
6 there? 13 through 17? 13 and 14. So it's 13 and
7 14. As I mentioned, I did not review Weiler,
8 although we became aware that it was hard to find.
9 14 is another Meltzer study, azelastine in the
10 management of seasonal allergic rhinitis. I do not
11 recall seeing that one either. It would have been
12 easy enough to find, but I did not read it, to my
13 knowledge, to my recollection. Eli Meltzer is
14 another friend, so I probably would have remembered
15 attaching it to his name.

16 Q. Okay. Are you aware of any other studies
17 or data that supports your opinion that azelastine
18 had an onset of action within 15 minutes?

19 A. My opinion is formed by reading -- informed
20 by reading the opinions of the world experts and in
21 studying this drug and who expressed that opinion in
22 major reviews in an ARIA. I'm not aware of other

1 studies. But as your sleuthing has indicated, I'm
2 not aware of all the studies either. And I would
3 definitely look at both of those Meltzer papers with
4 Weiler and suspect that one or both of them have
5 data that I'm unaware of. There may be other papers
6 as well, so I'm not aware of other studies. But
7 that doesn't mean they're not there.

8 (Schleimer Exhibit Number 13
9 marked for identification.)

10 BY MS. EVERETT:

11 Q. I'm handing to the court reporter to be
12 marked as Schleimer 13, an article titled:
13 Azelastine Nasal Spray as Adjunctive Therapy to
14 Azelastine Tablets in the Management of Seasonal
15 Allergic Rhinitis by John Weiler and Eli Meltzer.

16 A. Well, I haven't read it, but I've skimmed
17 it.

18 Q. Is this --

19 MR. WARNER: Actually, before you go, I want to
20 make an objection to lack of foundation to the
21 extent that he hasn't seen it before, and it's
22 beyond the expert report.

1 BY MS. EVERETT:

2 Q. And Schleimer 13, is that what we noted as
3 end reference 2088 in the ARIA guidelines?

4 A. Well, I would have to confirm that. But if
5 you tell me it is, I'll accept it.

6 Q. I believe it is. But why don't you go
7 ahead and check.

8 A. We have to go back. So that was 2088?

9 Q. Yes.

10 A. Is the reference? 2088, Weiler Meltzer
11 adjunctive '97, Page 327, that is it. All right.
12 Can I look at it for a couple more minutes?

13 Q. Sure. And my question is going to be
14 anywhere -- strike that.

15 My question will be: Isn't it correct
16 that there's nowhere in this article where the
17 authors say the onset of action of azelastine is
18 15 minutes?

19 MR. WARNER: Objection. Lack of foundation.
20 The document speaks for itself. It's beyond the
21 scope of the expert report.

22 BY THE WITNESS:

1 A. In my brief skimming of it, I don't see any
2 unequivocal kinetic data that look at azelastine by
3 itself. It's actually kind of an odd paper. It
4 uses both oral and intranasal.

5 Q. I won't tell your friend Eli Meltzer you
6 said -- called his article odd.

7 A. Oh, I'd tell him to his face.
8 Do you want me to keep looking at it?

9 Q. No, no.

10 A. Okay.

11 Q. That was my question.

12 A. But that's based on --

13 MR. WARNER: You already answered. Let her ask
14 another question.

15 THE WITNESS: Statute of limitations was up,
16 huh? Just how long is it?

17 MR. WARNER: That about covers it, Uma?

18 MS. EVERETT: No, not quite. I'm trying to
19 follow Dr. Schleimer, so ...

20 BY MS. EVERETT:

21 Q. Now I'm going to have you turn to
22 Paragraph 79 of your report.

1 A. Okay. Yes.

2 Q. Here you state: Counsel has provided me
3 with the deposition testimony of Dr. Accetta. I
4 have reviewed his testimony which confirms doctors
5 actually practiced this prior art by prescribing
6 both intranasal azelastine, Astelin, and an
7 intranasal steroid, often fluticasone, Flonase.
8 Then you have a number of citations to Dr. Accetta's
9 transcript.

10 A. Yes.

11 Q. Did you review the exhibits to
12 Dr. Accetta's testimony?

13 A. I read his deposition. But you mean are
14 there publications you're talking about?

15 Q. So like today, we've marked a number of
16 exhibits and there will be exhibits to your
17 deposition. That happens in Dr. Accetta's
18 deposition. Did you review those exhibits?

19 A. I may have reviewed some and not others. I
20 don't know. It depends on whether they showed up in
21 some of these other documents. Without seeing the
22 list, I can't tell you.

1 Q. Okay. You can go back to look at your
2 Materials Considered list. I think you have your
3 deposition today. It's on Page 2 of your Materials
4 Considered list.

5 MR. WARNER: I was going to say just let her
6 ask the question.

7 THE WITNESS: Yeah, I'm sorry. The statute of
8 limitations is shorter with your pauses than mine.

9 So ...

10 MR. WARNER: One second. What's the question?

11 BY THE WITNESS:

12 A. Yeah.

13 Q. Go ahead and turn to your Materials
14 Considered list --

15 A. All right.

16 Q. -- if you are having trouble remembering
17 if you reviewed his deposition exhibits.

18 A. I'm actually trying to understand the
19 question. So when you say his deposition exhibits,
20 do you mean a similar table in the back of his
21 deposition?

22 Q. So when you were --

1 A. Or something that would be within his
2 deposition, per se?

3 Q. So there would be documents attached -- So
4 you reviewed a written transcript, which is written
5 questions and answers of his deposition; is that
6 correct?

7 A. Yes, that I reviewed.

8 Q. And there were a number of documents that
9 were marked as exhibits with exhibit stickers, just
10 like for you today. Did you review those exhibits?

11 A. I may have. I don't recall. And I don't
12 know how I would figure out if I did or not.

13 Q. If you did, would you have listed it in
14 your materials considered?

15 A. I don't know. We already found one that
16 was in the body here and not in this table, so I
17 don't know. Without seeing them, that doesn't
18 guarantee I would remember them.

19 Q. You didn't cite any deposition exhibits in
20 Paragraph 79; is that correct?

21 A. Maybe I can help. When I read his
22 deposition, I did not go through the reference list

1 and pull references and read them. That helps. But
2 what I don't know is the exhibits that you're
3 talking about, if they would have been built into
4 his deposition in some way where they were actually
5 part of what was given to me, I would have read
6 them.

7 Q. Did you review his patient records?

8 A. Oh, no, I don't recall them being in his
9 deposition. I recall a discussion about his partial
10 search of his patient records and finding patients
11 to whom he had prescribed both intranasal azelastine
12 and intranasal fluticasone.

13 Q. And so when you say you recall the
14 discussion, you're referring to the deposition
15 transcript?

16 A. Did he have a declaration also? Was there
17 an Accetta declaration as well or just a deposition?

18 Q. That's what I'm trying to figure out, what
19 you have read of Dr. Accetta's.

20 MR. WARNER: Well, I don't think there was a
21 declaration. Let's not mislead him.

22 BY THE WITNESS:

1 A. There was one document Accetta was
2 involved. I don't recall if it was a deposition or
3 declaration. I read it in his entirety. And he
4 discussed how he at the time prescribed, with some
5 regularity, azelastine and intranasal steroid to the
6 same patient.

7 He also said some interesting things. He
8 apparently was on the formulary committee for his
9 hospital, and he said that he thought that the two
10 monotherapies prescribed to the same patient were
11 just as effective as mixing them together. And he
12 thought that if there was additional benefit found
13 in the combination that was not found by prescribing
14 both monotherapies, he would have recommended that
15 the formulary accept the Dymista.

16 But that's all that I recall. I don't
17 recall separate documents that were attached to that
18 or that I pulled.

19 Q. Okay. So you don't recall separately
20 reviewing Dr. Accetta's patients' records?

21 A. No.

22 Q. And you did not cite to any patient

1 records anywhere in your expert reports?

2 A. No.

3 Q. In your opening report, you do not cite to
4 Dr. Wedner; is that correct?

5 MR. WARNER: Objection. The document speaks
6 for itself.

7 BY THE WITNESS:

8 A. It may be correct. It may be that Wedner
9 came along in one of the later reports. I don't
10 have memorized which one has which reference. I
11 know in one of these reports, referencing Wedner --
12 and actually since then, it's come to my attention
13 that both Drs. Carr and Dr. Kaliner testified that
14 they prescribed both monotherapies to the same
15 patient at the same time prior to the date.

16 So there's Carr, Kaliner, Wedner, and
17 Accetta.

18 Q. Dr. Schleimer, my question was: In your
19 opening report, you did not cite to Dr. Wedner's
20 report?

21 MR. WARNER: One second. Objection. The
22 document speaks for itself. Asked and answered.

1 MS. EVERETT: I object to that. I move to
2 strike his answer because that was not an answer.

3 BY THE WITNESS:

4 A. We can go through the first report to see
5 if Wedner was not cited. But if you know where
6 Wedner was cited, that would be helpful.

7 Q. I believe you cited Wedner after your
8 first report. I just want to confirm, in your
9 opening report, you have not cited Dr. Wedner's
10 report?

11 A. And the only way I can confirm that and
12 know that it's correct is to either go through the
13 whole thing and not find it or find it elsewhere. I
14 believe you are correct that it's not mentioned in
15 the first document. It's one of the later ones.
16 But I can't state with certainty.

17 Q. Have you spoken to Dr. Wedner about this
18 case?

19 A. I have not.

20 Q. So you've just simply reviewed his report?

21 A. Yes.

22 Q. Have you reviewed any of Dr. Wedner's

1 patient records?

2 A. I have not.

3 (Schleimer Exhibit Number 14

4 marked for identification.)

5 BY MS. EVERETT:

6 Q. I'm handing to the court reporter to be
7 marked as Schleimer 14, a document bearing the Bates
8 CIP_DYM_00050955 through 961. It's actually through
9 962.

10 A. Yes.

11 Q. Do you recognize this article?

12 A. I do.

13 Q. What is this article?

14 A. It's a study by Ratner, et al. It was
15 performed in Texas using red cedar antigen where
16 they evaluated the effects of intranasal azelastine,
17 intranasal fluticasone, and the combination
18 administered separately in patients with seasonal
19 allergic rhinitis.

20 Q. And you in your reports compare the Ratner
21 2008 study with the Dymista studies; is that
22 correct?

1 A. Yes, and particularly -- particularly we
2 compare it to the Dymista Hampel study, which was
3 done by exactly the same group with exactly the same
4 antigen in exactly the same place 2 or 3 -- well, 3
5 years after this. The only difference is Hampel is
6 the first author and Ratner is second in that paper.
7 In this paper, Ratner is the first author and Hampel
8 is the second.

9 All others are identical and the model
10 system, the patient group is as similar as one can
11 possibly get. And it actually scientifically serves
12 as a very nice comparison in very similar patient
13 groups with identical antigen systems driving
14 disease.

15 Q. Do you know any of the authors -- strike
16 that.

17 Have you ever researched or published with
18 any of the authors in this study?

19 A. I don't believe so.

20 Q. Did you make any adjustments for
21 difference in dosing between the Ratner 2008 study
22 and the Hampel study?

1 A. Well, I focused on the therapeutic
2 pharmacologic effects of these two drugs. The
3 dosing differences were, in my opinion, modest. I'm
4 sure we'll talk about dosing later. But in my
5 opinion, both drugs were given at a
6 pharmacologically active dose in both studies.

7 Q. Do you know the difference in dosing
8 between the Ratner study and the Hampel study?

9 A. Well, I reviewed it a bit. There's some
10 issues with frequency of dosing. And when you
11 combine the two drugs into the same canister,
12 there's some what I consider to be fairly minor
13 compromises that have to be made in terms of total
14 dose and frequency. In the Hampel study, which is
15 Dymista, the total dose of azelastine is lower but
16 still quite an active dose so ... I mean, is that
17 what you had in mind?

18 Q. So just to be clear, the dose in Hampel is
19 half -- strike that.

20 The dose of azelastine is half the dose of
21 that in Ratner?

22 A. I believe that's true.

1 Q. And you don't believe that's a significant
2 difference?

3 A. I believe that the various documents
4 including, if I'm not mistaken, the Hench patent
5 discuss activity as low as 30 micrograms, and the
6 dose would have been 548 instead of 1,096 or no?
7 Yeah, I think I have it right.

8 Q. So you believe you can compare efficacy
9 where one set of patients receive twice as much
10 azelastine as the other set of patients?

11 A. So a principle of pharmacology is that dose
12 makes a very big difference when one's further down
13 in the dose response curve. Once you get to the top
14 of the dose response curve, a change in dose has
15 little or no effect. And in general, especially
16 with topical medications, companies and physicians
17 lean towards giving higher doses than are necessary
18 for a full pharmacologic effect because they're
19 relatively safe. They're so safe with topical
20 administration that they can have that luxury.

21 So I think that one -- there's a caveat
22 that you raised that the doses are different, but I

1 think they are comparable.

2 Q. Did you make any modifications or
3 adjustments in your conclusions based on the fact
4 that Ratner in 2008 had no placebo group?

5 A. So the main comparison here is twofold.
6 The comparison of each treatment to its baseline,
7 which is an acceptable alternative to placebo in
8 many studies, and the other is the comparison
9 between the groups. And specifically these studies
10 were designed to test where the combination was
11 superior to either monotherapy. So the lack of a
12 placebo group did not disturb me since we're looking
13 at an improvement from baseline, and the baseline
14 values for the different groups were similar. 19.6,
15 19.5, 19.5, and 19 -- yeah, were the total nasal
16 symptoms scores in the group, so they're similar.

17 Q. So no, you did not make any adjustments
18 for lack of a placebo group?

19 MR. WARNER: Objection. Asked and answered.

20 BY THE WITNESS:

21 A. I think I answered it. No, I'm not
22 concerned about that.

1 Q. In your comparison you compared TNSS
2 across Ratner -- strike that.

3 In your report, you compared the TNSS
4 scores of Ratner with Hampel, correct?

5 MR. WARNER: Go ahead and look in your report,
6 if you want to.

7 BY THE WITNESS:

8 A. Could you please tell me which part you're
9 referring to?

10 Q. Sure. In your opening, it's Paragraph 127
11 and continues to 128 and also in your rebuttal,
12 Paragraphs 33 --

13 A. It's also in the rebuttal. I think yeah,
14 we actually give the math in the rebuttal. Okay.
15 Thank you. What would you like to ask?

16 Q. You compared TNSS scores from the Ratner
17 2008 study with the Hampel 2012 study; is that
18 correct? Or excuse me. It's the Hampel 2010 study?

19 A. That sounds right, yes. We compared
20 changes in TNSS scores, normalized changes in TNSS
21 scores, meaning the relative improvement compared
22 with the monotherapy.

1 Q. You did not consider any improvements or
2 lack thereof in any individual symptom score in
3 Ratner versus Hampel, did you?

4 A. I don't think we broke it down to
5 individual symptom scores. We used a total score.
6 But as I recall -- I have Hampel in front of me.
7 But as I recall, the different domains were as one
8 would expect. And there was a similar magnitude of
9 improvement, but we would have to look at Hampel to
10 be sure.

11 Q. I'm going to have you look at table 2 of
12 Ratner.

13 A. Okay. Yes.

14 Q. In Ratner 2008, was there a statistically
15 significant improvement in runny nose for azelastine
16 nasal spray plus fluticasone nasal spray?

17 A. No.

18 Q. In Ratner 2008, was there a statistically
19 significant improvement in sneezing for azelastine
20 nasal spray plus fluticasone nasal spray?

21 A. No.

22 Q. Did you compare this with the results of

1 Hampel 2010?

2 A. As I said, I think we used the TNSS
3 composite. I don't recall breaking it down in each
4 domain.

5 Q. Oh, in your opening report, I'm going to
6 have you turn to -- still back to Paragraph 127.
7 Did you do anything to satisfy yourself that the
8 dosing methods in Ratner were actually those that
9 were practiced by -- strike that.

10 What, if anything, did you do to satisfy
11 yourself that the dosing methods practiced in Ratner
12 were the ones allegedly practiced by Dr. Accetta or
13 Dr. Wedner?

14 A. I didn't consider that question. But my
15 understanding of the Ratner study is they used the
16 commercially available Flonase and Astelin in the
17 study, and they used it according to the approved
18 indications for those. So I would have no reason to
19 believe that that would vary substantially from what
20 Drs. Accetta, Carr, Kaliner, or Wedner used.

21 Q. But you didn't actually look at anyone's
22 patient's records to see how it was prescribed --

1 strike that.

2 But you testified earlier you didn't look
3 at any patient records of Dr. Accetta, Wedner, and I
4 assume you've not looked at any patient records of
5 Dr. Carr or Kaliner?

6 A. That's correct.

7 Q. So you have no knowledge whether their
8 prescribing practices actually match the methods,
9 study methods of Ratner; is that correct?

10 MR. WARNER: Objection. Mischaracterizes his
11 testimony. Asked and answered.

12 BY THE WITNESS:

13 A. As I stated, I believe that the dosing and
14 the preparations that were used in Ratner were along
15 the lines of the commercially available FDA-approved
16 Flonase and Astelin, and I believe that those four
17 doctors that I mentioned would prescribe them
18 according to the FDA-approved guidelines. So I have
19 no reason to believe that they differ, but I did not
20 confirm that they were identical.

21 (Schleimer Exhibit Number 15
22 marked for identification.)

1 BY MS. EVERETT:

2 Q. I'm handing to the court reporter to be
3 marked as Schleimer 15, MED_DYN_00001345 through
4 353.

5 Do you recognize what's been marked as
6 Schleimer 15?

7 A. I do.

8 Q. What is it?

9 A. This is a study performed at McMaster
10 University in Hamilton by Elizabeth Juniper and her
11 colleagues, including the late Freddy Hargreave and
12 John Dolovich, who are leaders in this area. And
13 they compared the effects of beclomethasone
14 dipropionate, or BDP as it's known, with astemizole
15 or the combination of those two drugs in essentially
16 allergic rhinitis.

17 Q. And this article was published in JACI?

18 A. Yes, in 1989. So this was an early study.

19 Q. And we discussed earlier JACI publishes, I
20 think you called it the best research?

21 MR. WARNER: Objection. His testimony and
22 expert report speaks for themselves.

1 BY THE WITNESS:

2 A. It publishes excellent research.

3 Q. In -- I'm going to have you turn to the
4 end of the paper, Page 632.

5 A. Okay.

6 Q. And the -- on the second column, it says,
7 and I'm in the second column, first paragraph, the
8 last sentence: The results of the present study add
9 the further observation that beclomethasone nasal
10 spray alone is just as effective as beclomethasone
11 plus astemizole for nasal symptoms, suggesting that
12 nasal spray may be sufficient for optimal treatment
13 of symptoms.

14 Do you see that?

15 A. Uh-huh.

16 Q. So this was a study comparing the results
17 of beclomethasone alone -- strike that.

18 This was a study comparing the effects of
19 beclomethasone nasal spray alone with beclomethasone
20 nasal spray and astemizole.

21 A. Yes.

22 Q. And the effects on symptoms?

1 A. Yes.

2 Q. And there were no additional effects on --
3 or strike that.

4 There were no additional benefits to nasal
5 symptoms with the treatment of beclomethasone plus
6 astemizole as compared to beclomethasone alone?

7 MR. WARNER: Objection to the form of the
8 question. The document speaks for itself.

9 BY THE WITNESS:

10 A. So there's actually a fair amount to say
11 about this study and its relatives.

12 As oral antihistamines became more and more
13 popular, especially with the ones that had less
14 sedation effects, and as topical nasal steroids
15 became more popular because of their efficacy, they
16 started competing with each other.

17 And there were a number of studies, I'm
18 sure we'll discuss some of the others, that were
19 designed for the purpose of actually testing the
20 difference in the monotherapy of the steroid to the
21 oral antihistamines. These studies use fairly low
22 numbers of patients because the main goal is the

1 most of the studies were sponsored by the maker of
2 the intranasal steroid and they knew that the
3 steroids were superior to the oral antihistamines.
4 So they were primarily, in my opinion, designed to
5 test and/or prove that monotherapy of steroid was
6 superior to oral antihistamine. And they all
7 achieved that remarkably.

8 But it also means they weren't powered to
9 test the difference between the combination and
10 steroid alone because that's going to be a smaller
11 difference since the steroid is the more effective
12 drug and would require much larger number of
13 patients. So that's a caveat for this and the other
14 papers.

15 Having said that, in this paper, they
16 comment that there were beneficial ocular effects,
17 although they didn't reach statistical significance,
18 and they almost moaned about that because they said,
19 well, our study is underpowered. But they
20 essentially believed the combination improved eye
21 symptoms better than the steroid by itself.

22 So this same group, Juniper, et al.,

1 actually later made -- did a bigger study with the
2 combination of oral antihistamine and intranasal
3 steroid in more severe patients and made the
4 conclusion that 50 percent of them should benefit
5 from this combination and should be treated with it,
6 and that opinion was picked up in the practice
7 parameters documented by Mark Dykewicz and others.
8 So that's a little bit of the background.

9 The literal answer to your question is yes,
10 in this study, which was not powered to see a
11 difference between the combination and the steroid
12 alone, they did not see a difference.

13 Q. And you referred to the same group, the
14 Juniper group doing another study. You did not
15 include that in your reports; is that correct?

16 A. That's correct. But if I could, I would
17 like to say that the combination of oral
18 antihistamines and intranasal steroids continues to
19 be very popular to this day and is frequently
20 prescribed. These drugs in some cases are now
21 available over-the-counter, and patients are aware
22 of the benefits of these drugs.

1 Q. You mention that some of the patients in
2 Juniper had benefits to eye symptoms. Is that
3 correct?

4 A. Yes. They stated it a couple times in the
5 paper. And in the discussion, as I recall, they
6 themselves stated that they thought they were real
7 but that -- we can find it exactly. But that the
8 study was underpowered to answer the question. So
9 none of the eye -- so as I recall, the patients
10 required less eye medicines and reported less eye
11 symptoms on the combination, but the numbers were
12 too low.

13 Q. And the patients in this study took
14 astemizole, which is an oral antihistamine, correct?

15 A. That's correct.

16 Q. And earlier you testified how oral
17 antihistamines can affect multiple organs; is that
18 correct?

19 A. Oral antihistamines have access to organs
20 throughout the body, yes.

21 Q. So is part of the reason there are
22 benefits to eye symptoms because patients were

1 taking oral antihistamines?

2 A. That's a good question. It's different
3 from the point of whether the combination is better
4 than the steroid alone. But there are a lot of
5 investigators that are interested in this question
6 because there's some connection between the nose and
7 the eye through the nasal lacrimal duct. And
8 mediators and drugs can actually travel from one to
9 the other. If you put eyedrops in, it will end up
10 in your nose.

11 But I've not considered all of that in
12 this, so it wouldn't surprise me if oral
13 antihistamines in this study provided some benefit
14 to the eyes. But again, the question that I was
15 addressing is, is the combination superior in
16 benefit to the eyes compared to the oral
17 antihistamine alone. And they seem to think it is,
18 but it wasn't significant because the study is
19 powered to see the difference between the steroid
20 monotherapy and the antihistamine monotherapy, not
21 the combination versus the steroid, which is a
22 smaller difference.

1 And you see the same phenomenon in some of
2 these other studies, like Simpson or the earlier
3 Ratner study. They were all interestingly sponsored
4 by the companies that made the steroid. And they
5 were all designed to show that the steroid was
6 superior to the oral antihistamine, and they all
7 succeeded in that. But they also all inadvertently
8 showed that the combination is -- almost all, one
9 didn't -- is better than the intranasal steroid by
10 itself and far better than the antihistamine by
11 itself.

12 Q. In these studies that you say were funded
13 by the steroid companies to show that the steroids
14 were superior to the combination --

15 A. Yes.

16 Q. -- would a person of ordinary skill still
17 have considered the data and results from these
18 studies in their --

19 A. Absolutely. The reason why I mention that
20 is not to suggest that anything untoward is going on
21 or any crime or fraud, but rather that people of
22 skill in the art and clinicians as well understand

1 that studies -- that the study design itself can
2 influence the type of results that one gets. These
3 studies primarily looked at endpoints that were a
4 week or later.

5 And as we discussed, it takes many days for
6 steroids to reach their maximal effects. So they
7 don't want to pay money for a study that looks at
8 all these really early endpoint and shows that the
9 antihistamine is better than their steroid. So they
10 just don't do those points. There's nothing
11 unethical or wrong about that. But people in the
12 field, clinicians and investigators, understand that
13 the design of a study can be profoundly influenced
14 by the desires of the sponsor.

15 And the Simpson study was done in the U.K.
16 with budesonide sponsored by Astra Draco. This
17 study was done in Canada with beclomethasone funded
18 by GlaxoSmithKline. GlaxoSmithKline has BDP. Astra
19 Draco has budesonide. The Ratner study was a very
20 interesting study done with fluticasone and
21 loratadine.

22 Now, at the time of that study, which is

1 later in the '90s, fluticasone and loratadine were
2 the 800-pound gorillas in this field. Loratadine,
3 also known as Claritin, was selling several billion
4 dollars a year. It was a big market. And then
5 fluticasone, which in my opinion is the single most
6 effective drug available for allergic rhinitis, was
7 also -- had also become very popular as Flonase. So
8 that was almost a head to head comparison.

9 The sad thing about that study is that,
10 this is a little inside baseball, but loratadine had
11 no effect in that Ratner study. And the reason has
12 to do with the design and marketing of loratadine.
13 Schering-Plough was very interested in getting an
14 antihistamine that could have the label non-sedating
15 because all the doctors and all the patients wanted
16 non-sedating in their label. So what they did was
17 the lowered the dose of loratadine so low that it
18 could be considered non-sedating. It didn't tick
19 off the sedation markers. And by doing that, they
20 ended up with a drug that was not better than
21 placebo in a significant proportion of their Phase
22 III trials that led to approval by the FDA.

1 So that's the issue with that Ratner study.

2 So all these studies showed benefit of the
3 combination over the steroid alone, and certainly
4 over the antihistamine alone, but that was not their
5 major goal. Their major goal was to show the
6 superiority of the steroid, in my opinion.

7 MR. WARNER: Counsel, whenever it's a good
8 point, we should take a break.

9 MS. EVERETT: Okay. Let's take a break.

10 THE VIDEOGRAPHER: We are now going off the
11 record at 3:42 p.m.

12 (A short break was taken.)

13 THE VIDEOGRAPHER: We are now going back on the
14 record at 4:03 p.m.

15 BY MS. EVERETT:

16 Q. Dr. Schleimer, before the break, you had
17 testified that -- you said that loratadine was not
18 better than placebo in their Phase III trials that
19 led to FDA approval. Was that an accurate summary?

20 A. It's my understanding that some of the
21 trials, in some of the trials, it was not. But I
22 was referring to the Ratner study where loratadine

1 was not different from placebo. It's in one of the
2 exhibits in my reports. And I was commenting that
3 that -- well, the common discussed reason for that
4 is that it was a very low dose that was chosen in
5 order to get the non-sedating title for the drug.
6 And as a result, the efficacy is modest.

7 Q. Okay. In the second half, when you say it
8 was a low dose that was chosen to get a non-sedating
9 title, you're referring to the FDA clinical trials
10 at this point, correct?

11 A. Well, this is my understanding from
12 discussions with experts in the field about the
13 studies that were used for registration. I have not
14 reviewed all those studies.

15 Q. For a drug to receive FDA approval, does
16 it need to be more effective than placebo?

17 A. Absolutely.

18 Q. Okay. So -- and Claritin, loratadine,
19 does have FDA approval; is that correct?

20 A. Absolutely.

21 Q. So FDA at least believes it is a more
22 effective drug than placebo?

1 A. Yes. But usually a number of trials go
2 into that, a large number.

3 (Schleimer Exhibit Number 16
4 marked for identification.)

5 BY MS. EVERETT:

6 Q. I'm handing to the court reporter to be
7 marked as Schleimer Exhibit 16, MED_DYM_00001355
8 through 1364.

9 A. Yes. Yes.

10 Q. Is this the -- strike that.

11 Is Schleimer 16 the Ratner study of
12 fluticasone and loratadine that you were referring
13 to a few minutes ago?

14 A. Yes.

15 Q. And this is a study that compared
16 Flonase -- strike that. Excuse me.

17 This is a study that compared fluticasone
18 nasal spray with fluticasone nasal spray plus
19 loratadine; is that correct?

20 A. Yes.

21 Q. And it found that the combination of
22 fluticasone and loratadine were no more effective

1 than fluticasone alone; is that accurate?

2 A. Yes.

3 Q. And loratadine is an oral antihistamine,
4 as we've discussed; is that correct?

5 A. Yes. And I have to qualify my last answer
6 that there were some patient-reported outcomes where
7 the combination was better, as I recall in this
8 study, I can't remember if it was sneezing and itch
9 and things like that. But the major outcomes was
10 not different. The combination was not different
11 from the steroid alone. And loratadine was not
12 different from placebo.

13 Q. And loratadine is an oral antihistamine,
14 correct?

15 A. Yes.

16 Q. And oral antihistamines, like loratadine,
17 treat the early phase of allergic rhinitis; is that
18 correct?

19 A. If they're given in adequate doses, yes.
20 That's two words, in adequate.

21 Q. Understood. And fluticasone is a
22 corticosteroid that treats the late phase of

1 allergic rhinitis; is that correct?

2 A. Well, we've discussed that at some length.
3 It treats the late phase and, with prolonged use,
4 can also have some impact on the acute phase.

5 It's also a leading intranasal spray for
6 allergic rhinitis and probably the most popular
7 based on sales, et cetera. Certainly one of them.

8 Q. So is this fair to say this study took an
9 active that treated the early phase of allergic
10 rhinitis and an active that treated at least the
11 late phase of allergic rhinitis to determine whether
12 there was any benefit of the combination?

13 A. As I stated earlier before the break and
14 briefly just now, in my opinion, the lack of
15 efficacy of this dose of loratadine in this study
16 compared to placebo suggests that what you said is
17 not correct, that because of that issue, loratadine
18 was not apparently inhibiting the early phase or, to
19 the extent it did, it didn't show up in the symptom
20 results that were monitored.

21 Q. So your issue with my statement is the
22 effect of loratadine in the study, not generally

1 that -- you don't dispute that loratadine is known
2 to treat the early phase of allergic rhinitis?

3 A. I do not dispute that loratadine is an
4 antihistamine that will treat the early phase of
5 allergic responses.

6 Q. And I'm going to have you turn to the
7 first page, if you're not on it. You may be on it.

8 A. First page of Ratner?

9 Q. Of Ratner 1998.

10 A. Okay.

11 Q. Schleimer 16.

12 A. Yes.

13 Q. And I'm going to have you look at the
14 methods section.

15 A. Okay.

16 Q. It says: 600 patients with seasonal
17 allergic rhinitis were treated for 2 weeks with
18 either fluticasone ANS 200 micrograms once daily;
19 loratadine, 10 milligrams once daily; the
20 fluticasone proprionate ANS and loratadine regimens
21 combined; or placebo in a multicenter randomized,
22 double-blind dummy-parallel group study.

1 Do you see that?

2 A. Yes.

3 Q. So the patients that received loratadine
4 received 10 milligrams of loratadine?

5 A. Yes.

6 Q. Is that accurate? Is that an FDA-approved
7 amount?

8 A. I believe so.

9 Q. So again, the FDA believes 10 milligrams
10 would be more effective than placebo?

11 A. Yes.

12 Q. And if I understood your testimony
13 correctly, you're saying a person reading this
14 reference would question whether the loratadine was
15 effective?

16 A. Well, my reading of this paper was
17 loratadine was no better than placebo, so yes.

18 Q. And is it your testimony that the lack of
19 efficacy is due to the low dosage of loratadine?

20 A. That's my belief. But I also have to say
21 that there was a report from Dr. McCullough that
22 reviewed all these studies and critically evaluated

1 their design, et cetera. And if I'm not mistaken,
2 Dr. McCullough also pointed out this disappointing
3 feature of this study, that one of the comparator
4 drugs, for whatever reason, was not different from
5 placebo, making the combination, the test of the
6 combination moot since one of the drugs was not
7 contributing.

8 Dr. McCullough also reviewed the other
9 studies like the Benson and Ratner and Juniper and
10 others, so I defer to that report for the details of
11 the protocols of the evaluation.

12 Q. Do you have an independent opinion on the
13 protocol evaluation?

14 A. Well, I've expressed my views about some of
15 it already. I read that document carefully and did
16 not disagree with it, so I guess the answer is no.

17 Q. And just to be clear, when you say "that
18 document," are you referring to Dr. McCullough's
19 report?

20 A. Yes, I'm sorry.

21 (Schleimer Exhibit Number 17
22 marked for identification.)

1 BY MS. EVERETT:

2 Q. Okay. I've handed to the court reporter
3 to be marked as Schleimer 17, a document bearing the
4 Bates MEDA_APTX02173918 through 924.

5 A. Yes.

6 Q. Do you recognize what's been marked as
7 Schleimer 17?

8 A. Yes.

9 Q. What is it?

10 A. This is a paper by Brooks, et al.,
11 comparing topical beclomethasone with oral
12 loratadine and the combination in a seasonal
13 allergic rhinitis study.

14 Q. And this is one of the studies you have
15 cited in your report, I believe?

16 A. That's correct.

17 Q. And the conclusion of the study is that
18 beclomethasone alone is no different -- strike that.

19 And the conclusions of this paper are that
20 in certain domains, the combination of
21 beclomethasone alone -- strike that. That made no
22 sense, sorry.

1 A. I know what you mean.

2 MR. WARNER: Just read the conclusions.

3 BY MS. EVERETT:

4 Q. That in certain segments, the combined
5 treatment of beclomethasone and loratadine were
6 better than beclomethasone alone and in certain
7 segments, the combination was no better than
8 beclomethasone alone; is that accurate?

9 A. Yes.

10 Q. Okay. And so although we discussed it did
11 not -- strike that.

12 As we discussed, the combination did not
13 improve symptoms for runny nose and eye symptoms; is
14 that correct?

15 MR. WARNER: Objection to the form of the
16 question. And it's a mischaracterization of the
17 document.

18 BY THE WITNESS:

19 A. I think Table 3 and 4 are the most
20 relevant. Oh, I'm sorry. I was waiting for you to
21 formulate a question.

22 Q. Sorry. I thought you were in the middle

1 of it.

2 A. I was trying to help you out because you
3 were looking for your question.

4 MR. WARNER: Oh, let her figure out a question
5 for herself.

6 BY MS. EVERETT:

7 Q. No, I had a question.

8 A. Sorry. I'm waiting. It's my fault.

9 Q. The combination of -- the combination did
10 not statistically -- strike that.

11 The combination did not significantly
12 improve the symptoms, runny nose and eye symptoms,
13 versus beclomethasone alone; is that correct?

14 A. Well, no. I mean, if you look at Table 4,
15 which has the P values, eye symptoms were
16 significantly different in Segment 1, but it's
17 correct that in Segments 2 and 3, they were not
18 significantly different. Itching was significantly
19 different in Segments 2 and 3, and sneezing was
20 profoundly significantly different in the Segments 1
21 and 2.

22 To me, the more important table is Table 3.

1 That's overall patient assessment of treatment
2 effectiveness, where there's a statistically
3 significant improvement by the combination compared
4 to beclomethasone at .042. And this study is almost
5 an exception to what I was saying before because
6 Upjohn doesn't have a horse in this race as far as
7 I'm concerned. I don't know why they funded it.
8 But it did find superiority of the combination in
9 global assessment and several domains compared to
10 the beclomethasone alone.

11 Q. I'm going to have you turn to Page 194 --

12 A. Okay. Yes.

13 Q. -- where it says Experimental Drug
14 Treatment?

15 A. Okay.

16 Q. There it says: Patients who took
17 loratadine took 10 milligrams once a day.

18 A. Yes.

19 Q. Is that correct?

20 A. Yes.

21 Q. And that is the same amount they took in
22 Ratner 1998?

1 A. Yes.

2 Q. And it showed a benefit in the Brooks
3 study; is that your testimony?

4 A. The Brooks -- oh, this study?

5 Q. Yes.

6 A. So we weren't looking at that. Let me
7 look. I've got to find loratadine versus placebo.
8 I'm not sure where the data are in here for
9 loratadine versus placebo, but -- and sadly these
10 figures don't have P values on them. So I'm unsure.

11 Q. You're unsure whether loratadine was
12 effective in --

13 A. By itself, you know, without reading the
14 whole thing again.

15 Q. So would a person of ordinary skill
16 reading the Brooks study that administered
17 loratadine at 10 milligrams and then administering
18 the same amount at Ratner conclude that 10
19 milligrams is an ineffective dosage?

20 A. As I said, I don't see any data while
21 sitting here comparing loratadine to placebo. But
22 such a person would see the data that the

1 combination was better than the beclomethasone alone
2 and think loratadine was having some effect.

3 Q. So that person would likely think 10
4 milligrams was sufficient to have effect in the
5 combination?

6 A. Sufficient to have some effect, yes.
7 (Schleimer Exhibit Number 18
8 marked for identification.)

9 BY MS. EVERETT:

10 Q. I'm handing to the court reporter to be
11 marked as Schleimer 18, APOTEX_AZFL0060084 through
12 093.

13 A. Okay.

14 Q. And you rely on this article as well in
15 your opinion?

16 A. Yes.

17 Q. And just so we're clear for the record,
18 what is Schleimer Exhibit 18?

19 A. It's a paper by Drouin, et al., with Mel
20 Danzig is the last author, from Schering-Plough.

21 Q. And in this article, they evaluated the
22 effect of intranasal beclomethasone in combination

1 with loratadine as compared to beclomethasone alone;
2 is that correct?

3 A. Yes.

4 Q. And in this study, patients were
5 administered 10 milligrams of loratadine; is that
6 correct?

7 A. Yes.

8 Q. Looking at this study, would a person of
9 ordinary skill conclude that 10 milligrams was an
10 insufficient dosage of loratadine?

11 A. I don't see data on loratadine alone
12 compared to placebo. I'm not sure they did that.
13 But as with the last paper we just looked at -- is
14 that the Brooks paper? As with that paper, the
15 combination of loratadine plus BDP was superior to
16 BDP alone. So such a person would believe that the
17 loratadine had made a contribution to the
18 therapeutic benefit of the combination.

19 Q. And would a person of ordinary skill
20 understand that terfenadine was an effective oral
21 antihistamine?

22 MR. WARNER: What drug did you say?

1 MS. EVERETT: Terfenadine.

2 BY THE WITNESS:

3 A. Yes.

4 Q. Would a person of ordinary skill have
5 considered astemizole an effective oral
6 antihistamine?

7 A. Yes.

8 Q. Would they have considered cetirizine an
9 effective oral antihistamine?

10 A. Yes, but all these cases assume at an
11 adequate dose. But yes.

12 Q. And on Page 341, in the introduction, the
13 authors state in the second paragraph after the
14 introduction: Loratadine relieves most of the
15 symptoms related to SAR and is as effective as
16 terfenadine, astemizole, cetirizine.

17 Do you see that?

18 A. Where are you? Introduction in the last
19 paragraph?

20 Q. In the last sentence.

21 A. Last sentence. Yes, I see that.

22 Q. And reading this, would a person of

1 ordinary skill believe loratadine is an effective
2 oral antihistamine?

3 A. Yes.

4 Q. I'm going to have you turn back to your
5 opening report, Paragraph 88.

6 A. Okay. Okay.

7 Q. In the Paragraphs 88 and the ones that
8 follow, you provide a number of justifications that
9 a person of ordinary skill would know before the
10 date of the alleged invention that these
11 dual-therapy single-product compositions would
12 provide even more benefits than sequential
13 administration of steroid and antihistamine.

14 Do you see that?

15 A. Yes.

16 Q. And the first one you provide --
17 explanation you provide is related to excess fluid,
18 excess administration of liquids?

19 A. Uh-huh, yes.

20 Q. And how -- you say a person of ordinary
21 skill would have been motivated to combine them into
22 a single formulation?

1 A. Yes.

2 Q. To avoid -- is excess administration --
3 You say it might be less effective due to drainage.
4 Is that always the case?

5 A. Well, this is not a major problem with --
6 if you prescribe both of these drugs separately, but
7 optimally that means that the patient needs to
8 administer them at slightly different times to avoid
9 too much drug. So this is a modest, modest gain of
10 combining them into a single preparation.

11 But it also assumes that the volume of the
12 single preparation would be roughly the same as the
13 volume in either of the monotherapies, so therefore
14 half of the total volume if you had two
15 monotherapies. But again, it's a modest gain, but
16 it's one obvious motivation for combining them.

17 Q. In this second paragraph, you say the two
18 drugs combined is more convenient than taking the
19 drugs separately. Is that a separate point than the
20 excess administration of liquids or ...

21 A. Yes, it's a separate point. It means
22 carrying only one drug canister instead of two. It

1 means having only one to lose instead of two to
2 lose. It means actually slightly makes it more
3 likely that you might use it because it's more
4 convenient to have to only administer one instead of
5 two, things like that. Again, these are modest and
6 obvious.

7 Q. What do you -- What do you mean when you
8 just said "modest and obvious"?

9 A. Well, so we think that at the time of the
10 invention, patients had access to this, this through
11 the prior art, that by administering both
12 monotherapies separately, sequentially, that they
13 could get the full benefit of this combination of
14 drugs. And as we've discussed, we think that the
15 Ratner versus Hampel comparison supports that.

16 So -- but there are some gains to combining
17 them into a single canister, which we think are
18 fairly obvious. And these are some of them. But
19 the gains are modest, convenience being the biggest
20 one.

21 Q. So the gains of combining them into a
22 single fixed-dose formulation is modest?

1 A. Yes.

2 Q. Okay. At the beginning of your last
3 answer, you started "we think this at the time of
4 the invention, patients had access to this." Who
5 did you mean by "we"?

6 A. Well, I've had discussions with Elan and
7 Kevin about this. But this aligns with my opinion.

8 Q. Okay. In Paragraph 88, the first sentence
9 says: First, providing a combination of a known
10 antihistamine and a known steroid in a single
11 administration ensured that the dosing and
12 administration of each drug was optimal.

13 A. Yes.

14 Q. Are you aware of the dosing as of --
15 strike that.

16 Are you aware of the dosing and
17 administration schedules of azelastine and
18 fluticasone as of June 2002?

19 MR. WARNER: Objection to the form of the
20 question as vague.

21 BY THE WITNESS:

22 A. I believe so, and I think we discussed them

1 already.

2 Q. And at the time, fluticasone was
3 administered two sprays per nostril once a day; is
4 that correct?

5 A. Yes.

6 Q. And azelastine was administered two sprays
7 per nostril twice a day, correct?

8 A. Yes.

9 Q. How would combining these different dosing
10 schedules lead to an optimal dosing and
11 administration of each drug?

12 A. Well, there are many different ways of
13 looking at this. Having one canister instead of two
14 would make sure that the patient doesn't get
15 confused and double up on one instead of the other,
16 make sure that they got both drugs together as is
17 the desire of this combination. And make sure that
18 the concentrations or doses are within the
19 pharmacologically active range. And so those are
20 some of the factors that go into the statement about
21 optimal.

22 Q. A fixed-dose combination would not allow a

1 doctor or patient to vary the amount or timing of
2 the dose of the individual actives, correct?

3 A. There's a slight cost of the convenience,
4 and that is flexibility. But a physician or a
5 patient could easily go back to the monotherapies if
6 there was some sense that they needed more or less
7 of one of the components.

8 Q. So I want to make sure. I'm going to ask
9 it again. So if you have a fixed-dose combination,
10 that would not allow the doctor or patient to vary
11 the dose or timing of the dose of the actives unless
12 you discontinued the use of the product?

13 A. I don't think that's true. I think the
14 product could be used slightly differently than
15 indicated with some flexibility. We know that
16 200 micrograms of fluticasone is very safe. Higher
17 doses of fluticasone are not unsafe within a small
18 range, if there were more sprays. So there would be
19 less flexibility, no doubt, than the two
20 monotherapies.

21 Q. But you could not vary the amount of
22 active that was released per actuation; is that

1 correct?

2 A. That's correct. The proportion is fixed,
3 and you have to work within the paradigms of that
4 fact. It's an unalterable fact.

5 Q. In Paragraph 2, we talked about it
6 briefly, and you said convenience is a different
7 factor than the excess administration of liquids,
8 you know, patients don't have to worry about two
9 sprays.

10 MR. WARNER: I'm sorry. What paragraph,
11 Paragraph 2?

12 BY THE WITNESS:

13 A. 89.

14 Q. Oh, sorry. 89.

15 A. Yes, that's more convenient, and that's one
16 of the advantages.

17 Q. Are there other factors that you were
18 thinking of when you say two drugs combined is more
19 convenient?

20 A. I think I listed several already.

21 Q. Okay. I want to make sure that's the sum
22 of your opinion.

1 A. If I sat down with a pad of paper, I might
2 think of others. But those are the ones that were
3 on the top of my head that are defensible.

4 Q. And then Paragraph 90, there were
5 potential cost savings involved with using a single
6 product rather than two products sequentially?

7 A. Yes.

8 Q. How did you determine that there would be
9 a cost savings using a single product rather than
10 two products?

11 A. Well, the cost of the drug within the
12 preparation is only part of the total cost. The
13 packaging, the labeling, the marketing, all of those
14 things have real costs. And to have one preparation
15 would -- there would be a cost savings due to only
16 having to market, package, label one instead of two.

17 Q. And do you know, has there been cost
18 savings using a single product rather than two
19 products sequentially?

20 A. I'm not aware. I don't know of any
21 studies. I don't know if they share their data, so
22 I'm not aware.

1 Q. And a single product would still need to
2 go through the FDA approval process?

3 A. Yes.

4 MR. WARNER: Objection to the form of the
5 question. Vague.

6 BY MS. EVERETT:

7 Q. And that FDA approval process would likely
8 be very expensive; is that fair?

9 MR. WARNER: Objection to the form of the
10 question. It's vague. It's an incomplete
11 hypothetical. It's also assuming facts about the
12 claims.

13 BY THE WITNESS:

14 A. The combination would require FDA approval.

15 Q. And in your experience, is the efforts and
16 steps required to get FDA approval expensive?

17 A. Yes.

18 Q. Okay. I'm going to have you turn to your
19 rebuttal report, which is Exhibit 2.

20 A. Okay.

21 Q. And turn to Paragraph 11. The
22 Paragraph 11 begins: I further understand from

1 counsel that there was a so-called blocking patent,
2 which would have provided a strong disincentive for
3 a person of ordinary skill in the art, a POSA, to
4 develop a combination azelastine hydrochloride and
5 fluticasone propionate product.

6 A. Yes.

7 Q. Do you have any independent basis to
8 determine whether the Hettche patent and Phillips
9 patent referred to in Paragraph 11 are blocking
10 patents?

11 A. The principle of a blocking patent, as it's
12 been explained to me, is a patent that claims
13 intellectual property rights over a method or
14 composition or matter or what have you that would
15 interfere with the ability of another person skilled
16 in the art from using that compound or method in
17 their own development.

18 And I'm not a patent attorney. But I'm
19 aware that the Hettche patent states -- claims
20 protection of the use of azelastine in combinations.
21 And my attorney colleagues have explained to me that
22 that is considered a blocking patent for the use of

1 azelastine in combinations, or it was until 2011.

2 Q. And when you say you are aware that the
3 Hettche patent claims protection of the use of
4 azelastine in combinations --

5 A. Yes.

6 Q. -- is that your determination; or is that
7 something you learned from counsel?

8 A. I looked at that section of the Hettche
9 patent, but I'm not -- I don't believe I read the
10 Hettche patent from stem to stern.

11 Q. So is that your opinion based on your
12 review of the Hettche patent, or is that
13 counsel's -- what you have discussed with counsel?

14 A. Both, in concurment.

15 Q. You have not provided a basis in your
16 report for that, have you?

17 MR. WARNER: Objection. Mischaracterizes the
18 report.

19 BY THE WITNESS:

20 A. I'm not sure what you mean by a basis, but
21 I think this is the only discussion of the blocking
22 patent.

1 Q. This is your only discussion. And it
2 starts with you understand from counsel that there
3 are blocking patents?

4 A. Yes.

5 Q. Did you provide -- Did you undertake an
6 independent analysis to determine whether these are,
7 in fact, blocking patents?

8 A. No, I did not go out and hire separate
9 legal counsel to do that. No, I did not.

10 Q. And I'm not saying whether you did it with
11 other counsel or not. Did you review these patents
12 and satisfy yourself that they are blocking patents?

13 A. I'm not qualified as a patent review
14 officer. But I concur that there are claims for the
15 use of azelastine in combinations, and that
16 satisfies me with my minimal knowledge of patent law
17 that that could serve as a blocking patent.

18 Q. Did you undertake any other analysis to
19 determine whether Hettche or Phillips were blocking
20 patents?

21 MR. WARNER: Objection to the form of the
22 question. Other than reading the patents and the

1 claims?

2 MS. EVERETT: Well, as he talked about --

3 BY THE WITNESS:

4 A. As I said, I have not performed any further
5 analysis to investigate the strength of that --
6 those as blocking patents.

7 MS. EVERETT: Okay. I think now might be a
8 good time for a break.

9 THE VIDEOGRAPHER: We are going off the record
10 at 4:48 p.m.

11 (A short break was taken.)

12 THE VIDEOGRAPHER: We are now going back on the
13 record at 5:07 p.m.

14 BY MS. EVERETT:

15 Q. Welcome back.

16 A. Thank you.

17 Q. I'm going to have you go back just to
18 finish up a few questions on our previous
19 discussion. If you open up to Page 87 on your
20 opening report, I'd appreciate it. Are you there?

21 A. Yeah.

22 Q. We were discussing your opinion on the

1 benefits of a combination therapy over the
2 sequential administration of a steroid and an
3 antihistamine.

4 Do you recall that discussion?

5 A. I do.

6 Q. And we walked through the points disclosed
7 in 88, 89, and 90?

8 A. I'm sorry. Say that again.

9 Q. And we walked through Paragraphs 88, 89,
10 and 90?

11 A. Yes, uh-huh.

12 Q. And you have no additional benefits --
13 strike that.

14 And these are the sum of your opinion on
15 the benefits of a combination therapy as opposed to
16 a sequential administration of a steroid and
17 antihistamine; is that correct?

18 MR. WARNER: Objection to the extent it
19 mischaracterizes his previous testimony.

20 BY THE WITNESS:

21 A. The discussion was how these are some
22 modest benefits of combining them, the two drugs,

1 the intranasal steroid and the intranasal
2 antihistamine into a single drug.

3 Q. And you have not opined on any additional
4 benefits besides the ones disclosed in Paragraph 88,
5 89, and 90, correct?

6 MR. WARNER: Objection to the form of the
7 question to the extent it mischaracterizes his
8 previous testimony.

9 BY THE WITNESS:

10 A. I'm not aware outside of this, opining on
11 the additional benefits. There are discussion about
12 lack of unexpected results and lack of certain
13 benefits, but I think your statement is correct.

14 Q. Earlier today we talked about your
15 definition of a person of ordinary skill. Do you
16 recall that?

17 A. Yes.

18 Q. In your opinion in June 2002, how many
19 people in the United States were qualified as a
20 person of ordinary skill, in your definition?

21 MR. WARNER: Objection to the form of the
22 question. Beyond the scope of the expert report.

1 BY THE WITNESS:

2 A. Oh. You're asking for speculation, but I
3 would think it would be --

4 MR. WARNER: Don't speculate. You don't have
5 to.

6 THE WITNESS: No?

7 MR. WARNER: She doesn't want your speculation.

8 BY MS. EVERETT:

9 Q. Well, do you have an idea of how many it
10 would be?

11 MR. WARNER: Objection. Calls for speculation.
12 Beyond the scope of the expert report. Incomplete
13 hypothetical.

14 BY THE WITNESS:

15 A. A large number.

16 Q. What is a large number?

17 MR. WARNER: Same objections.

18 BY THE WITNESS:

19 A. I'm not going to speculate. Sorry.

20 Q. Are we talking thousands? Hundreds of
21 thousands?

22 MR. WARNER: Objection. Asked and answered.

1 Same objections.

2 BY THE WITNESS:

3 A. Yeah, you're asking for me to speculate. I
4 don't know.

5 Q. Okay. How did you prepare for today's
6 deposition?

7 MR. WARNER: You can answer the question. Just
8 in doing so, if you had any communications with
9 attorneys, don't reveal the substance of any of
10 those communications.

11 THE WITNESS: Okay.

12 BY THE WITNESS:

13 A. You're asking about after the preparation
14 of all these reports?

15 Q. Yes. I'll ask you about the reports in a
16 moment.

17 A. Okay. Well, I studied the materials, the
18 reports in particular, but also the documents and
19 key information and then spent a part of yesterday
20 discussing the case with Kevin and Elan.

21 Q. Okay. Did you do anything else -- strike
22 that.

1 Did you speak with anyone outside of
2 counsel about today's deposition?

3 A. No. It's my understanding that the
4 substance of this is confidential.

5 Q. So when -- or strike that.

6 Earlier today, you -- we discussed your
7 reports, the preparation of your reports?

8 A. Yes.

9 Q. How -- Did you draft your reports? Did
10 you actually type them?

11 A. I played an active role in the writing of
12 them. And in some cases, I wrote my opinions,
13 especially in the rebuttal and the reply, I wrote my
14 opinions out and sent them. And then they were used
15 to put them in an organized legal document and, yes,
16 I played an active role in writing them. But I
17 also -- I proofed every word many times and made
18 sure that I agreed with the statements that were
19 made.

20 Q. Did you meet with counsel to review your
21 drafts?

22 MR. WARNER: Are you talking about before they

1 were submitted?

2 MS. EVERETT: Yes, yes.

3 BY THE WITNESS:

4 A. No, just phone calls and emails.

5 Q. Okay. Your report cites a number of
6 pieces of literature. How did you -- strike that.

7 Did you search for the pieces of
8 literature that were cited in your report?

9 A. In many cases yes. In some cases, no, they
10 were presented to me with a request for my opinion.

11 Q. Did you direct your counsel -- strike
12 that.

13 Did you direct Apotex's counsel to search
14 for certain prior art?

15 A. I may have on occasion asked them to look
16 for certain things.

17 Q. We've had a number of breaks today. And
18 during those breaks, did you discuss the substance
19 of your testimony with counsel?

20 A. No.

21 MS. EVERETT: I have no further questions.

22 THE WITNESS: Thank you.

1 MR. WARNER: Nothing for me.

2 We'll reserve signature.

3 THE VIDEOGRAPHER: This concludes today's
4 deposition. We are going off the record at
5 5:14 p.m.

6 (Witness excused.)

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1 STATE OF ILLINOIS)
2) SS:
3 COUNTY OF COOK)

4 I, RACHEL F. GARD, RPR, CLR, CRR, CSR No.
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5 the State of Illinois, at large, do hereby certify
that DR. ROBERT SCHLEIMER, the deponent herein, was
6 previously duly sworn to tell the truth, the whole
truth, and nothing but the truth in the
7 aforementioned matter;

8 That the foregoing deposition was taken on
behalf of the Plaintiffs at Winston & Strawn, 35
West Wacker Drive, Chicago, Illinois, on the 29th
9 day of September, 2016, at 9:04 a.m., pursuant to
the applicable rules;

10 That said deposition was taken down in
stenograph notes and afterwards reduced to
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typewritten transcript is a true record of the
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signature was requested by the deponent and all
13 parties present;

14 That the parties were represented by their
counsel as aforementioned.

15 I do further certify that I am a disinterested
person in this cause of action, that I am not a
relative or attorney of either party or otherwise
16 interested in the event of this action, and that I
am not in the employ of the attorneys for any party.

17
18 IN WITNESS WHEREOF, I have hereunto set my
hand and affixed my seal on this _____
day of _____, 2016.

19
20
21

Rachel F. Gard

22

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WINSTON & STRAWN, LLP
2 35 West Wacker Drive
Chicago, Illinois 60601

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Date of deposition: September 29, 2016
5 Deponent: Robert P. Schleimer

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11 Page No. Line No. Change
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15 **See Exhibit A**
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21 
22 Signature Date

Exhibit A

Page	Line	Item
31	1	Countries strike
36	4	Strike project
50	19 and 20	Salvation = salivation
52	9	lucatroians = leukotrienes
55	20	fill = filled
58	14	topic = topical
61	11	and = or
84	1	Elan = Ilan
119	4	relative = relevant
120	4	...more potent than = more potent in
122	6	cite = site
123	16	acetylene = acetamide
131	7	we've = they've
158	21	Person = Persson
162	11	John = Jean
163	20	Bouskay = Bousquet
166	1	work = word
185	6	or no? = or so.
191	12	John = Jerry
200	17	the lowered = they lowered
220	6	Elan = Ilan
226	14	composition or = composition of
233	20	Elan = Ilan