

Page 1

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. MAUREEN DONOVAN, 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 9:06 a.m. on Friday, October 7, 2016.

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16 ALSO PRESENT:

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1

I N D E X

2

WITNESS

PAGE

3

DR. MAUREEN DONOVAN

4

Examination by Ms. Everett

6

5

Examination by Mr. Warner

280

6

7

E X H I B I T S

8

9

DEPOSITION EXHIBITS

PAGE

10

11

Exhibit 1

Expert Report of Maureen

38

12

Donovan, Ph.D.

13

Exhibit 2

Expert Rebuttal Report of

39

14

Maureen D. Donovan, Ph.D.

15

Exhibit 3

Expert Reply Report of

39

16

Maureen D. Donovan, Ph.D.

17

Exhibit 4

Imitrex label

96

18

Exhibit 5

Loyd Allen article

108

19

Exhibit 6

'194 patent

131

20

Exhibit 7

Report of Matthew Herpin,

173

21

Ph.D.

22

Exhibit 8

Cramer reference

176

23

Exhibit 9

Exhibit R, Pump Delivery

185

Shot Weight Raw Data

Sprayability Check

1	E X H I B I T S (Continued)		
2	DEPOSITION EXHIBITS		PAGE
3	Exhibit 10	Expert Report of	203
4		Ramprakash Govindarajan	
5		Ph.D.	
6	Exhibit 11	Exhibit C, Cramer	209
7		Example I	
8	Exhibit 12	Exhibit D, Dr.	209
9		Govindarajan Process	
10	Exhibit 13	PH reports for	209
11		Dr. Herpin's tests	
12	Exhibit 14	Feasibility assessment	222
13		plan	
14	Exhibit 15	Lab notebook	242
15	Exhibit 16	Chapter of Remington's	265
16			
17			
18			
19			
20			
21			
22			

1 THE VIDEOGRAPHER: This is videotape No. 1 in
2 the videotaped deposition of Dr. Maureen Donovan,
3 taken by plaintiffs' counsel in the matter of Meda
4 Pharmaceuticals, Inc., and Cipla, Limited, versus
5 Apotex, Inc., in the United States District Court
6 for the District of Delaware, Case No. 1:15-CV-785.

7 This deposition is being held at Winston &
8 Strawn, LLP, 35 West Wacker Drive, Chicago,
9 Illinois, on Friday, October 7, 2016. The time on
10 the video screen is 9:06 a.m.

11 My name is Kim Ortiz. I am the legal
12 videographer from Digital Evidence Group. The court
13 reporter is Rachel Gard, in association with Digital
14 Evidence Group.

15 Will counsel please introduce themselves
16 for the record.

17 MS. EVERETT: Uma Everett from Sterne, Kessler,
18 Goldstein & Fox on behalf of plaintiffs. With me
19 today is my colleague, Rami Bardenstein.

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

22 THE VIDEOGRAPHER: Will the court reporter

1 please swear in the witness.

2 (Witness sworn.)

3 WHEREUPON:

4 DR. MAUREEN DONOVAN,

5 called as a witness herein, having been first duly

6 sworn, was examined and testified as follows:

7 EXAMINATION

8 BY MS. EVERETT:

9 Q. Good morning, Dr. Donovan.

10 A. Good morning.

11 Q. Can you please state your name.

12 A. Maureen Donovan.

13 Q. What is your work address?

14 A. 115 South Grand Avenue, University of Iowa
15 College of Pharmacy.

16 Q. Have you ever provided deposition
17 testimony before?

18 A. Yes, I have.

19 Q. When did you do that?

20 A. Most recently about 6 months ago, and quite
21 a few years ago previous to that.

22 Q. What was the testimony you provided 6

1 months ago?

2 A. 6 months ago was in a pharmaceutical patent
3 litigation case.

4 Q. Who did you -- strike that.

5 Who retained you in that case?

6 A. I was retained by a number of firms, and
7 Winston & Strawn happened to be one of the group.

8 Q. What was the nature of your opinion in
9 that case?

10 A. My nature -- My opinion was -- well, it was
11 a solid oral dosage form. And my opinion was
12 directed primarily at the formulation development
13 aspects of that.

14 Q. You stated that you gave deposition
15 testimony several years ago as well?

16 A. Uh-huh.

17 Q. And what was the case for which you gave
18 deposition testimony?

19 A. I've had other -- well, several other
20 depositions. Most of them have been in the areas of
21 nasal sprays and some in ophthalmic delivery
22 systems.

1 Q. Where you provided deposition for nasal
2 sprays, what were the products at issue?

3 A. The one that's publicly available for
4 everybody to go view is Nasacort.

5 Q. And what was the nature of your opinion in
6 the Nasacort case?

7 A. In the Nasacort case, I was working with a
8 firm that was representing a generic company. And I
9 was again an expert witness regarding formulation
10 and nasal deposition.

11 Q. Who retained you in the -- strike that.
12 Have you provided opinion testimony in
13 other litigations related to nasal sprays?

14 A. Yes, I have.

15 Q. What products were at issue?

16 MR. WARNER: Actually, I'll let her answer.
17 But I guess if you've done deposition testimony or
18 trial testimony, then it's known. One of your
19 responses earlier made me think that there may be
20 some engagements that aren't public, ones you
21 haven't done testimony for them. We just need to be
22 careful about those. But things you testified under

1 oath, that's okay.

2 BY THE WITNESS:

3 A. We're kind of in the wayback machine on a
4 number of things whether I was deposed in those
5 cases or not. And there was a -- this is a long-ago
6 case where I was deposed, and that was -- the case
7 settled. And it was an intranasal product. And I
8 believe it was an antihistamine, if I remember that
9 case correctly.

10 Q. It was an intranasal antihistamine, you
11 said?

12 A. Yes.

13 Q. Was it any Astelin?

14 A. It was related to Astelin, yeah.

15 Q. Was it Astepro?

16 A. I don't think I've ever been deposed about
17 Astepro, no.

18 Q. In addition to Nasacort and the Astelin
19 cases, are there any other cases where you provided
20 opinion testimony related to a nasal spray?

21 A. I don't think any -- I've been involved in
22 other cases. I don't think I've ever been deposed

1 in any of them. Again, they've all been quite a few
2 years ago, and I don't remember necessarily which
3 one corresponded to which.

4 Q. Understood. In the Astelin case, who
5 retained you?

6 A. I'm pretty sure at the time it was Husch
7 Blackwell. But the lawyers involved have moved to a
8 different firm, so again it's way back there.

9 Q. Do you remember which company retained
10 you?

11 A. To be honest, I do not.

12 Q. Was it for a generic company?

13 A. Yes, I was representing a generic.

14 Q. For the -- you -- strike that.

15 You said you provided deposition testimony
16 for ophthalmic products?

17 A. Yes.

18 Q. Which ophthalmic products?

19 A. Most of them have surrounded olopatadine as
20 one of the agents.

21 Q. Which companies retained you to provide
22 deposition testimony?

1 A. Apotex has been one. I'm trying to
2 remember. There were probably several others
3 involved, but I -- and I think Sandoz was involved
4 with one of the ophthalmic cases with olopatadine.
5 Again, I don't remember exactly.

6 Q. It was generic manufacturers you
7 represented?

8 A. It was generic manufacturers that I
9 represented, yes.

10 Q. Have you ever represented a branded
11 pharmaceutical company in a patent litigation case?
12 Or strike that. Have you ever been retained --
13 strike that again.

14 Have you provided testimony on behalf of a
15 branded pharmaceutical company in a patent
16 litigation?

17 A. I have not provided testimony regarding --
18 for a branded company.

19 Q. Have you been retained to -- strike that.
20 Have you ever consulted with a branded
21 pharmaceutical company?

22 A. Yes, I have.

1 Q. Okay. In what context?

2 A. In a variety of contexts. In early
3 formulation development activities, in activities
4 regarding patent litigation.

5 Q. In -- You said in activities related to
6 patent litigation?

7 A. Uh-huh.

8 Q. In a consulting role?

9 A. Yes.

10 Q. Your deposition testimony has been on
11 behalf of generic companies so far?

12 A. I believe all of my deposition testimony
13 that's of record is on behalf of generic companies.

14 Q. Have you provided any trial testimony?

15 A. Yes, I have.

16 Q. And what was the nature of -- strike that.
17 Who -- what was the nature of the case in
18 which you --

19 A. Again, that was a nasal spray case.

20 Q. Which case was it?

21 A. That was the Nasacort case.

22 Q. Are there any other cases in which you

1 provided trial testimony?

2 A. No.

3 Q. So I will just go over some -- obviously
4 you know some of the basics on depositions. I think
5 we're falling into a little bit of this so it's
6 worth going over. Obviously we have a court
7 reporter here to take down my questions and your
8 answers.

9 I think we just have to be cognizant of
10 not speaking one over other. I'm sure there will be
11 plenty of times you anticipate my question. I think
12 you have already a few times this morning.

13 I will let you finish your answer. Please
14 let me finish my question. And that way we'll have
15 a clean record.

16 If there's any question you don't
17 understand, please ask for clarification and I will
18 endeavor to make my questions clear. If you answer,
19 I will assume you've understood the question.

20 Is that fair?

21 A. Sure.

22 Q. Is there any reason you can't testify

1 truthfully today?

2 A. No.

3 Q. If you need breaks at any time, please let
4 me know and we'll stop for a break. We intend to
5 take breaks about every hour or so anyway.

6 A. Okay.

7 Q. I just ask if you need a break, we just
8 finish the question that's pending and we'll get you
9 a break.

10 A. Sure.

11 Q. Dr. Donovan, in your background, have you
12 formulated a nasal spray?

13 A. Yes, I have.

14 Q. When you formulate a nasal spray -- How
15 many nasal sprays have you formulated?

16 A. I don't keep track because I'm not -- I'm
17 not formulating a product. I formulate nasal sprays
18 for research endeavors. So it could be in the
19 thousands if we count every single solution or
20 suspension or gel or film or whatever that I've
21 made, so ...

22 Q. Are there considerations that are unique

1 to the nasal sprays as opposed to another dosage --
2 or another delivery system?

3 MR. WARNER: Objection to the form of the
4 question. Vague. It's an incomplete hypothetical.
5 Go ahead.

6 BY THE WITNESS:

7 A. Okay. There are a number of factors that a
8 nasal spray needs to have as its characteristic and
9 its function. And a lot of any dosage form factor
10 is dependent on, you know, what the drug is, what
11 the intended use is. And we formulate around that
12 for hopefully the most convenient use and best
13 product, if we're actually trying to formulate for a
14 commercial use. I formulate a number of things
15 where I have no intention of them being a commercial
16 use. They contain materials that I want to include
17 as probe molecules to understand basic activities in
18 the nasal cavity.

19 Q. For a nasal spray that is going to be used
20 by a person or as a method of treatment, are there
21 unique characteristics to consider in a nasal spray
22 different from other dosage forms?

1 MR. WARNER: Same objection. It's vague, and
2 it's kind of an incomplete hypothetical.

3 BY THE WITNESS:

4 A. Okay. And yeah. I think I'm going to ask
5 for a clarification. Are you talking about a nasal
6 formulation that is intended to be delivered via
7 a -- some sort of spray unit? Is that what you're
8 trying to have me answer?

9 Q. Yes. Is there a different -- a nasal
10 spray that can be delivered differently that you're
11 thinking of?

12 A. Well, there are characteristics about any
13 formulation that require them to be compatible if
14 you need to essentially couple that with a device
15 for delivery. You have to address whether that
16 formulation is compatible with the device you intend
17 to have it be delivered with.

18 But there are a lot of devices available,
19 so you've got similarly to you have formulation
20 latitude; you've got device latitude. There are
21 characteristics, but a lot of them are
22 characteristics of a specific device that you're

1 trying to couple your formulation to.

2 Q. Are there characteristics that are unique
3 to the formulation separate from the device that you
4 would consider?

5 MR. WARNER: Same objections.

6 BY THE WITNESS:

7 A. The characteristics for a nasal spray or
8 for a nasal that's going to be formulated in -- or
9 for a nasal formulation, or a nasal formulation
10 that's going to be formulated for a spray?

11 Q. For a nasal spray formulation.

12 A. Well, there are characteristics of nasal
13 spray formulations that are well accepted in the
14 art, and formulators are aware of those. They're
15 not rigid rules. They're not legally enforceable.
16 There's latitude for formulation components and
17 styles, forms depending on again the drug product
18 and the intended use or intended strategy for
19 delivery.

20 And so yeah. There are general guidances.
21 And I'm not speaking to the FDA guidances in any
22 strict fashion, but there are generally recognized

1 strategies that people use for nasal spray
2 formulations. They look quite similar to strategies
3 that formulators use for a number of other delivery
4 systems or dosage forms.

5 Q. Understood. But I'm trying to focus on
6 what is unique about nasal sprays. For example,
7 isotonicity. Is that a consideration in a nasal
8 spray?

9 A. Isotonicity is a consideration in a nasal
10 spray, but it's not unique to formulation of nasal
11 sprays.

12 Q. But it's not something that's considered,
13 say, in solid dosage form?

14 A. No, because the administration or
15 application site differs in those -- between those
16 two. So it's not the same, but it's relatively the
17 same as an ophthalmic, for example. And it's
18 relatively the same as an oral mucosal delivery
19 system.

20 Q. And a moment ago you referred to general
21 guidelines. You said not FDA guidelines but
22 guidelines. What were you referring to?

1 A. Well, I'm referring to the number of
2 textbooks and book chapters and review articles and
3 so forth where authors have put down various
4 characteristics of nasal spray formulations that
5 guide individuals in approaches for developing nasal
6 formulations.

7 Q. In addition to isotonicity, are there
8 other characteristics that you consider for a nasal
9 spray when formulating a nasal spray?

10 A. Well, there's a lot of things that get
11 considered. There's everything from the dose that's
12 intended, the solubility, the volume you're going to
13 be able to administer, how you're going to be able
14 to administer that. And if you have -- if there's a
15 particular goal in mind regarding that formulation,
16 where you're actually formulating it potentially to
17 be administered to patients or potentially being
18 turned into a commercial product. There are some
19 additional factors regarding shelf life and drug
20 stability and ease of manufacturing, and there can
21 be a whole number of things that get considered,
22 again depending on what the goal is for the

1 particular formulation activity.

2 Q. For a nasal spray that will be
3 administered as a method of treatment to a human,
4 what are the characteristics you would consider in a
5 nasal spray?

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

8 BY THE WITNESS:

9 A. Essentially many of the things I just
10 finished listing. And questions about whether --
11 whether the dose is -- as a formulator, you'd need
12 to have at least a range of doses that you were
13 targeting. You have an idea of how that formulation
14 might be administered.

15 You have -- You'd likely be keeping in
16 mind, you know, is this going to be something that's
17 made at the patient's bedside? Is it something
18 that's going to be made an hour before? Is it
19 something that's going to be made a year before and
20 provided? And all of those things have different
21 levels of consideration regarding what might be
22 included in the formulation and formulation

1 approaches.

2 Q. When you said that you would consider the
3 doses that you -- that were targeted, what did you
4 mean by that?

5 A. Well, as a formulator, we need to know how
6 much drug it is that we're intended to deliver. And
7 typically that's whatever pharmacologic dose is
8 going to give the response that's desired.

9 Now, doses are a -- are often given as a
10 range that you don't -- that a specific number isn't
11 the only number that gives the desired response.
12 And so there's oftentimes a range of appropriate
13 doses, and we oftentimes need to or we'd like to
14 know what that range is to, again, give us again the
15 latitude on balancing chemical characteristics with
16 pharmacologic need and other issues regarding how
17 we're going to go about manufacturing or providing
18 that particular drug product or dosage form or
19 formulation kind of depending on where we are in the
20 process of evaluating its use.

21 Q. So if you determine that you are targeting
22 a particular dose or dose range, it's important that

1 the drug deliver that dose or dose range, correct?

2 A. It's important that the formulation deliver
3 that, the dose that you intend.

4 Q. Okay. Is that -- and that's an important
5 characteristic in all nasal spray products; is that
6 correct?

7 A. It's an important characteristic in any
8 drug product, including nasal sprays.

9 Q. Next, you said you would consider how the
10 formulation was administered. And I think we were
11 talking about nasal sprays. So what did you mean
12 specifically on how it's administered?

13 A. Well, if we're talking about nasal sprays
14 as a subcategory, the need to consider what spray
15 device it is that it's going to be administered in.
16 Is somebody going to empty out a Dristan bottle and
17 you're going to refill that Dristan bottle with your
18 formulation? Are you going to obtain other spray
19 devices from other vendors?

20 There's a number of them to pick from, so
21 you need to know which of the many that you might
22 use, whether you're going to use all of the above,

1 whether there's only a single one that you might
2 have access to, a number of factors that go into
3 selecting the spray device. And then formulating so
4 that it delivers the proper dose is another activity
5 that would become part of a plan for formulation
6 development if that spray device was required for
7 dose administration.

8 Q. And you also said it's important that when
9 a patient -- when the formulation would be made in
10 relation to when it was administered, for example, I
11 think you gave whether it's made up at the patient's
12 bedside or a year before, there would be various
13 considerations on that as well?

14 A. Is there a question there?

15 Q. Is that a correct summary? Is that
16 correct?

17 A. Well, I said those are certainly
18 considerations that the length of time over which
19 that formulation will rest before it's being
20 administered is a consideration that a formulator
21 addresses.

22 Q. Are there -- in addition to the three

1 we've just gone over, can you think of any other
2 considerations that you would think about when you
3 were formulating a nasal spray that will be
4 administered to humans as a method of treatment?

5 A. Well, one of the issues, again
6 eventually -- well, even if it's not a commercial
7 product, if it's going to be administered to humans,
8 it doesn't have to be sterile. But you -- your
9 strategy is best formulated -- bad word -- best
10 planned to attempt to either be able to sterilize
11 the product or have it as, quote/unquote, near
12 sterile as possible.

13 Q. Is that because of nasal sprays are
14 multiple use or just sterility is an important
15 consideration?

16 A. Sterility is an important consideration or
17 near sterility. There's a debate about whether it's
18 mandatory, necessary, or just important.

19 Q. What is your view on that?

20 A. My view is that a nasal formulation does
21 not need to be sterile to be administered. It does
22 need to be as low bioburden as possible.

1 Q. What is low bioburden?

2 A. Low bioburden is the population of bacteria
3 and pyrogens and potentially other fungi, other
4 contaminants that are what we're trying to avoid
5 when we actually sterilize products. And meeting
6 the requirements for sterile dosage form for a nasal
7 delivery system, again, I don't believe it's in all
8 cases to have it absolutely sterile. But it has to
9 be low bioburden. We shouldn't be inoculating
10 people with bacteria or fungi laden dosage forms.

11 Q. That sounds like a good approach.

12 A. Yes, usually is.

13 Q. Earlier you stated you may have formulated
14 in the thousands of nasal sprays. About how many of
15 those nasal sprays were for potential use for humans
16 as a method of treatment?

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

19 BY THE WITNESS:

20 A. Well, and I think I'll back up. I'm not
21 sure. I may have been presumptive in my answer.
22 I've formulated thousands of formulations, not all

1 of them nasal sprays. And so of the materials that
2 I've formulated as nasal sprays, some of them had a
3 goal of eventually being used in humans if
4 preclinical results looked worth -- looked like they
5 were worth going forward. But all of my formulation
6 activities are very early in the preclinical to
7 clinical assessment phases. So I have not
8 formulated directly a nasal spray product that was
9 absolutely moving forward into use in humans.

10 Q. Have you formulated a nasal spray with two
11 active ingredients?

12 A. I believe I have, yes.

13 Q. What were the two --

14 A. Actually, it wasn't a nasal spray. It was
15 a nasal formulation with more than one active
16 ingredient.

17 Q. How was it delivered if it was not a
18 spray?

19 A. It was probably delivered by drops, the
20 level we were working at.

21 Q. What were the two actives?

22 A. I'm trying to remember. There was likely

1 an anti-inflammatory. There was likely an
2 antihistamine. I don't remember whether there
3 were -- there was an antibacterial in it or not.
4 And any variety of a number of other sort of
5 combinations of drugs that you'd consider using
6 nasally, we may have combined at points in time
7 during our research.

8 In a lot of the research that I do, we
9 combine things that are the actual active and then
10 something else that could be considered an active
11 agent but we're using it as an inhibitor instead.
12 So it's sort of an anti-active.

13 Q. So you referenced an anti-inflammatory.
14 Which active was that?

15 A. I have no recollection on the detail of
16 which one specifically that was.

17 Q. And then you said there was an
18 antihistamine. Do you recall which?

19 A. I don't remember. We've used a series of
20 antihistamines in my lab. I've worked with private
21 sponsors on other antihistamines they were
22 interested in. I have no recollection of which ones

1 we've combined and what we've done with them.

2 Q. Is this --

3 A. Specifically.

4 Q. Oh, I apologize.

5 A. No, no, it's just I don't specifically
6 remember which ones and in what combinations.

7 Q. So is this nasal drop product the only one
8 you can recall where you combined multiple active
9 ingredients for use as active ingredients?

10 A. And again, you know, I'm struggling over
11 the term "active ingredient" because I just have a
12 different view on what the FDA labels as active
13 ingredient and what's active, so -- but to try to
14 meet the question you've asked, if we're talking
15 about two -- what the FDA would require, the
16 identification as the active agent, I'm sure we've
17 combined plenty of active agents in various
18 situations in my research program. I just struggle
19 to come up with the exact examples of when we did
20 that or what was the motivation to do it at the
21 time.

22 Q. Do you recall whether these active agents

1 that were combined were all in solution?

2 A. They were likely in solution. But I can
3 think of cases where we've dealt with materials in
4 the formulation that weren't in solution that we
5 intentionally retained in those formulations.
6 Whether they were the actives or not, I mean, we've
7 administered plenty of actives that weren't in
8 solution as individual agents. Try not to do that
9 because, again, it doesn't address mechanistically
10 many of the things we're interested in. But we set
11 up a lot of in vitro experiments where the active is
12 not in -- well, it's in solution and in suspension.
13 We have excess solid drug present for particular
14 reasons.

15 Q. So you've mentioned that occasionally some
16 of the formulations that you've studied, the active
17 would not have been in solution because there was
18 excess drug. Are there situations you can recall
19 where it was a suspension product that you were
20 studying, two suspensions, for example?

21 MR. WARNER: Objection to the form of the
22 question as vague.

1 BY THE WITNESS:

2 A. So are you asking whether both actives were
3 both in suspension?

4 Q. Yes.

5 A. I don't recall having done two actives,
6 both of which were, you know, in solution to their
7 saturated solubility and then excess drug being as
8 two solids. I don't recall that strategy ever.

9 Q. Have you formulated a nasal spray where
10 there were two actives, one in solution and one in
11 suspension?

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

13 BY THE WITNESS:

14 A. You know, I'm sure at some point in time
15 we've done that, that the -- it goes back to what
16 the required mass load for a particular one of the
17 actives was and the volume that we were planning on
18 using for the administration. And there easily
19 could have been one API that was in suspension so it
20 had excess solid present, and the other didn't have
21 excess solid present and both had some drug
22 concentration in solution.

1 Q. Can you recall a specific example of that?

2 A. I can't.

3 Q. Have you formulated any nasal spray
4 products using fluticasone as an active?

5 A. Fluticasone is not an active ingredient
6 I've chosen to use in my laboratory in our
7 investigations.

8 Q. Why is that?

9 A. I -- looking -- using steroid products is
10 not -- or selecting steroids as APIs is not a
11 simple -- they're not simple model compounds. Their
12 analytical methods are challenging. That's
13 primarily one of the reasons that I typically don't
14 choose to use them.

15 Detection in blood, even analysis of the
16 dosage form itself requires more challenging HPLC
17 assays than I like to run on a daily basis requires
18 often -- back in the day, I think a very, very long
19 time ago, I worked with some steroids. Fluticasone
20 was not one of them. And we were -- we needed
21 special solvent systems that weren't typically used
22 in a lab.

1 We had to -- you know, there's waste
2 disposal issues. We had to have dedicated
3 equipment. It becomes inefficient in a small
4 academic research lab. So there wasn't ever any
5 reason from a focus of my research program to need
6 to use a steroid as a model compound, so they're
7 just not typically the things I use to look at.

8 Q. You said that they needed a special
9 solvent system. What kind of solvent system did
10 they need?

11 A. Well, again, back in the day when I worked
12 on them, the standard methods to analyze steroids
13 was something using -- called normal phase
14 chromatography. And normal phase chromatography
15 uses solvents like toluene and dimethyl --
16 dichloromethane, other things I try not to have to
17 use in my lab.

18 And typically -- And I'm sure now, I don't
19 look at steroid analytical methods, but there are
20 other improved detection systems and better columns
21 than there were at the time. And so, you know, our
22 typical materials for reverse phase chromatography

1 now are acetonitrile and methanol. And while they
2 also have disposal issues, they don't have as many
3 exposure issues and disposal issues as toluene,
4 dichloromethane, and their friends that get used in
5 normal phase chromatography.

6 Q. And you said at the time. What are the
7 time frames?

8 A. This is back in the 1980s and potentially
9 into the early 1990s.

10 Q. And when you say that there's these
11 special solvent systems, is that to -- for -- as
12 you're describing the chromatography, you know,
13 assessing a steroid; or does it have a different
14 purpose?

15 MR. WARNER: Objection to the form of the
16 question. Compound and vague.

17 BY THE WITNESS:

18 A. Well, the analytical methods I was using
19 were high-performance liquid chromatography. And
20 the basic principle of that is you flow a solvent
21 system through a packed column of material, and your
22 separation of your material of interest from a

1 number of other materials that might be associated
2 with it is dependent on partitioning functions
3 between the solid phase and the flowing solvent
4 phase.

5 And so the solvents that I was referring to
6 are those flowing solvent phases that go through the
7 column, and it's the partitioning functions of the
8 steroids that then allow them to be separated out
9 and leave the column and be detected using some
10 analytical instrumentation. UVs comes to mind, very
11 frequently used. Fluorescence doesn't get used in
12 most steroid analyses unless we're doing some sort
13 of derivatization procedure, which is even more
14 arduous. So that's what I meant by those solvents
15 is the solvent systems that were flowing through the
16 analytical equipment that were responsible for the
17 partitioning functions to separate the steroid and
18 allow it to be detected by some analytical method.

19 Q. Have you studied or formulated azelastine?

20 A. No, I have not.

21 Q. Is there a reason for that?

22 A. It's not a model compound that I was

1 interested in using for the work in my laboratory.

2 It's ...

3 Q. Earlier, I believe you said that most of
4 your work relates to early formulation stages,
5 preclinical stages?

6 A. Yes.

7 Q. Is there special considerations that you
8 look for when formulating a nasal spray product in
9 the preclinical stages?

10 MR. WARNER: Objection to the form of the
11 question. Vague and incomplete hypothetical.

12 BY THE WITNESS:

13 A. Well, in preclinical stages, you're really
14 very early on in the formulation development where
15 you're identifying materials that may be useful,
16 where you're identifying systems and combinations of
17 materials that achieve a particular goal.

18 You may be working towards optimizing that
19 formulation based on particular, again, goals that
20 you usually set for the formulation to start with
21 before you even begin the plan or as you're
22 beginning the planning stages with the realization

1 that your final formulation is going to be a
2 compromise of the possibilities of the goals you
3 identified and goals you identified based on what
4 you find the compatibilities and the opportunities
5 in those formulations as you work with them turn out
6 to be.

7 Q. Earlier we talked about a few
8 considerations, such as dosing that you were
9 targeting. Do you recall that?

10 A. Yes.

11 Q. Is that a consideration in the preclinical
12 development stage?

13 A. In preclinical development stage, we need
14 to know -- we typically need to know the amount of
15 drug that's intended to be included in a dose or the
16 sequence of doses that's going to be in the product
17 or whether it's the product or whether it's in the
18 formulation that we're going to be studying.

19 So the amount that you intend on delivering
20 is one of the pieces of information that you start
21 with or at least a range of doses that you're
22 interested in looking at is something that's part of

1 the initial plan for what you're going to formulate.

2 Q. And how the drug is administered, is that
3 also important in the preclinical stage?

4 A. At preclinical stage, not necessarily. You
5 still have latitude based on what you learn about
6 the formulation and the behaviors of the particular
7 materials to potentially change the method in which
8 it would be administered based on what you learn.

9 Q. So would you change the method of
10 administration at that stage? Or what would do?

11 MR. WARNER: Objection to the form of the
12 question. Vague and incomplete hypothetical.

13 BY THE WITNESS:

14 A. Well, as I said, when we're starting
15 formulation development, we oftentimes have a goal
16 in mind for how the product might be administered.
17 We might learn along the way that that method of
18 administration is likely not going to be effective,
19 be possible, be a number of things. And we're aware
20 of potentially other methods for administration that
21 could accomplish the same goal. And you change the
22 formulation goal to then meet the needs of the

1 alternative method.

2 So the early preclinical development is
3 open to a lot of possibilities. Even if you are
4 staying in the same route of administration, you
5 have plenty of opportunities to select methods of
6 administration.

7 Q. In preclinical development, is when the
8 drug is formulated in comparison to when it is
9 administered important?

10 A. It's always important because when
11 you're -- if you're going to administer is to an
12 animal system, to a cell system, to a human, you
13 have to be sure that the drug and other things that
14 you're planning on measuring is still in the form
15 that you think it's in.

16 So you at least need to have a knowledge
17 that it's chemically stable enough to be the drug
18 that at the concentration that you had formulated or
19 had intended to be at when you administer it so that
20 you know what you're measuring against as you're
21 doing those tests to evaluate its performance.

22 (Donovan Exhibit Number 1 marked

1 for identification.)

2 BY MS. EVERETT:

3 Q. I'm going to hand to you your reports.

4 And the court reporter has marked as Donovan

5 Exhibit 1, the Expert Report of Maureen Donovan.

6 Just do them all at once.

7 (Donovan Exhibit Number 2 marked

8 for identification.)

9 BY MS. EVERETT:

10 Q. Donovan Exhibit 2 is Expert Rebuttal

11 Report of Maureen D. Donovan, Ph.D.

12 (Donovan Exhibit Number 3 marked

13 for identification.)

14 BY MS. EVERETT:

15 Q. Exhibit Donovan 3 is Expert Reply Report

16 of Maureen D. Donovan, Ph.D.

17 And, Dr. Donovan, please just take a

18 moment to look through Exhibits 1, 2, and 3, please.

19 What is Exhibit 1? Is this your opening

20 report?

21 A. Exhibit 1 is as labeled. It's the expert

22 report I provided in this case.

1 Q. And Exhibit 2 is your rebuttal report?

2 A. Yes.

3 Q. And Exhibit 3 is your reply report?

4 A. Yes.

5 Q. Together do these form the basis for your
6 opinions in the case?

7 A. These describe my opinions in this case,
8 yes.

9 Q. Well, what is the distinction you just
10 made between describes your opinion versus I said
11 the basis of your opinion?

12 A. I guess I just repeated in my own layman's
13 terms what I would define these as.

14 Q. Got it. Now, there's nothing -- this
15 is -- I just want to make sure this is the sum of
16 your opinions what we have in 1, 2, and 3.

17 MR. WARNER: Objection to the form of the
18 question. It's vague.

19 BY THE WITNESS:

20 A. Okay. I'll tell you what I'm wrestling
21 with. I have thousands of opinions, but they are
22 not necessarily as defined in legal terms what

1 opinions are. So that's what I'm struggling with,
2 what is it that I'm supposed to answer that I have
3 no other thought regarding anything that might be
4 related to anything in this case? That's not true.
5 I have plenty of thoughts. Whether they're legal
6 opinion, that I'll leave to somebody else to decide.
7 So the bulk of information that I believe is
8 relevant to this case is expressed as the opinions
9 in these reports.

10 Q. Are there any thoughts or information
11 related to this case that you have not expressed?

12 A. Not intentionally.

13 Q. Okay. If you have -- And you may want to
14 take a moment to look. You've attached Materials
15 Considered lists to each of your reports; is that
16 correct?

17 A. That's correct. At least I saw them as I
18 flipped through. At least the first one, yeah, the
19 second one, and yes, they're all there.

20 Q. So if you intend to rely on any
21 documentary evidence to support your opinion, have
22 you included it either in your report by citation or

1 on your Materials Considered list for each of your
2 reports?

3 A. Yes, unless it's just knowledge that I have
4 retained over my years of experience.

5 Q. Understood. And that's why I made the
6 distinction on documentary evidence.

7 A. Yes.

8 Q. Is there any other documents -- strike
9 that.

10 The documents you intend to rely on to
11 support your opinions have been disclosed either
12 through citation in your report or in your Materials
13 Considered list; is that accurate?

14 A. Yes.

15 Q. Great. I'm going to have you turn to your
16 opening report. We'll start at 22. My questions
17 will be a little bit later. They'll be on person of
18 ordinary skill.

19 MR. WARNER: Paragraph or page?

20 BY MS. EVERETT:

21 Q. Oh, paragraph -- person of ordinary skill
22 discussion starts at 22, although my questions

1 probably relate to later paragraphs.

2 A. Okay.

3 Q. In your definition of person of ordinary
4 skill, you said: A person of ordinary skill in the
5 art may have a master's degree in chemistry,
6 biology, chemical engineering, or pharmaceutical
7 sciences with 1 to 3 years of experience in
8 formulation development of nasal agents as well as
9 the ability to operate independently on formulation
10 activities.

11 A. Are you reading Paragraph 25?

12 Q. I am, yes.

13 A. Okay.

14 Q. Why in your definition of person of
15 ordinary skill did you include that that person
16 needed experience in development of nasal agents?

17 A. Well, because a person with a master's
18 degree in any of the areas that I have mentioned has
19 the intellectual background to understand the
20 strategies for formulation development and, in
21 particular, nasal formulation development. Yet if
22 they have not considered directly nasal formulation

1 development, then just because of their training,
2 their education, there's no assurance that they --
3 that they would be able to operate immediately as a
4 person of ordinary skill in the art without having
5 had some specific activities involving nasal dosage
6 forms.

7 Q. Is that because there are again unique
8 formulation considerations in developing a nasal
9 dosage form as opposed to another dosage form?

10 A. Well, there are considerations with any
11 dosage form. And one needs an awareness of what
12 those are in order to formulate a development plan
13 and carry that out to -- and be able to evaluate
14 appropriate modifications to the plan.

15 And, again, people who have general
16 knowledge and experience in other -- other areas of
17 formulation development certainly have the
18 appropriate background and intellectual -- well, if
19 they meet any of these descriptions of POSA, they
20 have the intellectual background to understand and
21 to learn to be a nasal formulator.

22 But as a person of ordinary skill in the

1 art in my definition, that person actually has to be
2 skilled in nasal formulation or have really
3 considerable education and similar experience in
4 other formulation development activities.

5 Q. When you say -- as I understood it, you
6 say a person has to actually be skilled in nasal
7 formulation or have similar education and similar
8 experiences in formulation development. What are
9 those similar experiences?

10 A. They would need to have other formulation
11 development activity experiences. Typically, I
12 mean, my preference would be in the area of some
13 sort of sterile dosage form. Those are the best
14 translatable dosage forms to some of the
15 considerations necessary for nasal dosage forms.

16 But I have seen and been aware of
17 formulators who don't have any sterile dosage form
18 experience who have other experiences who very
19 rapidly learn what the considerations are in nasal
20 drug development and operate as POSAs very quickly.

21 Q. But still in your definition of a POSA, if
22 a person had a master's degree and 1 to 3 years of

1 experience, they would need to have experience with
2 nasal agents?

3 A. They would need experience with developing
4 a nasal dosage form to be considered as a POSA, yes.

5 Q. You go in your definition to state: Such
6 a person may also have a Ph.D., in chemistry,
7 chemical engineering, or pharmaceutical sciences
8 with at least one year of experience in formulation
9 development of sterile dosage forms.

10 Is that correct?

11 A. Yes.

12 Q. And here you said they would require at
13 least one year of formulation development in sterile
14 dosage forms?

15 A. Correct.

16 Q. You didn't limit it to just nasal dosage
17 forms?

18 A. Correct.

19 Q. Why is that?

20 A. Well, because a person who has a Ph.D. in
21 any of those areas has the -- both the intellectual
22 capabilities and the awareness of the needs to

1 gather additional information prior to starting
2 whatever endeavor they're going to be starting
3 scientifically.

4 And so that person would have the ability
5 to quickly understand the literature and know how to
6 apply that literature, whether their experience had
7 been in more general sterile dosage form areas or
8 whether it had actually been specifically in nasal
9 formulation.

10 Q. And when you say "sterile dosage forms,"
11 can you define that further?

12 A. Well, there are dosage forms that are
13 available commercially or even any -- if they're
14 being used in humans, that they are free of
15 bacteria, fungi, other biological contaminants.
16 They're most typically the products that get
17 injected in people's bodies. Ophthalmic dosage
18 forms are sterile dosage forms. And pulmonary
19 nebulizer systems are sterile dosage forms, so there
20 are a number of different routes of administration
21 that a sterile dosage form would be used at or used
22 with.

1 Q. And I think we spoke a moment ago, you
2 said it was controversial whether nasal sprays fell
3 into the sterile dosage form category?

4 A. Well, it's not --

5 MR. WARNER: Objection to the extent it
6 mischaracterizes the previous testimony.

7 BY THE WITNESS:

8 A. It's not that they don't fall into the
9 category. The controversy is whether as provided to
10 the user, whether they are -- whether they must be
11 sterile or whether they just must be low bioburden.

12 Q. Okay. Now I'm going to turn to
13 Paragraph 26, please. In here, it appears you've
14 reviewed the report of Robert P. Schleimer, who has
15 defined a person of ordinary skill as someone having
16 an M.D., Ph.D., or PharmD in the field of allergy,
17 immunology, and/or pharmacology or the equivalent
18 and at least 3 additional years of experience in the
19 treatment or research for treatments of allergic
20 rhinitis, including nasally administered steroids
21 and antihistamines.

22 Do you see that?

1 A. I see that, yes.

2 Q. Do you have any opinion whether the POSA
3 as defined by Dr. Schleimer must have research for
4 treatments of allergic rhinitis?

5 A. Can you state that again? I'm going to
6 reread what this says, and then I'll ask you to
7 restate the question.

8 Q. Sure. Do you have any opinion --

9 A. No, wait, just a moment. Let me read.
10 Then you state it.

11 Q. Okay.

12 A. Okay. Please restate the question.

13 Q. Do you have any opinion whether a POSA as
14 defined by Dr. Schleimer must have the experience of
15 having researched treatments for allergic rhinitis?

16 A. I think both the statement and the
17 current -- as I explain that statement, they don't
18 have to have experience in research. That's one of
19 the possibilities of their experiences that would
20 qualify them as a POSA.

21 Q. Okay. In your report, you begin with the
22 proposition that a POSA would want to formulate a

1 nasal spray product using azelastine and fluticasone
2 as the active ingredients. Is that correct?

3 A. I guess that's a general starting point
4 that I'll accept, sure.

5 Q. And I'm referring to, if you want to look
6 at Paragraph 35 of your report where you state: I
7 began my analysis by considering the following: If
8 a POSA were asked immediately prior to the date of
9 the alleged invention to make a combination nasal
10 spray product using azelastine hydrochloride and
11 fluticasone propionate as active ingredients,
12 consistent with Dr Schleimer's report and the actual
13 prescribing practices at the time, what would be the
14 obvious way to proceed.

15 Do you see that?

16 A. I do see that.

17 Q. And is that where you started your
18 analysis?

19 A. Yes, that if I, as a formulator, had been
20 asked or was part of a team that was identifying a
21 product and we had decided that was going to be a
22 combination of azelastine and fluticasone, that's

1 where I would start.

2 Q. And you did not consider whether a person
3 of ordinary skill would even have selected
4 azelastine or fluticasone to begin with; is that
5 right?

6 A. Well, there's always a part of even when a
7 POSA is asked to perform something, there's usually
8 a thought process that goes along with that of, gee,
9 that's interesting, an interesting project or
10 whatever. Why didn't -- you know, it's usually not
11 why does that get suggested? It's does that make
12 sense and what an interesting pursuit, oftentimes.

13 So the POSA here in this situation didn't,
14 you know, wake up one morning and decide to do that.
15 The situation was posed that we're going to -- we're
16 going to develop a combination product of azelastine
17 and fluticasone propionate, but there's usually some
18 sort of POSA thought process that's, like, okay that
19 either makes sense or doesn't make sense or I
20 understand what the goals of this project are.

21 Q. For the POSA thought process to select
22 azelastine and fluticasone, did you rely exclusively

1 on Dr. Schleimer's report and, as you describe it,
2 actual practices, prescribing practices at the time?

3 MR. WARNER: Sorry. One second. Can you
4 repeat that?

5 BY MS. EVERETT:

6 Q. Sure. For the -- to determine the POSA's
7 thought process on -- strike that.

8 To -- When you -- a moment ago you
9 mentioned that there's a thought process a POSA has
10 when selecting ingredients or starting a project; is
11 that right?

12 A. Well, I think the POSA is engaged somewhat
13 in the thought process. Whether they're formally
14 the individual making the decision on what the
15 project is or whether they're receiving that project
16 and then beginning to develop a formulation plan for
17 how to go about developing those early formulations,
18 there's some engagement in the -- or at least an
19 understanding of the goals of that project.

20 Q. And for your starting point of selecting
21 azelastine and fluticasone, you did not disclose the
22 engagement or thought process of a formulator; is

1 that correct?

2 A. Well, again I --

3 MR. WARNER: Object to the form of the question
4 and mischaracterizes the testimony and the report.
5 You can answer.

6 BY THE WITNESS:

7 A. Okay. As stated here, I was -- both my
8 opinion and -- well, let me go back and say that the
9 POSA may not be the originator selector in all
10 cases. They can be at times. But I'm perfectly
11 willing to accept Dr. Schleimer's opinion that
12 combining these was something that a POSA could do
13 and there's a motivation to do that. As an
14 independent POSA that also makes sense to me that
15 that would be a combination to select and move
16 forward with.

17 Q. So I just want to make sure I understand.
18 For your opinion, you started with the proposition
19 that Dr. Schleimer's opinion that combining these
20 two was something a POSA would do? You started
21 with -- that was your starting point for your
22 analysis; is that correct?

1 A. For my analysis in this case, that was my
2 starting point. But it complemented my own
3 expertise and knowledge of nasal dosage forms. And
4 I share that same opinion, that combining these,
5 there would be a motivation to combine these two.

6 Q. Did you -- But you don't disclose -- your
7 opinion doesn't disclose why a POSA would select
8 azelastine and fluticasone, does it?

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

11 BY THE WITNESS:

12 A. I believe that in the report, I rely on
13 Dr. Schleimer's opinions for the actual selection of
14 azelastine and fluticasone. But again, they are
15 consistent entirely with my knowledge and
16 understanding of nasal sprays and treatments.

17 Q. You stated that you share Dr. Schleimer's
18 opinion that there would have been a motivation to
19 combine these two actives. What is the basis for
20 your opinion?

21 A. The basis for that opinion is I am trained
22 as a pharmacist. I've worked in various settings

1 dealing with patients. I've dispensed nasal dosage
2 forms, nasal sprays.

3 And I am -- as a formulator, I understand
4 some of the issues regarding combination products
5 and understand certainly some of the advantages to
6 combination products for patient use. So all of
7 those experiences and understandings complement
8 completely Dr. Schleimer's opinion.

9 Q. Did you take an independent review of the
10 literature to decide whether a POSA in June 2002
11 would have decided to select azelastine and
12 fluticasone to formulate into a nasal spray?

13 A. Again, I relied on Dr. Schleimer's opinion.
14 But I was a POSA in 2002 and would have -- if
15 directed as a POSA to formulate that, would have
16 found those to be choices that I or many others
17 would have made.

18 So to start this case, I didn't do an
19 independent review to confirm Dr. Schleimer's
20 opinion because it was completely in keeping with my
21 POSA experience in 2002.

22 Q. And again, just to clarify, you said if

1 you were directed to formulate these choices, you
2 would have done so; is that --

3 A. Well, I don't think that's what I said.
4 But what I'm trying to say is, again, I rely on
5 Dr. Schleimer's opinion. But all of my opinion are
6 certainly in keeping with his regarding the
7 selection of these two. And as the POSA formulator,
8 there's not the expectation that I would be the one
9 to necessarily select the agents but, at times, a
10 POSA formulator can be the individual to select the
11 particular agents.

12 I do that in my laboratory all of the time,
13 select the agents that are going to be included in a
14 formulation. So in this case, I am perfectly
15 willing to rely on Dr. Schleimer's opinion, but I
16 have a parallel opinion that's entirely consistent
17 with his.

18 MS. EVERETT: Okay. Now might be -- I think
19 we've been going for an hour.

20 MR. WARNER: Take a break?

21 MS. EVERETT: Is this a good time for a break?

22 THE VIDEOGRAPHER: This marks the end of DVD

1 No. 1. We are off the record at 10:09 a.m.

2 (A short break was taken.)

3 THE VIDEOGRAPHER: Here begins DVD No. 2. We
4 are on the record at 10:36 a.m.

5 BY MS. EVERETT:

6 Q. Welcome back, Dr. Donovan.

7 A. Thanks.

8 Q. Before the break, we were discussing
9 Paragraph 35. And you said that you were relying on
10 Dr. Schleimer's opinion that a POSA would have
11 selected azelastine and fluticasone propionate to
12 formulate a nasal spray.

13 Do you recall that discussion?

14 A. Yes.

15 Q. You also stated that you had a parallel
16 opinion that was consistent with that, with
17 Dr. Schleimer's opinion?

18 A. Yes.

19 Q. Okay. And what is your parallel opinion
20 on that?

21 A. My opinion is that azelastine and
22 fluticasone propionate were easily identifiable as

1 two materials to combine into a nasal spray product
2 in 2002.

3 Q. How did you arrive at the conclusion that
4 azelastine and fluticasone propionate were easily
5 identifiable as two materials to combine into a
6 nasal spray in 2002?

7 A. Because they were both successful
8 commercial products as individual entities in 2002.

9 Q. Did you have any other basis to arrive at
10 your opinion?

11 A. I would say that that's the majority of the
12 reason outside of my general knowledge of, you know,
13 they're clearly safe and they're effective as their
14 individual agents, and I would have had no basis to
15 suspect that they couldn't be combined.

16 Q. You qualified your answer that's the
17 majority of your reason. Is there any other reason?

18 A. I'm sure if I sat down and thought for a
19 period of time, I might be able to come up with some
20 other reasons that would motivate me or would assure
21 me that in 2002, I would have thought to combine
22 these. But again, their commercial success is the

1 very most top of the list.

2 Q. Are the reasons if you intend to testify
3 at trial about a reason a POSA would have combined
4 azelastine and fluticasone, are they disclosed in
5 your reports?

6 A. Well, again, I think in my report, I relied
7 on Dr. Schleimer's opinion as the reasoning for
8 combining those. And again, I said I have a
9 parallel opinion. I am perfectly comfortable
10 agreeing with Dr. Schleimer's opinion. I'm not sure
11 what in addition you'd like me to say.

12 Q. I just want to find out if you're going to
13 testify to any other bases, I would like to know
14 that today.

15 A. I don't anticipate adding in any other
16 bases to my opinion on this matter.

17 Q. Okay. Thank you.

18 Also in Paragraph 35 you state -- in
19 addition to we've talked about the selection of
20 azelastine and fluticasone being consistent with
21 Dr. Schleimer's report, you state: And the actual
22 prescribing practices at the time.

1 Do you see that?

2 A. Yes.

3 Q. What did you -- what were you referring to
4 when you said "actual prescribing practices at the
5 time"?

6 A. I was referring to the information provided
7 by Dr. Schleimer and others and just general
8 knowledge that there were individuals who were using
9 both of these products for treatment.

10 Q. How did you have general knowledge that
11 there were individuals who were using both of these
12 products for treatment?

13 A. Again, I am a pharmacist by original
14 degree. In 2002 I wasn't practicing, but I was
15 certainly aware of what people were using in nasal
16 therapeutics in particular. And there would be no
17 reason why a prescriber wouldn't combine both of
18 these in an attempt to modify patient symptoms, and
19 it was -- I had family members who have allergies
20 that were not using these in combination, but they
21 didn't need them, but that would have been a certain
22 next step if they did.

1 Q. So is it your testimony that you were
2 aware of people using these in combination, or is it
3 your testimony that there would be no reason
4 somebody would not use these in combination?

5 MR. WARNER: Objection to the form of the
6 question. Compound and mischaracterizes the
7 testimony.

8 BY THE WITNESS:

9 A. And it's actually both. I was aware that
10 they were used in combination in individuals, and
11 I'm aware that they could be used in combination in
12 individuals.

13 Q. So when you said you were aware that they
14 were used in combination in individuals, how did
15 that information come to you?

16 A. It comes to me from, again, general reading
17 and conversations with people that are, you know,
18 involved in patient therapy and information that
19 comes across my computer or my desk about
20 advertisements and other media and other casual
21 conversations with my colleagues.

22 There's a whole number of ways that

1 information about how patients are using and
2 prescribers are prescribing can enter into my
3 knowledge base.

4 Q. So you said general reading, started with
5 general reading. What did you read that told you
6 that patients were using azelastine and fluticasone
7 in combination prior to June 2002?

8 A. Again, I don't recall ever reading or
9 intentionally going to look for such information.
10 It's perfectly consistent with my knowledge base
11 that patients would be using both of these together.
12 Dr. Schleimer has stated an opinion or given
13 information that as a prescriber, he prescribed them
14 together. It's completely supported by general
15 knowledge base of these medications, so I didn't go
16 look for specific literature to support that. I had
17 no reason to.

18 Q. Did you -- Have you ever reviewed a
19 physician's patient records to confirm whether he or
20 she was prescribing azelastine and fluticasone
21 propionate in combination to a patient prior to
22 June 2002?

1 A. I do not generally review patient or
2 prescriber records. And I don't recall actively
3 reviewing prescriber records to confirm that
4 somebody actually had, when they said they
5 prescribed them together, they actually did.

6 Q. And do you recall anyone telling you that
7 they prescribed them together?

8 A. I'm -- certainly recently in this case,
9 I've seen reports of prescribers saying they used
10 them together. But in 2002 or prior to that, I
11 don't have any recollection of a specific prescriber
12 telling me that they prescribed these two together.
13 But I would have no reason to even ask that because,
14 again, it would have been an obvious combination
15 to -- for prescribers to combine.

16 Q. So you're saying in 2002, you have no
17 specific knowledge of whether this practice
18 occurred, that patients took azelastine
19 hydrochloride and fluticasone propionate in
20 combination?

21 A. No. What I said, in 2002 is I never talked
22 to individual prescribers about whether they were

1 prescribing these two in combination.

2 Q. In 2002 do you have any specific knowledge
3 of patients who took azelastine hydrochloride and
4 fluticasone propionate in combination?

5 A. As specific individuals, no. But I
6 certainly know that it was a practice, and there
7 were individuals who were receiving both of those.

8 Q. So I just want to make sure I understand
9 the basis for you to say that. You said you haven't
10 spoken to prescribers. You have no specific
11 knowledge of patients taking it, and you don't
12 recall it in any specific literature or publication.
13 So how do you know that this was occurring?

14 MR. WARNER: Objection. Asked and answered.

15 BY THE WITNESS:

16 A. Because, again, I have clinical training in
17 pharmacy. I have knowledge of commercial success of
18 products. I have knowledge of how patients and
19 prescribers combine medications to meet particular
20 needs, and so I didn't need to know a specific
21 prescriber. I didn't need to know a specific
22 patient. Conversations happen all the time about

1 general prescribing practices; and information about
2 general prescribing practices is available in plenty
3 of tertiary literature, not even under the guise of
4 prescribing practices.

5 So in 2002, I was aware generally that this
6 occurs. It's a possibility. But a specific
7 instance with a specific prescriber with a specific
8 patient is out of the realm of my daily activities.

9 Q. When you -- And to be clear, you say
10 you're generally aware. But you don't have a
11 specific recollection of how this information came
12 to you?

13 A. Again, I get lots of information all the
14 time about general use of products, preferences,
15 observations. So no, I don't have a specific
16 recollection of a single one point in time transfer
17 of knowledge of this specific fact.

18 Q. And I just wanted to clarify something you
19 said earlier. You said that you had learned about
20 some of the prescribing habits because Dr. Schleimer
21 prescribed. I just want to make sure, did you mean
22 Dr. Accetta was a prescriber?

1 A. I think if I would be pointed to the place
2 in my report where I refer to Dr. Accetta's report,
3 my recollection off the top of my head, but I would
4 take the opportunity to refer to that section about
5 prescribing practices.

6 Q. Sure. I was referring to your testimony a
7 moment ago. I think you referred to Dr. Schleimer
8 as a prescriber, which --

9 A. I may have been mistaken.

10 Q. Okay. So if you refer to your opening
11 report, Paragraph 95 --

12 MR. WARNER: 95?

13 MS. EVERETT: Yes.

14 BY THE WITNESS:

15 A. Okay.

16 Q. When you reviewed Dr. Accetta's
17 transcripts, did you review the exhibits attached to
18 the deposition?

19 A. I'm sure I glanced quickly at them, but I
20 didn't review them in detail.

21 Q. Have you reviewed -- strike that.

22 Do you recall reviewing Dr. Accetta's

1 patients records?

2 A. I don't recall reviewing his patient
3 records.

4 Q. Okay. So did you take into consideration
5 the amount of each active that Dr. Accetta
6 prescribed to a patient?

7 A. Not -- I didn't take that into specific
8 account, no.

9 Q. Did you take into account the reasons he
10 may have prescribed azelastine and/or fluticasone to
11 a particular patient?

12 A. Not to a particular patient, no.

13 Q. Did you take into account the suggestions
14 he may have made to a patient on how to use
15 azelastine and fluticasone in -- to a particular
16 patient?

17 A. I don't recall seeing any of those
18 suggestions in a particular patient, you know, as
19 notable. And a lot of that is because it's entirely
20 consistent with what all prescribers -- or not all
21 but many prescribers and many other people know how
22 to work with patients to increase their adherence to

1 a drug regimen.

2 Q. Do you recall whether he told patients to
3 use the two actives consistently? Strike that.

4 Do you recall whether he told his patients
5 to use azelastine and fluticasone together
6 consistently?

7 A. I'm -- I mean, I don't recall his specific
8 directions to individual patients. But I'm not sure
9 what you mean by consistently. And again, if we
10 want to talk about this in generalities, we can
11 continue to do that; but I don't recall his specific
12 instructions to specific individual patients.

13 Q. Do you recall looking at any other patient
14 records or any other prescribing habits to come up
15 with your view that physicians were prescribing
16 azelastine and fluticasone together for patients
17 before June 2002?

18 A. Again, I don't recall looking at the
19 specific details of individual records, but it's
20 because that prescribing habit or prescribing
21 activity is entirely consistent with what I knew was
22 going on and what I would have anticipated would be

1 prescriber behavior.

2 Q. Do you recall whether physicians were
3 encouraging patients to take azelastine and
4 fluticasone together consistently or just as needed?

5 MR. WARNER: Objection to the form of the
6 question. Asked and answered.

7 BY THE WITNESS:

8 A. Again, you need to be a lot more specific
9 about consistently. But there are a variety of
10 compromises physicians make with individual patients
11 to get them to use their medications as their
12 physicians would like them to.

13 Q. So do you know whether physicians in
14 June 2002 were telling patients to take azelastine
15 and fluticasone together on a daily basis, or were
16 they saying they could take them together as needed?

17 A. I think that's very dependent on the
18 particular individual. I think either case is
19 something that might be told to a patient. It's
20 very dependent on those patients' individual
21 symptoms and typical adherence patterns, ability to
22 afford, a number of other things. So there's all

1 of -- I'm sure there are physicians who have told
2 their patients any of the above.

3 Q. So do you have specific knowledge of
4 whether it was either or both or something else?

5 A. Again, I don't recall looking at a specific
6 physician note and the specifics of the instructions
7 for use of -- in a specific individual patient. But
8 I know general prescribing practices, I know general
9 adherence techniques, and there are likely a variety
10 of different ways that prescribers might have
11 adapted what may have been the optimal therapeutic
12 regimen to an individual patient's needs or use.

13 Q. In your report, you consider a number of
14 the inactive ingredients in the patents-in-suit. Is
15 that correct?

16 MR. WARNER: Objection to the form of the
17 question to the extent it mischaracterizes the
18 report, and it's vague.

19 BY THE WITNESS:

20 A. Okay. And since I'm on Page 29, the
21 paragraph -- above Paragraph 96 is labeled Inactive
22 Ingredients, I will agree we call things inactive

1 ingredients as I described them in the report to be
2 consistent with the typical FDA classification of
3 active and inactive ingredients.

4 But I've already spoken to the fact that as
5 a formulator, an ingredient is an ingredient.
6 They're in formulations for purposes, some of which
7 are intended pharmacologic activities, some are
8 intended to do other activities. Some do many
9 activities.

10 Q. Well, since inactive ingredient is the
11 words you've selected for your report, would it be
12 all right if we continue to refer to them as
13 inactive ingredients?

14 A. With the recognition that inactive
15 ingredients does not mean that they have zero
16 activity and zero role.

17 Q. Fair enough. In your report, you identify
18 a number of these inactive ingredients, correct?

19 A. Uh-huh.

20 Q. And on -- I'm going to turn you to
21 Page 30, Paragraph 101, where you discuss
22 surfactants. What is a surfactant?

1 A. A surfactant is a surface active agent. So
2 it's a material that has the ability to interact at
3 interfaces and change the properties of materials at
4 those interfaces.

5 Q. Is a surfactant also known as a wetting
6 agent; is that --

7 A. One of the roles surfactants can play is as
8 a wetting agent.

9 Q. And what does a wetting agent mean?

10 A. In pharmaceutical terms, usually a wetting
11 agent is a material that interacts at the surface of
12 a -- in typical cases of a hydrophobic material and
13 improves its interaction with polar materials,
14 typically water.

15 Q. And do all nasal sprays have surfactants?

16 A. You know, I can't speak to the components
17 of every single nasal spray in the world. But my
18 general knowledge tells me no, not all nasal sprays
19 contain surfactants.

20 Q. You state in 101, if it were not there,
21 and I think "it" refers to surfactant; is that
22 correct? Second sentence.

1 A. Yes, "it" refers to surfactant.

2 Q. If it were not there, one would expect the
3 inactive ingredient would form agglomerates and
4 separate out to such an extent that it would not be
5 evenly distributed and result in a variable amount
6 of drug delivered in each spray.

7 Do you see that?

8 A. I see that.

9 Q. Is that a consideration in all nasal
10 sprays?

11 A. Well, the ability to have a consistent dose
12 administered is a consideration in all nasal sprays.
13 The rest of the information in that sentence is
14 rather specific to the active ingredient in Flonase,
15 which is what is being discussed in that paragraph.

16 Q. So it is your opinion that the surfactant
17 is necessary because otherwise Flonase would form --
18 strike that.

19 In your opinion, you're saying the
20 surfactant is necessary because otherwise
21 fluticasone propionate would form the agglomerates
22 and separate out; is that correct?

1 A. That's my expectation as a formulator that
2 that is very likely to occur with fluticasone
3 propionate in water.

4 Q. In your report, you also discuss
5 thickening agents. Is that accurate? And --

6 A. Are you on a specific paragraph? Yes, we
7 discuss --

8 Q. And go ahead and look through your report.
9 I think there's a discussion on Page 33, but feel
10 free to look at wherever you need.

11 A. Okay. I just wanted to make sure that the
12 term was used, yes.

13 Q. What is a thickening agent?

14 A. A thickening agent is in general something
15 that increases the viscosity of a system.

16 Q. Why is viscosity of a system -- strike
17 that.

18 Why is viscosity important for a nasal
19 spray?

20 A. Well, there's a number of reasons why
21 viscosity can be important. It can be important
22 just in formulation itself, or it can be important

1 for nasal spray intended for a pattern of deposition
2 and retention in the nasal cavity. So there's
3 multiple purposes to thickening agents in nasal
4 spray formulations.

5 Q. When you said it can be important itself,
6 what did you mean?

7 A. I'm sorry? What can be important itself?

8 Q. There are a number of reasons -- I believe
9 you stated: There are a number of reasons viscosity
10 can be important. It can be important itself, or it
11 can be important for a nasal spray intended for a
12 pattern of deposition, retention. I just want to
13 focus on the first part.

14 A. Well, I mean --

15 MR. WARNER: Sorry. What's the question?

16 BY MS. EVERETT:

17 Q. What did you mean when you said viscosity
18 can be important itself?

19 A. That was referring to the formulation
20 itself, so the viscosity of the formulation can be a
21 key characteristic and component or parameter of the
22 formulation. In a nasal spray, there can also be

1 reasons why we might want increased viscosity
2 materials once administered to perform functions in
3 the nose.

4 Q. So when you said it's a key component in
5 the formulation, you -- are you referring to just
6 viscosity of the actual dosage form itself or the --

7 A. I'm referring to the viscosity of the
8 formulation itself, yes.

9 Q. Separate and apart from how it sprays, is
10 that -- are you drawing a distinction there?

11 A. Well, I'm drawing the distinction between
12 the formulation as it's formulated and is in the
13 container ready to be delivered and the formulation
14 once administered, its activities in the nasal
15 cavity.

16 Q. Why is viscosity important for the
17 formulation in the container?

18 A. For the formulation in the container, it's
19 a key -- especially if we're concerned with
20 suspension formulations, viscosity is a key
21 parameter to consider for suspension stability.
22 There may be other reasons why we'd want to modify

1 the viscosity of a particular formulation that --
2 and we might even want to do that with a solution
3 formulation.

4 There are interactions between the
5 viscosity and the devices. And again, there's the
6 goal oftentimes of increasing the viscosity with
7 hopes that it has some effect once administered into
8 the nasal cavity.

9 Q. So when you say it's a key component for
10 suspension stability, what are you referring to?

11 A. I'm referring to suspension physical
12 stability.

13 Q. It's important that a suspension -- strike
14 that.

15 Is it important -- it's important, isn't
16 that an active ingredient that is suspended
17 continues to stay suspended?

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

20 BY THE WITNESS:

21 A. Okay. It's important in a suspension that
22 the material either stay suspended or be readily

1 able to be resuspended with shearing.

2 Q. And it's viscosity that determines whether
3 the suspension stays suspended or is able to be
4 readily resuspended?

5 A. It's not only the viscosity that determines
6 that.

7 Q. It's one of the properties that determines
8 that, correct?

9 A. It's a property that can affect whether
10 that happens, how fast it happens, a number of other
11 aspects of the suspension settling or ability to
12 remain dispersed.

13 Q. What other -- strike that.

14 What other agents affect the ability of a
15 suspension to stay suspended or to be resuspended
16 upon settling?

17 MR. WARNER: Objection to the form of the
18 question. Incomplete hypothetical.

19 BY THE WITNESS:

20 A. There -- The standard considerations in
21 suspensions and suspension physical stability are
22 things like the particle size, sometimes the

1 particle shape, even the particle density. Other
2 materials that are added can potentially limit the
3 direct interaction between particles so we don't
4 start forming particle -- it's usually called an
5 agglomerate that is not easily broken apart.
6 Viscosity plays a role. Temperature we might leave
7 the formulation at might play a role. There's a
8 number of contributing factors to suspension
9 physical stability.

10 Q. Is there a target viscosity for a nasal
11 spray?

12 A. The -- There are I think -- I think people
13 have expressed targets for individual formulations.
14 But my experience is that if people claim there
15 should be a target, that that again is very
16 dependent on the formulation, the device, and the
17 intention for -- what the goal of that viscosity
18 change or parameter is. So there's not a one
19 viscosity for the universe of nasal dosage forms.

20 Q. Is there a range?

21 A. Again, it's very -- it's dependent on the
22 particular formulation parameter and use and need.

1 It's somewhat of a custom-determined characteristic.
2 We can make it even more complicated that it depends
3 on what you're measuring and calling viscosity. If
4 you're measuring viscoelastic behaviors and looking
5 at the viscous modulus and if you're measuring
6 complex viscosity, are you measuring kinematic
7 viscosity or are you measuring intrinsic viscosity?
8 What viscosity is it you're actually describing?
9 And because there are a number of ways of measuring
10 and describing viscosity, giving an absolute range
11 for viscosity for any particular group of dosage
12 forms that happens to get administered as nasal
13 sprays is not something that most people would even
14 anticipate would be -- it wouldn't be something that
15 a formulator would use to direct them in any
16 particular way.

17 Q. Is there a target viscosity for a nasal
18 spray that will be used for allergic rhinitis?

19 A. Again, it's very dependent on what the
20 materials are in the formulation, what the dose
21 might be, what the particle characteristics are, if
22 that material stays in suspension, what the other

1 agents in the formulation are and how it's going to
2 be administered.

3 Q. Where would a person of ordinary skill in
4 June 2002 look for guidance for determining what a
5 target viscosity should be?

6 A. Again, I think -- I don't think I agreed
7 that there was a target viscosity or that a
8 formulator would necessarily look for information
9 about a target viscosity. They might look for
10 information about other successful products and what
11 viscosities they happened to be.

12 But the formulator would certainly have a
13 knowledge that depending on what materials they were
14 using, targeting that specific viscosity was not a
15 rational formulation approach that they -- a
16 formulator would look at information, both about the
17 suspending agents that they might use. They
18 might -- again, they need to have a knowledge of the
19 materials they're trying to suspend and other agents
20 they might be including and what they might want --
21 how they might want that suspension to perform
22 during administration or following administration.

1 Then there's certainly information in
2 products that were available at the time, other
3 primary literature, other patent literature, and so
4 forth that could help inform them on how to approach
5 those formulation activities.

6 Q. You stated in addition to the formulation
7 itself, you would look to how the formulation was
8 sprayed into the nose; is that a rough
9 approximation?

10 A. Yeah, can you clean that up a bit? Because
11 that's not exactly what I said or intended to
12 communicate.

13 Q. So it's not just how the formulation
14 itself -- it's how it comes out of the spray is
15 important? It's the characteristics, the viscosity
16 characteristics once it's sprayed into the nasal
17 mucosa?

18 A. Well, there's a number of steps that are
19 important. The formation of the spray is dependent
20 on the spray device characteristics and the
21 compatibility of the formulation to function within
22 those particular performance parameters.

1 And then once sprayed, the interactions
2 between the viscosity-enhancing agents and the
3 secretions and the nasal mucosa give a particular
4 pattern of behavior that -- and at times formulators
5 try to optimize those interactions by including
6 those viscosity-enhancing agents to improve the
7 therapeutic outcome.

8 Q. And is there a target that a person of
9 ordinary skill would have looked to when determining
10 viscosity for a -- for how viscosity of the
11 formulation would behave when sprayed into the nose?

12 MR. WARNER: Objection to the form of the
13 question. Vague and incomplete hypothetical.

14 BY THE WITNESS:

15 A. And yeah. I don't understand the question.

16 Q. Obviously if a formulator is making
17 something in June 2006, they don't want it to have
18 such low viscosity it runs out of your nose. Is
19 that fair?

20 A. No, that's not fair.

21 Q. So they would potentially formulate
22 something where the dosage would run out of your

1 nose?

2 A. Well, that might not be the intent, but
3 that's certainly the outcome of a number of current
4 nasal formulations.

5 Q. Is it the outcome of Astelin?

6 A. That depends on how that product is being
7 administered and to whom it's being administered.
8 But it's conceivable that in some cases, some
9 fraction of the material that was administered could
10 run out of the anterior region of the nose.

11 Q. So but one -- it's conceivable it could
12 happen to a particular patient or population. But
13 that's not how it's designed; is that correct?

14 A. Well, there's no nasal formulation that's
15 really designed to not stay in the nasal cavity.
16 But by far, almost all of the nasal formulations
17 that are currently administered, fractions are
18 quickly lost from the nasal cavity, whether it be
19 from the anterior or the posterior regions.

20 So it's just a result of current
21 technologies and compatibility with the nasal
22 cavity. Not everything that is sprayed into the

1 nasal cavity -- we have a knowledge that not
2 everything that's sprayed in the nasal cavity is
3 retained in the nasal cavity for a very long period
4 of time shortly after spraying.

5 Q. Would a person of ordinary skill in 2002
6 formulate to minimize the amount of runoff?

7 A. Formulators attempted to do that. The
8 success of those attempts was not assured.

9 Q. And would a formulator look to viscosity
10 so -- strike that.

11 And would a formulator also consider
12 viscosity when considering how the formulation came
13 out? Was it a spray pattern, for example.

14 A. Well --

15 MR. WARNER: Objection to the form of the
16 question. Vague. You can answer, if you
17 understood.

18 BY THE WITNESS:

19 A. The relationship between the material
20 that's being sprayed and the spray device determine
21 that -- what the output looks like. And it's just a
22 consequence of when you match a formulation and a

1 device.

2 Q. Would a person of ordinary skill target a
3 particular output?

4 A. Well, you -- please ask the question, and
5 I'll answer the question asked.

6 Q. So you said it's just a consequence of a
7 match between the formulation and the device. Is
8 there a particular output from the device that a
9 formulator would target? And again, I'm referring
10 to properties related to viscosity.

11 A. I'm still confused regarding the -- because
12 the viscosity is the viscosity of the formulation,
13 but you're asking about output. So I'm not sure how
14 you're connecting those two.

15 Q. So if something is highly viscous, is it
16 likely -- will it affect -- so if you have a
17 formulation that is highly viscous and a formulation
18 that is low viscous, will they spray out of the same
19 device in the same pattern?

20 A. Likely not.

21 Q. So if it is highly viscous, what will the
22 spray be like out of a device?

1 A. It depends on the device.

2 Q. Is it more likely to be a jet?

3 A. It's possible that it could be a jet.

4 Q. Is it more likely to be a spray?

5 A. It depends on the device.

6 Q. So you can't determine whether it would be
7 more likely to be a jet or a spray based on the
8 viscosity?

9 A. Again --

10 MR. WARNER: Objection to the form of the
11 question. It's very vague, and it's a very
12 incomplete hypothetical.

13 BY THE WITNESS:

14 A. The form of the spray that is released from
15 the device depends entirely on the device design and
16 its operating parameters.

17 Q. It depends entirely on the device and the
18 operating parameters?

19 A. Well, in combination with whatever
20 formulation you put in and the formulation
21 characteristics.

22 Q. So formulation characteristics also affect

1 the form of the spray that's released; is that fair?

2 A. It's the combination of the material that's
3 being sprayed and the spray device design that
4 determines what the pattern of droplets or stream or
5 whatever that is released from the release orifice.

6 Q. And if someone were -- strike that.

7 Is there a standard device that's used in
8 a lot of nasal sprays, a certain pump?

9 A. There's a number of different spray
10 designs, spray device designs. I'm not sure whether
11 one particular type represents the majority of
12 devices used.

13 Q. Are you aware of the spray -- strike that.

14 Are you aware of the device for Astelin?

15 A. I don't think I specifically recall which
16 exact vendor and device and pump design that Astelin
17 uses.

18 Q. What about Flonase?

19 A. Same thing. I do not -- I don't recall the
20 specific device, vendor, and pump style that is used
21 in those products.

22 Q. Earlier I asked you whether a person of

1 ordinary skill in 2002 would formulate to minimize
2 the amount of runoff, and you responded that
3 formulators attempted to do that. The success of
4 those attempts were not assured.

5 Why were they not assured?

6 A. Because retention in the nasal cavity isn't
7 only a function of the viscosity of the formulation
8 or viscosity of the material that entered the nasal
9 cavity.

10 Q. Are there other characteristics of the
11 formulation that would affect runoff?

12 A. Yes.

13 Q. What are they?

14 A. Well, I may have -- where I was thinking is
15 the volume that enters the nasal cavity is a
16 significant determinant of what might run off in
17 your version of description.

18 Q. Anything else?

19 A. There's a number of things. Are you asking
20 about formulation components?

21 Q. Yes.

22 A. Or formulation ...

1 Q. Yes, I'm referring to the formulation.

2 A. Formulation parameters? Yeah, the
3 elasticity of the material is actually quite
4 important.

5 Q. And what is the elasticity of the
6 material?

7 A. It's very similar to what you might expect
8 from the word elastic. It's how able that material
9 is to not move in a dimensional sense under force.

10 Q. Are there any other characteristics of the
11 formulation that would affect runoff?

12 A. Well, I can think of a lot of user-based
13 effects. But, you know, it's really a function of
14 where the spray enters the nasal cavity and what
15 potential interactions there might be between the
16 formulation and the nasal cavity that determine what
17 amount stays, where amounts go.

18 Q. I'm going to have you turn to Page --
19 excuse me, Paragraph 85 of your report. And the
20 first sentence: A POSA would also know Loyd V.
21 Allen, The Art, Science, and Technology of
22 Pharmaceutical Compounding, 1998.

1 Do you see that?

2 A. Yes, I do.

3 Q. What is compounding?

4 A. Compounding, certainly in Dr. Allen's use
5 of the term, is essentially preparation of
6 pharmaceutical materials intended for administration
7 to something, animal or human, and it's the -- what
8 equivalently people would call formulation.
9 Compounding is oftentimes done or performed for
10 single individuals with needs that aren't met by
11 other products available.

12 Q. Does this compounding differ from other
13 types of formulation work?

14 A. They have the same basis. In general, I
15 mean, we typically use very similar materials in
16 compounding and in formulation development. The
17 intended use of a formulation that's intended for a
18 commercial product is different than the intended
19 use of a formulation, for example, that I use as a
20 research tool is different than a formulation that a
21 pharmacist might compound for an individual patient
22 to use.

1 Q. You said you typically use very similar
2 materials in compounding and formulation
3 development. Are there other similarities?

4 A. Oh, there's similarities in the dosage
5 forms that are prepared. There's certainly
6 similarities in the actives that are incorporated
7 between compounded -- compounded medications
8 intended for an individual patient versus
9 medications that are available in other forms.

10 So yeah, there's certainly similarities in
11 materials, in agents, in delivery systems.

12 Q. In the paragraph you continue. You say:
13 Chapter -- feel free to read what you need to. But
14 you continue on in your paragraph and it says: It
15 discusses pH and buffering stating that generally pH
16 in the range of 4 to 8 is considered optimum.

17 A. Yep, that's what it says.

18 Q. Do you agree with Dr. Allen that pH in the
19 range of 4 to 8 is considered optimum?

20 A. I'd agree that typically we see nasal
21 formulations whose pHs are in the range of 4 to 8,
22 and that's a generally recognized range by both

1 Dr. Allen and a number of other authors of an
2 acceptable range of pHs for nasal -- nasal
3 formulations.

4 Q. Would a nasal spray with a pH of 3 be an
5 acceptable pH?

6 A. It may be.

7 Q. In what conditions would it be acceptable?

8 A. One would have to do the experiments. It's
9 certainly not a common pH. It doesn't mean that for
10 a particular product under particular circumstances
11 for that product performance that it would be
12 unacceptable.

13 Q. When you say one would have to do the
14 experiments, what experiments are you referring to?

15 A. You'd need a biological compatibility type
16 set of experiments to determine the safety, the
17 efficacy, the acceptability of that formulation,
18 just like you do with every other formulation.

19 Q. Do you know of a nasal spray that is
20 administered to humans on a daily basis that has a
21 pH of 3?

22 A. Right now I'm not aware of one, no.

1 Q. The paragraph goes on to state -- it also
2 discusses tonicity explaining that a tonicity of 300
3 milliosmoles per liter is ideal, although a range of
4 200 to 600 milliosmoles per liter is acceptable.

5 A. Uh-huh.

6 Q. Do you agree with that statement?

7 A. I agree that it's a reasonable
8 generalization of what tonicity values could be.
9 But I'm certainly aware of systems that are outside
10 of the 200 to 600 milliosmolar per liter range.

11 Q. And when you say you're aware of systems
12 that have a tonicity outside of that range, what are
13 you referring to?

14 A. Well, I know of products that are actually
15 in the marketplace outside of that range. I have
16 conducted experimental investigations where I have
17 intentionally kept the tonicity outside of those
18 ranges.

19 Q. In your experimental investigations where
20 you purposely kept the tonicity outside the range,
21 what was the range?

22 A. It was below 100 usually.

1 Q. And how often in your -- strike that.

2 In your experiments, how did you -- strike
3 that.

4 In the systems where you kept the tonicity
5 under 100, what sorts of tests did you perform?

6 A. We performed both absorption tests -- at
7 the time, our primary endpoint was absorption of a
8 model, looking at absorption changes in a model
9 compound in an animal model.

10 Q. Did you look at whether it would be
11 unacceptably irritating to a patient?

12 A. That wasn't one of the parameters that we
13 investigated at the time.

14 Q. You -- is that, are those the only --
15 strike that.

16 You said that you had conducted some
17 models and experiments outside the tonicity range
18 200 to 600. Do you have any other examples?

19 A. Of the work that we did?

20 Q. Yes.

21 A. The work was intentionally investigating
22 the effects of osmotic pressure on the ability of a

1 model compound to change its absorption profile, so
2 we looked at a broad range of tonicity values to
3 investigate that.

4 Q. And but you were studying absorption
5 profiles; you weren't studying whether it could be
6 tolerated by a patient? Is that correct?

7 A. That's correct. We were studying
8 absorption profiles.

9 Q. You mentioned that you knew of other
10 products on the market with osmolality outside the
11 200 to 600 range; is that right?

12 A. Yes.

13 Q. What were you referring to?

14 A. There's a current product in the
15 marketplace who's tonicity measurement is above 700,
16 I believe.

17 Q. And are you referring to Imitrex?

18 A. Yes.

19 Q. And have you, outside of this litigation,
20 examined, studied, or researched Imitrex?

21 A. Not specifically, no.

22 (Deposition Exhibit Number 4

1 marked for identification.)

2 BY MS. EVERETT:

3 Q. I'm handing to the court reporter to be
4 marked as Donovan Exhibit 4, I think it's the
5 Imitrex -- it's the Imitrex label. The Bates are
6 cut off, so I believe it's APOTEX_AZFL0132818
7 through 842.

8 Dr. Donovan, take a few minutes to look
9 through Exhibit 4, please.

10 A. Okay.

11 Q. Do you recognize Donovan 4?

12 A. I recognize this as the Imitrex label, yes.

13 Q. And is this the product you were just
14 referring to a few moments ago that had an
15 osmolality above 600?

16 A. As the 20-milligram formulation, yes.

17 Q. And are -- we might just go there. Are
18 you on Section 11. Is that where you're looking?

19 A. I'm not, but I'll go there.

20 MR. WARNER: Is that what you're on? Section?

21 MS. EVERETT: Sure. We can just confirm.

22 BY MS. EVERETT:

1 Q. We were looking under the description.
2 The last sentence says: The osmolality of the
3 solution is 373 or 742 milliosmoles for the 5- and
4 20-milligram Imitrex nasal spray respectively.

5 A. That's what I was referring to.

6 Q. Yes. And how is Imitrex administered?

7 A. This particular dosage form is administered
8 as a nasal spray.

9 Q. Is it administered on an as-needed basis,
10 or is it something else?

11 MR. WARNER: Objection to the form of the
12 question. The document speaks for itself.

13 BY THE WITNESS:

14 A. The label indicates that it's for the
15 treatment of -- I actually looked, but I'm sure it
16 says it's for the treatment of migraine. And it's
17 used at the time that somebody would need to treat a
18 migraine.

19 Q. So it's used as needed?

20 MR. WARNER: Objection. Asked and answered.

21 BY MS. EVERETT:

22 Q. And please look at whatever you need to to

1 answer my question.

2 A. The label -- the label indicates that that
3 is the FDA-approved methodology for use.

4 Q. And if you look, I'm going to have you
5 turn to the Page 1 in the Indications and Usage
6 section at the top left --

7 A. Okay.

8 Q. -- of the page. It says: Limitations of
9 Use. Do you see that?

10 A. Okay.

11 Q. Use only if a clear diagnosis of migraine
12 headache has been established?

13 A. That's what it says.

14 Q. And not indicated for the prophylactic
15 therapy of migraine attacks. Do you see that?

16 A. I see that.

17 Q. And then next is the dosage and
18 administration?

19 A. Uh-huh.

20 Q. In there it says: Single dose of 5
21 milligrams, 10 milligrams, or 20 milligrams of nasal
22 spray?

1 A. That's what it says, yes.

2 Q. A second dose should only be considered if
3 some response to the first dose was observed?

4 A. Uh-huh.

5 Q. And it says: Separate by -- doses by at
6 least 2 hours?

7 A. Uh-huh.

8 Q. And finally: Maximum dose in 24-hour
9 period is 40 milligrams?

10 A. Yes.

11 Q. So this is -- As we discussed earlier, you
12 use it only when you have a migraine?

13 A. That's what the FDA label directs.

14 Q. Right. And it says not to use it more
15 than twice -- 40 milligrams a day, or twice a day if
16 you're using the 20-milligram strength?

17 A. That's what the label directs, yes.

18 Q. How does -- strike that.

19 This dosage differs from the Dymista
20 product; is that correct?

21 A. Yes, it's a different product.

22 Q. So the Dymista dosage, a person would

1 spray two sprays per nostril once a day; is that
2 right?

3 A. They could spray two sprays per nostril
4 once per day.

5 Q. Do you know how it's indicated?

6 A. I'd like to refer to the label.

7 Q. Okay.

8 A. For what the FDA label says.

9 MR. WARNER: Uma, it's also been an hour. I
10 don't know if the witness wants a break or if you
11 do. But just to let you know, I want to know what
12 your thoughts are.

13 MS. EVERETT: Now seems like a good break, and
14 we can look for the documents.

15 THE WITNESS: Okay. Great.

16 THE VIDEOGRAPHER: This marks the end of DVD
17 No. 2. We are off the record at 11:36 a.m.

18 (A short break was taken.)

19 THE VIDEOGRAPHER: Here begins DVD No. 3. We
20 are on the record at 11:56 a.m.

21 BY MS. EVERETT:

22 Q. Welcome back, Dr. Donovan.

1 A. Thanks.

2 Q. Before the break, we were discussing
3 Imitrex and its osmolality.

4 A. Uh-huh.

5 Q. And a few minutes before that, we had
6 discussed how Loyd -- the Loyd reference said that a
7 preferred osmolality is 300, though it could be
8 between 200 and 600. Do you recall that?

9 A. I think it's between 200 and 600 is
10 acceptable is what the quote is.

11 Q. Are there certain uses of the product that
12 would affect osmolality? Could a patient tolerate a
13 higher osmolality if they were using it once a year?

14 MR. WARNER: Objection.

15 BY MS. EVERETT:

16 Q. Than every day?

17 MR. WARNER: Objection to the form of the
18 question.

19 BY THE WITNESS:

20 A. I think patient tolerance for any
21 administration is a function of patient tolerance,
22 so I don't know that it's -- that anybody has ever

1 tried to correlate -- well, actually, I'm sure they
2 have correlated tolerance to some slightly
3 unpleasant effect versus frequency of use. But I'm
4 not aware of any strong rationale for pursuing that
5 in a formulation development sense.

6 Q. When you say you're not aware of any
7 strong rationale for pursuing it in a formulation
8 development sense, do you mean considering the
9 osmolality and the frequency of administration?

10 A. No. The ability of patients to accept a
11 less than invisible dosage form is a matter of
12 patient judgment acceptance, risk aversion, and a
13 lot of those are very patient-dependent. We can
14 generalize in some cases. But risk/benefits, extent
15 of pain response, discomfort, or whatever is not a
16 generalizable quantitative measure.

17 Q. When you formulate, do you consider sort
18 of an average patient response?

19 MR. WARNER: Objection to the form of the
20 question. Incomplete hypothetical.

21 BY THE WITNESS:

22 A. When we formulate, we consider what is --

1 what will be safe, what will enable a formulation to
2 be used, and there are aspects of acceptability that
3 are certainly considered. But until actual patient
4 use, those aren't necessarily the driving forces of
5 formulation development process.

6 Q. At what point do you consider patient
7 tolerability?

8 A. When patients have the ability to tell us
9 what their tolerance is or what their organoleptic
10 perceptions are. Or if we have the opportunity to
11 do some short-term first-in-human studies when we
12 can get that information.

13 Q. So if you were developing a nasal spray,
14 would you still target a 300 versus an 800
15 milliosmoles per liter.

16 A. Well, as I said a couple hours ago,
17 there's -- developing a formulation is a series of
18 compromises off the optimal or perfect
19 characteristics for every component, including the
20 pharmaceutically active material.

21 And so we can start out by assigning any
22 numerical value or parameter characteristic for

1 perfect performance at the start of a development
2 scheme, and we know that we're going to move off of
3 those as a result of how materials interact with
4 each other, how formulation performs, a number of
5 other things.

6 And so stating in this case if we want to
7 talk about tonicity, stating a number for tonicity
8 and never moving from that number is not how a
9 formulator approaches making a dosage form where
10 tonicity is an important consideration.

11 Q. Would a formulator start with the approach
12 of targeting 300 versus 800?

13 MR. WARNER: Objection to the form of the
14 question. Vague and incomplete hypothetical.

15 BY THE WITNESS:

16 A. Typically, especially in my experience as a
17 formulator, I do not initially target tonicity as a
18 driving force for the materials that are included in
19 my formulation. It's essentially a followup
20 consideration that certainly needs to be addressed,
21 but it's not the -- one of the primary factors that
22 drive other decisions.

1 Q. Would that also be true for a POSA in
2 June 2002?

3 A. I would anticipate that's, yes, that's true
4 for just about any POSA.

5 Q. When you say you did -- you would not
6 initially target tonicity as a driving force, at
7 what stage would you consider tonicity?

8 A. When I have enough of the formulation
9 developed that I'm relatively comfortable with a
10 reasonably small number of choices of excipients and
11 have determined that I have at least a shot at
12 chemical stability and the other performance
13 criteria for my formulation look like it's meeting
14 the performance criteria that were established, then
15 I will go back and evaluate tonicity and optimize a
16 number of the other characteristics, perhaps for the
17 seemingly best possible on-paper characteristics.

18 Q. Have you ever had a formulation where you
19 attempted to modify the tonicity and that affected
20 the stability or performance criteria of your
21 formulation?

22 A. Yes. But then we oftentimes choose a

1 different tonicity-adjusting agent and resolve that
2 issue.

3 Q. Have you ever had a -- strike that.

4 Have you ever formulated a product where
5 you were -- had to adjust more than the tonicity
6 agent due to effects on -- strike that.

7 As you were formulating, you said earlier
8 that you adjust tonicity after you have chemical
9 stability and determine the performance criterias of
10 your formulation. Is that accurate?

11 A. Well, that's a pretty brief summary of what
12 I said. I said tonicity is a consideration. I
13 don't start with tonicity as the No. 1 issue, but it
14 gets addressed oftentimes after I've got a feasible
15 formulation developed. And then, you know, how I
16 adjust tonicity is a matter of what I've got in the
17 formulation and what I think are the correct agents
18 to use to adjust tonicity with.

19 Q. And you said there have been instances
20 where you have adjusted tonicity and that affected
21 chemical stability or other performance
22 characteristics of your formulation.

1 A. Yes.

2 Q. Correct? And you chose another tonicity
3 agent?

4 A. Right.

5 Q. Have there been times where you've
6 selected a number of tonicity-adjusting agents and
7 each of them in some way have affected chemical
8 stability or performance of your formulation?

9 A. I think that's universally true. You add
10 any additional material into a formulation and it's
11 going to have some effect on some characteristic of
12 the formulation, and that's just accepted in
13 formulation development. And whether that's an
14 effect that you have to then modify or whether it's
15 an effect that's just fine is a matter of what that
16 formulation is and what its intended use is and what
17 the parameters, the design parameters are and what
18 the acceptable parameters for the final formulation
19 can be.

20 (Donovan Exhibit Number 5 marked
21 for identification.)

22 BY MS. EVERETT:

1 Q. I'm handing to the court reporter to be
2 marked as Donovan 5, document bearing the Bates
3 APOTEX_AZFL0132304 through 325. And please go ahead
4 and look through Donovan 5. I'm just going to ask
5 you to identify it.

6 A. This looks like what I'm familiar with for
7 Allen's text.

8 Q. And this is what we've been referring to
9 in your report where you say --

10 A. Uh-huh.

11 Q. And you cite Allen's text for the pH and
12 the tonicity that we just referenced, correct?

13 A. Yes.

14 Q. And you also cited Allen's text on
15 Page 233 and 235 for preparation of nasal products?

16 A. Yes. Or 234, do you mean?

17 Q. Oh, excuse me. 233 and 234, yes.

18 A. Okay.

19 Q. And do you -- if we look at the bottom of
20 233, do you agree that this is a way to prepare a
21 solution, steps 1 through 7 as he has outlined here?

22 A. What's described there is certainly one

1 method to prepare a solution. Most of this text is
2 directed at compounding pharmacists, and so some of
3 the steps that are included in here are there
4 purposefully to remind pharmacists of things that
5 they should do as they are preparing, in this case,
6 a sterile or -- I don't know. I guess I'm not going
7 to go to sterile product, and so it's one of -- it's
8 certainly a good suggestion for a methodology to
9 prepare a solution for a compounding pharmacist.

10 Q. Okay. And in this solutions example, it
11 assumes that all the ingredients will be in
12 solution? Is that accurate?

13 A. Well, by definition if it's a solution, all
14 the materials that you've put in there or, you know,
15 if everything is in solution, and it's a solution
16 prep, those materials are dissolved in the vehicle.

17 Q. And do you agree with his suggestion that
18 one should take a sample of the solution and
19 determine pH, clarity, and other quality control
20 factors?

21 A. Well, under -- as a pharmacist compounding
22 a solution or in what ...

1 Q. In preparation for the opinion -- I
2 believe you've relied on this in your opinion.

3 A. Uh-huh.

4 Q. So these are the steps a person of
5 ordinary skill would know how to take?

6 A. Right. But a person of ordinary skill in
7 the art would also realize that this is an example
8 of how to make the solution for a particular purpose
9 given the target audience of the text and, as a
10 result, you know, this is a fine operating procedure
11 to suggest. And taking the pH and clarity and other
12 quality control factors is something that should be
13 done in the preparation of a nasal product.

14 But is it something that gets done at step
15 No. 4 in all occurrences of preparing a solution
16 nasal product? Not necessarily.

17 Q. Should it get done before you determine
18 that you have an acceptable nasal product?

19 A. Again, if we're taking what a formulator
20 would develop for a nasal formulation that was
21 intended for a broader audience than a single use
22 individual patient product that gets used in

1 compounding, that step is -- again, it's important.

2 It would happen at some point in time in that
3 formulation development procedure. But there's a
4 lot of other steps that are not specified here for a
5 compounding pharmacist and also for a formulator.

6 Q. And I just wanted -- you said formulator.
7 But I assume you mean a person of ordinary skill as
8 of June 2002?

9 A. A POSA formulator, yes.

10 Q. You said there were other steps --

11 A. Sure.

12 Q. -- that were not specified here. What
13 steps are you referring to?

14 A. Things like in this particular case, since
15 it's being filtered through a sterile filter into a
16 sterile nasal container, my assumption is that the
17 intent was for this to be a sterile product, yet
18 there's no direction for making sure that any of the
19 weighing or measuring ingredients or equipment is
20 sterile, that this is conducted in a sterile
21 environment, and so those are all things that either
22 the compounding pharmacist would have to decide if

1 they're making a sterile preparation that they would
2 need or a POSA formulator if they're making a
3 sterile product would know to include, but they're
4 not specified here. So there's a lot of steps that
5 go in between a lot of these other steps. But the
6 person to whom this is directed or a person using
7 this information, if they're a POSA formulator,
8 would understand there are other activities that
9 could take place.

10 Q. In addition to the steps related to
11 sterility, are there other steps you were -- a POSA
12 formulator would understand were included here?

13 A. Well, for example, the POSA -- this says
14 other quality control factors. That's left to then
15 the compounding pharmacist or the POSA formulator to
16 determine what those quality control factors are.

17 Q. Are there -- who would -- strike that.
18 Who would determine the quality control
19 factors?

20 A. It depends on what purpose those quality
21 control factors are being defined for. If they're
22 simply a preliminary formulation development quality

1 control, you know, you might have weighing
2 assurances. You might have visual inspections. You
3 might have color evaluation, a whole host of things
4 that could be a quality control factor.

5 In a full manufacturing sequence, you would
6 have things that were in-process tested and
7 characterized and measured and you would have final
8 product characterization and you would have many
9 steps of characterization in between.

10 So it all depends on what the purpose is
11 and what appropriate quality control factors are,
12 which is why they're not specified, because it's up
13 to the individual using this to take this
14 information and apply it to the situation they're
15 using it for.

16 Q. Are there a minimum number of quality
17 control factors? Strike that.

18 A. No.

19 Q. Are there basic or minimum quality control
20 factors that a person of ordinary skill would take
21 into consideration in every formulation?

22 A. From an absolute quantitative number? No.

1 Every formulation or every compounded prescription
2 has particular performance characteristics that are
3 important to control or assure, and that's what
4 those are. It essentially defines what the minimum
5 number of quality control procedures would be.

6 Q. Must a person of ordinary -- would a
7 person -- strike that.

8 Would a person of ordinary skill in 2002
9 determine the pH for every nasal spray?

10 A. If it was being used for humans, they
11 should have at least an understanding of what the pH
12 was likely to be or perhaps a reference source of
13 what the pH of similar concentration system is. I
14 am aware of compounding pharmacists who do not check
15 the pH of every compounded prescription that they
16 make.

17 Q. Is that because they already have an
18 opinion on what the pH of that formulation would be?

19 A. They have an expectation of what the
20 formulation -- or what the pH of that system would
21 be or that the pH is not a critical factor in the
22 performance or quality of the medication that

1 they've provided.

2 Q. Is pH a critical quality or factor in a
3 nasal spray?

4 MR. WARNER: Objection to the form of the
5 question. Vague as to critical.

6 BY THE WITNESS:

7 A. It's a consideration regarding drug product
8 stability. It's a consideration regarding how the
9 product performs or its shelf life. It's a
10 consideration regarding patient use. So yes. pH is
11 a consideration in every nasal product.

12 Q. When a person of ordinary skill does not
13 have an expectation or know the pH of a formulation,
14 would you expect that he or she would determine the
15 pH?

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

18 BY THE WITNESS:

19 A. I'm trying to develop in my mind a
20 situation where a person of ordinary skill in the
21 art wouldn't have any expectation for what the pH of
22 a simple system would be. But the easiest way to

1 determine what it is is to measure it. But
2 sometimes simply measuring the pH does not actually
3 give you an accurate measure of what the negative
4 log of the hydronium ion concentration is. And if
5 that's what you need to know, you have to measure it
6 appropriately using appropriate equipment.

7 Q. In step 4, the next -- strike that.

8 In step 4 after pH, it says clarity, so
9 person of ordinary skill would determine the
10 clarity. What is the clarity?

11 A. Well, in the context of this is if it's a
12 solution, everything should be a homogeneous
13 mixture. And as a result, you shouldn't see any
14 particulate matter. And the term clarity is
15 referring to if there's extraneous particulate
16 matter, you have a contaminant in your system.

17 Q. How would that determination be made?

18 A. Usually for a compounding pharmacy, it's
19 made visually. In other situations, it can be both
20 visually and there are other analytical methods to
21 use that can be used to determine the number and
22 size of particulate matter.

1 Q. Will visual inspection capture all
2 extraneous particulates?

3 A. No.

4 MR. WARNER: Objection to the form of the
5 question. Incomplete hypothetical.

6 BY THE WITNESS:

7 A. Visual inspection will only capture or only
8 allow people to identify the size particles that
9 they're capable of actually discriminating in their
10 visual field.

11 Q. So to have a complete understanding on
12 whether there's any extraneous particles, a person
13 of ordinary skill would need to engage analytical
14 methods as well?

15 A. It depends on the performance criteria for
16 your product or what your intention is.

17 Q. Well, if you were going to administer a
18 nasal spray and you wanted to make sure there were
19 no extraneous particles, would a person of ordinary
20 skill need to conduct analytical testing to be sure
21 of that?

22 A. Well, again, there it depends on what your

1 product characteristics are and what extraneous
2 particles might be there and what their particle
3 size are and what their role is and whether that
4 affects the performance of that spray or solution or
5 whatever.

6 Q. Would a person of ordinary skill in 2002
7 administer a method of treatment to humans for nasal
8 spray without undertaking an analytical test to
9 determine whether there was extraneous particulates?

10 MR. WARNER: Objection to the form of the
11 question. Incomplete hypothetical.

12 BY THE WITNESS:

13 A. It entirely depends on what those
14 extraneous particulates might be, what their size
15 are, and whether it's deemed that that would be an
16 important factor in the performance or quality of
17 that product.

18 Q. If it was determined that the person of
19 ordinary skill wanted to administer a stable
20 formulation that's a method of treatment to humans,
21 would he or she perform analytical testing to
22 determine whether there were any extraneous

1 particulates?

2 A. It depends on whether that's again an
3 important criteria. What size those particles are
4 is a critical factor in whether they're considered
5 to be a problematic contaminant or whether they will
6 have limited effect following administration and are
7 not something that needs to be evaluated or that
8 somebody needs to be concerned with.

9 Q. How would a person of ordinary skill even
10 determine whether extraneous particles existed --
11 strike that.

12 It's possible to visually determine
13 whether there's extraneous particles in the
14 formulation; is that correct?

15 A. It's possible to determine whether there
16 are extraneous particles in a formulation visually
17 if those particles are of a size that your eye can
18 discriminate.

19 Q. And the only way for a person of ordinary
20 skill to determine whether those particles in a
21 formulation are smaller than the particles of a size
22 your eye can discriminate, a person of ordinary

1 skill would have to conduct analytical testing; is
2 that correct?

3 A. Oh, the person would have to conduct some
4 sort of testing that is capable of measuring
5 particle sizes that are smaller than what your eye
6 is capable of discerning.

7 Q. I'm going to have you turn to the next
8 page, 234. And here, Allen discusses the
9 preparation of nasal spray products that are
10 suspensions?

11 A. Uh-huh.

12 Q. And you included this in your report; is
13 that correct?

14 A. Yeah, that's correct.

15 Q. And do you agree that methods 1 and 2 are
16 methods that a person of ordinary skill in June 2002
17 would have employed when creating a suspension?

18 A. Those methods or variations on them are
19 methods that could be used to prepare suspensions,
20 yes.

21 Q. And step 4 in both methods 1 and 2 also
22 say take a sample of the suspension and determine

1 the pH under quality control factors. Is that
2 accurate?

3 A. Yeah, step 4 in one and step 5 in the
4 other, yes.

5 Q. Yes, yes. Do you agree with those steps?

6 A. I agree with that -- those are factors that
7 you need to know about your formulation, and
8 they're good -- the pH is a good quality test or
9 check on the characteristics of a formulation. And
10 again, the other quality control factors are left up
11 to the formulator to determine what relevant quality
12 control factors need to be tested.

13 Q. What other quality control factors would a
14 person of ordinary skill test for a nasal spray
15 that's designed to be administered to humans?

16 A. Well, I mean, the most basic is always a
17 visual test. Does it look like the material or the
18 formulation that's either been prepared before, or
19 does it look like the material that we anticipated
20 it would be upon devising that formulation. So you
21 do a lot of visual inspection.

22 You can do some other simple measurements

1 in the case of compounding to assure that you've
2 actually made that in a consistent manner to how
3 it's been made previously. And it very much depends
4 on what the final goal of whatever it was you
5 formulated and when during a process you formulated
6 it is. If it's release testing for a commercial
7 batch of a product, those are very different quality
8 control factors that need to be evaluated compared
9 to if it's a compounded prescription that's
10 administered to one patient versus if it's something
11 I make in my laboratory for a series of tests in a
12 group of animals.

13 Q. So for a pharmaceutical that's compounded
14 and will be administered to one patient, what
15 quality control factors would you look for in
16 addition to visual test?

17 A. In many cases, as long as there's -- you
18 know, if there's a reference for that compounded
19 preparation being made previously or other
20 experience, oftentimes a visual test is often the
21 quality control that's performed by compounding
22 pharmacists.

1 Q. If that reference or preparation has not
2 been made previously, is visual test sufficient for
3 a formulation that's administered to a human?

4 A. It depends on how that formulation is being
5 administered and what it's -- what it contains and
6 what the risks are to that individual based on the
7 materials and what potentially could be a
8 formulation that, you know, exceeds some standard
9 typical characteristic for a similar preparation.

10 Q. Would a person of ordinary skill
11 administer, when preparing -- strike that.

12 Would a person of ordinary skill in June
13 of 2002 when preparing a formulation for the first
14 time administer a nasal spray to a human without
15 conducting some sort of analytical testing?

16 MR. WARNER: I'm going to object to the line of
17 questioning as beyond the scope of the report. It's
18 also incomplete hypotheticals.

19 BY THE WITNESS:

20 A. For a compounding pharmacist, it is
21 possible. I can't speak to every compounding
22 pharmacist and their methods of preparing materials

1 and what they do check and what they do document. I
2 know that there are new requirements that mandate
3 that quality control factors are identified and
4 performed for those compounded prescriptions. Those
5 are relatively new, however. So in 2002, what was
6 going on, I can't speak directly to every
7 occurrence.

8 Q. So when you say you can't speak directly
9 to every occurrence, do you have opinion one way or
10 another on whether a person of ordinary skill would
11 have performed some sort of analytical before
12 administering a nasal spray formulation to a human
13 for the first time?

14 MR. WARNER: Objection. Beyond the scope of
15 the report.

16 BY THE WITNESS:

17 A. I think in my experience in speaking with
18 compounding pharmacists, they oftentimes, again
19 given their expertise, they may have a -- they may
20 have a couple of performance, actual analytical
21 tests complete. Full analytical testing is
22 oftentimes not -- hasn't been performed and still is

1 typically not performed, which is why we have
2 regulations regarding limits on shelf life and so
3 forth on compounded prescriptions where there is no
4 analytical data to demonstrate what a true shelf
5 life is.

6 Q. So the analytical testing you were just
7 referring to, you're referring to on -- relating to
8 shelf life stability, is that ...

9 A. Oftentimes we use changes in those
10 analytical tests to tell us that there have been
11 changes in our product that we may or may not be
12 able to visually observe. You know, a lot of this
13 comes down to what analytical testing is it that
14 you're making. Anything that you can quantify, in
15 my opinion, could be deemed an analytical test. So
16 we could weigh the material, and that could be an
17 analytical test.

18 Is that going to be meaningful regarding
19 the product performance 30 days from now? I would
20 doubt that. But it's meaningful regarding whether
21 somebody prepared that in the way that was
22 instructed.

1 What analytical test is it that you want me
2 to discuss? And there's plenty of possibilities.
3 Who chooses what to do depends very much on what the
4 materials are, what the risks are, and what the --
5 where the administration is, what the expectation
6 is, and the evaluation of the formulator.

7 Q. I want to understand whether a person of
8 ordinary skill in June 2002 would consider any other
9 tests besides visual inspection before administering
10 a pharmaceutical for the first time to a human?

11 MR. WARNER: Objection.

12 BY MS. EVERETT:

13 Q. And specifically a nasal spray.

14 A. They may consider a number of tests.
15 Whether they perform them or not is up to them to
16 have determined whether they're important enough
17 that they need that information before they
18 administer that to a patient.

19 Q. So you're saying a person -- person of
20 ordinary skill, as of June 2002, would administer a
21 nasal spray that they prepared for the first time to
22 a human without -- with simply visual analysis?

1 A. I'm -- In 2002 there were likely instances
2 of compounding pharmacists administering drugs with
3 well-known safety profiles as nasal sprays to humans
4 or providing those to humans for use.

5 Q. So you're saying they were providing them
6 to humans for use without conducting any tests
7 besides a visual inspection?

8 A. They may -- There may have been other
9 simple tests that were performed. I don't know.
10 But, you know, full-blown chemical analysis was
11 likely not the test that was performed.

12 Q. Are there any other quality control
13 factors a person of ordinary skill would have
14 considered for a suspension specifically in 2002?

15 MR. WARNER: Objection to the form of the
16 question. Incomplete hypothetical.

17 BY THE WITNESS:

18 A. Again, there's a number of quality control
19 factors that should be considered. Particle size is
20 a quality control factor that should be considered.
21 The rate of either creaming or flocculation or
22 settling could be considered. The dose uniformity

1 could be considered.

2 There's certainly a number of things with
3 suspensions that are, from a manufactured suspension
4 product are a mandatory criterion and from a
5 compounded formulation standpoint, are not
6 necessarily oftentimes measured but are assumed or
7 based in experience and risk assessment are believed
8 to be within safe, safe ranges for administration to
9 humans.

10 Q. So for a compounded formulation, the POSA
11 would make assumptions about the particle size, the
12 flocculation, and the dose uniformity; is that what
13 you're saying?

14 A. At some points they may. Compounding
15 pharmacists oftentimes don't have the information
16 available to them regarding particle size or
17 particle size distribution, and they use their
18 experience and professional judgment to determine
19 whether that -- whether an absolute knowledge of the
20 particle size or simply a knowledge and observation
21 of that particle size performance is adequate to
22 develop that formulation and provide it to that

1 single individual.

2 Q. Would a person of ordinary skill as of
3 June 2002 have that information available to them?

4 MR. WARNER: What information?

5 MS. EVERETT: Particle size, particle size
6 distribution, referring to Dr. Donovan's answer
7 she just gave.

8 BY THE WITNESS:

9 A. Again, as I said in my answer, oftentimes
10 compounding pharmacists don't have that information
11 available to them. So they rely on their
12 professional judgment. They rely on their skills
13 and observations to determine whether what they are
14 using is appropriate and safe for the individual
15 patient they're compounding that material for.

16 Q. Okay. I asked about a POSA in June 2002,
17 and then you responded about a compounding
18 pharmacist. Are you referring -- when you're
19 referring to a compounding pharmacist, are you
20 referring to a POSA as of June 2002?

21 A. If -- By my definition of POSA, only if
22 they had the experience I described in addition to

1 their education. And so if you want to know what a
2 POSA formulator developing a formulation would know,
3 they at a point in time during formulation
4 development would -- would likely know the particle
5 size and particle size distribution of materials
6 they intended on using in a suspension.

7 (Donovan Exhibit Number 6 marked
8 for identification.)

9 BY MS. EVERETT:

10 Q. I am handing to the court reporter to be
11 marked as Donovan 6, a document bearing the Bates
12 stamp APOTEX_AZFL0054360 through 365.

13 Do you recognize Donovan 6?

14 A. Yes, I do.

15 Q. What is it?

16 A. It's a patent describing azelastine
17 containing medicaments.

18 Q. And you opine that this patent is a
19 blocking patent; is that correct? I can help orient
20 you if you --

21 A. No. I found the section where I discussed
22 blocking patents. And I was informed by counsel

1 what that term means because that's not a
2 terminology that I typically use. And based on the
3 information I was provided, that Patent '194, which
4 is Donovan 6, is a patent that was in existence at
5 the time, that certainly would have been considered
6 by someone trying to develop a commercial product.

7 Q. When you say "I was informed by counsel
8 what the term means," what were you informed the
9 term means?

10 A. Well, that in -- my understanding is that
11 it's a patent that's in existence that would -- that
12 contains descriptions that are -- that may have
13 intellectual property rights that affect or that
14 are, you know, that there may be infringement if
15 someone would pursue a body of work because this
16 patent was in existence. It's a clunky way of
17 saying it, but it existed so somebody has the
18 intellectual property rights in the area.

19 Q. And then you also say based on the
20 information you were provided, Donovan 6 is a patent
21 that was in existence at the time, that certainly
22 would have been considered by someone trying to

1 develop a commercial product. What information were
2 you provided that you're referencing that?

3 MR. WARNER: Where is that?

4 MS. EVERETT: In her answer.

5 MR. WARNER: Oh, I thought you were talking
6 about in the reports.

7 BY THE WITNESS:

8 A. When I see patents and I see dates and then
9 I've been told that, well, that's really, you know,
10 not the date, there's a previous patent, there's a
11 bunch of other things. I have no way of knowing
12 just given a single patent whether that patent was
13 in force at the time of interest or whether it had
14 been modified into a separate. I don't know.

15 I get confused very quickly, and I rely on
16 counsel to tell me which patents are in effect and
17 which ones are not based on dates or other changes
18 that have been made. So that's the information they
19 provided to me that this was in existence and
20 enforceable at the time, and it would have been a
21 consideration.

22 Q. They told you it would have been a

1 consideration?

2 A. No. They told me that it was -- that it
3 was in existence and still had a patent lifetime
4 left to it. And my opinion is that would have been
5 a consideration to somebody who would be trying to
6 develop a commercial product that would potentially
7 have this patent and that they would be infringing
8 or needing to use the intellectual property
9 described.

10 Q. And when you say it's a consideration to
11 somebody who was trying to develop a commercial
12 product, what do you mean by that?

13 A. Well, it's the knowledge that if you
14 develop a commercial product and bring it into the
15 marketplace and there's a patent that has
16 intellectual property in that area that you're
17 infringing on, that likely you will be informed of
18 that and there will have to be some arrangement made
19 to properly compensate the holder of the
20 intellectual property.

21 There are -- just because the intellectual
22 property exists doesn't mean you can't partner with

1 whoever owns it or have other arrangements made to
2 utilize that information and still bring your
3 product forward. But you have to recognize that
4 somebody has that intellectual property and that you
5 have to, in the U.S. at least, respect that and go
6 either forward in partnership or in agreement with
7 or you can't move into the commercial space.

8 Q. So is it your opinion that in June 2002, a
9 product, if it were launched, containing azelastine
10 and fluticasone would infringe the Hettche patent?

11 A. It depends on the concentrations of
12 azelastine and the use of that product. But if the
13 use was for uses described in this patent in the
14 concentration ranges that are described in the
15 patent, then my opinion would be yes, it would
16 infringe on this.

17 Q. Did you review the prosecution history of
18 the Hettche patent?

19 A. I'd have to refer to my list of documents
20 because it doesn't come to mind. If it's on one of
21 my lists, you're free to tell me that it is and we
22 can move on. Otherwise, I will try to find it.

1 Okay. In my quick evaluation of the
2 materials considered, I don't see that. And I don't
3 recall seeing the prosecution history for that
4 patent.

5 Q. Is it fair to say that if you had reviewed
6 the prosecution history, you would have cited it or
7 put it on your Materials Considered list?

8 A. In this case, yes.

9 Q. Okay. So we can assume you did not review
10 the prosecution history for the patent?

11 A. I don't have a recollection of reviewing
12 the prosecution history.

13 Q. So I'm going to turn to Donovan 6 and to
14 column 8, and I'll have you look at the 12 claims.

15 A. Okay.

16 Q. They each appear to be methods, is that
17 correct, method of treatment? Strike that. Let me
18 ask that again.

19 Each of these appear to be a method for
20 treatment; is that correct?

21 A. Well, I mean, I have to let somebody else
22 make the determination of how the individual claims

1 relate to each other. But they all describe
2 methods, given that they start with the phrase "a
3 method."

4 But the dependency of claim 3, for example,
5 as a method set forth in claim 2 and the description
6 of what that medicament contains, if that
7 correspondence to the method of treatment described
8 in claim 1, then it does. And if it doesn't because
9 of how claims are described, then it doesn't. I'm
10 going to rely on counsel to tell me whether these
11 are all methods for the treatment.

12 Q. Do you know or understand whether there's
13 a difference in a patent claim that's a method of
14 treatment versus a composition claim?

15 A. Well, in the terminology you've described,
16 yeah, I could come up with my own version of
17 definition of what I would think the difference is.
18 Again, I would rely on counsel to tell me whether my
19 definition is in keeping with legal standard
20 regarding claims.

21 Q. Did you -- When you analyzed the Hettche
22 patent to determine whether it was a blocking

1 patent, did you consider whether it would have
2 prevented someone from developing a composition
3 claim?

4 MR. WARNER: Objection to the form of the
5 question. Beyond the scope of the report.

6 BY THE WITNESS:

7 A. I guess can you reask the question?

8 Q. Sure. All of the claims in the '194
9 directed to a method of treatment?

10 A. Uh-huh.

11 Q. We've talked about that. Did you consider
12 whether these claims, these method of treatment
13 claims, would have blocked a person of ordinary
14 skill from developing a composition claim?

15 MR. WARNER: Same objections. I just want an
16 objection to vagueness, developing a composition
17 claim. You can answer.

18 BY THE WITNESS:

19 A. I don't understand, that's -- I don't
20 understand the question. And I don't understand the
21 terms and the differentiation, so I can't answer.

22 Q. So you know there are three

1 patents-in-suit in this case, correct?

2 A. Yes.

3 Q. And some of those patents are directed to
4 methods of treatment; is that correct? You know
5 that?

6 A. There are descriptions of methods of
7 treatment in them is the way I've come to be
8 familiar with them.

9 Q. And there are certain claims that are
10 directed to compositions; do you understand that?

11 A. I understand there's claims regarding
12 compositions, yes.

13 Q. Did you consider -- And when you looked at
14 your -- the Hettche patent to determine your
15 blocking analysis, did you consider whether a person
16 would be blocked from developing a composition
17 claim?

18 MR. WARNER: Same objections. Vagueness as to
19 developing a composition claim.

20 BY THE WITNESS:

21 A. And what I would consider is I believe that
22 a person would be limited in their ability to

1 commercialize for profit such a composition. But it
2 depends on what you mean by "development." People
3 worked with azelastine in concentrations that are
4 described in this patent. So does it mean they
5 didn't ever conceive of -- or didn't try to use
6 these concentrations in anything, but the key is if
7 the goal or the intent is to commercialize
8 something, then one has to recognize the
9 intellectual property concerns of the '194 patent.

10 Q. And I don't mean to be vague, but -- so
11 I'll ask it again. Did you consider whether these
12 method of treatment claims would have prevented a
13 person of ordinary skill from developing and
14 patenting a composition of azelastine and --
15 azelastine and fluticasone?

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

18 BY THE WITNESS:

19 A. Well, and again, I'll leave it to others to
20 decide what really could be patented or not. But it
21 would be my impression that if somebody was going to
22 develop a composition that was intended to be used

1 in a manner described in the '194 patent and then
2 used the materials and methods described in that,
3 that they couldn't pursue a patent to do that during
4 the time frame that this patent was in effect.

5 Q. Do you -- You qualified your answer that
6 if a person is going to develop a composition that
7 was intended to be used in a manner described in the
8 '194 patent. Are you opining on whether the -- an
9 additional product would be a method of treatment
10 patent?

11 A. I can't form an answer to that.

12 Q. So you can't form an opinion on whether a
13 person of ordinary skill would have been able to
14 develop a composition product, just the composition?

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

17 BY MS. EVERETT:

18 Q. And I'll rephrase. We've been talking
19 about using Dymista, a method of treatment for using
20 an azelastine fluticasone product. And I want to
21 make a distinction. Now my questions are going to
22 refer to the composition itself.

1 A. Okay.

2 Q. In your opinion, would the method of
3 treatment claims here prevent a person of ordinary
4 skill from developing an azelastine fluticasone
5 combination product?

6 A. Well, you need to define for me "product."
7 Is that a product for the commercial marketplace, or
8 is that a system in a beaker in a laboratory?

9 Q. From developing a composition on which
10 they go and seek a patent.

11 A. Then I think they would be limited by the
12 existence of this patent, that it would limit the
13 commercial opportunity to have that work reach a
14 commercializable and hopefully profitable potential
15 and likely would use your resources in a different
16 manner that could bring you the opportunity to bring
17 product into the commercial marketplace.

18 Q. In your report, you state that -- I
19 believe you looked through claim 1, in fact, and
20 opine on that azelastine is -- contains a member
21 selected from the group consisting of azelastine and
22 its physiologically accepted salts.

1 A. Is there a particular paragraph in one of
2 the reports you're reading that from?

3 Q. So, I believe, and please, please, feel
4 free to look at anything, your blocking opinion is
5 Paragraph 62 and 63.

6 A. Okay. I thought I was just on my blocking
7 opinion. You mean Page 62 and 63?

8 MR. WARNER: It's on Page 23 and 24. Are you
9 in the right report?

10 THE WITNESS: I may not be.

11 BY MS. EVERETT:

12 Q. It's the rebuttal report.

13 A. That's why. I'm not in the right report
14 any longer. I switched over. Okay. I'm sorry.
15 Can you go back and ask the question?

16 Q. Sure. You -- In this section of your
17 report, you were looking at claim 1 of Hettche; is
18 that correct?

19 A. Yes.

20 Q. And you opined that Dymista and other
21 drugs contain a medicament which contains a member
22 selected from the group consisting of azelastine and

1 its physiologically acceptable salts?

2 A. Okay. That's what it says, yes.

3 Q. And you agree with that? And you agree
4 with that today?

5 A. Yes.

6 Q. What is a -- What does it mean to say
7 contains a member selected from the group consisting
8 of azelastine and its physiologically acceptable
9 salts?

10 MR. WARNER: Objection to the form of the
11 question.

12 BY THE WITNESS:

13 A. Well, I believe in the other introductory
14 material, in the '194 patent, there are descriptions
15 of potential antihistamine compounds in addition to
16 azelastine that come from similar chemical families
17 or similar -- similar other antihistamine action.
18 But I may be confusing that, but this may be limited
19 to simply azelastine.

20 Okay. Well, when I look at this more
21 closely -- Well, I don't know. That's
22 preservatives. So the introduction, even though --

1 as far as I can tell as I quickly review this, that
2 it's focused on azelastine. But in how one writes a
3 claim, I guess, perhaps they might concede that it
4 might include azelastine and prodrugs of azelastine,
5 and this would be sufficient to cover it or
6 something and its potential salts in addition that
7 you might make.

8 So it might consist of analogs that people
9 would recognize as leading to the same parent and
10 simple salt forms that are certainly numerous and
11 probably too numerous to name as the possibilities.

12 Q. If the phrase was construed to mean
13 azelastine or its salts can be used, would that
14 modify your opinion at all?

15 MR. WARNER: As opposed to what?

16 BY MS. EVERETT:

17 Q. I just want to be clear. If it's only
18 azelastine and its salts.

19 A. It wouldn't change the context of my
20 opinion. It would change perhaps how I used this
21 reference in support of that.

22 Q. How would it modify how you used the

1 reference?

2 A. Well, again, you know, if I can take the
3 time to reread this and make sure that there's not
4 any other attribution to potentially any other
5 antihistamines, I can answer specifically with
6 regard to azelastine.

7 And otherwise I have to allow myself the
8 opportunity that if what's really described by this
9 claim, not just my sitting-here interpretation of
10 this claim is broader than what I'm thinking at the
11 moment, I'd need somebody to explain to me what the
12 claim has been -- what the claim is viewed to mean
13 outside of my own personal opinion of what the claim
14 is -- what I'm interpreting it to mean today sitting
15 here because I haven't reviewed the context of the
16 patent recently.

17 Q. If it was limited to azelastine or other
18 antihistamines, would that modify your opinion?

19 MR. WARNER: Objection to the form of the
20 question. Vague as to what "it" is.

21 BY THE WITNESS:

22 A. Yeah, can you go back and help me remember

1 what the topic of your question is?

2 Q. Sure. We're looking at a phrase:

3 Contains members selected from the group containing
4 azelastine and its physiologically acceptable salts.

5 A. Yes.

6 Q. And we had talked about what -- what you
7 understood that to mean. And I think we talked
8 about azelastine and its salts and potentially
9 azelastine and prodrugs.

10 A. Or some form of something that will --
11 would be viewed as equivalent to azelastine, yes.

12 Q. Okay. So in your view, when it says it
13 contains a member selected from the group consisting
14 of azelastine and its physiologically acceptable
15 salts, it is azelastine or something that is
16 considered an equivalent or a salt of azelastine?

17 A. Are you asking me what my interpretation of
18 what this method claim is?

19 Q. Yes.

20 A. And I'm going to tell you that I need
21 counsel to tell me what the legal interpretation is
22 and such that I can align my opinion with that

1 because I respect that what I as a scientist read
2 and what is written may not -- I may not fully
3 capture what is intended in a claim, but I stand by
4 what I've written in my report as my opinion.

5 Q. So I just want to be clear because you've
6 given an opinion on this claim. And now you are
7 looking to counsel's assistance? I'm not sure I
8 understand why you need counsel's assistance.

9 A. Well --

10 MR. WARNER: Objection. Mischaracterizes her
11 testimony.

12 BY THE WITNESS:

13 A. Counsel provided me information about this
14 claim and, while I was describing my opinion in my
15 reports, I no longer remember the specifics
16 regarding what the legal expansion of this claim
17 are. And until I know that, I can't begin to tell
18 you whether my opinion is different than what I have
19 written or not.

20 Q. You said counsel provided you some
21 information about this claim. What information did
22 counsel provide you about this claim?

1 A. In discussions, I've been told about claims
2 constructions and what is typically meant by when we
3 write -- when a claim is written with these words,
4 this is what it encompasses. It doesn't mean that.
5 I don't remember any specific instance. I certainly
6 don't necessarily remember any specific instance
7 about claim 1. But, you know, I certainly know in
8 general that I oftentimes need counsel to tell me
9 what the legal interpretation of a claim is compared
10 to what my scientific interpretation of a claim is.

11 But I had that knowledge as I was preparing
12 my report, and I stand by the opinions that are
13 written in it.

14 MR. WARNER: Whenever you guys are ready for
15 lunch, is this maybe a good time?

16 MS. EVERETT: It's a good time, yeah.

17 THE VIDEOGRAPHER: This marks the end of DVD
18 No. 3. We are off the record at 1:02 p.m.

19 (A lunch break was taken.)

20 THE VIDEOGRAPHER: Here begins DVD No. 4. We
21 are on the record at 1:48 p.m.

22 BY MS. EVERETT:

1 Q. Welcome back.

2 A. Thanks.

3 Q. I'm going to have you turn to your opening
4 report again, please, back to the section on
5 thickening agents.

6 A. Paragraph or page?

7 Q. Starting at 111, but I'm going to point
8 you to Paragraph 112.

9 A. Okay.

10 Q. So just please refer to it, if you need
11 to. In paragraph 112 you state that Astelin uses
12 another thickening agent called hypromellose?

13 A. Right.

14 Q. And the use of this other ingredient would
15 not present a reason for a POSA not to try MCC and
16 CMC in a combination product.

17 And do you still agree with that sentence?

18 A. Yes.

19 Q. It would be viewed as another available
20 option to try as a thickening event in the event
21 there were any surprising incompatibilities with MCC
22 and CMC in the desired combination formulation. I

1 am not aware of any.

2 And do you still agree with those
3 sentences?

4 A. Yes.

5 Q. So are there any -- strike that.

6 Are you aware as of June 2002 whether
7 there were any incompatibilities between azelastine
8 or either MCC or CMC?

9 A. I'm not aware of any incompatibilities that
10 were known at that time or would have been
11 anticipated.

12 Q. And by "incompatibilities," do you -- does
13 that include any potential interactions between MCC
14 and CMC -- strike that.

15 And by "incompatibilities," does that
16 include any potential interactions between either
17 MCC and azelastine or CMC and azelastine?

18 A. No, that's not what an incompatibility is.

19 Q. What is an incompatibility?

20 A. Well, an incompatibility is the inability
21 of -- well, we'll leave it to two agents -- to
22 coexist without one influencing the performance

1 characteristics of another. So interactions can
2 happen all the time. And as long as they don't
3 change the performance characteristics, that
4 wouldn't be an incompatibility.

5 Q. As of June 2002, would a POSA have known
6 of any interactions between MCC and azelastine or
7 CMC and azelastine that would have affected the
8 performance characteristics of either?

9 A. I'm not familiar with any a POSA would have
10 known. There's always the possibility that
11 materials can interact. They may interact and not
12 be discernible. They may interact and may be
13 discernible. They may have no negative effect on
14 the product. But I'm not aware of anything in 2002
15 that indicated that any of those agents at any
16 concentrations had some sort of interaction that was
17 a -- would have a negative outcome.

18 Q. I'm going to have you turn to your
19 rebuttal report now, Paragraph 45. Just take a
20 minute to read through that.

21 A. Okay.

22 Q. In that, in that document, the first

1 sentence says -- first a document with the
2 handwritten title Solubility Trials For Azelastine
3 Hydrochloride, I'll skip the Bates: The
4 experimenter concluded that from these trials, that
5 probably azelastine hydrochloride remains in the
6 solution state in the final suspension but might be
7 making loose bonding with spending agent, Avicel
8 CL611, because the sodium salt of
9 carboxymethylcellulose is present in Avicel and
10 azelastine hydrochloride is itself a hydrochloride
11 salt.

12 Do you see that?

13 A. Yes.

14 Q. And then you have a footnote that states:
15 The sodium salt of carboxymethylcellulose can
16 disassociate and form a negatively charged polymer,
17 while the hydrochloride salt of azelastine can
18 disassociate to form positively charged azelastine.
19 The positive and negative charges may ionically
20 interact in the formulation?

21 A. That's what that says, yes.

22 Q. Do you agree with that?

1 A. I still agree with that, yes.

2 Q. What does it mean when the positive and
3 negative charges may ionically interact in
4 formulation?

5 A. That the positively charged azelastine may
6 interact with the negative charge regions of CMC.

7 Q. Would that have a negative affect on
8 performance characteristics?

9 A. It doesn't appear to. And we use those
10 kind of interactions to enhance formulations all the
11 time. So it wouldn't be anticipated even if we
12 thought that they would occur, that they would
13 necessarily be a negative and they might be a
14 positive.

15 Q. How far do you use them to enhance
16 formulations?

17 A. Well, oftentimes because we can get those
18 interactions to occur, they might act to chemically
19 stabilize things. They may act to separate
20 materials from interacting from other materials.
21 They may act to actually increase solubility.
22 That's a number of things that performing those

1 complexes could accomplish.

2 Q. What does it accomplish in this system
3 described here in Paragraph 45?

4 A. Well, again, the information I was provided
5 is simply a hypothetical from the report, and so I'm
6 not sure that that's actually going on. I just
7 agree that it could possibly happen and that there's
8 not necessarily a problem with that.

9 Q. Is the footnote your positioning or just
10 what you've gleaned from the documents you're
11 opining on?

12 A. Well, it's my explanation for what the
13 statement in the -- or what the scientific
14 explanation for the statement in the report was,
15 that the statement was pretty loose about it, you
16 know, it might be -- let me read what it's actually
17 saying.

18 Make loose bonding with the suspending
19 agent. That's really not a very scientifically
20 distinct way of describing what's going on. And so
21 I chose to clarify what I believe that that meant in
22 a more molecular-level mechanistic sense.

1 Q. Earlier, you said that the interaction,
2 positive and negative charges may ionically interact
3 and the formulation may have -- may enhance the
4 formulation?

5 A. Uh-huh.

6 Q. Have you seen instances where it
7 negatively affected performance of the formulation?

8 A. Well, you have to be more clear. Of this
9 formulation? Of any formulation?

10 Q. Any formulation.

11 A. Potential formulation? I have seen
12 instances where positive and negative charge
13 interactions leads to a negative effect on a
14 combination of materials in a formulation.

15 Q. In the instances where you have seen the
16 positive and negative interactions lead to a
17 negative effect, was that -- did you anticipate that
18 in advance?

19 A. It certainly was a possibility that was
20 identified could occur. And in the situations that
21 I'm most familiar with, it would have been very
22 difficult to predict based on data that were

1 available. Whether it would occur, at what
2 concentrations it would occur, or under what other
3 conditions it would occur, so the goal was design a
4 set of experiments to demonstrate whether it did or
5 didn't occur.

6 Q. I'm going to have you turn to your reply
7 report.

8 A. Okay.

9 Q. And I'm going to have you turn to the
10 section where you're talking about the amount of
11 azelastine to use. I think Paragraph 38 of your
12 reply report. Are you --

13 A. I'm on Paragraph 38, yes.

14 Q. And here you note that Dr. Smyth has
15 opined it would not have been obvious that because
16 of -- the labeling in Astelin recommended eight
17 doses per day, two per nostril twice per day, and
18 the labeling in Flonase recommended four doses per
19 day.

20 A. I see that part.

21 Q. Okay. And Dr. Smyth is talking about the
22 amount of azelastine and fluticasone that were

1 administered and how often they were administered as
2 per the Flonase and Astelin labels. Do you see
3 that?

4 A. Uh-huh.

5 Q. Okay. And you go on to talk about the
6 concentrations of Astelin and Flonase; is that
7 correct?

8 A. Yes.

9 Q. There's a distinction between the dosage
10 and the concentrations; is that accurate?

11 A. There's a relationship between the two of
12 them in these formulation, but there are distinctly
13 two different aspects of them.

14 Q. And you opine on the concentration -- when
15 you look at the labels, you're opining on the
16 concentration in Paragraph 38; is that correct?

17 A. I'm --

18 Q. It would be sort of in the same spot?
19 First, it would have been obvious to include the
20 concentrations described in the Astelin and Flonase
21 label because those concentrations were successfully
22 known to be formulated in Astelin and Flonase?

1 A. Right, that's in there.

2 Q. So that's a different consideration than
3 what Dr. Smyth said with dosage; is that accurate?

4 A. Well, again, one's the result of the other.
5 The particular concentration that your formulation
6 is developed at and the device that you use
7 determines the volume that's emitted. And the
8 volume that emitted at the concentration determines
9 the dose you delivered.

10 Q. Well, it isn't just the device that
11 determines the volume that's emitted; there's also a
12 recommended dosage from FDA here?

13 A. I think you need to clarify what you're
14 asking me.

15 Q. So it isn't -- concentration is in what
16 percent in the entire formulation -- well, strike
17 that.

18 Concentration is of the entire
19 formulation, what percent is azelastine?

20 A. Well, in terms of a percent, it's actually
21 in terms of a mass per volume usually. But you can
22 come up with the percentage, if you'd like.

1 Q. And that's distinct from how many
2 micrograms would you administer to a patient?

3 A. Well, in a nasal spray dosage form, the
4 concentration of the formulation is emitted from the
5 device in a particular volume. And the volume
6 that's emitted and the concentration that it's
7 formulated at results in the specific dose that gets
8 delivered from the product.

9 Q. But the amount of product delivered can
10 also vary just based on the number of times a person
11 uses it per day, not just -- so you're talking about
12 the formulation. I'm talking about usage.

13 A. So --

14 MR. WARNER: Hold on one second. Make sure
15 there's a question out there.

16 BY MS. EVERETT:

17 Q. Do you understand the distinction? Do you
18 understand the distinction I'm making?

19 A. Well, I think I do, but I'd appreciate --
20 if you're talking about mass of drug exposure, then
21 be specific about that and dose administered or dose
22 absorbed or dose whatever. But there's -- the

1 statements I'm making about concentration provide
2 information about what the amount of drug, which
3 would be equivalent to the dose administered is
4 provided from a nasal spray formulation device
5 system.

6 Q. So you were looking at the nasal spray
7 device formulation. Are you -- I understood to have
8 said that; is that correct?

9 A. Well, the formulation plus the device
10 determines the amount emitted per spray, which then
11 is utilized to effect whatever the desired dose is
12 to expose the patient to.

13 Q. Are you considering how many sprays a
14 person of ordinary skill would have administered to
15 a patient in June 2002?

16 A. In the same way that I as a formulator
17 would consider how many tablets a person might take,
18 or how many inches of a cream somebody might use,
19 the ability to multiply a dosage unit to meet a dose
20 requirement is commonplace.

21 Q. So -- And there's a difference between the
22 amount of active ingredients delivered per spray and

1 an amount that a doctor may prescribe a patient to
2 take?

3 MR. WARNER: Objection.

4 MS. EVERETT: I can modify.

5 MR. WARNER: Go ahead.

6 BY MS. EVERETT:

7 Q. So we're talking about the amount per
8 spray, and I'm trying to make a distinction here. A
9 doctor may tell you to spray it three times or four
10 times, and that affects the amount of an active that
11 a patient ingests. Is that accurate?

12 A. Are you supposing that the physician feels
13 that the number of sprays is the most important
14 factor and that whatever mass load of drug is
15 exposed as a result of that number of sprays is just
16 a random occurrence? Because that's what the
17 question sounds like, that it's the most important,
18 irrelevant of what the concentration of the product
19 is or the amount it delivers, that the key is to
20 just spray it three or four times.

21 Q. No, of course not. I'm making a
22 distinction between the amount of active ingredient

1 a doctor would want a patient to consume versus the
2 amount that physically comes out of the spray. Does
3 that distinction -- do you understand that
4 distinction?

5 A. Well, I understand the distinction, but I
6 don't understand the question.

7 Q. I want to make sure you've understood the
8 distinction between the amount of active a physician
9 would prescribe to a patient versus the amount of
10 active administered per spray?

11 A. But typically physicians don't prescribe
12 nasal sprays based on the amount of the drug they
13 want to be administered. They prescribe them based
14 on a knowledge of the concentration and the amount
15 delivered and how many of those individual dose
16 units they want the patient to receive to get to the
17 total dose that the patient should be administered.

18 Q. I think we might be talking past each
19 other. You just said that physicians don't
20 prescribe nasal sprays based on the amount of drug
21 they want the patient to be administered? That was
22 the statement you just made. I want to make sure.

1 A. They don't dose them based on the number of
2 sprays alone. They understand what the
3 concentration in the formulation is or in the
4 product and the amount of drug that gets released
5 per actuation of that particular dosage form, and
6 they prescribe based on how much drug they want the
7 patient exposed to and how that system delivers it.

8 So they're not unaware and not determining
9 their dose or their instructions to their patients
10 in the isolation of the knowledge of what the
11 concentration and the dose provided per spray is.
12 That's the key point. And they adjust their dosing
13 recommendations, one, two, three, four sprays
14 whatever based on the knowledge that three sprays
15 will get this amount of drug, two sprays will get
16 that amount of drug. And frequency based on
17 whatever their prescribing rationale is for that
18 individual patient.

19 Q. So ultimately a physician is prescribing
20 an amount of active per day to a patient?

21 A. Or.

22 Q. Is that the consideration?

1 A. Or per dose or per week or per month. It
2 very much depends on the particular drug product and
3 the dosing strategies that physicians use for those
4 products.

5 Q. So ultimately when a physician is
6 prescribing to a patient, he or she is considering
7 the amount of active ingredient his or her patient
8 will consume, not necessarily the concentration at
9 which it's delivered; is that accurate?

10 A. I think that depends on what type of
11 delivery system we're speaking of.

12 Q. Here, in this context, in Paragraph 38,
13 looking at Astelin and Flonase.

14 A. In the situation of nasal sprays, if you'd
15 rephrase or repeat your question regarding nasal
16 sprays specifically, I can answer that.

17 Q. Sure. In the context of nasal sprays, and
18 specifically Astelin and Flonase, a physician would
19 be most concerned with the amount of or micrograms
20 of azelastine or fluticasone delivered to his or her
21 patient rather than the concentration of them in a
22 bottle; is that correct?

1 A. Well, the physician understands that the
2 amount that they want administered is only the
3 result of the concentration in the bottle and what
4 the device can deliver. So I don't think physicians
5 think of them separately. They're a package deal.

6 Q. But ultimately a physician wants a patient
7 to have a therapeutically effective amount of any
8 dosage form; is that --

9 A. That's true.

10 Q. And it was no different when a physician
11 prescribed Astelin and Flonase in June 2002; is that
12 correct?

13 A. I would assume that's correct, yeah.

14 Q. So you go on to state in Paragraph 38: I
15 understand from Dr. Schleimer that although the
16 Astelin label recommended use twice daily, all that
17 was needed for the antihistaminic and
18 anti-inflammatory effects was a single dose.

19 Do you see that?

20 A. I see that, yeah.

21 Q. Do you have any basis for that statement
22 besides reliance on Dr. Schleimer?

1 MR. WARNER: Objection. The report speaks for
2 itself.

3 BY THE WITNESS:

4 A. Well, I mean, my understanding regarding
5 the antihistamine in that -- in Astelin is that for
6 the immediate response, which is what this is
7 describing, that that's a result of the previous
8 dose. So if somebody desired an immediate
9 antihistaminic response, they could administer a
10 spray of Astelin.

11 And whether they needed that spray because
12 they felt they needed treatment twice a day, that
13 was certainly possible with Astelin. But they would
14 get a response and a detectable immediate response
15 following one dose or following two doses depending
16 on what their symptoms were and their needs for that
17 medication.

18 Q. When you just said your understanding,
19 what is the basis of your understanding?

20 A. My basis of my understanding is in my
21 understanding of what local antihistamine delivery
22 does in the nasal cavity, the mechanisms of action.

1 Q. And have you studied the Astelin label
2 specifically for this?

3 A. I know that previous to reading the Astelin
4 label, I could read the Astelin label and probably
5 find areas in the clinical pharmacology section and
6 maybe a couple of other sections that would support
7 that.

8 Q. Have you done that, or you said you could?

9 A. I mean, I've read the label. I'm not sure
10 that I can tell you -- in fact, I'm sure I can tell
11 you now I don't remember the specific wording in the
12 label. And I'd be happy to go back and review that
13 label and show you where in the label I learned
14 that.

15 Again, I know from knowledge of
16 antihistamine use in the nasal cavity and the
17 cellular responses that one would anticipate a rapid
18 response to an antihistamine being present. So
19 you'd have a detectable therapeutic response
20 following each spray, whether it was once a day,
21 whether it was twice a day, however how many times
22 that therapy was prescribed.

1 Q. And you stated earlier that you had not
2 studied azelastine outside of this litigation; is
3 that correct?

4 A. I'm aware of azelastine. I've read things
5 about azelastine. I have not pursued azelastine as
6 a research project.

7 Q. And do you have -- you've referred to Dr.
8 Schleimer's -- Schleimer, and now you've referred to
9 the Astelin label. Is there any other basis for
10 you -- for your opinion that all that was required
11 for immediate antihistaminic and anti-inflammatory
12 effects was a single dose?

13 A. Well, I mean, my opinion is based in that
14 there is an antihistaminic response following the
15 delivery of Astelin or of azelastine into the nasal
16 cavity. And the frequency with which that delivery
17 occurs is -- the response is not dependent on the
18 frequency that that's delivered.

19 The magnitude of the response may have some
20 relationship to the frequency. But there still will
21 be a response after every single administration.

22 Q. And what is the basis for your saying that

1 one dose of Astelin will provide immediate
2 antihistaminic and anti-inflammatory effects?

3 MR. WARNER: Objection. The report speaks for
4 itself.

5 BY THE WITNESS:

6 A. And again, I understand both from
7 Dr. Schleimer and my own personal understanding of
8 antihistaminic responses, and I rely on Dr.
9 Schleimer for information about the
10 anti-inflammatory effects.

11 Q. And when you rely on your personal
12 understanding of the anti-inflammatory and
13 antihistaminic effects, were these effects known as
14 of June 2002?

15 A. The effects of antihistamines to effect
16 mast cells and histamine release and so forth at --
17 on mucosal surfaces was known in 2002. Various
18 antihistamines had been available. They may use
19 different mechanisms of action.

20 But the general limiting of histamine
21 release, the general limiting of perhaps other
22 secretory materials release was known, was available

1 from standard pharmacology texts. There were plenty
2 of products in the marketplace from an oral
3 antihistamine standpoint to understand their
4 activities.

5 Q. Did any of these texts refer to the amount
6 of azelastine that had to be delivered to have this
7 antihistaminic/anti-inflammatory effects?

8 A. Well, the text might not have. But I can
9 look at Patent '194 and get some of that
10 information.

11 Q. Did you look at the Astelin label?

12 MR. WARNER: At all?

13 BY THE WITNESS:

14 A. What do you mean did I look at?

15 Q. For this, does the Astelin label tell you
16 at what dose you'll get antihistaminic and
17 anti-inflammatory effects?

18 A. The Astelin tells what the FDA-approved
19 dose and dosing regimen is for the product or the
20 azelastine-containing product. And that was
21 demonstrated by the developers, and the FDA accepted
22 that that dose provides a safe and effective dose of

1 azelastine.

2 MR. WARNER: Rami signed off.

3 BY MS. EVERETT:

4 Q. Okay. I'm going to refer you to --
5 actually, it could be in any number. I don't want
6 to direct you. I'm happy to guide you, if you need
7 help.

8 You recall you've opined on the Cramer
9 reference?

10 A. Yes.

11 Q. And you're aware that Matthew Herpin
12 performed some tests on the Cramer reference?

13 A. Using the Cramer reference as a basis for
14 some of the tests, yes.

15 Q. And I think that you discuss that in your
16 reply report, if you need to refer to that.

17 A. It's the one that's open. Okay.

18 Q. In your report, you state that, Paragraph
19 42: By contrast, Dr. Herpin's tests were more
20 focused on characteristics that support a
21 formulation being developed into a commercial
22 product.

1 Do you see that?

2 A. That's what it states, yes.

3 Q. What tests did Dr. Herpin perform that you
4 thought focused on the product being developed into
5 a commercial product?

6 A. Well, I'm not going to give a complete
7 answer here because I'd like to refer back to
8 Dr. Herpin's report for all of the tests. But
9 certainly one of them that comes to mind are his
10 spray characterization tests.

11 (Donovan Exhibit Number 7 marked
12 for identification.)

13 BY MS. EVERETT:

14 Q. And I'm going to have the court reporter
15 mark as Donovan 7, Report of Matthew Herpin, Ph.D.
16 We have a number of exhibits too. I'm happy to pull
17 any of them. They're stapled separately. If you
18 just let me know you need them, I'm happy to get
19 them for you.

20 A. Okay.

21 Q. Dr. Donovan, first I have, if you can
22 identify -- Dr. -- strike that.

1 Let me start over. The exhibit that's
2 been marked Donovan 7, do you recognize that as the
3 report of Matthew Herpin we've been discussing?

4 A. Yes, I do.

5 Q. Can you point me to the tests you were
6 just discussing?

7 A. Let me familiarize myself with what's in
8 the report first.

9 Okay. And I'm going to focus on
10 Paragraph 7, since he gives a list of the tests that
11 he performed. And the tests that are primarily
12 focused on a product development approach for this
13 formulation are the test of sprayability; the
14 measure of pH days after preparation, and in
15 particular at least 7 days after; and the bulk
16 uniformity testing 7 days after; and visual
17 examination 14 days after are primarily tests that
18 would be conducted in a product development approach
19 to an activity but are not tests that would be
20 required in formulation development.

21 Q. What is the distinction between the
22 product development approach and the formulation

1 development approach?

2 A. I can formulate a composition and have that
3 administered immediately to an individual. Still
4 likely accomplish my goal of treating that patient.

5 If, on the other hand, I want to develop a
6 commercializable product that can be -- can undergo
7 transport, can remain on a shelf, can meet
8 particular tests defined by the FDA, that's a
9 product development approach and I need to conduct
10 tests appropriate to those requirements.

11 Q. And is it your testimony that it only -- a
12 person of ordinary skill would have only considered
13 whether a product could be formulated and
14 administered immediately?

15 A. It depends on the project goal. So a
16 person of ordinary skill in the art can consider a
17 lot of things about their activities. Some of them
18 may only reflect I'm making this so it can be used
19 in an hour. And in other situations, they're
20 formulating things that might have a desire to be
21 used over a 10-year period. It's dependent on the
22 particular drug, the desire for its future or its

1 use in the immediate sense to help further an
2 understanding of something.

3 Q. What would have a person of ordinary skill
4 as of June 2002 understood the project goal for
5 formulating Cramer Example III?

6 MR. WARNER: Objection. Lack of foundation.
7 Calls for speculation. The document speaks for
8 itself.

9 BY THE WITNESS:

10 A. Let's see. Let me find Cramer again.

11 MR. WARNER: I don't think you brought it out,
12 did you?

13 BY MS. EVERETT:

14 Q. I can get you Cramer if you need to see
15 Cramer.

16 MR. WARNER: Do you want to look at it?

17 THE WITNESS: Yeah, I would.

18 (Donovan Exhibit Number 8 marked
19 for identification.)

20 BY MS. EVERETT:

21 Q. I'm handing to the court reporter to be
22 marked as Donovan 8, APOTEX_AZFL0052951 through 960.

1 And, Dr. Donovan, do you recognize what's
2 marked as Donovan Exhibit 8?

3 A. Yes, I do.

4 Q. Is this the Cramer reference we've just
5 been speaking of?

6 A. Yes, it is.

7 Q. And my question was: What would a person
8 of ordinary skill as of June 2002 understand as the
9 project goal for formulating Cramer Example III?

10 MR. WARNER: Objection to the form of the
11 question. Lack of foundation. Calls for
12 speculation. The document speaks for itself.

13 BY THE WITNESS:

14 A. Again, you know, I don't know that there
15 was even a project associated with this discovery.
16 So at least as somebody might define a project with
17 a goal, this is a report that the inventors
18 discovered that you could combine these agents and
19 that they would, for the intent of providing
20 improved relief of symptoms generally associated
21 with either seasonal or perennial allergic
22 rhinoconjunctivitis. There's no mention of what

1 project this was part of.

2 Q. You stated earlier that many of
3 Dr. Herpin's tests were related to a commercial
4 product and, therefore, were inappropriate for
5 consideration in Cramer III. Is that correct?

6 MR. WARNER: Objection to the form of the
7 question. I think it mischaracterizes the
8 testimony.

9 BY THE WITNESS:

10 A. Yeah, what I believe I stated was that
11 Dr. Herpin conducted a number of tests that are not
12 simply testing the formulations that are described
13 or the formulation in Cramer III in particular, but
14 took the -- made the decisions to conduct a number
15 of additional tests that do not speak directly to
16 the formulation but, in many cases, speak to the
17 formulation's performance when joined with a spray
18 device or over a longer period of time than is even
19 described in Cramer.

20 Q. In Cramer, how -- what period of time
21 is -- strike that.

22 Does Cramer specify what period of time

1 should be considered for these formulations?

2 A. I don't recall Cramer making any statement
3 on an interval of utility for any of these
4 formulations.

5 Q. Is it your testimony that these examples
6 were meant to be made and delivered instantaneously?

7 A. My interpretation of these examples is
8 simply they're examples that you can formulate these
9 materials together for the intended use as
10 described.

11 Q. And are they intended to be used over a
12 longer period of time?

13 MR. WARNER: Objection to the form of the
14 question. Lack of foundation as to are they
15 intended. By whom.

16 BY THE WITNESS:

17 A. Yeah, I have no way of knowing what the
18 intention is. I know what's written. I know they
19 describe formulations that could be described for
20 use for topical nasal application.

21 Q. Do they -- Does Example III in Cramer
22 describe a formulation that could be prepared and

1 then used over a longer period of time, over an
2 instant?

3 MR. WARNER: Sorry. Over a longer period of
4 time or over an instant?

5 BY MS. EVERETT:

6 Q. Over an instant.

7 A. Cramer III simply provides an example of a
8 composition that can be prepared for the intended
9 use for topical nasal application. Cramer III
10 doesn't describe anything about the time frame over
11 which that composition would be used.

12 Q. Do you have an opinion regarding the time
13 frame over which the composition would be used?

14 MR. WARNER: Objection to the form of the
15 question. Lack of foundation and speculation to the
16 extent you're talking about "would be used."

17 BY THE WITNESS:

18 A. Yeah, I have no opinion on what the
19 inventors intended for the duration of time for this
20 composition to be used.

21 Q. Does Example III in Cramer use any
22 preservatives?

1 A. There are agents included in Example III
2 that are known to be used as preservatives.

3 Q. Are you referring to the benzalkonium
4 chloride?

5 A. I'm referring to both the benzalkonium
6 chloride and the ethylenediaminetetraacetic acid in
7 particular.

8 Q. And both of these are known to have
9 preservative qualities?

10 A. Yes, they are.

11 Q. And preservatives are known to increase
12 the shelf life of composition; is that true?

13 A. I don't know that I entirely agree with
14 that.

15 Q. Can you turn to Page 5 of the Cramer
16 reference, Line 16? There's a sentence, you see a
17 sentence that says: A pharmaceutically acceptable
18 preservative is generally employed to increase the
19 shelf life of the compositions of the present
20 invention?

21 A. I'll agree that it's generally employed to
22 do that. But I'm not sure in every single case that

1 the inclusion of a preservative is done in order to
2 prolong or -- let me get the word right -- increase
3 the shelf life, to increase the shelf life.

4 Q. Are you speaking generally or specifically
5 to the Cramer response?

6 A. Well, you asked me to respond regarding a
7 particular statement in Cramer, and I'm responding
8 that I agree with the statement that yes, they're
9 used generally to do that, preservatives are
10 generally used to do that. But there are instances
11 where I think the shelf life prolongation may not be
12 accomplished by the inclusion of preservatives, yet
13 other factors are accomplished by those, by the
14 inclusion of those materials.

15 Q. Do you have an opinion on whether Cramer
16 included benzalkonium chloride and ethyldimine --
17 I'm just going to say EDTA. So let me say that
18 again. Whether Cramer included EDTA and
19 benzalkonium chloride in Example III to increase the
20 shelf life?

21 A. Again, nothing in Example III describes
22 duration of use of the preparation. And Cramer, I

1 believe, included materials in these compositions
2 that would commonly be included in intranasal spray
3 dosage forms and is merely demonstrating this
4 composition is capable of being prepared and is a
5 unique composition.

6 Q. Do you have any reason to doubt that
7 Cramer included EDTA and benzalkonium chloride to
8 increase shelf life?

9 A. Again, I really have no idea why Cramer
10 included the materials that he did outside of these
11 are commonly used materials in nasal dosage forms.

12 Q. Would a person of ordinary skill as of
13 June 2002 reading Cramer Example III understand this
14 to be a nasal preparation that can be used longer
15 than the instant it is prepared?

16 A. I think a POSA, a formulator POSA would
17 anticipate that given the materials described in
18 Example III, that it could be used for a longer
19 period of time than a simple instant.

20 And I'll add one more thing regarding
21 Example III. I could take the time to read this
22 entire section, but I don't think anywhere in

1 Example III does Cramer suggest that it's
2 administered by a nasal spray. It's topical nasal
3 application. There are other ways of administering
4 to the nasal cavity, so there's ...

5 Q. Does that affect your opinion on whether
6 Cramer disclosed an application that could be used
7 longer than the instant it was prepared?

8 A. Again, I stated that a formulator POSA
9 would look at this composition and anticipate it
10 might be able to be used for a longer period of
11 time. But I have no way of knowing what the intent
12 of Cramer was when he made this composition.

13 Q. And I'm going to return to just the tests
14 that Dr. Herpin performed in Paragraph 7. Why do
15 you -- I believe earlier you stated that the test
16 that tests the sprayability was not a test for
17 formulation development; it was a test for
18 commercial development. Why is that?

19 A. Well, it's primarily a test for larger
20 scale or a number of batches of material as a
21 quality test characteristic. But if somebody
22 desires to administer a nasal spray, you should be

1 able to find a composition and container and spray
2 device that allow it to be sprayed. But the
3 extensive testing that Dr. Herpin did to
4 characterize those sprays is unnecessary to
5 demonstrate that the composition can be sprayed from
6 a spray pump device.

7 Q. When you say the extensive testing that
8 Dr. Herpin did to characterize those sprays, what
9 specifically are you referring to?

10 A. Well, do you have the actual appendix of
11 the visuals and the report that -- with the
12 numerical values that he reports?

13 (Donovan Exhibit Number 9 marked
14 for identification.)

15 BY MS. EVERETT:

16 Q. I'm handing to the court reporter,
17 Exhibit R, Pump Delivery Shot Weight Raw Data
18 Sprayability Check to be marked as Donovan 9.

19 Dr. Donovan, are these the tests you're
20 referring to?

21 A. They're some of the tests that I was
22 referring to. I seem to recall also seeing videos

1 of spray formations that Dr. Herpin used in his
2 analysis.

3 Q. And do you believe the video of the spray
4 formation is a test that would be performed in
5 formulation development?

6 A. It would be performed in product
7 development because it's a requirement for FDA
8 submission. But it would not necessarily be
9 performed during early formulation development
10 during composition development.

11 Q. Is the characteristics -- strike that.
12 And you understand that in the video,
13 Dr. Herpin videoed whether the spray came out as a
14 jet or a spray?

15 A. That's my general recollection, that you
16 could make some qualitative -- he drew some
17 qualitative descriptions of what the spray looked
18 like.

19 Q. And in your opinion, is it acceptable for
20 a nasal spray for allergic rhinitis to come out in a
21 jet?

22 A. Absolutely.

1 Q. And is it your opinion that a person of
2 ordinary skill would test whether a spray was a jet
3 before administering it to a human patient?

4 A. They -- If somebody were formulating for
5 immediate human use and they were using a spray
6 device, they would test to make sure that the
7 material came out of the spray device. They
8 probably observed what it looked like, and I would
9 assume that they would be -- they would make sure
10 that the volume delivered was the intended volume to
11 deliver the dose accurately.

12 Q. So when you said that the video spray
13 of -- strike that.

14 When you said that the video of the spray
15 was -- strike that again.

16 Earlier you said some of the tests related
17 to sprayability were excessive. Did you include the
18 video tests in that determination?

19 A. Well, I believe what I said was the testing
20 that Dr. Herpin conducted was far beyond what a POSA
21 formulator would conduct to both develop a
22 composition and potentially optimize the

1 composition.

2 Q. What tests would a POSA formulator in
3 June 2002 have conducted on Cramer -- Cramer Example
4 III to determine whether it was suitable for
5 administration to a human?

6 A. Suitability for administration would be
7 a -- the POSA formulator would want to know that the
8 materials could be delivered accurately and that the
9 composition was safe for administration to the
10 human.

11 Q. When you say "delivered accurately," what
12 do you mean?

13 A. Well, however it's administered, that the
14 amount administered contains the dose or the mass
15 amount of drug or drugs that was intended to be
16 administered.

17 Q. So it would be a test to determine the
18 dose that is administered to a human?

19 A. It would be a methodology to evaluate that
20 the amounts that were contained in the unit that was
21 administered contained the specified target amounts
22 of materials intended.

1 Q. And what tests would a POSA as of June
2 2002 have conducted to determine safety?

3 A. Well, typical safety testing is not
4 something that a POSA formulator is usually engaged
5 in directly. They oftentimes are working in
6 conjunction with others that, in the pursuit of
7 human use of a formulation, take that formulation
8 and do both in vitro and in vivo tests on it to be
9 at least comfortable that it would likely be safe if
10 a human were exposed to it. But those tests aren't
11 something a formulator typically does themselves.

12 Q. Would a POSA formulator as of June 2002
13 conduct -- strike that.

14 As -- what tests would a POSA formulator
15 as of June 2002 conduct on Cramer Example III to
16 determine whether it was -- the formulation
17 disclosed was pharmaceutically acceptable?

18 A. I believe that they would evaluate the
19 composition such that it had an acceptable
20 appearance in that one would anticipate that this is
21 a -- that some of the material is not completely
22 soluble in the vehicles and so you would anticipate

1 seeing solid material and you would anticipate a
2 fluid-like vehicle and you -- let's see.

3 Looking at the materials, you know, there
4 might be hopefully somebody -- well, I don't know.
5 I won't say that, that there is -- contains
6 materials that in 2002 were recognized as safe as
7 individual components and there is little
8 expectation on the part of a POSA formulator that
9 combining those materials in any way would then
10 result in an unsafe material being present.

11 So they would potentially simply make this
12 composition and probably -- well, depending on how
13 they are planning to actually administer it,
14 calibrate their administration system so that they
15 were sure that the intended dose to be administered
16 was administered from that delivery system.

17 Q. So to be clear, a POSA formulator in
18 June 2002, to determine whether Cramer Example III
19 was pharmaceutically acceptable would have conducted
20 a visual analysis, some type of safety analysis, and
21 some analysis to ensure that the amount of drug
22 delivered was the intended dose; is that accurate?

1 A. Well, the safety analysis is really a
2 composition mental check that a POSA formulator
3 would certainly check or select materials or would
4 have a preference to check or select materials that
5 were recognized as safe and use them at
6 concentrations that were recognized as safe.

7 And yes, indeed, there might simply be a
8 visual check of the formulation to make sure that it
9 appeared as anticipated and that there would be a
10 method developed to assure that however it was being
11 administered, that it was -- that it administered
12 the dose that was intended to be delivered from the
13 composition.

14 Q. And how would a POSA formulator as of June
15 2002 ensure that the dose that was intended to be
16 delivered was the actual dose that was being
17 delivered?

18 A. There are a number of ways that if you
19 absolutely wanted to characterize the absolute
20 amount of material that was in an individual dose,
21 you'd go and do chemical analysis.

22 On the other hand, most of the time if the

1 POSA formulator is satisfied that they've developed
2 a uniformly prepared composition such that any given
3 portion of it represents the same combination of
4 concentrations in materials that any other portion
5 of it has, then you can simply look at a volumetric
6 or a mass measurement of the unit to make sure
7 that -- and then project that it contains the
8 desired amounts of the materials.

9 Q. Okay. So a POSA formulator as of June
10 2002 wanted to determine that the amount of nasal
11 spray delivered in the intended dose could do a
12 chemical analysis or volumetric or mass measurement?

13 A. Uh-huh.

14 Q. Are there any other tests a POSA could
15 have undertaken to ensure that the dose being
16 delivered was what was intended?

17 A. There probably are, but those -- the ones I
18 stated are the ones that most likely come to mind.

19 Q. So to -- Sorry. Excuse me. Strike that.

20 So to determine whether a product was
21 pharmaceutically acceptable, we talked about the
22 visual analysis, the safety mental check and a check

1 on intended dosage. Are there any other tests a
2 POSA would have performed in 2002?

3 A. On Cramer III.

4 Q. To test whether it was pharmaceutically
5 acceptable.

6 A. I mean, clearly the POSA formulator has a
7 knowledge of what they define as pharmaceutically
8 acceptable. So whatever is part of their definition
9 certainly may add additional evaluations, but ...

10 Q. Are you saying that each POSA formulator
11 would have a different definition of what's
12 pharmaceutically acceptable?

13 MR. WARNER: Objection. Mischaracterizes the
14 testimony.

15 BY THE WITNESS:

16 A. Yeah, because there's not a given
17 definition of pharmaceutically acceptable. And so
18 pharmaceutically acceptable is, again, similar to
19 formulation. It's a combination of compromises from
20 perfect to acceptable.

21 And what you would compromise is you had to
22 undertake and how you weighed -- when you had

1 exceeded your limit on acceptability for a
2 particular compromise is a specific product
3 composition and formulator and intended use
4 question.

5 Q. Earlier you stated it would be acceptable
6 to have a nasal spray product that was administered
7 to humans come out as a jet. Do you recall that?

8 A. Yes, I did say that.

9 Q. Are you aware of any products that are
10 commercially available, nasal sprays, that come out
11 as a jet?

12 A. Yes.

13 Q. Which ones?

14 A. Zicam. And I believe Nascobal in its
15 original formulation. I don't know currently. But
16 it would be -- I think that would still be
17 considered close to, if you had a limited
18 vocabulary, a jet. And I'm not trying to be
19 offensive about anybody's vocabulary. But how you
20 define those spray shapes, we have spray and jet.

21 Q. Is there a different -- don't worry. I'm
22 not offended. I don't have clearly a pharmaceutical

1 formulator's vocabulary. But is there a different
2 term you would use to describe Zicam and Nas- --

3 A. Nascobal. And I'll be honest. It's been a
4 while since I've looked at Nascobal, so I don't have
5 a good description of what it appears as a nasal
6 administration device. But the last time I looked
7 at Zicam nasal spray, it was a jet.

8 Q. So jet it is, I guess.

9 A. I mean, it's a commonly used descriptor of
10 something that doesn't form a broad cone with
11 discernible droplets.

12 Q. Is pH something that a person of ordinary
13 skill would test to determine whether a product,
14 specifically Cramer III, is pharmaceutically
15 acceptable?

16 A. Certainly. And somebody could have checked
17 the pH of Cramer III, yet Cramer III has some
18 materials in it that would cause a pH measurement by
19 typical pH measurement means, which would either be
20 a standard pH electrode or a pH paper. It's got
21 materials in it that are going to cause that reading
22 to be inaccurate.

1 And so depending on what specifically the
2 formulator desired to know about what we commonly
3 define as pH, which is the concentration of
4 hydronium ion and what they were intending to
5 describe based on the measurement they took with
6 those conventional apparatus, is up to the
7 formulator to decide how meaningful that test would
8 have been.

9 Q. And when you say it's got materials in it
10 that's going to cause the reading to be inaccurate,
11 are you talking about Cramer Example III?

12 A. I'm talking about Cramer Example III, yes.

13 Q. And what material are you referring to
14 specifically?

15 A. Any of the non-aqueous liquid vehicles in
16 that composition will affect the measurement of pH
17 by a pH electrode. It may not effect it as much
18 from pH paper, but ionization is suppressed in the
19 presence of glycerin and other miscible, non-aqueous
20 solvent vehicles. And so then we have to seriously
21 consider what is it that our pH number is telling us
22 because it's not an accurate depiction of what the

1 hydronium ion concentration in that system is.

2 Q. By what magnitude would this affect the pH
3 measurement if you took it by electrode?

4 A. I wasn't asked to provide that opinion, and
5 I sitting here today can't tell you.

6 Q. Dr. Herpin performs a number of pH tests;
7 is that correct?

8 A. Uh-huh.

9 Q. And in your report, you don't dispute the
10 pH numbers, do you?

11 A. Not specifically, no.

12 Q. Okay. And is that still your opinion
13 today?

14 A. That my opinion is to not dispute those pH
15 numbers?

16 Q. Yes.

17 A. They are what Dr. Herpin reported them to
18 be, I assume.

19 MR. WARNER: Uma, is this a good time for a
20 break?

21 MS. EVERETT: Sure.

22 THE VIDEOGRAPHER: This marks the end of DVD

1 No. 4. We are off the record at 2:52 p.m.

2 (A short break was taken.)

3 THE VIDEOGRAPHER: Here begins DVD No. 5. We
4 are on the record at 3:06 p.m.

5 BY MS. EVERETT:

6 Q. Welcome back.

7 A. Thanks.

8 Q. Dr. Donovan, do you know Ramprakash
9 Govindarajan?

10 A. Yes, I do.

11 Q. How are you -- strike that.
12 How do you know him?

13 A. He works for the same organization I do.
14 He's an assistant professor and a staff member in an
15 area of our college called the University of Iowa
16 Pharmaceuticals.

17 Q. Have you ever researched together?

18 A. No. We've talked about potential funding
19 strategies together, but we've never conducted the
20 same research project together.

21 Q. Have you ever published anything together?

22 A. No.

1 Q. Have you spoken to him about this
2 litigation?

3 A. I know he's involved in the litigation
4 after I read his report, but I haven't spoken to him
5 about anything he did involving it.

6 Q. I'm going to have you turn to
7 Paragraph 187 of your opening report. The
8 concluding sentence on 187, you say: To the
9 contrary, using knowledge well within the grasp of a
10 POSA in June 2002, Example III can be made with ease
11 and results in a formulation that is in every
12 measured respect fully suitable as a pharmaceutical
13 for administration as an intranasal spray.

14 A. Okay. Yes, I'm sorry. I was ahead or
15 above in the paragraph. I was having a hard time
16 finding that. That's fine. Yes.

17 Q. Okay. And actually, it might be better,
18 we can start earlier in the paragraph. Earlier in
19 the paragraph, you say: I thus disagree with
20 Ms. Malhotra's position that Cramer III's example --
21 I'm going to start over. Sorry.

22 At the beginning of Paragraph 187, you

1 say: I thus agree with Ms. Malhotra's position that
2 Cramer's Example III is inoperable and unacceptable
3 as a pharmaceutical formulation in a form suitable
4 for nasal administration.

5 And then you go on to state the sentence
6 we just looked at: To contrary, using knowledge
7 well within the grasp of a POSA in June 2002,
8 Example III can be made with ease and results in a
9 formulation that is in every measured respect fully
10 suitable as a pharmaceutical for administration as
11 an intranasal spray.

12 Do you see that?

13 A. Uh-huh.

14 MR. WARNER: Uma, you were racing.

15 MS. EVERETT: I'm sorry?

16 MR. WARNER: You were racing.

17 MS. EVERETT: Oh, I'm sorry. I was just so
18 happy to get the sentence out almost coherently.
19 Sorry about that.

20 BY MS. EVERETT:

21 Q. Do you agree with that sentence today?

22 A. Yes, I do.

1 Q. Okay. What did you mean that Cramer III
2 results in a formulation that in every measured
3 respect is fully suitable as pharmaceutical for
4 administration as an intranasal spray?

5 A. Well, I meant that based on the report of
6 both Ms. Malhotra -- we're going to call him Dr. Ram
7 because it's just so much easier on us, even though
8 I'm about the only one in our unit that can say
9 Govindarajan. That he -- that the -- I lost my
10 frame of reference.

11 That based on the measures that they took
12 to characterize their attempts at Cramer III, that I
13 believe it represents a -- something that's fully
14 suitable for pharmaceutical administration by an
15 intranasal spray.

16 Q. And so you're referring just to the tests
17 that were conducted?

18 A. I'm referring to the information that was
19 provided from their testing and based on that,
20 drawing that conclusion.

21 Q. And so you draw your conclusion based on
22 just the tests that were performed by Ms. Malhotra

1 and Dr. Ram?

2 A. Well, previous to that, I mean, I will
3 recognize we've already discussed that I find the
4 composition in Cramer III to be made of materials
5 that are recognized as safe and at doses and
6 concentrations where they are recognized as safe, so
7 I have no reason to believe that that -- those
8 characteristics of the formulation are -- would not
9 be suitable.

10 And then the Paragraph 187 is really
11 describing in context the performance
12 characteristics of that formulation once it's
13 matched into a spray bottle system that has a pump
14 capable of administering a nasal spray. And based
15 on the quality descriptions provided by the two
16 investigators, I think that it meets those
17 performance characteristics, still tell me that it's
18 suitable as a pharmaceutical for administration.

19 Q. And neither -- strike that.

20 And Dr. Govindarajan didn't test pH; is
21 that correct? Or strike that. Let me ask it
22 differently.

1 Dr. Govindarajan did not report a pH for
2 his formulations; is that correct?

3 A. You know, I don't recall all of the data
4 that he reported. But I'm -- I guess I'm willing to
5 believe, if you want me to, that he didn't; or you
6 can provide the data, and I'll see if I find it.

7 MS. EVERETT: I'm handing to the court
8 reporter, Expert Report of Ramprakash Govindarajan
9 Ph.D., to be marked as Donovan Exhibit 10.

10 (Donovan Exhibit Number 10 marked
11 for identification.)

12 BY THE WITNESS:

13 A. In my brief review of this, I don't see any
14 place where he reports pH.

15 Q. If the formulations created in Dr.
16 Govindarajan's report had a pH of 3, would that be a
17 formulation that is fully suitable as a
18 pharmaceutical for administration as an intranasal
19 spray?

20 A. In this composition in particular, you'd
21 have to tell me how that pH of 3 was measured, and
22 I'd have to evaluate whether that was a meaningful

1 pH value that would tell me something about the
2 safety of that particular formulation.

3 Q. Would a person of ordinary skill as of
4 June 2002, would they believe that the formulations
5 disclosed in Govindarajan report if they had a pH of
6 3, would they view it as a pharmaceutical that was
7 fully suitable for administration as a nasal spray?

8 A. A POSA in 2002 should have sufficient
9 background regarding ionic equilibria and pH to have
10 a knowledge that in this composition that the number
11 read off of a pH meter may not accurately report the
12 hydronium concentration.

13 Q. If Dr. Govindarajan reports the pH of 3,
14 do you believe he has the skills necessary to report
15 an accurate pH?

16 A. Well, I think he has the skills certainly
17 to tell you the reading that came from the
18 instrument he used to -- that it gave a value for
19 pH. The interpretation of that value and its
20 pharmaceutical appropriateness is something other
21 than what just reporting a value is in terms of what
22 a POSA does with that value.

1 Q. So it's your testimony that a POSA would
2 take pH and then need to consider more than just the
3 number?

4 A. Absolutely.

5 Q. So is that -- was that understood in
6 June 2002?

7 A. Yes.

8 Q. Can you point me to a reference where it
9 states that?

10 A. I, at this point, can't point you to a
11 reference that would directly state that.

12 Q. I'm going to have you turn back to Donovan
13 5. Anywhere in Donovan 5 which we referred to
14 earlier as one of your sources and one of your
15 sources on appropriate pH, does that reference
16 explain what more should be considered for pH
17 besides the number?

18 A. The reference itself doesn't directly
19 contain that information. But again, a POSA has the
20 academic knowledge regarding what the definition of
21 pH is and has the opportunity to understand how
22 measurements of pH come about and need to make --

1 need to know or should be applying the measurement
2 of and the system that they're measuring
3 appropriately in order to evaluate the value that's
4 obtained correctly.

5 Q. So they, a POSA, would need to know how to
6 apply the measurement that is obtained? Is that --

7 A. No. The references tell us the pH range.
8 And one interprets that reference as what a
9 hydronium ion concentration in water would be, what
10 the appropriate range or what a reasonable range or
11 accepted range or -- I don't remember what Dr. Allen
12 used to describe the range. But whatever adjective
13 he used, we'll go with that. And that's a range of
14 essentially translated hydronium ion concentration,
15 and that's what a POSA understands that value to
16 mean.

17 Now, how a POSA interprets a number
18 obtained from a system where they're aware that that
19 system doesn't accurately measure the hydronium ion
20 concentration is up to the POSA to interpret
21 correctly for their particular purpose of why
22 their -- why that value is important to them.

1 Q. Where in your reports have you disclosed
2 that opinion?

3 A. That's -- It's really not an opinion. It's
4 what pH is, and I didn't feel that I needed to
5 explain the basics of pH in my report.

6 Q. You do explain pH in your report, though,
7 do you?

8 A. Right. I refer to Dr. Allen's description
9 of what a formulator POSA would use as a range,
10 target range for pH. But it didn't require me to
11 then redefine "and here's what I mean by pH, and
12 this is what pH is."

13 Q. And you did not anywhere disclose that the
14 reading could not -- may not be accurate depending
15 on the type of pH reading; is that correct?

16 A. Well, the value is always accurate. It's
17 the interpretation of that value being equivalent to
18 the hydronium ion concentration or being something
19 else.

20 Q. And you did not disclose that in your
21 report?

22 A. I did not disclose that in my report

1 because that's just a statement of fact. And you
2 have to know what equipment is being used to measure
3 pH. And in many places that's not described in
4 patents or anyplace else, so I don't have any basis
5 for determining what that number means reflective of
6 a useful pH range, except in my own POSA balance of
7 combinations of attributes of a composition that I
8 would find to be pharmaceutically acceptable.

9 Q. And in your report, and I could refer you
10 to some paragraphs, nowhere do you say -- strike
11 that.

12 So Dr. Herpin reports pHs in his
13 formulations lower than 4; is that correct?

14 A. I believe so, yes.

15 Q. Some are in their 2s, and some are in
16 their 3s, correct?

17 A. Does this one have the pHs? It's got spray
18 weight.

19 MR. WARNER: I don't know if she gave you the
20 one where those are reported.

21 BY MS. EVERETT:

22 Q. I can give you the one with pHs, if you

1 need it. I'll have these marked all at once.

2 MS. EVERETT: So I'm handing to the court
3 reporter Exhibit B, Malhotra Preparations. It's
4 part of Matthew Herpin's report to be marked as
5 Donovan 11.

6 (Donovan Exhibit Number 11 marked
7 for identification.)

8 MS. EVERETT: Handing to the court reporter
9 Exhibit C, Cramer Example I, which is an exhibit of
10 Matthew Herpin's report, to be marked as Donovan 12.

11 (Donovan Exhibit Number 12 marked
12 for identification.)

13 MS. EVERETT: Handing to the court reporter,
14 Exhibit D, Dr. Govindarajan Process, an exhibit in
15 Matthew Herpin's report, to be marked as Donovan 13.

16 (Donovan Exhibit Number 13 marked
17 for identification.)

18 BY MS. EVERETT:

19 Q. And, Dr. Donovan, these are the pH reports
20 for Dr. Herpin's tests, I believe. They include a
21 number of things including pH; is that right?

22 A. Yes, I see pH reported on a number of the

1 documents.

2 Q. And all of the pH in these documents are
3 between 2 and 3; is that correct?

4 A. Yes, that's correct.

5 Q. And nowhere in your reports have you said
6 that this is a pH for the Cramer formulation Example
7 III between 2 and 3 -- strike that. I'm going to
8 start the sentence over.

9 And nowhere in your reports have you said
10 that a pH of 2 to 3 for Cramer Example III is an
11 acceptable pH; is that correct?

12 MR. WARNER: Objection. The report speaks for
13 itself.

14 BY THE WITNESS:

15 A. I think I'll preface, I see pH reported
16 here, but I don't see any indication of what methods
17 were used to measure pH or what equipment was used,
18 so I accept the numbers. But I'm not entirely sure
19 how I am to interpret those pH values.

20 And to directly answer your question, there
21 is no direct statement in my expert report or
22 rebuttal report regarding those specific values.

1 Q. Nor did you say in your expert report you
2 were unable to interpret the pH numbers; is that
3 correct?

4 MR. WARNER: Same objection. The reports speak
5 for themselves.

6 BY THE WITNESS:

7 A. I did not highlight that in my expert
8 report.

9 Q. Are you saying today that you are unable
10 to interpret these pH numbers?

11 A. I am saying that I don't know how these pH
12 numbers were measured. And while they're labeled
13 pH, I know not to interpret them to tell me that
14 they represent exactly the hydronium ion
15 concentrations in the system being measured.

16 Q. Are you able to opine today whether a pH
17 as reported by Dr. Herpin of 2 to 3 is an acceptable
18 pH for Cramer Example III?

19 A. Well, it is whatever Dr. Herpin reported as
20 the pH for Cramer Example III, so I'm willing to
21 accept that that was the numerical value using
22 whatever equipment it is that he used to obtain that

1 pH. But what do you mean by -- it's an acceptable
2 value. It's what he measured.

3 Q. Is it a pharmaceutically acceptable value?

4 A. The value of the pH and what the pH -- the
5 necessity to control pH or sometimes limit
6 excursions of pH in a pharmaceutical formulation is
7 more complicated than just the number. So one
8 doesn't determine the acceptability or
9 non-acceptability of a pharmaceutical preparation
10 based only on a numerical value reported for the pH.

11 Q. What else would you need in addition to
12 the numerical value?

13 A. I would need information about what else is
14 in the composition, how often it's going to be used,
15 where it's being applied, whether there are any --
16 well, where it's going to be applied is going to
17 tell me a number of things about how that
18 formulation will be modified by the body.

19 Q. For a nasal spray that is to be
20 administered twice a day for 2 months, is a pH of 2
21 to 3 acceptable?

22 A. I would say you have to do the testing to

1 find out. There's not -- there's not an abundance
2 of literature available or reports available in --
3 to either explain that it is or that it is not.

4 Q. In this process, I've lost my notes.

5 And I'm going to go to your opening
6 report, Paragraph 185. You state -- and this is in
7 relation to Dr. Govindarajan's testing -- I can draw
8 several conclusions from his work. First, he made a
9 more accurate replication of Example III than
10 Ms. Malhotra did in as far as he used EDTA instead
11 of disodium EDTA.

12 A. Yes.

13 Q. Is that still your opinion today?

14 A. Yes. Based on what I read, yes.

15 Q. And is that because -- What do you mean
16 it's a more accurate replication of Example III?

17 A. Example III states as its component,
18 ethylenediaminetetraacetic acid, but I'm going to
19 check that to make sure. Why do I not find what I'm
20 looking for? Not finding papers is contagious.

21 Q. Let's spread it next to Kevin.

22 A. There we go. Okay. Cramer Example III

1 states the composition contains
2 ethylenediaminetetraacetic acid, which I recognize
3 to be abbreviated frequently as EDTA.

4 Q. And then is it your testimony the more
5 modifications one makes to Cramer, the less accurate
6 of a replication it is?

7 MR. WARNER: Objection to the form of the
8 question. It mischaracterizes the record.

9 BY THE WITNESS:

10 A. And I think it depends entirely on what --
11 what modifications might be -- you might be
12 concerned with versus what's described in Cramer
13 Example III.

14 Q. Would you -- Do you view the modification
15 of disodium EDTA versus EDTA as a significant
16 modification?

17 A. Well, it's chemically significant. It will
18 have an influence on the -- on the composition
19 itself. Do I believe that it's significant
20 regarding EDTA's ability to be effective as a
21 preservative? Probably not.

22 Q. When you say it's chemically significant,

1 is that because the change will affect the
2 characteristics of the composition?

3 A. Yes.

4 Q. Is any change that will affect the
5 characteristics of a composition significant?

6 A. It depends on what that change is and the
7 magnitude of the change.

8 Q. I'm going to have you turn back to the
9 Govindarajan report. And if you can look to
10 Paragraph 9 of his report.

11 A. Okay.

12 Q. Did you contribute in any way to the tests
13 that were conducted in Dr. Govindarajan's report?

14 A. No. I was unaware he was even performing
15 those tests.

16 Q. Did -- strike that.

17 At any time did you suggest certain tests
18 should be conducted to determine whether Cramer III
19 is pharmaceutically acceptable?

20 A. Did I suggest to whom?

21 Q. To Apotex, to counsel.

22 MR. WARNER: And I'll let you answer the

1 question, although only to the extent that it's
2 disclosed in any of the reports. Otherwise, that
3 would be an off the -- an undiscoverable
4 conversation.

5 BY MS. EVERETT:

6 Q. Yeah. I'm trying to understand what
7 you -- if you were performing these tests, what you
8 would have considered necessary. So just with that
9 background ...

10 MR. WARNER: Sorry. Can you say the question
11 again.

12 BY THE WITNESS:

13 A. It would be better for you to ask that
14 specifically, I guess.

15 Q. Well, I'm going to go back to my original
16 question.

17 At any point, did you suggest any tests
18 should be conducted of Cramer Example III?

19 A. I don't recall making any specific
20 suggestion of that.

21 Q. Earlier today you testified that a product
22 can be a jet and still be pharmaceutically

1 acceptable. Do you recall that?

2 A. Yes, I recall that.

3 Q. Do you know why Dr. Govindarajan would
4 then determine whether his formulations sprayed as a
5 jet or a spray if that didn't affect pharmaceutical
6 acceptability?

7 MR. WARNER: I caution you not to speculate.

8 BY THE WITNESS:

9 A. Yeah, I -- Dr. Govindarajan wrote down
10 observations in his data book. What he chose to
11 write was his choice.

12 Q. And -- But I'm referring to what
13 observations he was asked to make. Do you see in
14 Paragraph 9, if I was able to make the
15 pharmaceutical formulation as described in Example
16 III, I was asked to make the following observations?

17 A. Uh-huh.

18 Q. And do you have any insight into why if
19 that's not -- does not -- a jet or a spray does not
20 affect pharmaceutical acceptability, why he would
21 have tested that?

22 MR. WARNER: Objection to the form of the

1 question. I caution you not to speculate about why
2 he did or didn't do some things.

3 BY THE WITNESS:

4 A. Yeah, I wasn't part of these instructions,
5 I take his report and the information that he has
6 written into account when I form my opinions in this
7 matter.

8 Q. When did you first see Dr.
9 Govindarajan's -- the results of Dr. Govindarajan's
10 Cramer testing?

11 A. At the time that I was preparing -- Let's
12 see. Okay. So at the time I was preparing my
13 expert rebuttal report is the time at which I was
14 provided Dr. Govindarajan's opening report.

15 Q. I think you made reference in your opening
16 report as well. So if you want to look at that
17 report and see if it provides you any insight.

18 A. Okay. Then I saw it shortly before I
19 completed my expert report.

20 Q. Did you ask for any additional tests to be
21 performed on the formulations Dr. Govindarajan
22 created?

1 A. I saw his report, similar to other reports.
2 I typically don't -- I wasn't part of asking him to
3 do the work to begin with. I didn't even consider
4 asking him to do anything else.

5 Q. Do you -- and -- strike that.

6 Looking through Dr. Govindarajan's report,
7 do you have any evidence of whether the formulation
8 disclosed in the report would provide a nasal spray
9 that had uniform dosing?

10 MR. WARNER: 10.

11 THE WITNESS: Thank you.

12 MR. WARNER: Can I have the question back too?

13 BY MS. EVERETT:

14 Q. Sure. Looking through Dr. Govindarajan's
15 report, do you have any evidence that the
16 formulation disclosed would be a nasal spray that
17 had uniform dosing?

18 A. Well, I've gotten as far as Page 7 in
19 Dr. Govindarajan's lab book, and I have found the
20 conclusion that I was looking for, at least
21 regarding his first preparation, that it's a uniform
22 suspension product and that I would, as a POSA,

1 anticipate that since it was a uniform suspension
2 product that, as dosed as a uniform suspension
3 product, that it would have -- and I'm trying to
4 remember the exact question terminology you used,
5 but I would anticipate it was -- it contained all of
6 the components throughout the mixture in equal
7 concentrations at each point and that it would -- it
8 would deliver a reproducible dose as that uniform
9 suspension.

10 Q. So Dr. Govindarajan's observation was made
11 on visual inspection; is that correct?

12 A. That's correct.

13 Q. And is visual inspection sufficient to
14 determine whether all of the components throughout a
15 mixture deliver concentrations in an equal
16 reproducible dose?

17 A. It's suggestive that for simple
18 experimentation, that that would probably be
19 acceptable. But it's not sufficient to prove that
20 it's a uniform and equal dose of material.

21 Q. So you can't actually conclude based on
22 Dr. Govindarajan's visual observation alone that the

1 dose, that the -- strike that.

2 So you can't conclude based on
3 Dr. Govindarajan's visual observation alone that
4 the formulations in his report actually provide a
5 uniform dose?

6 MR. WARNER: Objection. Mischaracterizes her
7 testimony.

8 BY THE WITNESS:

9 A. Well, I'm also going to look at a couple
10 other things in addition to respond to that
11 question. And there's -- I don't see definitive
12 proof in Dr. Govindarajan's reports that allows me
13 to say with absolute certainty that each spray would
14 contain the -- would contain equivalent amounts of
15 the materials prepared in the composition.

16 Q. Dr. Donovan, in your report you comment on
17 some testing performed by MedPointe Pharmaceuticals.
18 Do you recall that?

19 A. Could you say specifically what comments,
20 about what testing to help me remember?

21 Q. Sure. It's contained in your rebuttal
22 report, I believe. And it's MedPointe. But I think

1 in places in your report, you might refer to it as
2 Meda, so that might be more familiar to you.

3 A. Yeah, and I knew who you were asking about.
4 The content of the specific comments I wanted to
5 narrow down.

6 Q. Do you recall that in your report?

7 A. I'm looking at some of the report where I
8 have some analysis, and I recall there's comments
9 about work that they conducted, yes.

10 Q. Okay. Great.

11 MS. EVERETT: Handing to the court reporter to
12 be marked as Donovan 14, a document bearing the
13 Bates stamp MEDA_APTX01645706 through 07.

14 MR. WARNER: What was the exhibit number again?

15 MS. EVERETT: 14.

16 (Donovan Exhibit Number 14 marked
17 for identification.)

18 BY THE WITNESS:

19 A. Okay.

20 Q. Do you recognize -- strike that.

21 Dr. Donovan, do you recognize the exhibit
22 marked Donovan 14?

1 A. Yes, I do.

2 Q. What is it?

3 A. It is as titled, the feasibility assessment
4 plan for do you want me to say MedPointe or Meda?

5 Q. Either is fine.

6 A. For their Astelin/Flonase product, which I
7 understand to really mean combination of azelastine
8 and fluticasone propionate.

9 Q. And you opine on this document; is that
10 correct?

11 A. Yes, I do.

12 Q. You note that there are three plans, Plan
13 A, Plan B, and Plan C in this document?

14 A. Yes.

15 Q. And is it your understanding that
16 MedPointe attempted Plan A when it developed --
17 attempted to develop an azelastine fluticasone
18 product?

19 MR. WARNER: You can go ahead and answer. I'll
20 just remind you, if you need to refresh yourself in
21 your report, you're free to do that.

22 BY THE WITNESS:

1 A. Okay. But my opinion is that MedPointe
2 attempted part of Plan A, and I don't recall that
3 there was anything in anything I reviewed that
4 indicated they attempted anything about Plan B or
5 Plan C.

6 Q. And it's your testimony, I believe, that
7 they should have gone on to Plan B and Plan C; is
8 that accurate?

9 A. No, that's not accurate. My testimony --
10 Well, let's go to the section where I'm actually --
11 I've written what I wanted to communicate. From
12 what I can recall and find in my report, I describe
13 how MedPointe addressed step 1 in their Plan A. But
14 they don't describe clearly all of the work they may
15 have done or should have done to complete step 2;
16 and there's certainly nothing describing -- nothing
17 in their reports describing what they did to get to
18 step 3.

19 Q. Just to be clear, I think you're on
20 Plan A?

21 A. Yes, I'm on Plan A.

22 Q. I think my question was a little bit

1 different. It was: Is it part of your opinion that
2 MedPointe should have also attempted Plan B and
3 Plan C?

4 A. Well, in my opinion, I think I describe
5 that they identified three plans, and they failed to
6 address completely any of them. But I didn't take a
7 directive approach in what they should have done. I
8 acknowledged what they did, which does not
9 completely address any of the plans they describe.

10 Q. In Plan B, the first step is identify a
11 water-soluble corticosteroid compatible with
12 azelastine hydrochloride. As of June 2002, what
13 would a POSA have identified as a water-soluble
14 corticosteroid compatible with azelastine
15 hydrochloride?

16 MR. WARNER: Objection. Beyond the scope of my
17 report.

18 BY THE WITNESS:

19 A. I wasn't asked to provide an opinion on
20 that, but there were water-soluble corticosteroids
21 available in 2002.

22 Q. I'm going to have you turn to Paragraph 20

1 of your report.

2 MR. WARNER: The rebuttal?

3 MS. EVERETT: Yes.

4 BY MS. EVERETT:

5 Q. Here you say: MedPointe's Dr. Kale came
6 up with three different approaches for making the
7 combination. Do you see that?

8 A. Yes. And it's my recollection that Donovan
9 14 is Dr. Kale's document. Right?

10 Q. Yes. And are you on Paragraph 20?

11 A. I'm on Paragraph 20.

12 Q. You go on to state two of them, and I
13 believe "them" is the approaches, Plan B and Plan C,
14 two of them were apparently never tried by
15 MedPointe, so we cannot know whether they would be
16 successful using them.

17 A. That's what it says, yes.

18 Q. You say: My opinion, however, is that
19 they would have been successful because making the
20 proposed combination formulation is not difficult
21 for a POSA as I explained in my opening report.

22 A. Yes.

1 Q. But the very fact that Dr. Kale was aware
2 of three possibilities reflects the numerous
3 formulation options available.

4 Is that still your opinion?

5 A. That is still my opinion.

6 Q. So it is your opinion that -- am I to
7 understand that options 2 and 3 would have been --
8 strike that.

9 Am I to understand your opinion is that
10 Plan B and Plan C would have been successful because
11 making the proposed combination is not difficult for
12 a POSA?

13 MR. WARNER: Objection to the form of the
14 question. Vague as to successful.

15 MS. EVERETT: I'm using Paragraph 20 of Dr.
16 Donovan's report.

17 BY THE WITNESS:

18 A. My opinion and my statement is that a POSA
19 would accept the ability to successfully formulate
20 azelastine with a corticosteroid using Plan A,
21 Plan B, and Plan C and the variety of materials
22 available for formulation.

1 Q. So --

2 A. And it was demonstrated that some version
3 of a plan was successful. And there's no reason to
4 believe that Plan B or C which weren't attempted or
5 Plan A if it had been fully completed would not have
6 been equally successful.

7 Q. So then back to my question on Plan B.
8 Can you identify a water-soluble corticosteroid
9 that's compatible with azelastine hydrochloride?

10 A. I can identify water-soluble
11 corticosteroids that were -- that I'm vaguely aware
12 of that I would anticipate would be compatible with
13 or I would have no reason to anticipate it would not
14 be compatible with azelastine hydrochloride.

15 Q. And would a POSA have been able to
16 identify these water-soluble corticosteroids that
17 were compatible with azelastine hydrochloride as of
18 June 2002?

19 A. They were chemically available, they were
20 well known in the repertoire of corticosteroids. I
21 would anticipate a POSA would be able to find those.

22 Q. What are the water-soluble corticosteroids

1 that were compatible with azelastine hydrochloride?

2 A. Again, I wasn't really asked to provide an
3 opinion on which ones, but in 2002, there were
4 phosphate prodrugs of corticosteroids that are
5 injected into people and they're in solution
6 formulations. So they are water-soluble to some
7 extent, solubility being in the eye of the beholder,
8 how much material you need to be soluble.

9 Q. So these are phosphate prodrugs; is that
10 what you --

11 A. Of corticosteroids, yes.

12 Q. Okay. Had they been used in allergic
13 rhinitis?

14 A. I'm -- I have no way of knowing that.

15 Q. And these phosphate prodrugs, they are
16 separate from fluticasone propionate; is that
17 correct?

18 A. Fluticasone propionate is not recognized as
19 a water-soluble prodrug or as a water-soluble
20 phosphate prodrug.

21 Q. Are there any other water-soluble
22 corticosteroids that were compatible with azelastine

1 as of June 2002?

2 A. I'd have to consider the full body of
3 corticosteroids that were known in 2002 and evaluate
4 their water solubilities. Sitting here today, I'm
5 at a loss. I wasn't asked to provide an opinion
6 about the availability of them, and I -- but I do
7 know that there were some available.

8 Q. Well, your opinion in Paragraph 20 is that
9 Plan B would be successful?

10 A. Yes.

11 Q. So what drug would a POSA have selected?

12 MR. WARNER: Objection. Asked and answered.

13 BY THE WITNESS:

14 A. A POSA, me as a POSA, I would initially
15 select a phosphate prodrug corticosteroid.

16 Q. Are there any others that a POSA would
17 have selected?

18 A. That's -- that would be my starting point.
19 And I would reflect on whether I needed to select
20 something else based on the results of my initial
21 formulation attempts.

22 Q. I'm going to have you turn to Plan C.

1 A. Okay.

2 Q. The first step says: Increase the
3 solubility of fluticasone propionate by various
4 solubility enhancement technologies. How would one
5 go about enhancing the solubility of fluticasone
6 propionate?

7 A. Using various solubility enhancement
8 technologies, one would evaluate appropriate
9 technologies and apply them and/or evaluate the
10 increase in solubility of fluticasone propionate in
11 the presence of those systems.

12 Q. And are you aware of any studies or
13 literature disclosing, as of June 2002, methods to
14 increase the solubility of fluticasone propionate?

15 A. The solubility of fluticasone propionate in
16 what compared to what?

17 Q. Well, here it says increase the solubility
18 of fluticasone propionate.

19 A. Okay.

20 Q. So I'm referring to that.

21 A. And are we increasing it in the Flonase
22 formulation, or are we increasing it in the proposed

1 combination product? Or I'll tell you where my
2 frame of reference is. You can ask further
3 questions, if you'd like.

4 So I read that as to increase the aqueous
5 solubility of fluticasone propionate by using
6 various solubility-enhancement technologies. And
7 there's information in the fluticasone propionate
8 Flonase label that leads me directly to at least
9 one, and if not more than one, potential method.
10 And it tells me what materials fluticasone
11 propionate is freely soluble in, which is more
12 soluble than practically insoluble. And I may
13 choose to look at some of those materials or
14 technologies around those materials to increase the
15 solubility of fluticasone propionate.

16 Q. And in addition to looking at the Flonase
17 label, what other literature or steps would you
18 consult to increase the solubility?

19 A. A POSA would likely look at literature that
20 was available, whether it be other patent
21 literature, whether it be publications about
22 fluticasone propionate and its chemical properties

1 and its known solubilities or chemical behaviors and
2 match those to what the POSA was aware of for
3 various solubility enhancement technologies.

4 Q. How would increasing the solubility of
5 fluticasone propionate affect its effectiveness?

6 A. Well, the only thing that's effective about
7 fluticasone propionate is whatever fluticasone
8 propionate is in solution at the receptor where it's
9 acting, so I'm not sure I understand about --
10 increasing solubility just means there's drug in
11 solution that can act at the receptor, and it means
12 that it will be effective.

13 Q. So you don't understand that it would --
14 you don't understand -- strike that.

15 So you don't believe that increasing
16 solubility of fluticasone propionate would affect
17 its effectiveness?

18 A. What do you mean by "its effectiveness"?

19 Q. The effectiveness of fluticasone
20 propionate when administered to a person.

21 A. How much fluticasone propionate is being
22 administered to that person? And what is its

1 solubility in the vehicle it's being administered
2 in?

3 Q. Would solubility of making fluticasone
4 propionate, make -- if a hundred milligrams of
5 fluticasone propionate was administered, would it be
6 less effective if it was -- if you would increase
7 the solubility?

8 A. Okay. You need to be quantitative. If
9 there's a hundred milligrams administered and a
10 hundred milligrams is in solution in the vehicle,
11 then a hundred milligrams is available to be
12 effective. If we increase the solubility and still
13 administer a hundred milligrams and a hundred
14 milligrams is in solution, then it's the same
15 effect.

16 Q. Would increasing the solubility of
17 fluticasone affect its stability?

18 MR. WARNER: Objection. Incomplete
19 hypothetical.

20 BY THE WITNESS:

21 A. Would increasing the solubility of
22 fluticasone propionate increase its stability?

1 Q. Affect its stability.

2 A. Affect its stability. It depends on what
3 the instability mechanisms are for fluticasone
4 propionate and whether they're
5 concentration-dependent mechanisms.

6 Q. Would you consider increasing the
7 solubility of fluticasone propionate routine
8 optimization?

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

11 BY THE WITNESS:

12 A. I'm struggling because routine optimization
13 is usually performed on a composition that meets
14 many of the performance criteria desired and then
15 we're trying to improve all of the possible
16 characteristics towards our perfect composition
17 characteristics. Determining the concentration of
18 drug in solution in that composition is a step
19 that's performed before optimization is
20 contemplated.

21 Q. So would you consider this development
22 work?

1 A. If I had -- If I were evaluating the
2 concentration of drug that was present in a number
3 of different potential vehicles, that would likely
4 be considered at, you know, an early formulation
5 development stage.

6 MS. EVERETT: I think now's a good time for a
7 break. We've been going for an hour.

8 THE VIDEOGRAPHER: This marks the end of DVD
9 No. 5. We are off the record at 4:07 p.m.

10 (A short break was taken.)

11 THE VIDEOGRAPHER: Here begins DVD No. 6. We
12 are on the record at 4:22 p.m.

13 BY MS. EVERETT:

14 Q. Dr. Donovan, now I'm going to have you
15 turn back to your rebuttal expert report. And
16 I'm -- strike that.

17 I'm at Paragraph 31. You were commenting
18 on tests and experiments run by Meda
19 Pharmaceuticals. Let me know when you're there.

20 A. Okay.

21 Q. In Paragraph 31, you state. The next
22 morning, April 27th, the experimenters note that a

1 major portion of azelastine had not gone into
2 solution. There was no indication of what portion
3 that is.

4 Is it pharmaceutically acceptable to have
5 a product where any portion of the azelastine does
6 not go into solution?

7 MR. WARNER: Objection to form. Incomplete
8 hypothetical.

9 BY THE WITNESS:

10 A. Depends entirely what the purpose of that
11 composition is, what its goals are. And the only
12 material that can be active in a pharmaceutical
13 composition is the part of the material that's in
14 solution at the point of the receptor interaction.

15 So it's certainly possible that there could
16 be solid -- any compound in a composition. It
17 doesn't make it pharmaceutically acceptable or
18 unacceptable. And having all of the composition in
19 liquid or in solution may be advantageous in some
20 situations.

21 Q. For a pharmaceutical product that's a
22 nasal spray that includes azelastine hydrochloride

1 and fluticasone propionate, is it acceptable if any
2 part of the azelastine is not in solution?

3 A. Under certain conditions, it certainly may
4 be. It depends. And again, the composition has to
5 be effective, which means that at the site of
6 action, sufficient azelastine has to be in solution
7 to be able to interact with the target receptors.
8 But outside of that, if there's additional
9 undissolved azelastine, there isn't any reason that
10 would necessarily be unacceptable.

11 Q. But there is a portion, a certain portion
12 of azelastine that must be in solution for the
13 pharmaceutical to be effective; is that accurate?

14 A. The active -- the pharmacologically active
15 agent to interact with its receptor or at the target
16 site of action has to be in solutions. Whether it's
17 azelastine or fluticasone or any other API, to
18 actually exert its activity, a molecule has to be in
19 solution to do that.

20 Q. In Paragraph 32, you note that no analysis
21 was done to determine how much of the solid had
22 precipitated out, parentheticals, they noted that

1 only some had or what material in the sample had
2 precipitated.

3 Do you see that?

4 A. I see that, yes.

5 Q. Is there an acceptable level of
6 precipitation in a solution?

7 A. Again, by definition, a solution is a
8 homogeneous mixture of material that is molecularly
9 dispersed in the vehicle. So there wouldn't be
10 solid material, which is what likely individuals are
11 referring to as precipitate.

12 Q. So for a solution, there should be no
13 precipitation; is that accurate?

14 A. The solution has to be a homogeneous
15 molecularly dispersed system, which means everything
16 has to be molecularly dispersed within the vehicle.

17 Q. And if there is a formulation that is
18 intended to be a solution and there's some
19 precipitation, is that an unacceptable formulation?

20 A. Not necessarily. It wouldn't be classified
21 as a solution, but it doesn't mean that it's an
22 acceptable composition.

1 Q. And earlier I believe you stated the
2 solution appears clear. Is that ...

3 A. I may have sort of overgeneralized that.
4 But oftentimes we think of solutions as being clear.
5 But most solid solutions aren't. So a solution by
6 thermodynamic definition is a molecularly dispersed
7 homogeneous system.

8 Q. If something that -- strike that.
9 If there's a formulation that was not
10 clear, would you say that that either was
11 unacceptable or not actually a solution?

12 A. You know, I'm not able to agree that
13 just -- that clarity is a definition or mandatory
14 attribute of a solution.

15 Q. Okay. In Paragraph 34, you state in
16 relation to the formulation that Meda has made, it
17 is highly probable that the precipitate was not
18 azelastine hydrochloride, which is sparingly soluble
19 material but rather the MCC from the Avicel in the
20 Flonase; is that correct?

21 A. That's what that states, yes.

22 Q. Is that still your opinion?

1 A. It's my opinion that that's certainly a
2 possibility, yes.

3 Q. And what is your basis for saying that it
4 may not be azelastine hydrochloride?

5 A. Well, the basis is azelastine hydrochloride
6 is a sparingly soluble material, and
7 microcrystalline cellulose is an insoluble
8 material. The particulates in microcrystalline
9 cellulose in general are smaller than the filter
10 size used to filter out solid material in this
11 activity. So azelastine has higher solubility than
12 MCC, and there's no reason to believe that MCC was
13 removed from the system.

14 Q. Just a moment ago you stated that it was
15 one possibility that the precipitate was not
16 azelastine hydrochloride. In your report, you say
17 it's highly probable that the precipitate was not
18 Astelin hydrochloride.

19 What is your view on the probability that
20 the precipitate is Astelin hydrochloride -- that the
21 precipitate is azelastine hydrochloride?

22 A. Well, there was no evidence provided in the

1 report regarding this set of experiments that there
2 was confirmatory evidence that it was azelastine
3 hydrochloride. So I leave myself open to it's
4 probable that it could be a number of things. I
5 can't give you the odds. I have no idea what the
6 odds are. I wasn't -- the information documented
7 about this experiment is limited and confusing, so I
8 can't clearly discern exactly what was done, exactly
9 what was observed. I can't give you odds under
10 those conditions.

11 Q. The technician who noted it in the lab
12 notebook recorded it as azelastine hydrochloride; is
13 that correct?

14 A. I guess I'd like to see the lab notebook
15 pages because that's my recollection that there are
16 probably some other things written around that.

17 MS. EVERETT: Handing to the court reporter to
18 be marked as MEDA_APTX03470948 through 970 as
19 Donovan 15.

20 (Donovan Exhibit Number 15 marked
21 for identification.)

22 BY THE WITNESS:

1 A. Do you have a specific page and section
2 you'd like to refer me to?

3 Q. I'm going to refer you to lab notebook
4 Page 118.

5 A. Okay.

6 Q. I mean, there are a few entries here. But
7 specifically: The following morning, April 26,
8 2006, it is observed the fact that some of the solid
9 has, in fact, precipitated out of the 1044 sample.

10 MR. WARNER: So what's the question.

11 MS. EVERETT: She -- Dr. Donovan asked to see
12 the lab notebook. I asked her whether the
13 technician made the observation that azelastine had
14 precipitated out.

15 BY THE WITNESS:

16 A. And I --

17 MR. WARNER: One second. I've got to object to
18 the form of the question. And are you asking her is
19 that sentence -- are you referring her to that
20 sentence?

21 MS. EVERETT: I asked her whether the
22 technician had recorded that azelastine had

1 precipitated out. She asked to see the lab notebook
2 and be referred to that sentence. I've now referred
3 her to that sentence.

4 BY MS. EVERETT:

5 Q. Isn't this what the technician recorded at
6 that time?

7 MR. WARNER: I object to the form of the
8 question. I don't recall her asking to be referred
9 to a particular sentence. Go ahead.

10 BY THE WITNESS:

11 A. Anyway, I'm to look in context at the
12 statements above that, which describes the system
13 looking white and opaque and that it was allowed to
14 settle and observed for precipitation, which if it's
15 opaque, I'm not sure how you observe additional
16 precipitation.

17 And the following statement is that
18 observed some of the solid had, in fact,
19 precipitated out. I am not directed to believe that
20 that is azelastine by any confirmatory method, nor
21 do I understand how something that was white and
22 opaque now somebody can differentiate a solid that

1 they're calling a precipitate as a specific
2 component of that mixture.

3 Q. I'm going to have you look at Page 117 as
4 well, the bottom, where it says: The following
5 morning, the sample was observed for clarity and
6 solubility, and it was found that there was still a
7 major portion of the azelastine hydrochloride that
8 had not gone into solution.

9 A. I'm not sure where -- so it's 117. Let me
10 see that again.

11 Q. Yes. Do you see that?

12 A. Well, I'm going to read all of Page 117 for
13 a moment, just to get myself oriented to this
14 section of reporting.

15 Okay. And the question?

16 Q. The technician on April 26th noted that a
17 major portion of the azelastine hydrochloride had
18 not gone into solution. Is that correct?

19 A. That's what's written. I don't understand
20 how the technician determined that what he or she
21 was observing was azelastine hydrochloride.

22 Q. Why is that?

1 A. There's no confirmatory analysis that the
2 material of the solid material observed is
3 azelastine hydrochloride.

4 Q. Why isn't visual inspection enough?

5 A. Because it's a solid material. I can't
6 identify chemically what any given solid material
7 is, and I don't anticipate the technician is capable
8 of doing that either.

9 Q. Well, if there wasn't a solid material --
10 strike that.

11 In this experiment, you understand that
12 the technician took the Flonase system and removed
13 the solid particles of fluticasone propionate?

14 MR. WARNER: Objection to the form of the
15 question. Assumes facts.

16 BY THE WITNESS:

17 A. And based on the description, they removed
18 the solids that were able to be removed by
19 centrifugation or by filtering through, at the
20 smallest, a .45-micron filter.

21 Q. And then the technician added azelastine
22 to that supernatant?

1 A. Yes.

2 Q. And so it's your testimony that a
3 technician who removed the solids and then added
4 azelastine would not be able to determine whether
5 the remaining solid was azelastine?

6 MR. WARNER: Can you repeat that?

7 THE COURT REPORTER: Yeah, could you repeat it?
8 I need it too.

9 BY MS. EVERETT:

10 Q. So it's your opinion that the technician
11 who removed the solids from the Flonase system and
12 then added azelastine, he would not be able to
13 determine that any undissolved solid was azelastine?

14 MR. WARNER: Objection to the form of the
15 question. Mischaracterizes the document. Assumes
16 facts.

17 BY THE WITNESS:

18 A. Based on this description and what I
19 previously just said was what was removed from the
20 Flonase formulation was any solid particles that
21 could be centrifuged out and any other particulate
22 matter that was greater than .45 micron in diameter.

1 It doesn't mean that everything was removed from
2 that vehicle.

3 And as a result, there are other materials
4 still remaining in that supernatant and azelastine
5 was added. And I don't believe that a technician or
6 anyone else can without a doubt determine after a
7 period of time that what they observe as a solid
8 material in that is azelastine hydrochloride.

9 Q. If the supernatant was passed through a
10 .45-micron filter, would a human be able to observe
11 particles that were smaller than .45 micron?

12 A. I believe that that's -- you might see a
13 Tyndall effect at that size, I think, but you
14 wouldn't be able to discern individual particles.

15 Q. So the microcrystalline cellulose that was
16 remaining was smaller than .45 micron?

17 A. On one axis, it would have been smaller
18 than .45 micron.

19 Q. What do you mean by one axis?

20 A. Well, there's nothing that says
21 microcrystalline cellulose is a sphere. So it has
22 dimensions that are both length and width. So one

1 portion of that molecule has a radius less than
2 .45 microns because it could go through a .45-micron
3 filter because it's typical particle size is
4 characterized as less than .45 microns.

5 Q. So is it your opinion that a person, a
6 human, looking at the supernatant that had gone
7 through a .45-micron filter would see particles of
8 microcrystalline cellulose?

9 A. They wouldn't see individual particles.
10 But if there's a multitude of them, there's going to
11 be an observable something about that supernatant.
12 And I refer to Page 116 where under a nearly
13 identical methodology with slightly different filter
14 sizes, it's clearly stated that the supernatant is
15 not clear, whereas on Page 117, there's no
16 indication. There's nothing that says the
17 supernatant was clear.

18 Q. I'm going to refer you to the bottom of
19 Page 116. It says: Attempting to pass the sample
20 through the .45-micron filter was extremely
21 difficult. After approximately 3 milliliters of the
22 sample had passed through and was seemingly clear

1 now -- do you see that?

2 A. Okay.

3 Q. So the technician is reporting that the
4 sample was clear after passing through the filter;
5 is that correct?

6 MR. WARNER: Objection. Form of the question.
7 It incompletely states the document.

8 BY THE WITNESS:

9 A. The technician is reporting some fraction
10 of the sample that they recovered appeared to be
11 clear before they spilled it.

12 Q. If a person could see the microcrystalline
13 cellulose -- or strike that.

14 If a person could observe the
15 microcrystalline cellulose after the supernatant had
16 gone before the .45-micron filter, is that because
17 the microcrystalline cellulose particles were
18 clumped together?

19 A. It may be. Other -- It's merely a matter
20 of can those particles scatter enough light so your
21 eye detects a difference in that vehicle. And why
22 they're doing that and what size they're doing that,

1 you need further investigation.

2 Q. If the particles were visible after
3 passing through the .45-micron filter, is it --
4 strike that.

5 So I want to go back to your basis for
6 stating that the material observed may not be
7 azelastine. You noted the difference in solubility
8 between MCC and azelastine; is that correct?

9 A. Yes.

10 Q. What other basis do you have to suggest
11 that what is recorded as azelastine is not, in fact,
12 azelastine?

13 A. The basis is there's no convincing evidence
14 in the laboratory notebook that it is azelastine
15 hydrochloride. So I have to hold open the
16 possibility that it could be azelastine
17 hydrochloride or any of the other materials present
18 in the system.

19 And by adding azelastine hydrochloride to
20 the system, it changed materially the
21 characteristics of the system. I don't know what
22 that means regarding the other materials in the

1 system based on the information provided in the
2 laboratory notebook. There's inconsistent
3 documentation of what happened and on what basis the
4 technician assigned particular observations to
5 specific entities without any regard for what the
6 other entities in the system were.

7 Q. We were just referred to in Paragraph --
8 Page 116 where the supernatant was clear.

9 A. On 116? Okay.

10 Q. Yes. Do you see that?

11 A. I see that, yeah.

12 Q. So assuming the supernatant was clear
13 before the addition of azelastine, what would you
14 conclude the visible solid the technician refers to?

15 A. I don't know based on this report. I can't
16 conclude when there's no attempt at control
17 experiments, no attempt at other experiments that
18 would eliminate the possibility that there are other
19 materials that could be forming that precipitate,
20 automatically assuming that it's the thing I thought
21 would precipitate or wanted to precipitate or
22 whatever did, is unscientific.

1 Q. If the supernatant was clear before the
2 addition of azelastine and the visible solids were
3 MCC, wouldn't MCC have had a negative interaction
4 with the azelastine?

5 A. I don't know. What do you mean by negative
6 interaction?

7 Q. Well, before the addition of azelastine,
8 the supernatant was clear?

9 MR. WARNER: Objection to the form of the
10 statement.

11 BY MS. EVERETT:

12 Q. And --

13 A. We're assuming that it was clear. But
14 anyway, if we go with that assumption, the
15 supernatant was clear and azelastine was added. And
16 do you want me to then project that there was a
17 negative interaction between MCC and azelastine?

18 Q. No. If the supernatant was clear and you
19 added azelastine and there was some solids in the
20 resulting formulation such that it was clumping or
21 some sort of agglomeration of MCC, is this a
22 negative interaction between azelastine and MCC?

1 A. It's a result of the system change induced
2 by azelastine under the conditions of merely the
3 supernatant being present. So, you know, if that
4 were really the case, there may be ways to resolve
5 that issue if it really was a negative interaction.

6 Q. If it was the azelastine that had not been
7 dissolved -- strike that.

8 I think earlier you testified that it
9 would not be pharmaceutically unacceptable to have a
10 product where all of the azelastine didn't go into
11 solution?

12 A. That's not what I said. So actually maybe
13 I misheard what you just restated. But do you mean
14 the entirety of the azelastine was not in solution,
15 or that some of the azelastine was not in solution
16 and some was?

17 Q. The latter.

18 A. Okay.

19 Q. So I believe you stated that it's not
20 pharmaceutically unacceptable where some of the
21 azelastine is in solution and some is not?

22 A. It's no more pharmaceutically unacceptable

1 to have some azelastine in solid form and some in
2 solution form than it is to have fluticasone, some
3 in solid form and some in solution form. It has
4 nothing to do with the pharmaceutical acceptability
5 of those systems.

6 Q. Would it affect the uniform dosing of a
7 pharmaceutical composition if azelastine was partly
8 in solution and partly not in solution?

9 A. In the same way that we addressed dose
10 uniformity with suspensions, the dose uniformity if
11 azelastine was some in solid form, some in solution
12 form could be addressed using formulation techniques
13 and optimization.

14 Q. So your answer is it would affect dosing?
15 I think you're going on to state but you may do
16 other things about that?

17 MR. WARNER: Objection to that form of that
18 question. Asked and answered.

19 BY THE WITNESS:

20 A. And I didn't state it would affect dosing.
21 I would say in the same way we consider dose
22 uniformity, something to address with suspension

1 formulation, we would address it if azelastine was
2 as a suspension in the formulation.

3 Q. So would it affect -- I hear you that you
4 could consider it. Would it -- My question is: If
5 azelastine is in -- partly in solution and partly
6 not in solution, would it affect the uniformity of
7 the dosing?

8 MR. WARNER: Objection. Asked and answered.

9 BY THE WITNESS:

10 A. And I -- unless I know the type of
11 dispersion of the azelastine solid in that system, I
12 have no way of projecting whether it would or
13 wouldn't. If it acts as a typical suspension, it
14 would be something at least would be evaluated and
15 addressed whether it could lead to dose uniformity
16 under certain circumstances or dose uniformity
17 issues under certain circumstances. But there are
18 suspensions that stay, you know, stay suspended and
19 dispersed for long periods of time and there's some
20 that don't. Some lead to dose uniformity issues as
21 a result if they don't stay uniformly dispersed.

22 Q. Would a person of ordinary skill as of

1 June 2002 have knowledge of azelastine's behavior as
2 if it was a solid in the system?

3 A. Well, I think one of the things -- you
4 know, in 2002, something available to a POSA is the
5 Hettche reference. And the Hettche reference gives
6 a broad range of concentrations of azelastine to be
7 used and that are effective. And knowing what a
8 POSA could do to determine the solubility, the POSA
9 might determine that some of those concentration
10 ranges represent suspensions.

11 Q. Would a POSA understand that the Hettche
12 reference is disclosing using azelastine as a
13 suspension?

14 A. Well, the POSA would need to evaluate the
15 concentration ranges disclosed in the Hettche
16 reference and either, by routine experimentation,
17 determine the solubility of azelastine, which would
18 then allow them to draw the conclusion about whether
19 some of those ranges describe suspensions or not.

20 Q. I'm going to have you turn to
21 Paragraph 40. Here you discuss some techniques a
22 POSA would have taken to make azelastine more

1 soluble.

2 A. I'm describing -- it's pH-dependent
3 solubility, yes. In Paragraph 40?

4 Q. Yes.

5 How would you -- how -- strike that.

6 How would a POSA have modified -- strike
7 that.

8 What pH would a POSA have adjusted
9 azelastine to to increase its solubility?

10 A. Well, Paragraph 40 is describing the
11 experiment the POSA would conduct to determine just
12 that, that you would like to determine what pH -- a
13 pH where azelastine or, you know, what the pH
14 dependency of azelastine solubility is so that that
15 would inform the pH of the system based on what it
16 is that you want -- how you want to present
17 azelastine in the system.

18 So this doesn't specify a pH, and the POSA
19 would know well how to do a pH solubility
20 determination to inform them about pH effects on
21 azelastine solubility.

22 Q. Would the POSA have conducted this

1 experiment on azelastine hydrochloride by itself?

2 A. Well, in order to conduct these
3 experiments, you need to put them into controlled
4 vehicles where the pH is constant, azelastine in
5 addition to the materials in the vehicle that allow
6 you to hold the pH constant.

7 Q. So would this have been conducted putting
8 azelastine in the Flonase vehicle?

9 A. No, it would not. A pH solubility
10 experiment is conducted in vehicles that don't have
11 an abundance of additional formulation excipients
12 if you really want to understand the pH solubility
13 behavior of just the active substance.

14 Q. And is that because -- because of the
15 other components, it would -- and is that because
16 having other components in the system would affect
17 learning what the actual pH of azelastine is?

18 A. Azelastine doesn't have a pH, so I don't
19 understand the question.

20 Q. So you stated that you would want to
21 conduct these tests in the presence of a vehicle
22 without a lot of components?

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

2 Q. Why is that?

3 A. Because if you're really investigating the
4 pH dependence of solubility of an API, you want the
5 pH to be the only variable in the system. You don't
6 want other components because they represent other
7 variables in the system that you are not
8 controlling.

9 Q. So once you determined the -- when you've
10 investigated the pH dependence of the API, how would
11 that affect -- how would you take that and then
12 translate that into putting azelastine into the
13 Flonase vehicle?

14 MR. WARNER: Objection to the form of the
15 question. Incomplete hypothetical.

16 BY THE WITNESS:

17 A. The pH dependence, the knowledge of the pH
18 dependence informs a POSA about the concentrations
19 of azelastine that are in solution at specific pHs.
20 What that means regarding the Flonase vehicle, if
21 you know the pH of the Flonase vehicle, you can
22 probably calculate how much azelastine would be in

1 solution if it were only the pH that was affecting
2 the solubility of azelastine in that vehicle.

3 But there are other materials in that
4 vehicle that can have an influence, both on pH, as
5 we define it as hydronium ion concentration, and on
6 chemical interactions that may alter the solubility
7 of azelastine.

8 Q. And a POSA would need to consider the
9 effect of the variabilities of the other materials
10 in the Flonase vehicle as well; is that correct?

11 A. Only if the only methodology the POSA knew
12 was to take the Flonase vehicle and add azelastine
13 to it. Otherwise, all of the materials in the
14 Flonase vehicle are just other materials that could
15 be included or not included in a final formulation,
16 and there are plenty of other materials that could
17 be substituted for those.

18 So, you know, what a POSA needs to do
19 regarding the Flonase vehicle is just a very strange
20 question or approach for formulation development.

21 Q. A POSA would need to consider the
22 variabilities of azelastine -- strike that.

1 A POSA would need to consider the
2 variables of any vehicle that would be used with the
3 azelastine; is that fair?

4 A. A POSA needs to consider the interactions
5 and material properties of all of the materials that
6 get included in a formulation that's being developed
7 or optimized.

8 Q. In 41, Paragraph 41, you suggest the use
9 of a co-solvent?

10 A. Yes.

11 Q. And here you state that it was known that
12 azelastine hydrochloride was more soluble in
13 glycerin than water?

14 A. Yes.

15 Q. Okay. And you refer to your opening
16 report, Paragraph 41.

17 A. Okay.

18 Q. Here in 41, I believe you're referring to
19 azelastine. You say: Sparingly solubility and
20 slightly soluble in glycerin?

21 A. Yes, I'm referring to the statements in the
22 label that's reproduced above.

1 Q. And you may want to look at Paragraph 42.

2 Is azelastine more soluble -- if azelastine --
3 strike that.

4 If azelastine is sparingly soluble in
5 water and slightly soluble in glycerin, which
6 vehicle is it more soluble in?

7 A. Azelastine hydrochloride is more soluble in
8 the slightly soluble vehicle as compared to a
9 vehicle where it's only sparingly soluble.

10 Q. It's more soluble in slightly soluble than
11 sparingly soluble?

12 A. Yes. Though it's more soluble in glycerin
13 than it is in water as described by it being
14 sparingly soluble in water and slightly soluble in
15 glycerin.

16 Q. And looking at the arrangement of the
17 descriptive terms, slightly soluble appears below
18 sparingly soluble; is that correct?

19 A. Well, in the ranking there, yes.

20 Q. And it needs more parts of solvent needed
21 for one part of solute?

22 A. Yes, you're right. I'm sorry. I was --

1 it's getting late.

2 Q. I hear you. I just want to make sure
3 we're on the same page.

4 So is that reversed, azelastine is
5 actually more soluble in water than in glycerin?

6 A. Yes, based on the information in this
7 table, that would be how you would interpret that
8 information.

9 Q. Okay. So when you said in Paragraph 41 of
10 your reply that azelastine was more soluble in
11 glycerin than water thus making glycerin an option
12 as a co-solvent in an aqueous nasal formulation, do
13 you still agree with that statement?

14 A. Based on the information in the table, I'm
15 going to -- I think I'm going to need the
16 opportunity to reconsider that because my
17 understanding of the descriptive terms and the
18 descriptive terms and the parts of solvent needed
19 are not -- are not aligning at this point. So if I
20 could refer to Remington's or another -- or USP,
21 which are the two places where these terms are
22 typically included, that might be helpful to me.

1 MS. EVERETT: I'm handing to the court reporter
2 a document bearing the Bates APOTEX_AZFL0132974
3 through 992 to be marked as Donovan 16.

4 (Donovan Exhibit Number 16 marked
5 for identification.)

6 BY MS. EVERETT:

7 Q. I'm handing to you what I believe is a
8 chapter of Remington's, but please confirm and take
9 a look.

10 A. This does look like a chapter from
11 Remington's. Okay. And it looks like the
12 information in the table in Chapter 42 is a
13 reproduction of the information in this Remington
14 chapter.

15 Q. So based on that, would you say that
16 azelastine hydrochloride is actually more soluble in
17 water than glycerin?

18 A. Yes, the azelastine hydrochloride is, based
19 on those qualitative descriptions, somewhat more
20 soluble in water than in glycerin.

21 Q. Is it your opinion still that glycerin
22 would be a useful co-solvent?

1 A. Yes, it is.

2 Q. How much glycerin would one need to add to
3 the azelastine to make it all in solution?

4 A. It depends on the pH of the system and
5 whether there's entire azelastine hydrochloride or
6 the hydrochloride salt will dissociate, so whether
7 there's the protonated form of azelastine in the
8 system or whether there's azelastine free base in
9 the system.

10 Q. You would need to add more glycerin to the
11 system to make azelastine hydrochloride dissolve
12 than you would need to add water; is that correct?
13 Let me ask that again.

14 A. I don't think that's what I said.

15 Q. You would need to add more glycerin than
16 water to the system to make azelastine hydrochloride
17 soluble; is that correct?

18 A. Again, it depends on what pH the system is
19 at because the pH of the system defines whether it's
20 azelastine hydrochloride or the protonated form of
21 azelastine that's present or whether it's azelastine
22 free base, and we're not provided information here

1 regarding the solubility of the free base.

2 Q. What is the form that's in Astelin?

3 A. What's the pH of Astelin?

4 Q. I think you list it in this report.

5 A. It's 6.8?

6 Q. 6.8, yes.

7 A. Okay. And the pKa of azelastine is, do we
8 have that information? It's the only way I can tell
9 you what form is in the system.

10 Q. Well, let me ask you it a different way.
11 If everything is equal in the system except for the
12 solvent, water versus glycerin, would you need more
13 glycerin than water?

14 A. It entirely depends on what the proportion
15 of azelastine hydrochloride versus azelastine is in
16 the system.

17 Q. And that would -- the amount you would
18 need of the solvent would -- strike that.

19 And depending on the amount of azelastine
20 hydrochloride versus azelastine in the system, that
21 would affect the amount of the solute you would use,
22 excuse me, the co-solvent you would use?

1 A. Well, let me correct one thing that you
2 said. It's whether the protonated form of
3 azelastine or azelastine free base, which
4 proportion -- which proportion they are present in
5 that particular system. And their proportions and
6 their solubilities in those solvent determine which
7 solvent you need to add more of to solubilize
8 whichever form has the lowest solubility.

9 Q. In your report, you did not distinguish
10 between analysis of azelastine in the protonated
11 form or azelastine free base in determining that
12 azelastine hydrochloride, whether it was more
13 soluble in glycerin than water, did you?

14 A. No, because I described how a POSA would
15 simply do the pH solubility study, which is the more
16 straightforward way of obtaining that information.

17 Q. So now are you able to comment on
18 whether -- sitting here today, are you able to
19 comment on azelastine hydrochloride as it is found
20 in Astelin, whether that would require more --
21 whether -- strike that.

22 Whether azelastine hydrochloride is more

1 soluble in water than glycerin?

2 A. Well, by the label description and by the
3 definitions that azelastine hydrochloride, as the
4 salt form, is more soluble in water than in
5 glycerin.

6 Q. And you're not able to opine on how much
7 more glycerin would have been added, needed to be
8 added to a system versus water?

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

11 BY THE WITNESS:

12 A. I don't understand the question.

13 Q. So if azelastine is slightly soluble in
14 glycerin, how -- strike that.

15 In Paragraph 42 of your report, you've
16 reproduced part of Remington's where it says
17 slightly soluble, and then in the right-hand column
18 it says: Parts of solvent needed for partly
19 solubility. Do you see that?

20 A. Yes.

21 Q. And it says 100 to 1,000 parts of solvent
22 needed for one part of solute.

1 A. Correct.

2 Q. And do you agree that that is the amount
3 of glycerin that would be needed to dissolve
4 azelastine hydrochloride?

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

7 BY THE WITNESS:

8 A. I interpret the table -- let me see the
9 right value here. That for azelastine
10 hydrochloride, in azelastine hydrochloride glycerin
11 system, that I would need somewhere between 100 and
12 1,000 parts of glycerin to dissolve 1 part of
13 azelastine hydrochloride.

14 Q. And glycerin is also known as a
15 tonicity-adjusting agent; is that right?

16 A. It's used in tonicity adjustment in some
17 formulations, yes.

18 Q. And how would adding 100 to 1,000 parts of
19 glycerin to dissolve 1 part of azelastine
20 hydrochloride affect the tonicity of a formulation
21 of azelastine hydrochloride and fluticasone
22 propionate?

1 A. Can you reask that question?

2 Q. Sure. How would adding glycerin at the
3 quantity of 100 to 1,000 parts per 1 part of
4 azelastine hydrochloride affected -- affect the
5 osmolality of the nasal spray?

6 MR. WARNER: Objection. Vague as to the nasal
7 spray.

8 BY THE WITNESS:

9 A. Because, I mean, you're describing a system
10 where you have one part of azelastine hydrochloride
11 and 100 to 1,000 parts of glycerin. And do you have
12 anything else?

13 Q. Assuming you have everything the same --
14 you have a system and you replaced the water with
15 the glycerin, how would that have affected the
16 osmolality?

17 A. I'd need the molecular weight of water and
18 the molecular weight of glycerin to tell you that.

19 Q. So it's not -- you couldn't say whether
20 adding 100 to 1,000 parts to 1 part of azelastine
21 hydrochloride would affect the osmolality of a
22 formulation?

1 MR. WARNER: Objection. Mischaracterizes her
2 testimony.

3 BY THE WITNESS:

4 A. Yeah, that's not what I said at all.

5 Q. I asked you how would it affect the
6 osmolality. How would it affect the osmolality?

7 A. You asked me if I substituted glycerin for
8 water in the, I'm assuming the Flonase formulation,
9 how that would affect the osmolality. And I told
10 you I could tell you that if I knew the molecular
11 weights of the two, and I believe I'd need to know
12 the either L iso or E value for glycerine to make
13 that determination.

14 Q. Is water a tonicity-adjusting agent?

15 A. Water is typically the vehicle that -- that
16 all of the other materials are within. And so the
17 frame of reference for tonicity is the number of
18 additional molecules in the aqueous vehicle. So
19 water is the default vehicle. We don't really
20 usually pay attention to the number of water
21 molecules. It's all of the other molecules that
22 contribute then to the tonicity.

1 Q. Would adding glycerin make the formulation
2 more hypertonic?

3 A. Well, if you have a system and you add
4 something else to it which provides molecules in
5 solution in the system, then there will be more
6 molecules. And if you want to compare that to
7 isotonic, then, well, there's just going to be an
8 increase in the tonicity value.

9 Q. So if you substituted glycerin for water
10 as a co-solvent, then you would have a higher
11 tonicity value?

12 A. Because you've reduced the amount of water
13 in the system.

14 Q. In Dr. Smyth's report, he -- strike that.
15 Do you recall in Dr. Smyth's report that
16 he opines that Dymista is an embodiment of the
17 asserted patents?

18 A. I'm sorry. Can you say that again?

19 Q. Yeah. Do you recall that he said --
20 Dr. Smyth opines that Dymista meets the claims of
21 the asserted patents?

22 A. I don't -- I don't know that I really

1 recall much of the phraseology in Dr. Smyth's
2 report. So I'd like to see whatever phrase it is
3 that you're referring to.

4 Q. Do you -- do you recall Dr. Smyth opining
5 that Duonase meets the limitations of the asserted
6 patents?

7 A. Again, sitting here right now, I don't
8 recall the phrasing in Dr. Smyth's reports.

9 Q. Do you recall Dr. Smyth stating that there
10 are a number of azelastine fluticasone products that
11 are available in India?

12 A. I recall seeing that information. I don't
13 recall whether I saw it in Dr. Smyth's report or in
14 a different version of information I reviewed.

15 Q. You're not challenging that the product --
16 fluticasone azelastine products available in India
17 meet the asserted claims, are you?

18 MR. WARNER: You can look at the reports if you
19 need to. The reports speak for themselves.

20 BY THE WITNESS:

21 A. I don't believe I expressed an opinion
22 whether any, some, or all of the Indian copycat

1 products meet the specified claims. And I would
2 have to go through all of the product details to
3 make that determination, and that's not an exercise
4 that I conducted.

5 Q. You don't intend to offer an opinion on
6 whether the Indian products meet the asserted
7 claims, do you?

8 A. My opinion states that there were a number
9 of different formulations that contained azelastine
10 hydrochloride and fluticasone propionate with a
11 number of excipients, many of which are described in
12 the '194 patent -- or not the '194 patent, I'm
13 sorry -- the patent at issue, patents at issue.

14 Exactly -- whether exactly all of them meet
15 all of the claims again is something I would have to
16 actually go back and look at the details and reflect
17 on. And I understand that Dr. Smyth feels that they
18 don't all meet the claims of the patent-in-suit.
19 That's all I can say at the moment. I wasn't asked
20 to provide an opinion on whether each of those
21 formulations met or did not meet the given claims.

22 Q. In Paragraphs 44 through 48 of your

1 report, you look through some Cipla/Meda documents
2 to support your opinion that the invention was
3 obvious. Is that correct?

4 MR. WARNER: Could you restate that?

5 MS. EVERETT: Sure.

6 BY MS. EVERETT:

7 Q. In Paragraphs 44 through 48, you cite some
8 documents to support your general opinion that these
9 patents are obvious?

10 A. Well, I think the substance of 44 through
11 48 is that in those development reports, it was
12 clear that Meda didn't have any significant problems
13 in formulating Dymista.

14 Q. Are you using these to rely -- support
15 your opinion?

16 MR. WARNER: Which opinion?

17 BY MS. EVERETT:

18 Q. Your basic opinion is that these patents
19 are obvious; is that correct?

20 A. I drew -- I developed my opinion on the
21 patents being obvious and expressed that opinion in
22 my initial expert report. I was provided these

1 other documents at a time later than that and
2 reviewed them and found that in many cases, exactly
3 what appeared in their development documents
4 supported my opinion that a POSA formulator could
5 take things that were known in the art, used in the
6 art, and easily come up with a formulation that
7 combined fluticasone propionate and azelastine
8 hydrochloride.

9 Q. Did you look at the dates of these
10 documents?

11 A. I don't recall looking at the dates of the
12 documents specifically, no.

13 Q. Did you ask what dates they were
14 generated?

15 A. Not directly. And I can -- well, no, I
16 didn't.

17 Q. So do you know whether they were generated
18 after the critical date?

19 A. I don't know that.

20 Q. Do you know whether they were generated
21 after launch of a commercial product?

22 A. I have no way of knowing that if I didn't

1 look at the dates.

2 Q. Are you aware that when you consider your
3 opinion, you can't -- on whether it -- strike that.

4 You're aware that you can't use hindsight
5 to determine whether the invention is obvious; is
6 that correct?

7 A. I've had the term hindsight explained to me
8 by counsel. And yes, I'm aware that you can't use
9 what's currently defined as hindsight in an
10 evaluation of obviousness.

11 Q. And what do you understand hindsight to
12 be?

13 A. That you take the information provided
14 about the pertinent question and then simply reflect
15 on how each of those points is obvious in an absence
16 of how an individual at the time that that
17 intellectual property or the patent or whatever or
18 when the invention was initially identified.

19 So to make it less maybe circuitous is that
20 in order to evaluate obviousness, you have to use
21 the materials that were available to a POSA at the
22 time of the invention without direct regard for the

1 information that's provided in the description of
2 the invention.

3 Q. And I believe you stated that the
4 documents you reference in Paragraphs 44 through 48
5 were provided to you by counsel?

6 A. Yes, that's the only -- yes.

7 Q. Did you ask for these documents to be
8 provided to you?

9 A. Not directly, no.

10 Q. Did you ask counsel to search the database
11 looking for development documents?

12 A. I may have. I don't recall in
13 conversations. Those are always valuable for me to
14 refer to just to know that their development
15 processes met what -- my expectation of what a POSA
16 would perform or approach.

17 Q. I'm going to have you look at your reply
18 report now.

19 MR. WARNER: You know, actually this has been
20 another hour. Can we take a break here?

21 MS. EVERETT: Sure.

22 THE VIDEOGRAPHER: This marks the end of DVD

1 No. 6. We are off the record at 5:28 p.m.

2 (A short break was taken.)

3 THE VIDEOGRAPHER: Here begins DVD No. 7. We
4 are on the record at 5:32 p.m.

5 BY MS. EVERETT:

6 Q. I actually do have one more question.
7 Dr. Donovan, we had a number of breaks today.
8 During those breaks, have you discussed the
9 substance of your testimony with your counsel?

10 A. No, I have not.

11 MS. EVERETT: No further questions.

12 MR. WARNER: Okay. I have just a few,
13 Dr. Donovan.

14 EXAMINATION

15 BY MR. WARNER:

16 Q. We were talking some today about the work
17 that Dr. Ram or Dr. Govindarajan did. Do you recall
18 that?

19 A. Yes, I do.

20 Q. Did the work and the data that he reported
21 provide a person of ordinary skill in the art the
22 basis to form a reasonable expectation that the drug

1 in the spray would be uniformly distributed as it
2 was in the bottle?

3 A. As a preliminary set of experiments, yes,
4 there would be a reasonable expectation to assume
5 that there would be dose uniformity and it would be
6 uniform in suspension.

7 Q. Okay. There were also some questions
8 today about using solubility enhancement techniques
9 to improve solubility of certain drugs. Do you
10 recall that?

11 A. Yes.

12 Q. In the -- And then there was also, related
13 to that, some discussion about a distinction between
14 optimizing a product and, before that, developing a
15 product. Do you recall that?

16 A. Yes.

17 Q. In the development stage, would using
18 known solubility enhancement techniques to improve
19 solubility, would that be a routine experimentation
20 for a POSA during the development stage?

21 A. Essentially yes. You know, they use a very
22 common sequence of materials to investigate those

1 solubility changes. So I think you could probably
2 classify even at that early development stage that's
3 routine experimentation, similar to conducting a pH
4 solubility profile is routine experimentation. It
5 just gets done early in the development stage.

6 MR. WARNER: Very good. Nothing further.

7 MS. EVERETT: No further questions.

8 THE VIDEOGRAPHER: This marks the end of DVD
9 No. 7 and the deposition. We are off the record at
10 5:35 p.m.

11 (Witness excused.)

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1 STATE OF ILLINOIS)
) SS:
2 COUNTY OF COOK)

3 I, RACHEL F. GARD, RPR, CLR, CRR, CSR No.
084-3324, a Certified Shorthand Reporter in and for
4 the State of Illinois, at large, do hereby certify
that DR. MAUREEN DONOVAN, the deponent herein, was
5 previously duly sworn to tell the truth, the whole
truth, and nothing but the truth in the
6 aforementioned matter;

That the foregoing deposition was taken on
7 behalf of the Plaintiffs at Winston & Strawn, 35
West Wacker Drive, Chicago, Illinois, on the 7th day
8 of October, 2016, at 9:00 a.m., pursuant to the
applicable rules;

9 That said deposition was taken down in
stenograph notes and afterwards reduced to
10 typewriting under my direction, and that the
typewritten transcript is a true record of the
11 testimony given by the said deponent; and that
signature was requested by the deponent and all
12 parties present;

That the parties were represented by their
13 counsel as aforementioned.

I do further certify that I am a disinterested
14 person in this cause of action, that I am not a
relative or attorney of either party or otherwise
15 interested in the event of this action, and that I
am not in the employ of the attorneys for any party.
16

IN WITNESS WHEREOF, I have hereunto set my
17 hand and affixed my seal on this _____
day of _____, 2016.

18
19
20
21

Rachel F. Gard

22

COURT REPORTER

Page 284

1 Maureen D. Donovan c/o
 WINSTON & STRAWN, LLP
2 35 West Wacker Drive
 Chicago, Illinois 60601

3
4 Case: Meda Pharmaceuticals Inc., et al. v. Apotex Inc.
 Date of deposition: October 7, 2016
5 Deponent: Maureen D. Donovan

6
7 Please be advised that the transcript in the above
8 referenced matter is now complete and ready for signature.
9 The deponent may come to this office to sign the transcript,
10 a copy may be purchased for the witness to review and sign,
11 or the deponent and/or counsel may waive the option of
12 signing. Please advise us of the option selected.
13 Please forward the errata sheet and the original signed
14 signature page to counsel noticing the deposition, noting the
15 applicable time period allowed for such by the governing
16 Rules of Procedure. If you have any questions, please do
17 not hesitate to call our office at (202)-232-0646.

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4 SIGNATURE PAGE

Case: Meda Pharmaceuticals Inc., et al. v. Apotex Inc.
5 Witness Name: Maureen D. Donovan
Deposition Date: October 7, 2016

6

7 I do hereby acknowledge that I have read
and examined the foregoing pages
8 of the transcript of my deposition and that:

9

10 (Check appropriate box):

() The same is a true, correct and
11 complete transcription of the answers given by
me to the questions therein recorded.

12 () Except for the changes noted in the
attached Errata Sheet, the same is a true,
13 correct and complete transcription of the
answers given by me to the questions therein
14 recorded.

15

16

17 DATE

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18

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6 ERRATA SHEET
7

8 Case: Meda Pharmaceuticals Inc., et al. v. Apotex Inc.
9 Witness Name: Maureen D. Donovan
10 Deposition Date: October 7, 2016

11 Page No. Line No. Change
12
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21 _____
22 Signature Date