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UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE PATENT TRIAL AND APPEAL BOARD

ARGENTUM PHARMACEUTICALS LLC,

Petitioner

v.

CIPLA LTD.

Patent Owner

Patent No. 8,168,620

IPR2017-00807

Deposition of MAUREEN D. DONOVAN, PH.D., at
the offices of Foley & Lardner, 321 North
Clark Street, Chicago, Illinois, before
Janice M. Kocek, IL-CSR and CLR,
commencing at the hour of 9:07 a.m. on
Tuesday, March 27, 2018.

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Exhibit CIP2176

Second Declaration of

134

4

Hugh David Charles

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Smyth, Ph.D.

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(Argentum vs. Cipla)

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Exhibit CIP2177

Direct Examination

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Demonstratives of

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Maureen Donovan, Ph.D.

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DDX 5.00 - 5.56

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(Meda and Cipla vs. Apotex)

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1 (Witness sworn.)

2 MAUREEN DONOVAN, Ph.D.,

3 called as a witness herein, having been

4 first duly sworn, was examined and

5 testified as follows:

6 EXAMINATION

7 BY MR. LAROCK:

8 Q. Good morning. Can you state your full
9 name for the record, please.

10 A. Maureen Donovan.

11 Q. And my name is Adam LaRock. I
12 represent Cipla. And do you understand you're here
13 on behalf of Argentum Pharmaceuticals?

14 A. Yes.

15 Q. And you've been deposed previously?

16 A. Yes, I have.

17 Q. Yeah. About how many times?

18 A. About ten times.

19 Q. Okay. And you were deposed a couple of
20 times on the '620 patent that is at issue?

21 A. On things relevant to the '620 patent,
22 yes.

1 Q. Your opinions on the '620 patent?

2 A. Yes.

3 Q. Would you say you're familiar with the
4 deposition rules in general?

5 A. In general, yes.

6 Q. Okay. Well, as a refresher, I'll ask
7 some questions, you'll provide answers to those
8 questions.

9 If I ask a question, you provide an
10 answer, I'm going to assume that you understood it,
11 that you heard it.

12 Is that fair?

13 A. Sure.

14 Q. And Mike may have some objections at
15 times. But unless he instructs you not to answer,
16 you're supposed to answer my questions.

17 A. Okay.

18 Q. Okay. And is there any reason why you
19 can't provide truthful testimony today?

20 A. No.

21 Q. So I've just handed you what's been
22 previously marked Exhibit 1165. And do you

1 recognize this exhibit?

2 (Witness examining document.)

3 THE WITNESS: Well, I recognize it
4 except for the redacted portion.

5 BY MR. LAROCK:

6 Q. Do you recognize -- do you understand
7 that at one point in time you had cited to
8 confidential information?

9 A. Yes.

10 Q. And then I think your counsel redacted
11 out a portion of it when it was publicly filed.

12 A. Okay. I'll -- then -- then -- I mean,
13 yes. This -- this looks to be, without me reading
14 every word, my second declaration. And I'll --
15 I'll leave it to understanding that that was
16 redacted before it went public.

17 Q. Okay. But I'm saying, besides that
18 redacted -- redaction, you're familiar with --
19 that's right?

20 A. Yes.

21 Q. And that's your signature on the last
22 page, page 41?

1 A. Yes, it is.

2 Q. Okay. And in paragraph 3 of 1165, you
3 say that you considered patent owner's response,
4 right?

5 A. Yes.

6 Q. And then Dr. Smyth's second
7 declaration, right?

8 A. That's correct.

9 Q. Dr. D'Addio's second declaration,
10 right?

11 A. Yes.

12 Q. Dr. Heperin's declaration?

13 A. Yes.

14 Q. And then the documents cited in those?

15 A. Correct.

16 Q. So I want to understand what you mean
17 by that. So you -- in preparing your -- first of
18 all, let me back up.

19 So your second declaration, is it fair
20 that we just call it either your second declaration
21 or reply declaration?

22 A. Either is fine. I'll know what you're

1 talking about.

2 Q. So in preparing your reply declaration,
3 you reviewed Mr. Smyth's second declaration,
4 Mr. D'Addio's second declaration, Dr. Heperin's
5 declaration, and the documents cited in those,
6 right?

7 A. Yes.

8 Q. And you reviewed them to see where you
9 had disagreements with what their opinions were and
10 the documents they cited, right?

11 A. Well, I -- I reviewed what the
12 documents said themselves.

13 Q. Okay.

14 A. And on various cites, citations,
15 references, that -- that appeared in any of those,
16 if I wasn't quite familiar with the area or was
17 wondering what reference it is that that individual
18 was referring to, I went and referred to the
19 citations.

20 Q. You said -- so you said that when you
21 were reviewing Dr. Smyth's second declaration,
22 Dr. D'Addio's second declaration, and Dr. Heperin's

1 declaration, if you found something you weren't
2 quite familiar with, you kind of dug into that?

3 A. Well, that or I just wanted to expand
4 my understanding what basis those statements were
5 being made. You know, a number of things, a
6 statement of fact that I'm well aware of, I don't
7 need to go check the cite for.

8 Q. And -- and what areas in Dr. Smyth's
9 second declaration, Dr. D'Addio second declaration,
10 and Dr. Heperin's declaration did you have to go
11 back and look into a little bit to familiarize
12 yourself?

13 A. I don't have any recollection on what I
14 looked into.

15 Q. Okay. Okay.

16 So I think where we were with -- you
17 had reviewed Dr. Smyth's second declaration,
18 Dr. D'Addio second declaration, Dr. Heperin's
19 declaration, and you found where you had disagreed
20 with what their opinions were?

21 A. I don't think that's a -- a fair
22 description of what I said.

1 Q. Okay.

2 A. I said I read their materials. I
3 broadened my knowledge based on what citations they
4 were using to support their arguments. I evaluated
5 what I thought of the -- the statements being made
6 in those declarations, what I understood from the
7 references, a whole number of things. But it
8 wasn't just focused on what I might have disagreed
9 with.

10 Q. Okay. So what areas of Dr. Smyth's
11 declaration do you agree with?

12 A. I would have to see Dr. Smyth's
13 declaration to recall what things I -- I understand
14 or are simply a statement of fact in his and which
15 are his opinions and which of those are -- are
16 commonly held and which are unique to Dr. Smyth.

17 Q. Would it be fair to say that your
18 second declaration, Exhibit 1165, highlights some
19 differences between what Dr. Smyth thought and what
20 you think?

21 A. I believe there's discussion in this
22 declaration where I clearly state that Dr. Smyth

1 states something or relies on information that I --
2 I consider in a different light and have a
3 different opinion.

4 Q. Okay. That's -- that's all I'm trying
5 to get is that you reviewed these things and then
6 where you had a different viewpoint you then wrote
7 it down.

8 A. That might be an overgeneralization of
9 the process. But there are places in this document
10 where I provide my opinion which might not be in
11 alignment with Dr. Smyth's opinion.

12 Q. Okay. And you provided your second
13 declaration for the Patent Office to rely on in
14 making a decision about the '620 patent? Is that
15 fair to say?

16 A. In some general manner, as best I
17 understand how IPR proceedings work.

18 Q. And if you had a -- a viewpoint that
19 was different from either Dr. Smyth or Dr. D'Addio
20 or Dr. Heperin that you thought was meaningful, you
21 would want to make sure that the -- you wrote it
22 down in your second declaration, that the Patent

1 Office was aware of it?

2 A. Well, my second declaration was
3 composed under advice and work with counsel. And
4 I'm not the only expert in this case that I'm aware
5 of. And so, you know, I made comments in this
6 report that I thought were reflective of the -- the
7 information that were the bases for my opinions.
8 I've expressed other opinions in previous reports
9 in this case that might not have recurred in this
10 one.

11 Q. So within your field of expertise, when
12 you're reviewing Dr. Smyth's second declaration,
13 Dr. D'Addio's second declaration, Dr. Heperin's
14 declaration, and your viewpoints were different and
15 you thought it was a meaningful difference, would
16 you have written them down in your second
17 declaration?

18 A. I don't know. I mean, I'm sure I would
19 have thought about them. I would have thought
20 about them in context of the claims of the '620.
21 And things I might have differed on might not be
22 relevant to those claims. And so, you know, there

1 are -- there are a number of instances of how I
2 would have selected the -- the information that's
3 contained in this second declaration.

4 Q. So if there were instances where you
5 agreed with Dr. Smyth and Dr. D'Addio and
6 Dr. Heperin, you would have said I agree or --

7 A. Not in every instance. A lot of --
8 there again, many of the statements of fact are
9 statements of fact that I don't differ with. So I
10 didn't feel the need to report in that, yep, I -- I
11 agree with that, everybody agrees with that. It's
12 a statement of fact.

13 Q. But I just want to make sure that your
14 second declaration, 1165, contains what you think
15 was meaningful to write down and point out to the
16 Patent Office.

17 A. Well, these are key elements in my --
18 of my responses or my -- my reflections on the
19 information I looked at and I think key elements
20 where I needed to express my opinion to the Patent
21 Office.

22 Q. Because you wanted the Patent Office to

1 rely on --

2 A. Well, I wanted them to understand what
3 -- what my opinion was as an expert in this case.

4 Q. Okay. Okay.

5 And if there were some fundamental flaw
6 with Dr. Smyth's second declaration, Dr. D'Addio's
7 second declaration, or Dr. Heperin's declaration,
8 you would have pointed that out in your second
9 declaration?

10 A. I -- I guess I need to understand what
11 you mean by "fundamental flaw."

12 Q. Well, if you thought they were -- one
13 of these guys was completely wrong on the science,
14 would you -- and because of that, their opinion you
15 thought was inaccurate, would you have highlighted
16 that in your second declaration?

17 A. Each of -- each of these individuals of
18 these -- each of these individuals has a long
19 history as a scientist. So I -- I -- I'm starting
20 from a point where I respect their scientific
21 ability. So I don't think anybody any of them, you
22 know, doesn't understand science and understand the

1 world.

2 They -- they have their opportunity to
3 evaluate things, communicate that, have me decide
4 whether I agree with their evaluation of -- of
5 those facts or not. But -- and -- and in areas
6 where I thought relevant to the '620, relevant to
7 my opinion that needed to be communicated to the
8 Patent Office, that's what's in this declaration.

9 Q. Okay. Yeah, I think that's what I was
10 getting at, which is what you thought was going to
11 be relevant to your opinion that you wanted the
12 Patent Office to hear, you wrote those down after
13 looking at Dr. Smyth's second declaration,
14 Dr. D'Addio's second, and Dr. Heperin's
15 declaration, and then you put forward that opinion
16 and the basis for that opinion in your second
17 declaration.

18 A. In essence, yes. There may be other
19 things that I've even further considered since that
20 time and have many -- in many cases I have
21 additional questions about how opinions were
22 arrived at or how things were done that would allow

1 me to then form other opinions. But at the time
2 that -- this is -- these were the areas that I felt
3 were relevant to the '620 patent that I had an
4 opinion that I wanted to express in the document.

5 Q. Okay. Okay. That's fair.

6 And you also -- besides your second
7 declaration, you also submitted a first
8 declaration; is that right?

9 A. Yes.

10 Q. And that was sometime in early 2017.
11 Does that sound about right?

12 A. Yeah. February-ish or something like
13 that.

14 Q. And that document was submitted in
15 support of Argentum's petition to the Patent
16 Office; is that right?

17 A. Again, I am not an expert in IPR
18 mechanisms and --

19 Q. Okay.

20 A. So if that's -- if that's the legal
21 version of how that supports things, then yes.

22 Q. Okay. And I think you said earlier

1 that you had been deposed a couple of previous
2 times on the '620 patent. Does that sound about
3 right?

4 A. Well, I was deposed regarding my first
5 declaration.

6 Q. Right. Sorry. I didn't mean to cut
7 you off.

8 A. That's all right. And then I was
9 deposed in a previous case where the '620 patent
10 was one of the patents at issue.

11 Q. And that was a district court case --

12 A. Yes.

13 Q. -- where you were then retained on
14 behalf of Apotex, right?

15 A. That's correct.

16 Q. And I think you said it involved the
17 '620 patent that's also at issue here?

18 A. It did, yes.

19 Q. And then it also involved endista
20 (phonetic) that's also at issue here?

21 A. Yes.

22 Q. And you had been retained on behalf of

1 Apotex in that case?

2 A. Yes.

3 Q. And your opinion there in that -- I'll
4 just call that the Apotex case. Is that fair?

5 A. Sure.

6 Q. And then your opinion in that Apotex
7 case was that the '620 patent was obvious; is that
8 right?

9 A. I mean, I guess I'd like to refer to
10 what my opinion clearly was. There were different
11 patent claims. There were different patents and so
12 forth. It's been a long time since that case.

13 Q. Okay.

14 A. So I -- before I can just blatantly
15 state the entire patent was obvious, I'd need to
16 refer to my opinion.

17 Q. Okay. But generally speaking, you --
18 your opinion was that -- I understand that there
19 was other patent claims at issue, maybe even other
20 patents at issue, but that the '620 patent was not
21 valid? That was your very overarching opinion?

22 A. Again, there were -- there was either

1 -- there were specific claims or whatever, but
2 there were portions of the '620 patent that I
3 believed were either -- yeah, that I believed were
4 obvious.

5 Q. And those were the portions of the '620
6 patent, whichever ones they were, that were in that
7 Apotex case?

8 A. That's my recollection.

9 Q. Okay. And then in the Apotex case you
10 went to trial, right?

11 A. That is correct.

12 Q. In December 2016?

13 A. Yes.

14 Q. And then you testified under oath in
15 front of the District of Delaware I think it was?

16 A. Yeah, that's correct.

17 Q. And then you expressed your opinions
18 there?

19 A. Yes.

20 Q. Dr. Donovan, I'm going to ask you to
21 turn to paragraphs 68 and 69 of your second
22 declaration.

1 A. I'm ready.

2 Q. Okay. So is it fair to say -- so in --
3 in paragraph 68 and 69, it's your opinion that the
4 person of ordinary skill in 2002 would have avoided
5 using sodium chloride and dextrose as tonicity
6 adjusters in combination formulation of azelastine
7 hydrochloride and fluticasone propionate?

8 A. Well, a person of ordinary skill, when
9 they're trying to adjust the tonicity of a
10 formulation, is aware of -- of -- you know, several
11 possible materials that they might be able to
12 consider. And so the POSA thinks about what
13 attributes they think might be best or what
14 attributes might -- might limit their formulation.

15 So what I've expressed in paragraph 68
16 and 69 are some of the issues that a POSA would
17 have considered regarding sodium chloride, using it
18 as a tonicity adjuster. It could have been used.
19 But it's got some drawbacks as being an ionic
20 material and potentially wanting to avoid adding
21 additional extraneous ionic compounds, the POSA
22 would likely select against that initially.

1 Same thing with dextrose. Dextrose has
2 issues in low concentrations in formulations,
3 especially formulations that were trying to remain
4 sterile. And so the POSA would likely select
5 against that also.

6 If -- if other agents turned out to be
7 totally unworkable, you could consider these. But
8 initially, there would likely be choices other than
9 those two for specifically the -- the reasons I
10 point out here and maybe some additional reasons
11 that. Those would not necessarily have been the
12 first choices.

13 Q. So just to unpack your answer a little
14 bit, though there's multiple tonicity adjusters
15 that the person in 2002 -- that the person of
16 ordinary skill could potentially have used?

17 A. Yes.

18 Q. But you write here that the person of
19 ordinary skill would have been motivated to avoid
20 sodium chloride. That's in paragraph 68 and 69, "a
21 POSA would have been motivated to avoid using
22 dextrose."

1 A. That's what they say, uh-huh.

2 Q. So -- so it would have been obvious --
3 would sodium chloride and would dextrose have been
4 obvious to use in a combination formulation of
5 fluticasone propionate and azelastine
6 hydrochloride, given what you've articulated in
7 paragraph 68 and 69 of your --

8 A. Well, both sodium chloride and dextrose
9 are known agents that get used to adjust tonicity.

10 Q. Right.

11 A. So a POSA would certainly be aware of
12 them and -- and know that they -- they could choose
13 them. What I said was a POSA knows of these
14 agents, knows of their characteristics, knows of
15 the goals of the formulation, and essentially
16 prioritizes the -- the selection or the -- the
17 investigation of them. And there were several --
18 there were characteristics of both sodium chloride
19 and dextrose that a POSA would have known that
20 would have motivated the POSA to select a different
21 tonicity adjusting agent.

22 Q. So what I'm trying -- what I'm trying

1 to get to the bottom of is, if the POSA was
2 motivated to avoid sodium chloride and avoid
3 dextrose, would they have been obvious tonicity
4 adjusters to use in an azelastine fluticasone
5 formulation?

6 MR. HOUSTON: Objection. Asked and
7 answered.

8 THE WITNESS: As I said, the -- a POSA
9 is aware that sodium chloride gets used to
10 adjust tonicity. They're aware that dextrose
11 gets used to adjust tonicity. They're aware
12 of other materials that get used to adjust
13 tonicity. They're aware that every material
14 that they use that's in solution adjusted the
15 tonicity.

16 So what they -- if they feel that they
17 need to add a material to a formulation to
18 increase the tonicity of that formulation,
19 they then consider characteristics of those
20 materials and choose among them or test
21 several of them to determine which one they
22 want to finally use.

1 Again, I've identified why dextrose and
2 sodium chloride in the case of these -- in
3 the case of the formulation or -- so let me
4 -- and in paragraph 68, the issue with sodium
5 chloride primarily that would cause a
6 formulator to avoid it in -- in this system
7 is that the suspending agent is -- is known
8 to -- hydrates better or continues its
9 hydration -- or gives it the -- the desired
10 characteristics when it has sufficient water
11 activity to hydrate. And it -- it --
12 additional high concentrations of ions
13 reduces the water activity and -- and that
14 becomes -- it may become an issue.

15 BY MR. LAROCK:

16 Q. What --

17 A. And so it's knowing that about sodium
18 chloride. You've -- you've sort of asked general
19 questions about a blank-blank formulation. I don't
20 know, depends on what else is in there.

21 The -- the dextrose issue is about
22 bacterial growth. Other -- the formulations

1 containing dextrose can contain sufficient
2 antimicrobial preservatives to ward against that.
3 So I can't answer in an all general, all
4 formulations.

5 It's about a specific formulation
6 process and how a POSA goes about identifying which
7 are -- which are the -- the -- which agents they're
8 going to look at first of potentially a group of
9 materials that they likely feel would give the
10 result that they're looking for.

11 Q. And that group of agents that's being
12 looked at first, those would be obvious?

13 A. Well, they would be known.

14 Q. Right. I mean, it would be -- it would
15 be known. And would it be obvious for the person
16 of ordinary skill to use those agents as tonicity
17 adjusters?

18 A. Which agents --

19 Q. You said --

20 A. -- specifically?

21 Q. You said that there was prioritization,
22 right? So you said there was a group of agents

1 that the person of ordinary skill would look at
2 first that would likely give the -- likely feel
3 that they would give the result that they're
4 looking for.

5 Does that sound about right?

6 A. I'm not sure. So either if there's a
7 -- if there's a particular phrase you want to back
8 to and you want to have it reread to me, that's
9 fine. Otherwise, if we can just clarify a question
10 that I can answer, that would -- I can -- I can
11 answer.

12 Q. Okay. So I think you said that there's
13 prioritization of excipients that the POSA in 2002
14 was going through in order to figure out whether
15 they're going to -- what tonicity adjuster they're
16 going to use in a formulation.

17 Is that --

18 A. Well, they -- they're aware of -- of
19 agents that are used as tonicity adjusters and they
20 -- they make a decision about which ones they're --
21 they're going to focus on to start with.

22 Q. Uh-huh.

1 A. Doesn't mean that they exclude all of
2 them forever. But you narrow down your initial
3 approaches.

4 Q. And the group of those known tonicity
5 adjusters that the person of ordinary skill is
6 focusing in on, those would be obvious tonicity
7 adjusters to use in the formulation?

8 A. Well, again, there's lots of materials
9 that can be used as tonicity adjusters. A POSA
10 would consider the tonicity adjusters that are used
11 in -- in similar products, in -- that they've used
12 before, that are used frequently. So -- and then
13 they would select based on those characteristics
14 and the characteristics and goals of their
15 formulations which ones they thought would be best
16 suited for the specific formulation that they were
17 concerned with.

18 Q. And if a tonicity adjuster wasn't going
19 to give the -- didn't have or wasn't going to give
20 the characteristics that the person of ordinary
21 skill wanted, that would either -- that would be
22 crossed off the list of tonicity adjusters to use

1 or put at the bottom of the list? How would that
2 work?

3 A. I think it's -- it's, again, an order
4 of prioritization. The tonicity adjuster that the
5 POSA thought would be most advantageous would be
6 looked at first. And if that turned out to be not
7 as advantageous, then based on what was observed
8 about why that didn't give the intended results, a
9 different agent would be selected based on its
10 properties that wouldn't have duplicated what the
11 POSA thought was the negative effect of the one
12 that was initially selected.

13 Q. Okay. So let's take, for example,
14 sodium chloride. And you have a combination
15 formulation of azelastine hydrochloride fluticasone
16 propionate. You're trying to look for a tonicity
17 adjuster for the -- to use in that formulation.

18 A. Okay.

19 Q. And where would sodium chloride be on
20 the list of tonicity adjusters that the person of
21 ordinary skill would be thinking of?

22 A. Depends on what else is in the

1 formulation.

2 Q. Well, there was -- there would be
3 preservatives in the formulation.

4 A. Which ones?

5 Q. Say, for example, EDTA.

6 A. Okay.

7 Q. Phenyl ethyl alcohol.

8 A. Okay.

9 Q. And benzalkonium chloride.

10 A. Okay. Anything else in the
11 formulation?

12 Q. There is polysorbate 80.

13 A. Okay.

14 Q. So, if that's our formulation, you're
15 looking for tonicity adjuster to use in that
16 formulation. That's the situation.

17 Do you understand?

18 A. Azelastine, hydrochloride, fluticasone
19 propionate, at I'm assuming the concentrations near
20 where we've been concerned with regarding the
21 concentration ranges of the '620 patent,
22 polysorbate 80.

1 Q. Uh-huh.

2 A. And benzalkonium chloride, phenyl ethyl
3 alcohol, and EDTA. Those are my formulation
4 components. I already know that's not an optimized
5 formulation. So I --

6 Q. And -- go ahead.

7 A. Why I would want to adjust tonicity at
8 that point is un- -- I'm not sure why that is.

9 Q. Okay. And why isn't that an optimized
10 formulation?

11 A. Well, the fluticasone propionate is not
12 going to be in solution in that. And if -- if it's
13 as a suspension, I'd like to have a suspending
14 agent in there.

15 Q. So let's add Avicel in.

16 A. Which Avicel?

17 Q. Does it -- would it matter?

18 A. Avicel is a whole family of materials.

19 Q. Okay.

20 A. So I need to know which Avicel it is
21 that you are proposing to add.

22 Q. Hypothetically, let's add the Avicel

1 grade that is used in the commercial Flonase
2 formulation so that we know that it thickens.

3 A. Okay.

4 Q. And suspends.

5 A. And my -- my recollection is that's
6 Avicel RC-591. But -- and it's a combination of
7 methylcellu- -- or a combination of
8 carboxymethylcellulose and microcrystalline
9 cellulose. We're going to add that?

10 Q. Yes. Okay.

11 So now we have our formulation that's I
12 think somewhat optimized according to what you
13 would --

14 A. Well, I don't -- I don't know. I mean,
15 we haven't really talked about specific
16 concentrations and so forth. But -- so it sounds
17 to me like it's our first attempt at a formulation.
18 We're -- we're working on paper identifying the
19 materials that we might want to incorporate into
20 that.

21 Q. Okay. Yes.

22 And you're thinking about incorporating

1 a tonicity adjuster.

2 A. Okay.

3 Q. And you're trying to find which one to
4 use?

5 A. Right.

6 Q. Where would sodium chloride be on the
7 list of tonicity adjusters to use?

8 A. It would be on the list. But as I said
9 in paragraph 68, because the formulation has the
10 Avicel in it, the microcrystalline cellulose,
11 carboxymethylcellulose, the formulator is going to
12 be motivated to limit the number of extraneous
13 electrolytes they incorporate into the formulation.
14 So they would likely not choose sodium chloride
15 first.

16 Q. Okay. Given the concern that you
17 articulate for sodium chloride in paragraph 68 of
18 your second declaration, is it possible that sodium
19 chloride isn't even on the list, given this
20 concern?

21 A. No, I don't think that's the case.

22 Q. Okay. And why not?

1 A. Because depending on concentrations of
2 materials, depending on formulations, depending on
3 the characteristics of the formulation, you can
4 oftentimes adjust concentrations of -- of materials
5 to adapt to the -- the entire composition. So it
6 wouldn't be an immediate exclusion, but a
7 formulator would be motivated not to -- not to
8 perhaps start there.

9 Q. Okay. And given the fact that the --
10 the person of ordinary skill would be motivated not
11 to start there, would it be obvious to have used it
12 as the tonicity adjuster?

13 MR. HOUSTON: Objection. Asked and
14 answered.

15 THE WITNESS: Sodium chloride is a
16 commonly used agent to adjust tonicity of a
17 number of formulations. So a formulator
18 would be well aware of the use of sodium
19 chloride as a tonicity adjuster.

20 BY MR. LAROCK:

21 Q. And so it would be obvious to use?

22 A. Well, again, obvious to use is in

1 context of how you're -- how you're planning on
2 using it. And it -- it -- if -- it could be used
3 as a -- as a tonicity adjuster in this case. A
4 formulator would just be motivated to select an
5 alternative on initial formulation to avoid some of
6 the problems that they might later face with sodium
7 chloride being in the formulation.

8 Q. So would it to be fair to say sodium
9 chloride was obvious to think about using but may
10 not actually be used ultimately in the -- in the
11 formulation given the concerns that -- at least the
12 concerns that you articulated in paragraph 68?

13 A. It would have been identified as a
14 tonicity adjuster that a formulator would have been
15 aware of.

16 Q. Okay. That didn't answer my question.
17 So is it a fair characterization to say that sodium
18 chloride would have been obvious to think about
19 using as in this hypothetical formulation we've
20 been talking about?

21 A. Well, it kind of depends on -- on how
22 we're picturing somebody thinking.

1 Q. Okay.

2 A. Is -- is thinking I saw that, my
3 initial reaction is no, I want to select against
4 that. Is -- is that thinking or is -- is that just
5 as it crossed my mind? You know, I considered it
6 but I quickly dismissed it versus I considered it
7 -- considered it for a long period of time. What
8 -- what do you want to use as our definition of
9 thinking so I can answer the question?

10 Q. Well, I'll rephrase it.

11 Is it fair to say that sodium chloride
12 would have been an obvious tonicity adjuster to use
13 -- to consider using in the hypothetical
14 formulation that we've been talking about but may
15 not actually have been used given the concerns
16 here?

17 MR. HOUSTON: Objection. Asked and
18 answered.

19 THE WITNESS: Well, again, it -- it
20 could have been considered as we were
21 considering materials that were going to be
22 incorporated into this formulation; and --

1 and due to some of its limitations regarding
2 the proposed formulation, it likely wouldn't
3 have been selected as the -- the optimum
4 tonicity adjuster to -- to pursue.

5 BY MR. LAROCK:

6 Q. Okay. Okay.

7 So we've been talking about this line
8 of questioning with respect to sodium chloride. Is
9 it fair to say that in the context of dextrose --
10 same hypothetical formulation but in the context of
11 using dextrose as the tonicity adjuster, that it
12 likely -- it wouldn't likely have been selected as
13 the optimum tonicity adjuster to pursue?

14 A. Based on my --

15 Q. Based on -- sorry. Based on what you
16 -- at least the issues that you articulate in
17 paragraph 69?

18 A. Based on my -- my statement in
19 paragraph 69 and my understanding that -- that low
20 concentrations of dextrose are a wonderful
21 nutritional source for bacteria. And as a result,
22 not incorporating them into a formulation that

1 contains -- that's going to be exposed to areas
2 where there are significant bacteria, it might be a
3 -- a better idea than including it.

4 Again, I leave open that there are many
5 formulations with dextrose in them that have
6 antimicrobial preservatives in them, are certainly
7 capable of limiting microbial growth. But as
8 you're thinking about a formulation, if you can
9 avoid a potential problem with that early on by
10 selection of -- of a different agent, that's always
11 a smart thing to do.

12 Q. And then the concerns -- so was that a
13 "yes" to my -- so you said previously in the
14 context of the hypothetical formulation using
15 sodium chloride as the tonicity adjuster that,
16 given the issues that you articulate in paragraph
17 68, that it wouldn't likely have been selected as
18 the optimum tonicity adjuster to pursue.

19 And my question is, does the same
20 conclusion that it's not an obvious tonicity
21 adjuster to use apply to using dextrose in the
22 hypothetical formulation?

1 A. That's it's not an obvious or that it's
2 not an optimal?

3 Q. That it's not an optimum tonicity
4 adjuster to use.

5 A. Well, I think it has some potential
6 negative characteristics for this formulation. And
7 I think other POSAs would -- would also consider
8 perhaps using a different agent to replace dextrose
9 to avoid those issues.

10 Q. And the issues with sodium chloride and
11 the issues with dextrose that you articulate in
12 paragraph 68 and 69, is it your opinion that those
13 would have been readily apparent to the person of
14 ordinary skill in 2002?

15 A. I believe that a person in -- that a
16 POSA in 2002 has access to the same information
17 sources that I looked at and -- and know of and
18 were aware of in 2002 and they would have drawn the
19 same conclusions.

20 Q. But is it your opinion that they would
21 have drawn the same conclusions?

22 A. I -- I have no basis to be able to form

1 that opinion. But as a -- as a POSA, they have the
2 same information, the same knowledge and skills of
3 a POSA, and they would have this -- use the same
4 considerations.

5 Q. I ask because, I mean, you write in
6 paragraph 68 and you write in paragraph 69 that the
7 person of ordinary skill would have been motivated.
8 So I'm just trying to understand.

9 A. They -- they --

10 Q. They would have access to the same
11 information and then they would have been motivated
12 to avoid using sodium chloride and avoid using
13 dextrose?

14 A. Correct. Based on the information that
15 I've used to -- to evaluate their -- the use of
16 sodium chloride or the use of dextrose, a person of
17 ordinary skill would have had that same information
18 and also have been motivated to avoid potential
19 problems with their formulation and select another
20 tonicity adjusting agent that they felt could avoid
21 those problems or avoid other problems.

22 Q. And is it possible, given the issues

1 surrounding sodium chloride and the issues
2 surrounding dextrose that you articulate in
3 paragraph 68 and 69 that the person of ordinary
4 skill would have been so motivated to avoid using
5 those tonicity adjusters in this hypothetical
6 formulation that we're talking about that they
7 would have not considered them at all?

8 A. No, I don't -- again, I -- as I said
9 over and over again, these are certainly possible
10 tonicity adjusters. They are certainly possible to
11 use under these situations. They just have
12 potential issues that a POSA might desire to select
13 a different tonicity adjuster to avoid as they're
14 moving forward in a formulation process.

15 But it doesn't mean that there's --
16 these are never -- that, you know, it doesn't mean
17 that sodium chloride has never have been used in a
18 formulation with Avicel RC-591. It has. It's been
19 used successfully. But it might not be the best
20 choice for a future formulation.

21 Dextrose has been used as a tonicity
22 agent in a lot of formulations. It's still a good

1 tonicity adjusting agent. A POSA would have been
2 motivated to avoid the potential problems that
3 these are known to -- to possess in these -- in a
4 formulation specific to what we've been describing
5 and select a different tonicity adjuster as they
6 come up with a new formulation.

7 Q. Okay. Now, Dr. Donovan, is it your
8 opinion that the use of glycerin as a tonicity
9 adjuster in this hypothetical formulation that
10 we've been talking about, that would have been
11 obvious?

12 A. Yes, because glycerin was even noted in
13 a number of the pieces of prior art regarding the
14 -- the materials that are being included in this
15 formulation, and glycerin is a well known tonicity
16 adjuster to a person of ordinary skill.

17 Q. Now, the same that we've been talking
18 about with sodium chloride and dextrose, that it
19 would have been on the list of tonicity adjusters
20 to use for this hypothetical formulation but there
21 might be downsides to using it, you articulated
22 some for sodium chloride and dextrose.

1 Would the same apply to glycerin?

2 A. Well, there are likely always
3 interactions of a material with other things in a
4 formulation that could lead to a negative
5 consequence or could lead the -- the formulation
6 not to give the attributes that you wanted.

7 Glycerin is a neutral species. So I
8 wouldn't anticipate that at low concentrations that
9 it would have any negative effects on
10 carboxymethylcellulose, microcrystalline cellulose
11 suspending agents.

12 It's typically not used as a microbial
13 nutrient source, so it avoids the issues that --
14 that dextrose had. And it has some positive
15 attributes. It's well known as a humectant, which
16 may serve as a -- as a positive attribute to its
17 selection in use in a nasal spray or use in other
18 topical agents. So it -- it -- it both avoids the
19 problems that were associated with sodium chloride
20 and were associated with dextrose and it also has
21 some positive attributes that would motivate a POSA
22 to select it.

1 Q. So my question was, it's your opinion
2 that using glycerin as the tonicity adjuster for an
3 azelastine hydrochloride fluticasone propionate
4 combination was obvious?

5 A. That the -- the combination we were
6 expressly were talking about, right?

7 Q. Yeah. Say the hypothetical
8 formulation, it was your opinion that glycerin
9 would be an obvious tonicity adjuster to use?

10 A. It was, again, suggested in the art
11 that it could be added to those formulations. A
12 POSA understands it's a tonicity adjusting agent
13 and it has positive attributes that would cause a
14 POSA to strongly consider its use as the tonicity
15 adjusting agent.

16 Q. And so, therefore, it's your opinion,
17 given these positive benefits that you say come
18 along with the use of glycerin, that it would have
19 been an obvious choice to use in this hypothetical
20 formulation?

21 A. It's -- again, glycerin is well known
22 as a tonicity adjuster. It has positive

1 attributes, doesn't possess the same negative
2 attributes of the other two tonicity adjusters that
3 I excluded from -- from initial consideration. A
4 POSA would certainly consider and be motivated to
5 use glycerin in this formulation.

6 Q. So you'd be motivated to use glycerin
7 in this formulation and, therefore, it would have
8 been obvious to use in this hypothetical
9 formulation?

10 A. Is an obvious tonicity adjuster.

11 Q. Okay. And when you say it's obvious --
12 obvious tonicity adjuster to use in this
13 hypothetical formulation, is it -- do you say that
14 even though there are potential drawbacks to using
15 glycerin as a tonicity adjuster in a formulation?

16 MR. HOUSTON: Objection. Form.

17 THE WITNESS: There may be potential
18 drawbacks to any material that you include in
19 a formulation. It's a consideration of the
20 likelihood of those drawbacks, the impact of
21 those drawbacks that -- that cause you to
22 select a particular material, always with the

1 understanding that, you know, there either
2 may be anticipated or unanticipated drawbacks
3 to the addition of that material.

4 (Donovan Deposition Exhibit 2177
5 was marked for identification.)

6 BY MR. LAROCK:

7 Q. Do you recognize what document 2177 is?

8 A. I'm going to -- these look like a set
9 or subset or something of some of the
10 demonstratives that were used at the Apotex trial
11 about my testimony.

12 Q. Okay.

13 MR. HOUSTON: I'm going to place a
14 hearsay objection on the record as to Exhibit
15 2177.

16 BY MR. LAROCK:

17 Q. And I think you confirmed that these
18 were your direct examination demonstratives?

19 A. I mean, it's been a long time since the
20 trial. I haven't reviewed the demonstratives in a
21 long time. But this is what they strike me as.

22 Q. Okay. And you -- did you help put

1 these together?

2 A. I did.

3 Q. Okay. And you agreed with the contents
4 of what was in these documents?

5 A. To the best of my recollection, yes.

6 Q. And I think you said that these were
7 used during your testimony at trial?

8 A. They were prepared to use at my
9 testimony, yes.

10 Q. Do you recall actually using them?

11 A. I do recall using some of them, yes.

12 Q. Okay. And these demonstratives were
13 prepared to help educate the Court on what your
14 opinions were in the Apotex trial?

15 A. Yes. Yes, and provide context for how
16 I came about drawing that -- or proposing -- or how
17 -- how my opinion is supported by the -- the
18 information that's provided on the demonstratives.

19 Q. Okay. So -- and you intended the Court
20 to consider and rely upon what the information was
21 here in educating itself, both about the science
22 and understanding what the basis of your opinion

1 was?

2 A. I'm sorry. Can you say that again?

3 Q. You intended the Court to consider and
4 rely upon your demonstratives in understanding both
5 the science and the basis of your opinions that you
6 testified to at trial -- in the Apotex trial?

7 A. I guess I'm not expert enough to know
8 how the Court handles demonstratives in -- in their
9 considerations and rulings. These were prepared to
10 -- to demonstrate what the -- what the -- the
11 specific pieces of information I was testifying
12 about were and were a way of providing a framework
13 of information around them.

14 But there was plenty more information
15 in my reports regarding that and I assume that the
16 Court would refer to those in addition to relying
17 on the demonstratives.

18 Q. Yeah. I didn't -- I didn't mean to --
19 to suggest that the Court was only relying on --
20 upon your demonstratives and not anything else.

21 It was just you prepared these to help
22 the Court understand and familiarize what your

1 opinion was as a -- whatever you want to call it,
2 as a framework for your opinions but it was to help
3 kind of compartmentalize so that it was easy to
4 discuss both at the time and for the Court to
5 understand piecemeal what your opinion was?

6 A. I guess, in a very general way, I'll
7 accept that that was one of the reasons to prepare
8 these demonstratives.

9 Q. Okay. Do you have a -- do you have an
10 alternate reason why you would prepare
11 demonstratives?

12 A. I -- you know, again they -- they help
13 me -- you know, I'm a faculty member. I'm used to
14 teaching from PowerPoint slides. So -- so it's
15 sort of a natural way for me to present
16 information.

17 How the Court would prefer to have
18 information presented to them I think is -- is not
19 the same as how I prefer to -- to present it to --
20 to undergraduate professional and graduate
21 students. But it's a -- it's a -- it's an easy
22 way. And if we felt the Court would be -- would

1 benefit by seeing these, it -- it -- it was away
2 for me to communicate that I was comfortable with
3 and hopefully a way that made it easier for the
4 Court to understand.

5 Q. That's fair. That's what I was trying
6 to get at. Okay.

7 How about we turn to the bottom right
8 corner. You'll see it says DDX. Those are page
9 numbers. We'll turn to DDX 5.33.

10 And do you see this is a -- a chart or
11 a matrix that's shown on DDX 5.33?

12 A. Yes, I see that.

13 Q. Then we have three columns. One column
14 is Flonase. One column is Astelin, correct?

15 A. Correct.

16 Q. One column is Flonase, right?

17 A. And that column, it represents the
18 components in the Flonase product as described by
19 the left-hand column.

20 Q. Yeah. So I'll just -- I'll go through
21 the columns first and then I'll go through the
22 rows.

1 A. Okay.

2 Q. So we have one column is the "Flonase"
3 is the header of that column.

4 A. Okay.

5 Q. And then another column is "Astelin."
6 And another column is "Obvious Combination
7 Formulation."

8 A. Yep.

9 Q. Right? So those are the three columns.
10 Then we have one, two, three, four, five, six --
11 seven rows, right?

12 A. I think you need to count that again.

13 Q. One, two, three, four, five, six, seven
14 -- eight.

15 A. And if you count the header row.

16 Q. So eight to nine columns.

17 A. Eight to nine rows.

18 Q. Eight to nine rows, sorry.

19 And each of these rows represents a
20 component in a formulation. Is that fair to say?
21 There's no header on this column but there's --

22 A. Represents a category of formulation

1 components.

2 Q. Okay. So we have that first row is
3 active ingredient as a category of component in a
4 formulation, right?

5 A. Yes.

6 Q. Next one -- next one down is particle
7 size, right?

8 A. Yes.

9 Q. Then vehicle?

10 A. Yes.

11 Q. One, two, three -- so the fourth one
12 down is preservatives?

13 A. Yes.

14 Q. And then the fifth one down is
15 surfactants?

16 A. Yes.

17 Q. Sixth one down is thickening agents?

18 A. Yes.

19 Q. Seventh one down is tonicity adjuster?

20 A. Yes.

21 Q. And then pH is the last row?

22 A. Yes.

1 Q. And then populating the columns, the
2 corresponding column and row for the Flonase and
3 Astelin, and each one of these rows of categories
4 of components of the formulation are the components
5 of Astelin and Flonase that were commercially
6 available. Is that right?

7 A. I'm sorry.

8 Q. I'll strike that.

9 So those are the headers of the
10 columns. And those are kind of the headers of the
11 rows that we just discussed.

12 And can you describe for me what is in
13 the rest of the cells of this matrix?

14 A. Well, under the Flonase column, all of
15 the information in the cells corresponds to the
16 component of the formulation Flonase and the
17 material that brings that about.

18 Same thing for Astelin. The component
19 in the formulation that is best attributed to the
20 -- the category is included in the cell and the
21 obvious formulation combination are things that
22 would have been obvious to include in a combination

1 formulation of fluticasone propionate and
2 azelastine hydrochloride.

3 Q. So you beat me to the punch. But the
4 obvious combination formulation being the component
5 that would be obvious to include in a combination
6 formulation of these, right?

7 A. Yes.

8 Q. And you testified at trial -- well,
9 under demonstrative, you list as an obvious
10 tonicity adjuster to use -- to include in this
11 combination formulation, dextrose and sodium
12 chloride.

13 Do you see that?

14 A. I see that.

15 Q. Do you still stand by that opinion
16 today?

17 A. I think I've said that for the last
18 hour, that they were well known tonicity adjusting
19 agents. They had some drawbacks for inclusion in a
20 -- in a combination formulation.

21 I've identified a number of -- of
22 potential tonicity adjusting agents that could have

1 been included in a combination formulation.

2 I've identified weaknesses for dextrose
3 and sodium chloride as the agents that I -- that
4 might have been preferred in that combination
5 formulation. So I've said that for the last hour.
6 I said it at trial.

7 Q. Well, you don't say here that the --
8 the dextrose and sodium chloride would be obvious
9 to include, but the person of ordinary skill would
10 be motivated to avoid using them?

11 A. That's not what the purpose of this
12 chart was for. If I wanted to express all of the
13 potential reasons and communicate it to the Court
14 what -- how a POSA might find advantages or
15 disadvantages in each one of those tonicity
16 adjusting agents, I probably would have had a
17 different demonstrative prepared regarding that
18 information.

19 Q. But looking at this demonstrative, it
20 was your opinion that dextrose and sodium chloride
21 were obvious tonicity adjusters to include in --
22 the --

1 A. They were -- they were known tonicity
2 adjusters. They were included in two other
3 formulations that are sitting here on this chart.
4 You know, they could have been considered. I think
5 there were materials that had better properties for
6 the combination formulation that would have -- that
7 a POSA would have been motivated to consider over
8 dextrose or sodium chloride. It doesn't mean that
9 they couldn't have considered dextrose or sodium
10 chloride or any of the other agents in that list.

11 Q. But your current opinion as to why the
12 person of ordinary skill would be motivated to
13 avoid using dextrose and sodium chloride is not
14 contained in DDX 5.33?

15 A. None of my opinions about why any of
16 the materials that I've stated or that the
17 demonstrative states were -- could be used in the
18 obvious combination formulation are included in
19 DDX 5.33.

20 Q. Okay. That didn't answer my question.
21 My question was -- DDX 5.33, you told the Court
22 that it was obvious to use dextrose and sodium

1 chloride in the obvious combination formulation.
2 And it does not say that the person of ordinary
3 skill would be motivated to avoid using those,
4 dextrose and sodium chloride, as tonicity adjusters
5 in this obvious combination formulation?

6 A. DDX 5.33 has a column that says
7 "obvious combination formulation" and it contains
8 materials that would have been obvious to include
9 in that -- in a -- in a combination formulation of
10 fluticasone propionate and azelastine.

11 There is nothing in that table that
12 describes on any of the formulation components how
13 a POSA would have selected from among the choices
14 given.

15 Q. It was your intention to tell the
16 Court, using DDX 5.33, that dextrose and sodium
17 chloride were obvious tonicity adjusters to
18 include, right, in the -- in this -- in this
19 combination formulation of azelastine and
20 fluticasone propionate?

21 A. The cell regarding obvious combination
22 formulation and tonicity adjuster contains a list

1 of potential tonicity adjusters that were -- were
2 taught in the art for a POSA to consider for a --
3 either a combination formulation or a formulation
4 containing one or the other of those agents.

5 Q. And you didn't tell the Court in this
6 demonstrative that sodium chloride and dextrose
7 would have been obvious to consider using but not
8 actually use and maybe avoid using altogether; is
9 that right?

10 A. I don't remember exactly what I told
11 the Court. I'm talking about what's showing in
12 this demonstrative. If you want to show me my
13 testimony from the Court, I will refresh myself
14 about what it is that I testified regarding the
15 tonicity adjuster and be able to an answer your
16 question.

17 Q. But looking at DDX 5.33, there's
18 nothing on DDX 5.33 that says don't use or -- that
19 the person of ordinary skill would be motivated to
20 avoid using dextrose and sodium chloride?

21 A. There's nothing on DDX 5.33 that
22 indicates anything about any of the choices in that

1 column regarding whether it should be used or
2 shouldn't be used. They were all materials that --
3 that were identified as obvious materials to
4 include in a combination formulation.

5 Q. This still doesn't answer my question.
6 So you testified that the obvious combination
7 formulation column was a listing of components to
8 use -- components to include in an azelastine
9 hydrochloride fluticasone propionate combination
10 formulation?

11 A. As I said, I don't remember exactly
12 what I testified. This is a demonstrative that was
13 provided to the Court. As part of my oral
14 testimony, the demonstrative includes in the column
15 obvious combination formulation agents that would
16 have been obvious to a POSA at the time to include
17 in a combination formulation.

18 Q. And it doesn't say obvious to include
19 but not use or be motivated to not use?

20 MR. HOUSTON: Objection. Asked and
21 answered.

22 THE WITNESS: None of the -- none of

1 the information in that column has any
2 additional instruction to the POSA regarding
3 how to select from among the choices.

4 BY MR. LAROCK:

5 Q. Was it your intention in preparing this
6 obvious combination formulation to -- that's shown
7 here on this demonstrative, DDX 5.33, to convey
8 that it would have been obvious to use any one of
9 the tonicity adjusters listed as the tonicity
10 adjusters in the obvious combination formulation?

11 A. Again, this was prepared a year and a
12 half ago. I don't remember all of the details
13 about how it was that I felt this was the -- a good
14 way of communicating the information. So you asked
15 the motivation for doing it. It's a year and a
16 half ago. I don't recall.

17 MR. HOUSTON: Adam, before you start a
18 new topic, it might be a good time for a
19 break.

20 MR. LAROCK: Okay. Let's take a break.
21 (Whereupon, a recess was taken
22 from 1:08 p.m. to 1:22 p.m.)

1 BY MR. LAROCK:

2 Q. Welcome back.

3 A. Thanks.

4 Q. So can you -- can you explain to me
5 what a preservative challenge test is?

6 A. A preservative challenge test is
7 something that's prescribed by -- I actually think
8 there's a USP standard for it. But it's certainly
9 looked to by the FDA when they're approving a
10 commercial product that they -- you take your
11 product and you expose it to a known titer of well
12 characterized bacteria. And I'm not sure what else
13 is included in that -- in the mixture or multiple
14 of -- of assays. And you challenge the
15 antibacterial level that's in your product. Is it
16 capable of -- of killing or not providing a growth
17 source for the bacteria that you've placed into it.

18 And the idea is that similar loads of
19 bacteria will be exposed to your product during the
20 product's use time and you need to assure that
21 you'll have sufficient antibacterial or
22 antimicrobial coverage in there to -- to keep -- to

1 render it such that it doesn't grow and provide a
2 -- a -- a community of bacteria that you then
3 reinoculate upon administration. But there's --
4 there's details that I just don't recall.

5 Q. Okay. You said it was looked to by
6 FDA. Is it -- is it FDA required? Do you know?

7 A. It's my understanding that the FDA
8 will --

9 Q. Want you to do this?

10 A. Well, I -- essentially, I think in your
11 -- in the chemical manufacturing controls package
12 for an FDA-approved project that you have to
13 demonstrate that your antimicrobial preservative
14 for a multiuse system is adequate.

15 If you decide to do something
16 different, than the prescribed test, you may be
17 able to justify that to the FDA. Each -- each
18 dosage form and its site of application or whatever
19 might be unique and might be a reason to deviate
20 from the exact prescribed test.

21 Q. Got it.

22 A. But the FDA is going to ask for a

1 demonstration that the -- that commercial product
2 is -- is able to sustain a -- essentially, a
3 zero-bacteria burden during its shelf life under
4 normal uses.

5 Q. I think we were on the same page about
6 that. So the FDA wants to know whether or not
7 whatever preservatives you're using in your
8 multidose formulation will be sufficient to inhibit
9 the bacterial growth that's expected during shelf
10 life.

11 And whether you show that by
12 preservative challenge test or some other way,
13 they're going to want to see that your
14 preservatives are doing what they're supposed to
15 do.

16 A. Yes. They need data to demonstrate
17 that.

18 Q. So is it safe to assume then that when
19 you have an FDA-approved product, that it's either
20 passed a preservative challenge test or somehow
21 sufficiently been shown to the FDA that that
22 multidose product does not have unacceptable

1 bacterial growth in it?

2 A. I think it's to -- to understand that
3 it passed whatever test or there was experimental
4 data to support the -- the lack of bacterial growth
5 under whatever conditions it was -- it was -- those
6 tests were performed.

7 Q. But the FDA would have ultimately
8 concluded -- if we're dealing with an FDA-approved
9 product, the FDA would have ultimately come to the
10 conclusion that the preservatives that are in the
11 system are functioning as they should and
12 inhibiting bacterial growth as they should?

13 MR. HOUSTON: Objection. Form.

14 THE WITNESS: Yeah, that's potentially
15 more analysis that the FDA likely concludes
16 about things. They -- they have -- whatever
17 data was presented to them, they found that
18 to be sufficient to demonstrate that the
19 product would not be a source of bacterial
20 contamination to the user during the shelf
21 life that it's labeled for.

22 BY MR. LAROCK:

1 Q. Okay. And by 2002 Flonase was a
2 multidose nasal spray that was FDA approved?

3 A. That's my understanding, yes.

4 Q. Okay. And it contained multiple
5 preservatives to inhibit bacterial growth, right?

6 A. I can check. I can use this or I can
7 use my report. It's a better thing to rely on.

8 Q. Sure.

9 A. Okay. As I state in my report, Flonase
10 contained --

11 Q. Where are you looking, first?

12 A. Paragraph 60.

13 Q. Sorry. Continue.

14 A. That Flonase contained the
15 preservatives benzalkonium chloride and phenyl
16 ethyl alcohol.

17 Q. Okay. And those were the two
18 preservatives that are contained in the commercial
19 Flonase product in 2002?

20 A. Those are the two agents that are
21 intentionally added to that product as
22 antimicrobial -- antimicrobial preservatives.

1 Q. And dextrose is also in -- contained in
2 the commercial Flonase product in 2002 as a
3 tonicity adjuster, right?

4 A. That's my recollection, yes.

5 There's multiple pages so I don't get
6 messed up here.

7 Yes, Flonase uses dextrose as a
8 tonicity agent -- tonicity adjusting agent.

9 Q. Okay. Now, the dextrose in Flonase
10 isn't a source of -- is not a source of
11 unacceptable -- unacceptable microbial growth in
12 the Flonase product?

13 A. Well, Flonase contains antimicrobial
14 preservatives that have been demonstrated to
15 maintain the lack of growth. They kill or -- or
16 render harmless, somewhat harmless, bacteria that
17 -- that can enter into that formulation. So
18 there's likely no bacteria there to need the
19 dextrose to feed off of.

20 Q. Okay. So if the person of ordinary
21 skill were going to use in a combination
22 fluticasone azelastine formulation the

1 preservatives from Flonase, the concern about
2 dextrose being a source of unacceptable microbial
3 growth wouldn't be an issue. Right?

4 A. I don't agree. There's always a
5 concern that your antimicrobial preservatives will
6 fail under some use challenge that you don't mock
7 up in your -- in your evaluation of your
8 preservatives as you're filing your -- your CMC
9 documents with the FDA.

10 So the -- a POSA always holds out the
11 possibility that they will have some undesired
12 failure of their system and then the dextrose will
13 serve as a great growth media.

14 Q. But at least in the context of Flonase,
15 the preservatives contained in the Flonase product
16 were sufficient to show the FDA that dextrose was
17 not a source of unacceptable -- unacceptable
18 microbial growth?

19 A. In that formulation, in that package,
20 they were shown to provide -- the two preservatives
21 were shown to provide sufficient coverage against
22 the test bacteria to assure the FDA that it met the

1 FDA's preservative effectiveness guidelines,
2 whatever they call them.

3 Q. Okay. And the two preservatives that
4 are in Flonase were shown to provide sufficient
5 coverage against the test bacteria to assure the
6 FDA that it met the FDA's preservative
7 effectiveness guidelines, that was done even though
8 dextrose was in the Flonase product?

9 A. Can you ask that again?

10 Q. So you had said that the two
11 preservatives in Flonase were shown to provide
12 sufficient coverage against the test bacteria to
13 assure the FDA that it met the FDA's effectiveness
14 guidelines -- preservative effectiveness
15 guidelines.

16 A. But I think I said things about the
17 container that the Flonase was provided in and the
18 concentrations that were in that formulation.

19 Q. The concentrations of the --

20 A. Antimicrobial preservatives and the
21 other materials that are in that formulation,
22 including the dextrose.

1 Q. Well, it's your opinion that the
2 components of Flonase would have been obvious to
3 use in a combination, fluticasone propionate
4 azelastine -- azelastine hydrochloride combination
5 formulation, right?

6 A. Based on -- do you want to make that a
7 bit more detailed, or ask me each component or
8 something?

9 Q. So Flonase contains fluticasone
10 propionate?

11 A. Yes.

12 Q. And you think that was -- would be an
13 obvious active ingredient to use in a fluticasone
14 propionate azelastine hydrochloride?

15 A. Yes.

16 Q. Water as a -- water is the vehicle in
17 Flonase. You think that would have been obvious to
18 use?

19 A. Yes.

20 Q. And the preservatives benzalkonium
21 chloride and phenyl ethyl alcohol that are
22 contained in Flonase, you think those would have

1 been obvious to use?

2 A. Yes.

3 Q. And the surfactant polysorbate 80, you
4 think that would have been obvious?

5 A. Yes.

6 Q. And the thickening agent Avicel?

7 A. Yes, yes. RC-591, yes.

8 Q. And my question is -- so setting aside
9 the tonicity adjuster of Flonase, all the other
10 components of Flonase you think would have been
11 obvious to include in a combination azelastine
12 fluticasone formulation?

13 A. Yes.

14 Q. And my question is, the preservatives
15 that were in Flonase had been sufficient to
16 overcome any concern about dextrose being a source
17 of unacceptable microbial growth?

18 A. I guess I don't know that. There are
19 plenty of product reports that are -- are given to
20 the FDA, are given to the manufacturer, that I
21 don't follow. So I have -- I have no knowledge of
22 whether there were product reports of -- of

1 microbial failures of Flonase.

2 Q. And in putting together your reply
3 declaration, did you look and see whether there
4 were any public reports about failures of Flonase
5 to control microbial growth?

6 A. Not specifically, no.

7 Q. Okay. And I'm looking specifically at
8 paragraph 69 of your second declaration. You don't
9 cite any prior art or examples of -- or instances
10 of Flonase failing to adequately inhibit microbial
11 growth.

12 A. Paragraph 69 is merely a description of
13 -- of dextrose being included in formulations at
14 low concentrations and how that can aid and -- and
15 provide a medium for good bacterial growth. It
16 doesn't say anything about the performance of the
17 Flonase product.

18 Q. Right. And so what I'm trying to get
19 at is, was the flow -- was there -- were there
20 failures of Flonase to adequately control microbial
21 growth such as the dextrose would be a source of --
22 of microbial growth as you talk about in paragraph

1 69?

2 A. I don't know. But I -- I don't need
3 those reports to -- to confirm to me that dextrose
4 serves as a growth medium for bacteria. And that
5 is always a risk, that you could be formulating a
6 growth medium for bacteria that are exposed to your
7 formulation somehow.

8 Q. And this concern that dextrose would be
9 a source of microbial growth, that was a concern
10 even before the Flonase product?

11 A. Yes. It's a -- it was -- I mean, it's
12 well known that low concentrations of dextrose
13 support bacterial growth.

14 Q. Okay. But yet the Flonase product was
15 able to sufficiently -- or the FDA was sufficiently
16 satisfied with the data on Flonase to find that it
17 adequately inhibited microbial growth even in light
18 of the fact that it contained dextrose?

19 A. The Flonase product must have passed or
20 provided sufficient data to the FDA to assure the
21 FDA that it -- it could resist microbial growth
22 during its shelf life.

1 Q. So just the simple fact that multidose
2 product contains dextrose doesn't necessarily mean
3 that there is concern, an incurable concern, that
4 dextrose would be a source of microbial growth?

5 A. Well, I think it means that there's --
6 there's always a concern. A POSA understands that
7 you can -- you can address that concern through the
8 use of adequate antimicrobial preservatives.

9 Q. I'm handing you what's been marked
10 Exhibit 1007. Are you familiar with this exhibit?

11 A. Yes, I am.

12 Q. And what is it?

13 A. This is a patent that is -- the
14 inventor is Helmut Hettche.

15 Q. And you've reviewed this patent a
16 couple of times?

17 A. I've seen this patent before, yes.

18 Q. Okay. And is it fair to -- today if we
19 call this either the Hettche patent or the '194
20 patent?

21 A. Sure.

22 Q. Okay. So Hettche discloses a number of

1 suitable preservatives for use with azelastine
2 formulations; is that right?

3 A. I don't know. Do you want to point me
4 to a column and lines or would you like me to find
5 that information?

6 Q. Well, I mean, you have reviewed the --
7 the Hettche patent?

8 A. I have.

9 Q. Previously?

10 A. You know, I don't remember where and in
11 what places things are described in here. So if
12 there's particular things you'd like to point out,
13 I would be happy to go to those sections.
14 Otherwise, I will take the time to familiarize
15 myself with the patent and then we can continue.

16 Q. Sure. So Column 2, roughly line 46.

17 A. Okay.

18 Q. And so my question was, Hettche
19 discloses a number of suitable preservatives for
20 use in a fluticasone formulation; is that right?

21 A. Yes.

22 Q. And how many preservatives are listed

1 here?

2 A. I don't know. I've -- I don't know
3 that I've ever taken the time to count them. I can
4 do that now.

5 Well, a number of things that Hettche
6 also lists are sort of general categories. So I'm
7 just going to --

8 Q. So if it's -- so just -- I recognize
9 that fact. And would it be fair to just -- if
10 there's a general category and then it specifically
11 lists a preservative that we just talked about, the
12 ones that are specifically listed?

13 A. Oh, the for "example parts" of them?

14 MR. HOUSTON: Objection.

15 THE WITNESS: Or I got confused.

16 BY MR. LAROCK:

17 Q. Right. I'm just -- I'm trying to get
18 an understanding of you of how many preservatives
19 are listed here as being acceptable.

20 A. Like I said, I haven't counted them.
21 There's several. I mean, I count what I would
22 consider five sort of general families of

1 preservatives and then analogs within those
2 families are -- are included in some of the lists.

3 Q. Okay. So one family is -- edetic acid.
4 Is that --

5 A. That's -- that's used as one of the
6 examples, yes.

7 Q. And then there's, for example, the
8 disodium salt, the calcium salt, and the calcium
9 sodium salt.

10 A. That's what's stated, yes.

11 Q. So are those three different
12 preservatives?

13 A. Well, they're all based on EDTA
14 basically. There's salt forms, so how they're
15 commercially provided, how you would -- salt forms
16 oftentimes have a more rapid dissolution rate. So
17 might choose the salt form rather than the acid
18 form during a formulation process, but people use
19 either.

20 And yes, they -- they all provide --
21 edetic acid in solution and edetic acid, in and of
22 itself, is typically not a sufficient preservative

1 in most -- certainly most nasal sprays, most --
2 many other aqueous-based formulations. It, in and
3 of itself, doesn't have a broad enough spectrum of
4 coverage to be suitable by itself, but it's used in
5 combinations with other materials quite frequently.

6 Q. And it's listed here as being a -- a
7 preservative?

8 A. Preservative and stabilizer.

9 Q. So is it fair to characterize the
10 specific examples of edetic acid as three different
11 preservatives or stabilizers that can be used in a
12 Flonase formulation -- sorry, in an azelastine
13 formulation?

14 A. Well, they are three distinct chemical
15 species but they're just a way of arriving at the
16 very same edetic acid in solution. And it's a
17 formulator's preference which one they -- they use
18 as a starting material.

19 Q. Okay. So should we count that as three
20 or should we count that as one?

21 MR. HOUSTON: Objection. Form.

22 THE WITNESS: You can count it however

1 way -- however you would like to.

2 BY MR. LAROCK:

3 Q. Let's -- there's three examples here,
4 so let's count three. Okay. Is that fair?

5 A. Sure.

6 Q. The next one is lower alkyl
7 p-hydroxybenzoates?

8 A. Parahydroxybenzoates.

9 Q. Para, yeah. Sorry.

10 A. Yes.

11 Q. That's a preservative?

12 A. The -- the family. Some of the members
13 of the parahydroxybenzoate family are used as
14 preservatives.

15 Q. So that would be a fourth in the -- in
16 our list of acceptable preservatives?

17 A. Sure.

18 Q. Then the -- the next one, the
19 chlorhexidine?

20 A. Uh-huh.

21 Q. That's another preservative that can be
22 used?

1 A. It can be used in certain -- in certain
2 circumstances. It's certainly not preferred in
3 topical -- topical mucosal delivery systems. But
4 it's certainly known as a preservative.

5 Q. And then phenylmercuric borate?

6 A. Yep, it's a known preservative. It's
7 also not currently used in pharmaceutical
8 preparations.

9 Q. Okay. My question just is it's being
10 listed as an acceptable -- the Hettche patent lists
11 phenylmercuric borate as a -- as an acceptable
12 preservative.

13 A. It -- it provides examples. I'm not
14 sure that I read what the Hettche patent tells me
15 as all of those are preferred.

16 Q. Okay. But it's a -- it's a possible --
17 it's a suitable -- Hettche disclosed it as being
18 suitable?

19 A. Hettche discloses them as an example.

20 Q. And -- okay. So that's -- now we're up
21 to four or five?

22 A. I think chlorhexidine was probably

1 five.

2 Q. So we're up to five now?

3 A. Correction. We passed phenylmercuric
4 borate, so six.

5 Q. And then thimerosal, line 55?

6 A. Uh-huh. Which, again, has fallen out
7 of favor as a preservative since 1992.

8 Q. So that's seven preservatives?

9 A. Yes.

10 Q. This then right around line 1, 2 -- 58,
11 it says "other suitable preservatives are," and
12 then it lists a number of other preservatives.

13 A. Right. The quaternary ammoniums.

14 Q. And so the -- how many preservatives
15 are listed there?

16 A. Well, there's three in the initial list
17 and then the -- starting at page -- or at line 68
18 and continuing to Column 3, it describes preferred
19 preservatives among the quaternary ammoniums
20 compounds. So already Hettche is establishing that
21 not every one on his list is preferred.

22 There are -- well, there were three in

1 the initial description and then there are --
2 describes the preferred preservative is
3 benzalkonium chloride.

4 Q. Okay. So is that in addition to the
5 other three, so four?

6 A. That would be a distinct chemical from
7 the other three, yes.

8 Q. And so four plus the additional seven
9 that we had already discussed earlier in that
10 paragraph?

11 A. Yeah.

12 Q. So we're up to 11.

13 A. Okay. But, again, he's already
14 identified benzalkonium chloride as preferred
15 compared to the rest of the preservatives.

16 Q. And then Hettche also discloses in
17 Column 4 suitable isotonization agents; is that
18 right?

19 A. On line 47.

20 Q. I was looking specifically 31 to 35.

21 A. Okay. I'll look at those lines. Okay.

22 Q. And how many isotonization agents are

1 listed there?

2 A. Six.

3 Q. Then further down, Column 4, right
4 around line 51, we have possible thickening agents
5 for use in an azelastine formulation, right?

6 A. Yes.

7 Q. Then starting at line 54, we have such
8 thickening agents may, for example, be -- and then
9 it lists a whole host of thickening agents?

10 A. Correct.

11 Q. And how many thickening agents are
12 listed there?

13 A. I haven't counted them.

14 Q. Can we?

15 A. Well, the -- I'll count the specific
16 names that he's called out for -- in the examples.

17 Q. Rather than the families, you're
18 saying?

19 A. Yes. I count 11.

20 Q. Okay. So we have 11 thickening agents,
21 six isotonization agents, and 11 preservatives
22 disclosed in Hettche for use in an azelastine

1 formulation?

2 A. Sure. Yep.

3 Q. And I want to direct your attention to
4 paragraph 60 of your second declaration.

5 Specifically the table you have in paragraph 60.

6 You have -- page 25 or 28 of your report, depending
7 on what number you're looking at.

8 A. I've got page 25.

9 Q. And my question is, you have a chart,
10 Flonase label, Hettche, and '620 patent Claims 42
11 through 44 are listed in the columns, right?

12 A. Okay.

13 Q. And your chart under Hettche is missing
14 for preservatives the 11 preservatives that we
15 already discussed with the exception of
16 benzalkonium chloride and edetate disodium, right?

17 A. Well, I believe the chart highlights --

18 Q. It's just a yes-or-no question.

19 A. Then why don't you reask the question,
20 please.

21 Q. So would you agree that with the
22 exception of benzalkonium chloride and edetate

1 disodium, the chart you have in paragraph 60 is
2 missing the other 11, or I guess nine now,
3 preservatives that Hettche discloses?

4 A. Okay. Yet, if you read the -- the
5 context for the table, at least in the paragraph
6 directly above the table, and I'd have to go back
7 and somewhat review the -- the couple of paragraphs
8 before that, but in that text, the Hettche (Example
9 I)/Astelin are a combined moniker.

10 So, in essence, that table heading
11 should have said Hettche (Example I)/Astelin. And
12 what's included in the table are, in essence, the
13 components of the Astelin product from the label.

14 Q. Okay. But it just says Hettche, right,
15 in your chart in paragraph 60?

16 A. Yeah. All of the text above clearly
17 indicates that Hettche (Example I)/Astelin are --
18 are what's being referred to.

19 Q. So you -- should we ignore everything
20 in Hettche except for Example I?

21 A. That's not what I'm saying. I'm saying
22 if we read the table as it was intended, we can

1 read the information.

2 "The table below further illustrates
3 this. A formulator would reasonably expect using
4 all three preservatives in a formulation combining
5 the active ingredients in Flonase and Hettche
6 (Example I)/Astelin."

7 And that's exactly what the table
8 contains as the formulations that are described by
9 the Flonase label, formulation that's described by
10 the Astelin label, which happens in the table to be
11 labeled Hettche instead of Hettche (Example I)/
12 Astelin which is really what it refers to.

13 Q. So when considering Hettche, you're
14 only considering Example I?

15 A. That's not what I'm saying. I'm just
16 saying, if you -- if we want to talk about what's
17 in the chart, that's what's in the chart is the
18 components from the Astelin label that are also
19 described in Hettche (Example I).

20 If we want to discuss Hettche as a --
21 as a body of work, we can do that. But it's not
22 what was -- it's not what is summarized in that

1 table.

2 Q. But there's disclosures from Hettche
3 that are missing from the table and then I think
4 we've established that, correct?

5 A. The table describes Hettche (Example I)
6 and -- and/or the Astelin product and its
7 components. That's what -- that's what that table
8 describes or contains, which is clearly described
9 in the paragraph above the table.

10 Q. And why are you focusing in on
11 Example I of Hettche?

12 A. Because I believe I've come to know
13 that the embodiment of that is -- or very close to
14 the Astelin product. That's my recollection at
15 least. But let me -- at least my report indicates
16 that the -- the patent, the Astelin, the commercial
17 embodiment of that patent.

18 Q. What paragraph are you looking at?

19 A. I'm looking at paragraph 60.

20 Q. So because Astelin is the commercial
21 embodiment of that patent, how does that relate to
22 Example I of Hettche?

1 A. It's -- again, it is a my understanding
2 that Example I with potentially minor modifications
3 is, in essence, the Astelin formulation and
4 describes the Astelin -- the components that are
5 described in the Astelin label.

6 Q. Okay. And what's that understanding
7 based on?

8 A. My previous reading of the Hettche
9 patent and discussions I've had with -- with
10 counsels regarding what the -- what the commercial
11 embodiment of this patent is.

12 Q. And so my question is, is it your
13 opinion that Example I of Hettche is the commercial
14 embodiment of the Astelin product?

15 A. I guess I'd like to --

16 Q. Or did you learn that information from
17 somewhere else?

18 A. I -- it -- my -- my recollection -- I
19 mean, it's certainly both. I mean, I'm -- I'm not
20 the one to determine that something is the
21 commercial embodiment of something. So I need that
22 information from others. But I can look at the --

1 at the Astelin label and I probably would need some
2 additional information about the specific details
3 of the concentrations of materials in the Astelin
4 product. I know I have seen those in the past.

5 But I -- to be absolutely certain that
6 this Example I describes the exact or with only
7 minor modifications the Astelin product, I'd
8 needing to go back and refer to those. But I've
9 seen them in the past. And, again, it's my
10 recollection and I -- I've been -- been told and I
11 -- that this is the commercial embodiment of -- of
12 Hettche is the Astelin product.

13 Q. And why is the fact that Hettche
14 (Example I) embodies Astelin important, or I guess
15 is it important that -- that Astelin commercial
16 product is an embodiment of Hettche (Example I)?

17 A. Well, Hettche's more than just the
18 commercial embodiment that we see as the Astelin
19 product. So there are -- there's information in
20 Hettche that's more detailed about azelastine, more
21 detailed about formulation possibilities, other
22 possible routes of administration for azelastine

1 that's provided in the '194 patent that a POSA can
2 learn from for a number of different things.

3 And so the -- the -- the commercial
4 embodiment is certainly an important characteristic
5 if we're thinking about -- about how it came to the
6 market and what it contains and what it's -- what's
7 approved for use and what it's stable in and so
8 forth, what components are stable. But Hettche --
9 the '194 has more information in that. And, you
10 know, that complete description of the Hettche
11 patent and its utility was outside of the -- of the
12 -- the pages that I wanted to add to my
13 declarations.

14 Q. Why is it important that Astelin -- why
15 is it important that Astelin is an embodiment of
16 Hettche (Example I) and why is that important to
17 your analysis?

18 A. Well, it just provides an example.
19 Astelin is a -- is a commercial product that's been
20 successfully formulated and its basis was the
21 Hettche patent. So the materials that were
22 described in Hettche, the -- and in fact very close

1 to Example I, was brought forward and brought into
2 the marketplace.

3 So already a POSA would learn from that
4 that these particular components are -- are stable
5 for the time period that product is labeled for and
6 have -- have met various regulatory bodies'
7 approval processes.

8 Q. So -- so is there some sort of --
9 because the person of ordinary skill and I take it
10 that you're saying would understand that Astelin is
11 a commercial embodiment of Hettche (Example I),
12 that there's some sort of added meaning to
13 (Example I) as opposed to the rest of the Hettche
14 patent?

15 A. Well, it demonstrates that Example I,
16 in addition to being an example that was certainly
17 provided in the patent -- but that there's no
18 indication that -- let's see. There are some
19 things in the -- in the description of the
20 Example I text that aren't complete to help
21 somebody understand or -- to help someone know
22 exactly how to take the information from Example I

1 and convert that into a -- into a commercial
2 product.

3 So for example, the pump sprayer is not
4 disclosed. And so there would need to be some
5 evaluation of that to determine really whether this
6 could become a -- an approved product or not. So
7 this Example I is a -- a great brief description
8 of -- of a formulation.

9 The POSA learns from the fact that it
10 becomes a commercial embodiment that with
11 appropriate materials selected, other
12 investigations conducted, that it was those
13 materials were compatible and allowed it to be
14 brought into the commercial marketplace.

15 Q. But my question is, is there some sort
16 of added meaning to the person of ordinary skill
17 knowing that Hettche embodies Example I -- or that
18 Astelin embodies Example I of Hettche?

19 A. Outside of -- well --

20 Q. So --

21 A. Hettche describes an example. He
22 teaches a lot of information in the -- in the '194.

1 And Hettche provides an example of how to -- to
2 select among some of the lists and materials and so
3 forth to give an example of a nasal drop or eye
4 drop containing 0.1 percent azelastine
5 hydrochloride system. Somebody happened to take
6 that Example I and study it, develop it, and put
7 together the -- the appropriate regulatory packages
8 to have it approved as a commercial product.

9 Q. But compared to the rest of the
10 disclosures of Hettche, is Example I more important
11 because it embodies a commercial product or less
12 important?

13 A. It -- it teaches a POSA that those
14 combinations of materials have been studied
15 sufficiently, have a data package around them to
16 have reached -- to have -- to have received
17 regulatory approval. That's all it -- it --
18 knowing that that's the commercial embodiment,
19 that's what it tells a POSA.

20 Q. So because there's more information in
21 this data package that would be known about
22 Example I, given the fact that it -- it's a

1 commercial embodiment of Example I, that would have
2 extra meaning to a person of ordinary skill looking
3 to Hettche compared to the rest of Hettche's
4 disclosure?

5 MR. HOUSTON: Objection. Asked and
6 answered.

7 THE WITNESS: It -- Example I simply
8 gives the components that -- and knowing that
9 Example I has become the commercial
10 embodiment known as azelastine -- known as
11 Astelin, it just simply tells a formulator, a
12 POSA, that you can combine these materials
13 all described in the '194 patent and it was
14 able to receive regulatory approval as a
15 commercial product.

16 BY MR. LAROCK:

17 Q. And given the fact that taking the
18 disclosures of Hettche, putting them together in a
19 certain way to come up with Example I, the fact
20 that resulted in FDA-approved product, does that
21 have more meaning to the disclosure of Example I or
22 less meaning?

1 A. It doesn't have -- it's not a gradation
2 of value. It has meaning.

3 Q. So equally as important to the rest of
4 Hettche's disclosure?

5 A. It just describes an example and that
6 example has then been taken and developed
7 sufficiently and other investigations done
8 appropriately to convince a regulatory body to
9 approve that for human use in several countries.

10 Q. So unlike some of the disclosures in
11 Hettche, the fact that you have more data about
12 what is disclosed in Example I means that it was --
13 the person of ordinary skill looking at Hettche
14 would be more focused on Example I as opposed to
15 the other --

16 A. We don't necessarily have more data.

17 Q. -- parts of Hettche?

18 Well, you have the FDA data that you've
19 been talking about.

20 A. I don't necessarily have access to it.
21 I have an understanding of the -- of the
22 information the FDA requires a -- a sponsor to

1 provide for it to approve a drug for use in the --
2 and sale in the United States. But I don't
3 necessarily have access to it nor do I need access
4 to it.

5 Q. Just the fact that you know Example I
6 resulted in an FDA-approved product?

7 A. It's just -- it's a working example of
8 the '194 patent, what the '194 patent teaches.
9 It's a working example and it's actually a
10 commercial example.

11 Q. And my question is, because it's a
12 working example and as you put it a commercial
13 example, is Example I more or less important to the
14 person of ordinary skill when looking at Hettche?

15 MR. HOUSTON: Objection.

16 BY MR. LAROCK:

17 Q. Compared to the rest of Hettche's
18 disclosure?

19 MR. HOUSTON: Objection. Asked and
20 answered.

21 THE WITNESS: That's not how a POSA
22 looks at the information provided in the '194

1 patent.

2 BY MR. LAROCK:

3 Q. How would the person of ordinary skill
4 look at the information provided in the '194
5 patent?

6 A. How would they?

7 Q. Yes.

8 A. Hettche teaches about azelastine.
9 Hettche teaches about a number of methods for
10 administration of -- of azelastine. Hettche
11 teaches about a number of components that are
12 suggested for inclusion with those, all based on
13 how a -- how somebody would take azelastine and
14 combine it with materials to accomplish a
15 particular purpose. That's how a POSA looks at the
16 information in '194.

17 Q. So there's -- there's no more or less
18 importance given to any of Hettche's disclosure
19 compared to those?

20 A. It's just a recognized fact that
21 Example I was -- was described in '194 and then a
22 formulation very similar to Example I was -- was

1 brought forward and is now a commercial product.

2 Simple as that.

3 Q. And the question is, compared to the
4 rest of Hettche's disclosure, is Example I more or
5 less important?

6 MR. HOUSTON: Objection. Asked and
7 answered.

8 THE WITNESS: A POSA doesn't put more
9 or less value on a material that's -- that's
10 presented in the patent.

11 BY MR. LAROCK:

12 Q. So all of Hettche's disclosure,
13 Example I, II, and everything else that's disclosed
14 is all on an equal playing field in terms of its
15 importance to the person of ordinary skill?

16 A. Well, it depends on what the person of
17 ordinary skill in the art is learning from
18 components of the material in the Hettche patent.
19 And there are a number of purposes for reading the
20 '194 and learning from it. What's -- what's more
21 important to the particular POSA reading is very
22 dependent on what their -- what -- what are they

1 learning. What -- what is it that the '194 is
2 teaching them that they can now bring to -- bring
3 to bear on some challenge that they're -- they're
4 facing.

5 Q. So going back to paragraph 60 of your
6 declaration, when you list Hettche (Example I)/
7 Astelin as your discussion of the Hettche patent,
8 why did you limit that discussion to Example I?

9 A. Well, I'm going to read paragraph 60.
10 (Witness reviewed document.)

11 THE WITNESS: Okay. Can you restate
12 your question?

13 BY MR. LAROCK:

14 Q. In paragraph 60 of your second
15 declaration, why do you list Hettche (Example I)/
16 Astelin when you discuss Hettche as opposed to the
17 other disclosures of the Hettche patent?

18 A. The Hettche patent discloses a number
19 of -- of -- of things again about Astelin, about
20 formulations, about potential routes of
21 administration, and so forth. Astelin itself is
22 the -- is the specific nasal spray dosage form

1 that's described in Example I. And since many of
2 the topics in -- in my declaration and as described
3 in paragraph 59 even, that -- looking at multidose
4 nasal spray formulation.

5 So the -- the Astelin -- the Example I
6 of Hettche is the -- is certainly one aspect of the
7 '194 that a POSA would -- would look to and -- and
8 -- and evaluate as they're evaluating the rest of
9 the '194 patent. So it's just a -- it's a -- it's
10 a highlight, not necessarily a magnitude of
11 importance, but -- but that -- to draw attention to
12 Example I clearly describes a nasal spray
13 formulation.

14 Q. Okay. So in your discussion of
15 Hettche, you're not limiting yourself to
16 specifically Example I, the disclosure of
17 Example I?

18 A. In what sense?

19 Q. Well, all through paragraph 60 and the
20 table in paragraph 60, all -- I think you've been
21 testifying now for a while, all relate to Example I
22 and not the other disclosures of Hettche.

1 A. That's -- it's certainly a focus, which
2 is why it's highlighted there. It doesn't mean
3 that I've -- a POSA would ignore all of the other
4 teachings in the '194. But it's a -- it's a
5 focused description of one clearly described aspect
6 in the '194 patent.

7 Q. And because of that, would the person
8 of ordinary skill be more or less likely to look at
9 Example I compared to Example II?

10 A. Well, the person of ordinary skill in
11 the art is going to look at all of the information
12 that's provided in Hettche.

13 Q. So if -- if the person of ordinary
14 skill is looking at all of the information in
15 Hettche, is the person of ordinary skill also
16 focusing in specifically on Example II as a -- as a
17 focused discussion of Hettche's disclosure?

18 A. Possibly. And I'm sure the POSA would
19 have read that, would have made -- would have
20 learned about materials that would be appropriate
21 for nasal ointments. Would have -- would have
22 learned about other materials that were added to

1 that formulation to make that a -- to at least
2 demonstrate that that can be made. And whether
3 they reflected on anything else related to a nasal
4 spray formulation is -- is up to their particular
5 read and evaluation. But they would have certainly
6 read that information, learned from it. What they
7 did with that knowledge is entirely up to them.

8 Q. So the person of ordinary skill is
9 looking to make a combination formulation of
10 azelastine hydrochloride fluticasone propionate as
11 a nasal spray and they're looking at Hettche. Are
12 they interested in Example I to the same extent
13 that they're interested in Example II?

14 A. Well, Example I gives a specific
15 example of a nasal spray. So that's -- if that's
16 what the POSA is intending to also formulate,
17 they're going to pay attention to that example.
18 Then they may look at Example II or Example III and
19 note any distinct differences or similarities in
20 those formulations as they -- as the formulator
21 POSA determines how they're going to approach
22 either making Example I a modification of

1 Example I, a modification of Example II, or they'll
2 look throughout Hettche for other information to
3 guide them for the formulation that they desire or
4 think would be best to make.

5 Q. So if there was an inconsistency
6 between Example I which the person of ordinary
7 skill would focus in on and another disclosure
8 within Hettche, how would the person of ordinary
9 skill resolve that inconsistency?

10 A. You have to give me an example. I -- I
11 mean, it depends on what the inconsistency is and
12 really whether it's inconsistent. You've defined
13 it as that. But perhaps others might not find it
14 to be inconsistent.

15 Q. Well, would there be more or less
16 emphasis put on Example I because it's a nasal
17 spray and you know it's an embodiment of a
18 commercial product or you know a commercial product
19 embodies it compared to the rest of Hettche's
20 disclosure?

21 MR. HOUSTON: Objection. Asked and
22 answered.

1 THE WITNESS: Example I teaches a POSA
2 that combining these materials results in a
3 nasal spray. And further information about
4 Example I now tells us that nasal spray went
5 through further development, went through
6 additional testing, and became available as a
7 commercial product. That's what the
8 information a POSA knows about the '194, the
9 place of Example I in the '194, and the fact
10 that Example I has now become the commercial
11 embodiment of the -- or at least of one --
12 one part of the '194 patent.

13 BY MR. LAROCK:

14 Q. So my question is, because the person
15 of ordinary skill has more information, further
16 information, about Example I knowing that it's -- a
17 commercial product embodies it, are they more or
18 less likely to follow Example I as opposed to some
19 other portion of Hettche?

20 A. The only thing Example I becoming a
21 commercial embodiment tells a POSA is that those
22 materials combined in that formulation have met

1 regulatory standards, the amount of the active
2 ingredient along with those materials at their
3 concentrations in the dose -- in the packaging that
4 was provided, in the shelf life that was given
5 passed regulatory standards and must have
6 demonstrated safety and efficacy. That's what a
7 POSA understands a commercial embodiment of
8 Example I or some other aspect of the patent to
9 mean.

10 Q. And because you have more information
11 about Example I, given the fact that you knew it
12 was a commercial embodiment, is that given some
13 sort of additional focus compared to other portions
14 of Hettche?

15 A. I -- I just said what -- what Example I
16 becoming a -- commercial embodiment tells a POSA is
17 that they -- the materials in that formulation were
18 demonstrated to be safe, the -- the active agent
19 was demonstrated to be effective for the indication
20 that was sought by the product, the product in its
21 packaging meets the regulatory standards for the
22 country that it's -- that it's being commercialized

1 and approved in. That's what -- that's what the
2 commercial embodiment aspect of Example I tells a
3 POSA.

4 Q. And because the person of ordinary
5 skill -- you keep saying what a commercial
6 embodiment of Example I means. It means you have
7 more information potentially about Example I.
8 Either you have the data or you just simply know
9 that there's a commercial product out there that
10 embodies Example I, right?

11 A. I know that, yes.

12 Q. And because Example I was able to
13 combine the disclosures of Hettche in such a way
14 that it would get regulatory approval, does the
15 disclosure of Example I have more or less -- would
16 the person of ordinary skill be more or less
17 focused on Example I as opposed to another portion
18 --

19 A. And again, I've said many times it's
20 not -- it's not a magnitude. It's what the POSA
21 learns from the information provided in the '194,
22 in the patent. And the example provides a working

1 example, and the POSA, if they know that's become a
2 commercial embodiment, knows a few additional
3 pieces of supplementary information about what was
4 -- about stability, about safety, about efficacy,
5 but in a very general sense. And that's what they
6 -- that's what they interpret from this
7 information.

8 Q. But that information would be on the
9 same level playing field as all of the rest of
10 Hettche's disclosure in terms of the person of
11 ordinary skill looking at it and evaluating it?

12 A. It's not a magnitude. The Hettche --
13 the '194 patent provides information. And how a
14 POSA wants to use that information is a -- is their
15 own choice based on why they're reading it, what
16 they're thinking about, what -- what they decide to
17 do with the information.

18 But it's not a magnitude of this is
19 any -- you know, that every POSA would agree that
20 one column is more important than another column in
21 the patent. It has entirely to do with the '194
22 patent provides information teaching in the art and

1 how a POSA would -- would take that teaching and do
2 whatever they wanted to do with it.

3 Q. That wasn't my question. My question
4 was all of Hettche disclosures on the same level
5 playing field, not --

6 A. But nobody evaluates things as a more
7 or less as far as the -- as far as a patent or any
8 other piece of -- of information. It's a matter of
9 -- an individual POSA with an individual plan or
10 idea or lack of knowledge or something may have
11 found one information source to be useful or more
12 useful to them and one part of it. But that's
13 their own personal view. A POSA in general reads
14 the information provided in the art and learns from
15 all of it.

16 Q. Okay. So looking at Example 60, why
17 then is your discussion of Example 60 when talking
18 about Hettche limited to Example I?

19 A. Because in Example I, it is an example
20 of an aqueous-based nasal spray and -- and it's --
21 Example I does provide that it's -- it has a
22 preservative in it, so the intention of that was

1 likely a multidose nasal spray system. And -- and
2 if a POSA was intending on developing a different
3 aqueous-based nasal spray containing azelastine,
4 the information provided in Example I shows them an
5 example of components that have -- that could be
6 selected for such a formulation.

7 Q. The person of ordinary skill would know
8 that those excipients worked at least because they
9 had worked for their intended purpose because they
10 were already a part of the commercial product that
11 was embodying Example I?

12 A. I think that might be more than the
13 POSA would know. Yeah, because in Example I,
14 there's nothing specific about the particular
15 plastic or glass bottle that was used, the pump
16 sprayer that was used, and so forth.

17 Q. But from a -- from a formulation
18 perspective, the person of ordinary skill looking
19 at Example I would know that those preservatives
20 were acceptable, knowing the fact that you have a
21 commercial product out there that embodies
22 Example I, you would know that these preservatives

1 would have been useful for -- for at least what it
2 discloses here?

3 A. Well, in the container and packaging
4 selected for that commercial product, yes.

5 Q. And the person of ordinary skill
6 wouldn't have that same level of understanding
7 about any of the other 11 preservatives, for
8 example, of Hettche because they were not included
9 in that commercial product that embodied Example I?

10 A. I -- I -- I don't think I agree with
11 that. I mean, the difference between the example
12 being a nasal spray and teaching a POSA and other
13 things that were done and added to Example I to
14 make a commercial product is -- those other things
15 are not part of the '194 and it's not what a POSA
16 would learn from the '194.

17 So how I would read Example II and
18 understand it, if it had become a commercial
19 product, I would probably read it the same way and
20 also have the same questions of, well, you know,
21 you don't tell me what kind of -- of final
22 packaging. And that's an important aspect of a

1 commercial product.

2 There -- there may be -- I would have
3 to look closer at Example II but I'm sure there are
4 a number of things in Example II I could point out
5 that -- that are not specific. And if there were a
6 commercial product of -- that embodied Example II
7 that I would have to think about how much I -- you
8 know -- whether a -- just what that information
9 provides me and how I learn from that as a POSA in
10 -- in taking that information in and either just
11 joining it into my general knowledge base or using
12 it for another purpose.

13 Q. So going back to the table of
14 Example 60, I think it was your testimony that this
15 table was mislabeled, specifically the column of
16 Hettche?

17 A. Well --

18 Q. That it should be Hettche Example I?

19 MR. HOUSTON: Objection.

20 Mischaracterizes the witness's testimony.

21 THE WITNESS: Yeah, I -- I don't recall
22 that I used the term "mislabeled." I think

1 perhaps the -- the label on the table could
2 have been more informative. But in the table
3 description in the text it's clear that that
4 column refers to Hettche (Example I)/Astelin.
5 And so the table plus the table description,
6 which is how someone always reads a -- a
7 graphic, it's clearly described what the
8 contents of that table are.

9 BY MR. LAROCK:

10 Q. Do you draw a distinction between
11 Hettche Example I and Astelin or are they kind of
12 synonymous in your view?

13 A. In terms of their components, they're
14 synonymous.

15 Q. So they may have other differences but
16 how you're using them would be the same for the
17 components?

18 A. In the case of this table, they're the
19 same. There's actually some additional components
20 I believe in the Astelin label, which is why this
21 isn't labeled Astelin label. But those components
22 are also given in the -- in Example I.

1 Q. And I think you said you focused in on
2 Example I because it was an example of a nasal
3 spray?

4 A. That's what I -- a starting point, yes.

5 Q. And then you also knew that it was
6 approved, there was a product out there that had a
7 lot of the information that was in Example I, at
8 least the components of the formulation, setting
9 aside the bottle, setting aside what pump actuator
10 you're using, and the container?

11 A. I mean, I learned at a later point that
12 Example I -- that is the commercial embodiment of
13 Example I.

14 Q. When exactly did you?

15 A. I don't recall.

16 Q. Did you have that understanding during
17 the Apotex case?

18 A. I -- I expect that I did.

19 Q. Okay. So at least as of that time you
20 knew that Hettche (Example I) and Astelin --

21 A. That's my recollection.

22 Q. Okay. And when you've been using

1 Hettche throughout, both in your first declaration,
2 your second declaration, have you been using it to
3 describe Hettche's entire disclosure or just
4 (Example I)/Astelin?

5 A. I would need to go back and refer to
6 that. But I think -- if there are -- there are --
7 I know that there is information provided in the
8 '194 that maybe in shorthand I refer to as the
9 Hettche patent that has -- that describes other
10 things besides Example I.

11 So I would need to back and actually
12 check my -- the consistency. But I think,
13 especially in section -- in Section 8, that the
14 (Example I)/Astelin is intended to describe the --
15 the components described in Example I or known as
16 the commercial embodiment of azelastine.

17 Q. And when you're -- and when you're
18 labeling the Hettche (Example I)/Astelin, you are
19 focusing the reader in on Example I to the
20 exclusion of other -- other disclosures in Hettche,
21 right?

22 A. No, I'm just -- we're -- we're -- the

1 -- Section 8 is describing preservatives in a
2 general sense, okay. And we've already discussed
3 that there are other preservatives described in the
4 '194. Okay. But the '194 also has an example of a
5 nasal spray where a selected preservative along
6 with the EDTA was included in the example.

7 Q. So you wanted to make sure to highlight
8 that?

9 A. Well, it's -- it's -- Hettche already
10 described benzalkonium chloride as a preferred
11 preservative. It's well known in the --
12 benzalkonium chloride is well known in the art,
13 benzalkonium chloride plus EDTA is well known in
14 the art. And so it's merely a way of -- of
15 highlighting that, yes, everybody knows that
16 benzalkonium chloride is a preservative, Hettche
17 identified it as a preferred, he included it in his
18 example of a nasal spray, along with EDTA. And
19 many POSAs are aware of that combination of
20 preservatives.

21 Q. So the fact that Example I used EDTA
22 as a preservative was a reason that you wanted to

1 highlight that when you were writing about the
2 Hettche patent?

3 A. It was just for completeness, too, that
4 Example I includes EDTA. And it includes
5 benzalkonium chloride and it's a nasal spray. And
6 if I'm comparing information in the '194 and the
7 nasal spray example in the '194 in particular,
8 benzalkonium chloride and EDTA were the
9 preservative -- were -- could -- could act as a
10 preservative combination in that example.

11 Q. And that's how the person of ordinary
12 skill would read Hettche as -- knowing that there's
13 a more general disclosure of -- of preservatives,
14 for example, but then knowing that Example I used
15 those preservatives to come together as a nasal
16 spray that eventually was approved?

17 A. Well, the POSA simply understands that
18 that's how Hettche designed that first example
19 nasal spray. Doesn't mean that it couldn't have
20 been designed a different way or a different nasal
21 spray couldn't have been designed a different way.
22 But that's how Hettche chose to -- to provide an

1 example of a nasal spray which, again, tells us
2 that Hettche, in 1992, knew that benzalkonium
3 chloride was preferred and that benzalkonium
4 chloride got used with EDTA.

5 Q. And given the fact that Example I is a
6 working example, that means that there was -- the
7 person of ordinary skill would understand that and
8 be focusing on those disclosures knowing that
9 there's another disclosures of the Hettche patent
10 but Example I tied everything together as a select
11 way of coming up with a formulation that worked?

12 A. Well, it tells a POSA that Hettche knew
13 the same thing about preservatives that other POSAs
14 know about preservatives and that benzalkonium
15 chloride is a preservative. And, in fact, in nasal
16 sprays it's one of the most frequently used
17 preservatives.

18 Hettche knew that EDTA is a
19 preservative stabilizer and gets used in
20 combination with benzalkonium chloride and with
21 other preservatives and chose to -- in -- in the
22 example formulation chose to combine benzalkonium

1 chloride and EDTA.

2 Q. What happens when azelastine
3 hydrochloride is put in the solution?

4 A. Can you be more specific?

5 Q. Well, does it -- would you agree that
6 it disassociates as azelastine and hydrochloride?

7 A. What use are we putting it into?

8 Q. Sorry. Water.

9 A. Okay. What pH?

10 Q. Does it matter?

11 A. Potentially. How much are we putting
12 in water?

13 Q. Well, just as a general exercise, the
14 salt would, when put in water, disassociate?

15 A. Again, if I'm putting a salt form into
16 water and I've put material in that's below the
17 solubility of the -- of the salt, at a reasonable
18 pH range, if it's a strong acid salt form, it
19 disassociates.

20 Q. Okay.

21 A. So the chloride ion leaves the --
22 leaves the salt molecule structure and for a very

1 small infinitesimal short period of time I am left
2 with a protonated or cationic form of the drug
3 which then re-equilibrates based on the pH of the
4 solution.

5 Q. So those disassociated ions, one's a
6 cation and one's an anion?

7 A. If I've hydrochloride salt, the
8 chloride that disassociates as an anion and the
9 drug form if it retains the proton is a cation.

10 Q. Got it. And those are examples of
11 electrolytes, cations and anions?

12 A. Electrolytes are species that are
13 charged.

14 Q. Okay. So those are examples of a
15 larger category of things called electrolytes?

16 A. Yes.

17 Q. Generally speaking?

18 A. They have -- as long as they have a
19 charge, they could be classified as an electrolyte.

20 Q. Okay.

21 MR. HOUSTON: Adam, we've been going
22 about an hour 20. Before you pull out a new

1 exhibit, I thought I might ask if now would
2 be a good time for a break.

3 MR. LAROCK: Sure.

4 (Whereupon, a lunch recess was taken
5 from 11:48 a.m. to 12:46 p.m.)

6 A F T E R N O O N S E S S I O N

7 BY MR. LAROCK:

8 Q. Welcome back.

9 A. Thanks.

10 Q. During lunch, did you talk to your
11 counsel about the substance of the testimony that
12 you've already gave?

13 A. No.

14 Q. Or anticipated testimony?

15 A. No.

16 Q. Okay. Where we left off before lunch,
17 there was a discussion of azelastine hydrochloride
18 being dissolved into an aqueous solution and we had
19 come to an agreement on the chloride ion comes off
20 -- or the -- the azelastine hydrochloride
21 disassociates from the chloride ion and then the
22 azelastine molecule?

1 A. Positively charged.

2 Q. Positively charged. And those are --

3 A. Which then equilibrate.

4 Q. And those are examples of cations and
5 anions, which are broadly classified as
6 electrolytes?

7 A. Yes.

8 Q. And so you had said that -- a previous
9 discussion that it depended upon what the pH was of
10 the solution?

11 A. Uh-huh.

12 Q. And why does that matter?

13 A. Well, because whether the -- the -- the
14 -- if we have a drug that's a hydrochloride salt,
15 when the -- when the salt disassociates and you
16 have the charged form of the drug, depending on
17 what the pH of the environment is, that proton can
18 come off of that drug and leave you an unchanged
19 form.

20 Q. Okay.

21 A. And likely will do so.

22 Q. And if the environment of the solution

1 is less acidic, meaning it's more basic, how does
2 that affect the -- that protonation equilibration
3 you were talking about?

4 A. Well, the equilibrium is based in a
5 thing we call the PKA, which is the acid
6 disassociation constant and its logarithm. And
7 depending on what the acid disassociation constant
8 of that protonated species is will tell you exactly
9 how much of the proton will come off and what ratio
10 of charged and uncharged specie you have. So as
11 you -- if you have a protonated base compound and
12 you start increasing the pH, more and more of that
13 protonated species will form the neutral
14 unprotonated species.

15 Q. So in a basic aqueous environment, that
16 protonated species will either be less or exist for
17 less time because of the -- of ion is going to come
18 off?

19 A. It depends entirely what the PKA is, so
20 it depends on what the pH and what the PKA is but
21 it's very straightforward after you know those two
22 values.

1 Q. Okay. And then on the flip side, if
2 the aqueous solution that is -- that azelastine
3 hydrochloride is being dissolved in was acidics
4 that had a pH of 1, what effect would that have on
5 the protonated species?

6 A. Proton would be retained.

7 Q. Okay. And then where is the proton?

8 A. As long as -- again, depends entirely
9 what the PKA is.

10 Q. Yeah. And then in the -- in the
11 context of azelastine, where is that proton bonding
12 to or associating with?

13 A. It's bonded to a -- an atom, in
14 essence, on the molecule itself.

15 Q. And one of those -- so it's bonding to
16 a tertiary amine part of azelastine?

17 A. I'd have to take a look at the
18 structure of azelastine and discern that. But if
19 azelastine has a tertiary nitrogen, that's
20 certainly a likely possibility for where it's going
21 to be.

22 Q. You don't know --

1 A. I don't have the structure.

2 Q. Without looking at the --

3 A. I don't have the structure of
4 azelastine memorized, no.

5 Q. If you look at your declaration, your
6 second declaration, paragraph 28.

7 A. Okay.

8 Q. Do you agree there that there's a
9 tertiary amine binding site of azelastine would be
10 where azelastine protonates?

11 A. Yeah, based on this paragraph, when I
12 wrote the paragraph I certainly was referring to
13 the structure of azelastine and tertiary.

14 Q. How many tertiary amine does azelastine
15 contain?

16 A. I don't recall.

17 Q. I'm going to hand you what's been
18 marked Exhibit 1008. So on the second page --
19 first of all, are you familiar with this exhibit?

20 A. I'm familiar with the PDR and it seems
21 like it's the -- at least part of the azelastine --
22 PD Astelin section of the PDR, 2000 edition.

1 Q. So you're familiar with it?

2 A. Yeah, I'm familiar with the PDR.

3 Q. And do you see on the second page under
4 the column Astelin, it gives a description but it
5 also gives the structure?

6 A. Right.

7 Q. So looking at the structure of
8 azelastine as contained in 1008, Exhibit 1008,
9 you'd agree that the structure of azelastine has
10 three tertiary amines?

11 A. No, I wouldn't agree with that.

12 Q. Okay. Why not?

13 A. Because the -- the other two nitrogens
14 associated with that ring structure really aren't
15 tertiary nitrogens.

16 Q. And your basis for that?

17 A. Just my general understanding of
18 chemistry. Those have other functional properties
19 that differ from what we anticipate the tertiary
20 nitrogen, how it behaves, and they're classified as
21 a different functional group species compared to
22 the -- the one in the big ring on the bottom, which

1 is a classic tertiary nitrogen.

2 Q. So because these two nitrogens in the
3 central ring structure you say are -- they have
4 different properties?

5 A. Well, they're conjugated. Again,
6 identifying functional groups in -- in chemical
7 molecules is not something I'm prepared to do about
8 azelastine or other structures today.

9 And I can read from the chemical name
10 various functional groups that I might be able to
11 -- to associate with various parts of that
12 molecule. But I would need some other reference
13 texts to help me identify what -- what a chemist
14 would actually label those nitrogens to be. And I
15 just don't have the appropriate reference materials
16 to do that today.

17 Q. So you don't actually know whether --
18 you think they might be classified as -- as a
19 different functional group than a tertiary amine
20 but you don't know for certain whether they are or
21 aren't, having not looked at this other reference
22 material?

1 A. I haven't made a systematic analysis of
2 the other functional groups contained in azelastine
3 to both name them and be able to tell you what sort
4 of electronic structure contributions they make.
5 I'm aware that the protonated form of the molecule
6 or the salt form is made off of the tertiary
7 nitrogen as shown in this picture -- in the -- in
8 the diagram.

9 Q. So having not made that systematic
10 analysis of these other functional groups, the two
11 other tertiary amines that I identified, which do
12 you think may not be classified as tertiary amines
13 -- may or may not be protonated, you just don't
14 know the answer to that question?

15 A. No, I haven't been asked to form an
16 opinion on that. I know that the salt form that is
17 known as azelastine hydrochloride has the salt
18 structure, the protonated nitrogen being the
19 nitrogen indicated in the diagram on this page.

20 Q. Okay. But you haven't done an analysis
21 to determine whether or not any other functional
22 groups like the two other tertiary amines would be

1 protonated in an aqueous environment?

2 A. As a POSA in 2002, I have not seen in
3 the art that I've looked at any information about
4 that.

5 Q. And how do you determine -- and by you
6 I'm talking about the person of ordinary skill.
7 How would the person of ordinary skill determine
8 whether or not one of these functional groups was
9 protonated?

10 A. I -- I think you need to clarify that.
11 Whether one of many is protonated, whether -- which
12 one is protonated? What are you asking?

13 Q. So if the person of ordinary skill in
14 2002 wanted to determine whether these two other
15 tertiary amines were protonated, how would that
16 person of ordinary skill go about doing that?

17 A. Well, a formulator acting as a POSA
18 wouldn't be the person doing that. I haven't been
19 asked to provide an opinion on how a formulator or
20 a chemist would go about doing that. So at this
21 point in time I am not prepared to -- to start
22 describing accurately how that would be

1 accomplished.

2 Q. Okay. So in forming your second
3 declaration you said that you considered
4 Dr. Smyth's deposition transcript; is that right?

5 A. Yes.

6 Q. And do you recall in that deposition
7 transcript where he was asked whether azelastine
8 could be protonated at more than one site?

9 A. I'd like to see that.

10 Q. You don't remember that?

11 A. There were many things in Dr. Smyth's
12 report and other reports. I don't know that I
13 remember which report I may have or may not have
14 seen information about protonation of azelastine or
15 whether it was in prior art.

16 Q. So it's your opinion that azelastine is
17 monovalent but it could also been di- and
18 trivalent, you just don't know whether or not these
19 other amine structures -- tertiary amine structures
20 would be protonated having not made that systematic
21 analysis of the prior art on that issue?

22 A. Well, the -- the information about

1 azelastine that I'm aware of and that was -- well,
2 that -- the information about azelastine that I'm
3 aware of reports that azelastine has one PKA value,
4 which leads me to believe that, unless I'm under
5 very extreme conditions, there will be only one
6 protonation site in that molecule.

7 And extreme conditions are extreme
8 values of pH. And exactly what the PKAs of the
9 other functional groups that have acidic and basic
10 nature in that molecule, I'm unaware of what they
11 are and I can't speak to when they would be
12 protonated or not.

13 Q. Okay. What would be an example of an
14 extreme -- an extreme value of pH? How about a pH
15 of 3?

16 A. I wouldn't consider a pH of 3 extreme.

17 Q. Okay. Below -- below a pH of 3, would
18 that be extreme?

19 A. Well, certainly if -- 3 is not extreme.
20 Some value below 3 approaches what I might call
21 extreme. I'll volunteer that maybe below 1, maybe
22 below zero. And then, conversely, near 14 and

1 perhaps above.

2 Q. So looking at paragraph 28 of your
3 second declaration, you quote Dr. Smyth in the
4 second sentence.

5 A. Okay.

6 Q. Right?

7 A. Let me read that.

8 Well, with the understanding it depends
9 on what the pH of the solution disassociated into
10 is. But if we assume it's below 8, there will be a
11 reasonable fraction of monovalent cation drug or
12 monovalent form of the cation drug -- or protonated
13 azelastine.

14 Q. And so -- do you agree with his
15 position that would occur?

16 A. Yes.

17 Q. I mean --

18 A. I agree with what's stated in that
19 paragraph. And what was stated by Dr. Smyth is
20 that, in aqueous solution, as long as I'm below pH
21 8, the tertiary amine will be protonated or a
22 significant number of molecules of azelastine will

1 have that tertiary amine in a protonated form.

2 Q. And in the second paragraph of -- the
3 second sentence of paragraph 28, you've -- it says
4 "tertiary amine of azelastine will have a" -- and
5 then singular, you put brackets around "singular,"
6 "positive charge."

7 A. Okay.

8 Q. Why did you put brackets around
9 "singular"?

10 A. I guess I'd like to see the quote that
11 I'm using from Dr. Smyth and I can tell you why the
12 brackets are there.

13 Q. The quote that you're using from
14 Dr. Smyth is the one you just quoted in paragraph
15 28.

16 A. Right, but you're asking me why the
17 brackets are there. I guess I'd like to see the
18 quote so I can tell you exactly why the brackets
19 are there. Because sitting here, I don't remember
20 the grammatical choices I made when I wrote this
21 report.

22 Q. Well, before we do that, is it your

1 common practice to put brackets around a word like
2 singular that doesn't actually appear in what
3 you're quoting but you're adding that in?

4 A. I put brackets around a lot of things.
5 I put brackets around parentheticals. I put
6 brackets in a number of situations. So --

7 Q. So you don't agree that -- well, you're
8 not sure whether the word singular shows up in
9 Dr. Smyth's quote or whether that --

10 A. I'd like to refer to Dr. Smyth's quote
11 to figure -- to decide why it is those brackets are
12 -- have been placed around the word "singular."

13 Q. And what would the additional context
14 of looking at Dr. Smyth's report give you about why
15 you added singular around -- you added brackets
16 around the word "singular" or inserted singular
17 into this sentence?

18 A. I don't know. I'd like to see the
19 quote and the section to help me remember what it
20 was -- why it was that I felt I wanted to place
21 brackets around that word.

22 Q. So is there -- I think we asked this

1 earlier -- a test that you would run to determine
2 the -- the valency of azelastine, whether it's a
3 monovalent, divalent, trivalent?

4 A. I think that's kind of -- that's a very
5 generalized question regarding the charged form of
6 a chemical species. There are experimental methods
7 to test those properties. Whether it's a single
8 experimental method or whether it's a series of
9 them depends on a lot of characteristics of the
10 compound. And again, I wasn't asked to provide an
11 opinion about that.

12 Q. So you don't know sitting here today
13 whether or not the word "singular" was used by
14 Dr. Smyth in the sentence that you quoted in
15 paragraph 28?

16 A. If I could refer to the document that I
17 used to base my report on, I can tell you exactly
18 why the brackets were placed around "singular."

19 Do I have every sentence of Dr. Smyth's
20 report memorized, committed to memory? No. So
21 I -- I will be happy to provide an answer to your
22 question if I am given the citation paragraph that

1 I referred to so that I can answer your question.

2 Q. So I'm going to hand you what's been
3 marked CIP2176. I'll stipulate to you that this is
4 the redacted form of Dr. Smyth's declaration. You
5 can see there are redactions in there. I can point
6 them out if you want me to.

7 A. Okay. If they become important I'll
8 ask you about them.

9 Q. But for the purposes of our discussion,
10 paragraph 47, which you cite here in paragraph 28
11 of your second declaration, paragraph 47 of
12 Dr. Smyth's second declaration is under there.

13 So my question is, do you agree that
14 the word "singular" does not appear in the quote
15 that you've taken from Dr. Smyth's report?

16 A. Yes, based on the first couple of
17 sentences of Dr. Smyth's paragraph 47, which appear
18 to be where this quote is drawn from, both he -- it
19 is the beginning of sentence so obviously "i" in
20 brackets is indicative of whether it was the start
21 of the sentence or placed in the middle of his
22 quote, and then "singular" has been added as a

1 term.

2 Q. But you're not sure -- you think as a
3 singular positive charge but you're not sure given
4 the -- you haven't been asked to take a systematic
5 review of azelastine and how it's being protonated
6 at certain pHs?

7 A. I know that unless I'm in a -- in a
8 region of extreme pH in -- in the -- on the pH
9 scale, that azelastine below at least pH 8, many of
10 the molecules will be in a singularly charged form.

11 Q. And is that meaning that there's not
12 one molecule of azelastine that's in a divalent
13 form or a trivalent form?

14 A. Since there haven't been other PKAs
15 reported for azelastine, I'm going to base my -- my
16 answer on that, that I'm only aware of one PKA
17 being reported, which tells me that within typical
18 ranges in the pH scale that we're using in the
19 pharmaceuticals that there is -- that there is only
20 one charged functional group in the molecule and
21 that charge will be on that molecule at pH's
22 below -- well, certainly below the PKA, and at --

1 at significantly below the PKA nearly all of the
2 molecules will be in the charged form.

3 Q. So in drafting your second declaration,
4 did you go and look to see whether there were other
5 PKAs reported for azelastine?

6 A. I did.

7 Q. And you did not find any?

8 A. I did not find any.

9 Q. So I want to direct your attention to
10 Section III of your second declaration.

11 MR. HOUSTON: I'm sorry. Did you say
12 Section III?

13 MR. LAROCK: Yes, Roman numeral III.

14 BY MR. LAROCK:

15 Q. Are you there?

16 A. I am, uh-huh.

17 Q. Can you point me in Section III where
18 you disagree with Dr. Smyth's claim construction
19 for the term "suitable for nasal administration"?

20 (Witness reviewed document.)

21 THE WITNESS: Okay. Well, I briefly
22 looked at Section III. And Section -- and

1 Dr. Smyth doesn't really -- doesn't describe
2 a -- an opinion. I can look at his report
3 and see.

4 But Dr. Smyth is merely, I think,
5 quoting what Cipla documents were -- and
6 statements in Cipla document that were
7 provided to the patent examiner.

8 BY MR. LAROCK:

9 Q. So it's your opinion that he -- he
10 doesn't actually come to an opinion about what the
11 term "suitable for nasal administration" means?

12 A. I don't know. Let me look -- is it in
13 his second declaration?

14 Q. I'll direct you to paragraph 23 of
15 Smyth's second declaration. Specifically page 12.
16 Last sentence where it says, "A POSA, therefore,
17 would have understood the claim phrases 'dosage
18 form suitable for nasal administration' and 'nasal
19 spray' to require pharmaceutical formulations that
20 are tolerable to patients, that are homogenous" --

21 A. I'm going to stop you because your
22 pagination and mine must be different. Where

1 you're reading is not at the bottom of my page 12.

2 Q. No, it's the bottom of paragraph 23.

3 The section that's on page 12. It would be the

4 last sentence before Roman numeral --

5 A. Okay. All right. I see where you're

6 at.

7 Okay. So this suggests to me that

8 Dr. Smyth has adopted the -- or adopted the

9 phrasing and it is now his opinion that is what the

10 term "dosage form suitable for nasal

11 administration" and "nasal spray" mean to him.

12 Q. And do you disagree with that opinion?

13 A. I have a different opinion on what the

14 claim terms "nasal spray" and "suitable for nasal

15 administration" mean, yes.

16 Q. But do you disagree with what he said

17 they mean, is my question.

18 A. Yes.

19 Q. So is it your opinion that a "dosage

20 form suitable for nasal administration" does not

21 have to be homogenous?

22 A. I believe at the time that it's

1 administered that it has to be able to administer
2 the dose that was intended to be administered.

3 Q. Okay.

4 A. If it does so and it's not in a
5 homogenous manner, then we can -- if it's capable
6 of doing that accurately, it doesn't have to be
7 homogenous.

8 Q. And how do you determine whether or not
9 you are delivering the dose of the drug that you're
10 intending to administer at the time you're
11 administering?

12 A. Can you rephrase that, please.

13 Q. So you said that at the time it's
14 administered you would need to administer a dose
15 that is intended to be administered.

16 A. Okay.

17 Q. My question is, how do you determine
18 that you're administering the amount you intended
19 to administer?

20 A. It depends on what I'm administering it
21 from.

22 Q. So you have a nasal spray. You have a

1 nasal spray pump actuator and you have an aqueous
2 formulation. How are you determining whether or
3 not your spray is admitting and administering the
4 amount you're intending to administer of the drug?

5 A. Okay. I may have a system where the
6 units of administration are -- are separate from
7 each other and that I -- as long as the -- the unit
8 has passed through the spray device, I know I've
9 administered the dose that was intended.

10 Q. What are the units of administration?

11 A. Well, the units of administration is
12 the volume of vehicle that contains the dose or
13 doses of material that I'm intending to administer.

14 Q. Okay. So you -- you spray it. Then
15 what are you testing? I guess I didn't follow what
16 your system was of figuring out whether your --

17 A. If my -- if my system has -- is
18 designed such that I have a unit of volume that
19 contains the amount of materials that I intend to
20 administer into the nose --

21 Q. So say -- just can I stop you there for
22 a second so that I understand?

1 A. Uh-huh.

2 Q. Would that mean you're intending to
3 administer a hundred microliters?

4 A. Okay.

5 Q. So that would be your --

6 A. Unit of volume.

7 Q. Okay.

8 A. And in 100 microliters is contained the
9 amount of material that I intend to administer into
10 the nose. And if I'm able to administer that 100
11 microliters as a separate unit, as a spray into the
12 nose, and I can visually see that the unit is now
13 empty, I've administered 100 microliters into the
14 nose.

15 Q. So the unit being empty, that would
16 imply some sort of unit dose?

17 A. Could be. Some sort of discrete unit
18 of availability of material.

19 Q. But I guess how do you know that you're
20 administering the amount that you intended to
21 administer? I mean, there's a situation where --

22 A. The device that I'm administering from

1 would have been qualified to demonstrate that that
2 is the amount that's being administered.

3 Q. Okay. So if you have a formulation
4 where you're not sure what's in it but you know
5 there's a drug in it, someone just hands it to you,
6 doesn't matter what drug is in it but it's some
7 sort of suspension, and you're supposed to
8 administer 50 micrograms per spray, and you spray
9 it, how do you know you've administered
10 50 micrograms?

11 A. Well, that's a purely hypothetical
12 situation. We've been talking about what "nasal
13 spray," "suitable for nasal administration
14 homogeneous" means. What does -- ask me that
15 question in your hypothetical formulation world
16 about how --

17 Q. Well, I'm trying to figure out -- you
18 said it had to be homogenous -- or you said it had
19 to -- yeah, I think you said it had to be
20 homogenous at the time that you were administering
21 it?

22 A. No, I didn't say -- if it -- if it

1 could be administered and given and provide the
2 dose that was intended, it doesn't necessarily have
3 to be homogenous while it's doing it.

4 Q. And if you have a nonhomogenous
5 mixture, how is that -- strike that.

6 If you have a nonhomogenous composition
7 in a spray container and you spray it, how do you
8 know you're administering the amount that you
9 intend to administer given the fact that you know
10 you have a composition that's now homogenous?

11 A. Again, what I proposed to you is a unit
12 of -- of formulation, which when that unit was
13 filled it was filled such that a known amount of
14 the drug went into that unit. Okay. So -- so 100
15 microliters of my system got filled into my unit.
16 When I filled that, I filled it in a process where
17 it was verified that a 100 microliters contained
18 the amount of material that I desired to administer
19 of that 100 microliters into the nose.

20 Q. In that process, though?

21 A. Well, what do you mean "in that
22 process"?

1 Q. Well, you verified that you had 100
2 microliters and that everything works out and then
3 you fill the unit dose with it or you fill the
4 sprain container with it under your hypothetical?

5 A. Or -- or perhaps I filled this -- the
6 unit container with the amount of drug I wanted and
7 then I filled the rest of the formulation around
8 it.

9 Q. Okay.

10 A. I have a unit. I have -- and whether
11 it's homogenous or not, if I have a device that's
12 capable of placing that volume in that unit into
13 the nose, I've administered -- and my device was a
14 spray, I've administered the dose I wanted into the
15 nose via a nasal spray. And it -- it was not
16 necessarily homogenous when I did it.

17 Q. So how about a different hypothetical
18 where you have a drug in a composition that every
19 molecule of the drug rather than being suspended or
20 dissolved has caked down to the bottom. So you
21 just have drug that's caked and then you have the
22 rest of that vehicle of the composition above.

1 When you spray it, you're not spraying
2 the -- your spray doesn't contain the dose that
3 you're intending to administer, right?

4 A. Well, in most situations one wouldn't
5 be spraying out of that kind of composition. We
6 have a -- if you're talking about a suspension
7 system, formulators know very well how to make
8 suspension systems such that if the particles
9 settle, whether they rise to the top or settle to
10 the bottom, based on their density, that you shake
11 or sheer or provide some mixing mechanism to reform
12 a well-distributed suspension that then you're
13 aware that each and every unit volume in that is --
14 is equivalent and your spray wherever you draw to
15 or however you're getting the volume into your
16 spray device contains the amount of medicine or
17 whatever you were trying to spray.

18 Q. So in the situation where you have a
19 solution -- sorry, a suspension, the drug
20 suspended, you have some sort of settling but you
21 don't go back before administering it and remix it
22 to provide the uniform suspension, are you

1 administering the -- the dose of the drug that you
2 intend to administer?

3 A. Well, if you're going to spray under
4 those -- or you're going to actuate the device
5 under those conditions, you're not actuating the
6 device under the conditions that were -- that it
7 was designed to deliver the drug for. So you've --
8 you've proposed a situation that is outside of the
9 construct of a formulation that is -- is known to
10 settle -- every POSA knows that nearly every
11 suspension is going to settle or -- or -- or
12 rise -- again, all about density -- over some
13 period of time. And every suspension user is told
14 to shake before they dispense from that unit.

15 So what you've proposed of spraying
16 that without shaking is -- is -- is not even a
17 relevant situation.

18 Q. My question is, if you're spraying it
19 out of a -- out of a situation where we have a
20 composition, you have settling of -- of the
21 suspended drug, you don't shake it, you don't mix
22 it to provide a uniform suspension again, and then

1 you actuate it, that spray is not suitable for
2 nasal administration because you don't know whether
3 or not it's administering the drug you intend to
4 administer, right?

5 A. I think you've built a whole lot of
6 things, conditions, into a specific situation about
7 a particular nasal spray that wouldn't even be
8 conceived of by a formulator or a regulator.

9 For me to agree that that's what a
10 POSA would understand, a "nasal spray suitable for
11 administration," you have too many qualifiers that
12 are irrelevant to how a formulator would -- would
13 be designing and moving towards a formulation,
14 whether it had a shelf life of 3 seconds or a shelf
15 life of 30 years.

16 So not shaking a suspension before it's
17 administered is -- is probably -- or at least
18 having some form of mixing step prior to
19 administration is counter to every suspension that
20 I'm aware of.

21 Q. Okay. What if you mix it and it mixes
22 some -- so same hypothetical. You have a

1 composition, it's a suspension, settling occurs,
2 you do mixing. How do you know whether that mixing
3 has provided a uniform suspension again before you
4 actuate it?

5 A. In formulation development those are
6 the things that we address all the time. We define
7 formulations. We develop them so that over a
8 period of time that we identify that we understand
9 that that formulation should be sufficient that
10 it's going to deliver the intended dose to the
11 individual. In this case via a nasal spray.

12 Q. But my question is, how do you know
13 it's -- so during the formulation development
14 process, you're running either tests or experiments
15 to figure out how you get a uniform suspension once
16 settling occurs, right?

17 A. Likely.

18 Q. Okay. In what test were you doing
19 that?

20 A. I -- I wasn't asked to opine on what
21 tests we use to -- to certify dose reproducibility
22 in a suspension. Your other -- other investigators

1 or other experts have opined on them. I'm
2 certainly familiar with them.

3 And you're right, there's a number --
4 you can chemically analyze the amount of spray
5 that's been -- been emitted. You can do other
6 things. You know, maybe microscopically analyze
7 things. It depends on the formulation.

8 There are -- there are -- for
9 commercial products, if this is actually going to
10 become a commercial product, there are suggested
11 methods that the FDA uses. If I'm a pharmacist
12 whose -- I'm extemporaneously compounding a
13 formulation like this, chances are I'm going to use
14 a visual analysis.

15 Q. But my question is, in all of those
16 settings, how do you know whether you're getting a
17 uniform suspension prior to actuating?

18 A. Well, either I -- I -- as a POSA
19 formulator, I would have likely in my development
20 scheme built in an analysis of looking at spray
21 devices as a variable, looking at spray volumes as
22 a variable, looking at formulation components,

1 potentially the suspending agent, potentially
2 particle size, potentially a number of other things
3 into a design matrix where that's exactly what I
4 would have evaluated.

5 Whether I'm -- whether as I spray out
6 of -- out of a series of sprayers, a series of
7 formulations, which ones provide -- and I
8 chemically analyze for the drug potentially or for
9 the drug plus some other agents that I felt were
10 important also to be administered, I mean, the
11 simplest thing is to chemically analyze that.

12 But that's part of a formulation
13 development scheme. It's not a -- or it's actually
14 part of a -- a product development scheme. It's
15 not necessarily part of an initial formulation
16 development scheme.

17 Q. So if you're doing the product
18 development portion of working with a -- a
19 particular composition and you're trying to figure
20 out whether you're getting upon shaking or -- or
21 some sort of redistribution that you're getting a
22 uniform suspension, what tests are you running --

1 what chemical tests are you running to determine
2 that?

3 A. So in my product development schemes as
4 I'm moving my product towards determining its final
5 packaging, I need to -- and you're asking me how
6 I'm measuring the amount of drug that's being
7 emitted?

8 Q. No. When you have a -- you have a -- a
9 suspension -- a composition. It's a suspension.
10 You have settling. You've mixed up your
11 composition to redistribute the settled particles.
12 How do you know what tests you're running?

13 How do you know that you're getting a
14 uniform suspension after that?

15 A. Again, am I in a spray bottle? Am I in
16 a beaker? Am I -- what's -- where am I in my
17 formulation development process? Because that very
18 much determines what tests I'm likely to use.

19 Q. Well, so, if you're in a beaker, what
20 tests would you use?

21 A. If I'm in a beaker, very early
22 formulation development stage, my first test is

1 visual. And I can probably eliminate or at least
2 identify where I might want to optimize my
3 formulation and make changes until I'm satisfied
4 that -- that visually I have the outcome I want,
5 that -- that I disperse for whatever time it was
6 that I felt necessary for that -- that suspension
7 or those particles to redisperse.

8 If I'm -- and then if I -- if I want to
9 get quantitative, if I'm much further along in my
10 product development scheme and I'm evaluating again
11 spray devices and their spray uniformity patterns
12 and possible formulation changes I might need to
13 make around the particular spray device I choose,
14 then I likely would start doing chemical analyses
15 around what was sprayed from the device.

16 And I'd do temperature studies to see
17 whether I get this -- you know, if -- if somebody
18 is in Chicago today and in Chicago in July, what
19 are those temperature differences might affect
20 that.

21 There's a lot of testing that would go
22 into a final product specification that would use

1 those exact chemical tests. But it depends where I
2 am along the product development scheme to
3 determine which one it is that I need to use or
4 which one is sufficient enough to tell me the
5 information I need to know.

6 Q. And so back to the situation where you
7 have the -- the -- you're in the beaker, you're at
8 the beginning of the formulation development
9 process.

10 A. Okay.

11 Q. You said you would use visual analysis,
12 visual observation, to see whether you had obtained
13 uniform suspension?

14 A. Well, I'd certainly use my visual
15 skills to determine whether I redisperse -- whether
16 there really is a cake that forms. I can probably
17 visually observe how long it might take for
18 materials to settle.

19 What that has to do with my final
20 product performance, I'd have to evaluate. Again,
21 it very much depends on -- on what kind of
22 container it is that I'm going to be using in my

1 final product to determine what my settling rate
2 might mean regarding how -- how important it is or
3 what rate I -- what rate I'm targeting.

4 Q. And so when the beaker -- so you went
5 through some visual observation. But would you do
6 any other tests, any other analysis on suspension
7 at the beginning of your formulation process
8 development to see whether you would obtain a
9 uniform suspension?

10 A. It depends -- you know, as I started
11 my -- as I would start a formulation development
12 process, I would at least have in mind what my
13 performance characteristics were going to be for
14 my -- that I would have moved towards. Okay.
15 So if -- if -- when I make that suspension, then
16 I'm -- I think it's a reasonable place to -- to
17 start with --

18 Q. Can I stop you for one second?

19 A. I guess.

20 Q. Sorry. What do you mean -- by
21 performance characteristics, what do you mean by
22 that?

1 A. When I'm developing a formulation, what
2 do I want that formulation to do. Those are my
3 performance characteristics. What do I want it to
4 be able to do. Do I need to just have it be able
5 to deliver two drug compounds. Do I need to have
6 it deliver only one drug compound.

7 Do I -- you know, in the terms of nasal
8 sprays. I don't know. What kind of sprays device
9 am I planning on using. What am I -- is it going
10 to be in a clear bottle. How are patients going to
11 perceive settling.

12 I don't know. There's a whole series
13 of things that I evaluate why I'm doing this and
14 what are my preferred outcomes and sort of what are
15 the ranges around those outcomes that are
16 acceptable enough to continue to move forward as
17 I -- as I build in the materials I want into my
18 formulation. Okay.

19 So if I -- if I've decided that I'm
20 administering two -- two drug compounds, even stay
21 in the -- in the context of this particular '620
22 patent, one of them is in solution, one of them is

1 in suspension, I am going -- and I need to make
2 sure that I'm able to reproducibly deliver both
3 drug components, I start formulation, design. And
4 as long as I can redisperse the solid and have it
5 dispersed for long enough that I think it can draw
6 a draw-to, then I'm probably satisfied that was a
7 nice starting point.

8 Is that my end point? Probably not.
9 So then -- I don't know, if I didn't like -- if I
10 didn't like the particle size, if I thought that
11 that was influencing the rate at which the -- the
12 particles were settling, I might choose to reduce
13 the particle size of the -- the lower solubility
14 drug until that doesn't have as much as an effect.
15 If I -- you know, there's -- it all depends on what
16 I observed the next steps I take.

17 But I have plenty of options to --
18 and -- and system to -- to systematically improve
19 my formulation, to get it to behave or perform the
20 way I had desired it to perform.

21 Q. So just to go back to one of the things
22 I think you said earlier, that it was your opinion

1 that to be suitable for nasal administration, the
2 formulation had to be I think homogenous at the
3 time of delivery or at the time it was
4 administered?

5 A. I don't think I said that.

6 Q. Okay.

7 A. It -- the formulation just has to be
8 able to administer the -- from the spray device
9 administer the amount of drug that's labeled that
10 it will administer.

11 Q. And at the beginning of your
12 formulation process, how do you know that you're
13 going to be able to administer the amount of drug
14 that you intend to administer?

15 A. I do formulation development, product
16 development activities that demonstrate that. But
17 that's what formulation development is all about.

18 Q. So you would do those -- the -- the
19 formulation development activities would be the
20 things that you would do to go from your starting
21 formulation to --

22 A. To my final product.

1 Q. To the final?

2 A. And, I mean, really, those are called
3 product development activities.

4 Q. Product development activities. So if
5 you have your initial formulation that you're
6 working with and it shows some settling of the
7 suspended agent and it has problems, how do you
8 know at that point in time that -- that this
9 formulation will be able to deliver the amount of
10 drug that it's intended to deliver?

11 A. That's not even --

12 Q. Without having done --

13 A. That's not even an appropriate question
14 to ask me at that point.

15 Q. Okay.

16 A. If I haven't completed my formulation
17 development activities such that I believe, based
18 on -- on my work as a POSA and variables, that I
19 would start evaluating and the devices I would
20 start evaluating first, I wouldn't ask that
21 question --

22 Q. That's just too early in the process?

1 A. -- initially.

2 Yes.

3 Q. So you have your initial formulation.
4 You have your product development activities. You
5 have formulation?

6 A. Final product.

7 Q. That's the spectrum that we've been
8 kind of talking about.

9 A. Okay.

10 Q. And at what point in time do you -- on
11 that spectrum, from beginning formulation through
12 the activities to the final product, at what point
13 in time do you know that you're going to have a
14 formulation that when you administer it it's
15 administer the amount of drug that you're intending
16 to administer?

17 A. I think that would likely be the time
18 at which I've decided on my final formulation
19 components, their final concentrations, my final
20 device, my final -- and -- and what my -- probably
21 close to what my manufacturing specifications would
22 be.

1 Q. So if we think about the spectrum from
2 the beginning formulation to the final product and
3 then you have your product development activities
4 in between, the time that you would know that you
5 would have a formulation that is delivering the
6 dose that you intend to deliver is more near the
7 end than it is near the beginning, generally
8 speaking?

9 A. Well, that would be the time that --
10 that you would be -- you work towards assuring
11 that --

12 Q. Yeah.

13 A. -- during your other formulation
14 development activities. But again, as I mentioned
15 before, there are a number of variables that a
16 formulator/POSA can -- can change to work towards
17 that uniformity goal.

18 You know, whether it's changing the
19 spray devices, whether it's changing the suspending
20 agent, whether it's changing the particle size.
21 Or, you know, those are all things that get done in
22 the early phases of product development working

1 towards -- we know that that's a final goal. So
2 it's certainly something to keep in mind. But you
3 have lots and lots of opportunity to optimize the
4 formulation to get you to that goal.

5 Q. Right. And -- and throughout the
6 product development cycle you're doing lots of
7 things to make sure that you get a formulation that
8 will deliver the drug that's -- the amount of drug
9 that's -- that you're intending to administer.

10 But my question is, you don't know
11 you're going to get a formulation that is
12 delivering the amount of drug that you intend to
13 deliver until you do the test or analysis to figure
14 that issue out. Right?

15 A. Well, I mean --

16 Q. You can't know you have a -- a
17 formulation that when administered will administer
18 the amount of drug that you intend to administer
19 until you do the test to determine it?

20 A. Well, once again, you've piled so many
21 hypotheticals into that that, you know, we can
22 go -- we can go back and unpack these things and

1 think about back to my single unit of spray
2 formulation and how I would approach that and
3 how -- how much and when I need to be concerned
4 with the dose uniformity. It's a very different
5 question than if I'm thinking about formulating a
6 multispray, multiunit, dose system.

7 Q. So we're formulating a multiuse system
8 and we're going through from our initial product
9 to -- or the initial formulation to the final
10 product. And at what point in time in the product
11 development cycle are you -- do you know that you
12 have a formulation that's administering the amount
13 of drug that you intend to administer?

14 A. When I test it and show it.

15 Q. Okay. Whenever that is?

16 A. Well, when I know -- when I know that
17 I -- when I test and show it on my -- my final
18 optimized formulation. But I have optimized my
19 formulation around my device to be able to give me
20 that anyway. So exactly when I know is when I --
21 I'm essentially writing my final product
22 specifications. But when I've been testing to make

1 sure that my -- I get there happens earlier.

2 Q. Yeah, the testing happens earlier. You
3 just don't know whether -- you're building up to
4 the final point where you're like, aha, I have a
5 formulation that's delivering the amount of drug
6 that you've intended to deliver?

7 A. I probably along the path identify
8 multiple formulation variances and several devices
9 that all give me the same good result that I want.

10 Q. Uh-huh.

11 A. Which is dosing uniformity in this
12 case.

13 Q. And there's specific dose uniformity
14 tests that you can run to determine the dose
15 uniformity?

16 A. We've talked about that already. You
17 can do that by what the FDA describes as a way to
18 do dose uniformity testing. You can set up your
19 own testing methodologies. Depends on potentially
20 what it is that you're spraying out of the device.

21 Q. And if you have a multidose formulation
22 where there's a suspension, there's been some

1 caking, or settling, you redisperse it, you spray.

2 How do you know at that time that you're

3 spraying -- that that spray is designed -- that

4 that spray is administering the amount of drug you

5 intend to administer?

6 You haven't done -- you haven't done

7 the product development scheme. You haven't done

8 anything. You've just made a formulation and

9 you've put it into a multidose spray container and

10 then you've sprayed it.

11 How do you know -- how do you know that

12 it's delivering the amount of drug you intended it

13 to deliver?

14 A. If that's the specific question I'm

15 asking, I guess I'll -- I'll chemically analyze for

16 the amount of drug that was sprayed into whatever

17 container I sprayed it into.

18 (Whereupon, a recess was taken

19 from 1:45 p.m. to 1:56 p.m.)

20 BY MR. LAROCK:

21 Q. Dr. Donovan, welcome back.

22 A. Thanks.

1 Q. Did you talk with your counsel about
2 the substance of your testimony or anticipated
3 testimony --

4 A. No.

5 Q. -- during the break?

6 A. No. I saw him in the hallway as we
7 walked back in so you were with him more than I
8 was, I think.

9 Q. I'm going to ask that you turn to
10 paragraph 46 of your second declaration. And my
11 question is, you don't cite to any prior art in
12 this paragraph, correct?

13 A. Let me read the paragraph.

14 (Witness reviewed document.)

15 THE WITNESS: Well, I mean there's
16 citations to Dr. Govindarajan -- or
17 Dr. Herpin's report on Dr. Govindarajan's
18 testing. The '620 patent is cited. There's
19 a citation from Dr. Smyth's deposition.

20 So what is it that's not cited?

21 BY MR. LAROCK:

22 Q. Oh, my question was you don't cite to

1 any prior art.

2 A. Paragraph 46?

3 Q. In paragraph 46.

4 A. You're correct. There's not a -- that
5 paragraph -- I didn't write it to need to start
6 referring to prior art.

7 Q. Okay. Now, in putting together your
8 second declaration, you studied Dr. Govindarajan's
9 testing and then you studied Dr. Herpin's testing?

10 A. I referred to the patent owner's
11 response, Dr. Smyth's second declaration,
12 Dr. D'Addio's second declaration, and Dr. Herpin's
13 declaration.

14 Q. And the documents cited therein, right?

15 A. Yes.

16 Q. And you yourself cited
17 Dr. Govindarajan's testing in putting together your
18 second declaration, right?

19 A. Yes. I believe that was cited in
20 probably Dr. Herpin's declaration. That's my
21 suspicion where that came from.

22 Q. So just as a table sitting, I just

1 wanted to make clear that you studied both
2 Dr. Govindarajan's testing in preparing your second
3 declaration and Dr. Herpin's testing in preparing
4 your second declaration.

5 A. I -- I referred to them, yes.

6 Q. Okay. So you didn't -- you didn't
7 study, you just referred to them?

8 A. I -- reading somebody else's data book
9 is reading somebody else's data book.

10 Q. Considered them; is that fair?

11 A. I considered them certainly.

12 Q. And you had -- do you recall that
13 Dr. Govindarajan's testing had been done as part of
14 the Apotex litigation, right?

15 A. Yes.

16 Q. And were you involved in putting that
17 together?

18 A. No.

19 Q. Okay. But --

20 A. You mean outside of -- I work with
21 Dr. Govindarajan. I gave his name to Apotex
22 counsel. That's all I know.

1 Q. And then as part of the litigation, do
2 you remember criticizing Dr. Herpin's testing at
3 all?

4 A. I remember having questions about some
5 of the things Dr. Herpin did.

6 Q. Okay. Because you disagreed with some
7 of the things that he did or --

8 A. You need to be more specific about
9 that.

10 Q. Okay. Well, if you saw a major flaw in
11 Dr. Herpin's testing, would you have identified it
12 in your -- any of the times that you had written an
13 expert report or a declaration involving
14 Dr. Herpin's testing?

15 A. Well, I have a number of questions
16 about Dr. Herpin's motivations, Dr. Herpin's
17 selections of things. But there -- they're not
18 questions on his -- on his scientific capabilities.
19 They're just questions that aren't included in the
20 details in his report.

21 Q. And if it was a meaningful question
22 that you had about something having to do with his

1 report, you would have raised it at any time point
2 in time?

3 A. I -- I will consider that I think I've
4 raised the -- what I would consider the main global
5 issues and questions I have with Dr. Herpin's
6 testing. Within those global issues, there's a lot
7 of minutia questions that I may not have actually
8 specified but they still remain.

9 Q. So I'm going to hand you what's been
10 marked 2016, CIP2016. Do you recognize CIP2016,
11 Dr. Donovan?

12 A. There's a title on it. In my quick
13 review, this looks like a report that was submitted
14 in the previous litigation prior to that litigation
15 going to trial.

16 Q. Okay. And on page 25 of CIP2016,
17 that's your signature there?

18 A. Yes, it is.

19 Q. Okay. And it's page 18 of the report.
20 There's also a paragraph 19 at the bottom. At the
21 top it says Subsection E?

22 A. Paragraph 18?

1 Q. Sorry. Page.

2 A. Okay.

3 Q. You see it's Subsection E?

4 A. Yes.

5 Q. And you can review Subsection E if you
6 need to. But my question is, do you see in
7 paragraph 41 where you are responding back to
8 Dr. Smyth who is basing his opinion on Dr. Herpin's
9 testing?

10 A. Okay.

11 Q. Do you see that in paragraph 41?

12 A. I see that, yes.

13 Q. And you see that this section relates
14 to your criticisms of Dr. Herpin's testing and
15 Dr. Smyth's opinion based on that testing.

16 Is that -- is that a fair
17 characterization?

18 A. I don't know. I'm going to stop and
19 look at this. It's dated August 2016 and about the
20 last time I looked at it was December of 2016. So
21 I have no idea really.

22 Q. Okay.

1 (Witness reviewed document.)

2 THE WITNESS: Okay.

3 BY MR. LAROCK:

4 Q. So my question was Section E of
5 CIP2016 is where you criticize Dr. Herpin's
6 testing. Is that a fair characterization of what
7 that section is?

8 A. Well, I think criticize is not
9 necessarily an appropriate term. I describe
10 portions of his testing that I don't believe were
11 performed in the way that a POSA formulator would
12 have approached a problem. I call into question
13 perhaps some of the things he failed to do and some
14 of his other choices. But, you know, I call into
15 question some of the things that he did. I'm not
16 sure that criticize is a fair description.

17 Q. Okay. But you -- in this section you
18 call into question some of the things that he had
19 done?

20 A. Yes.

21 Q. And were you thorough in coming up with
22 the things that you wanted to take issue with in

1 Dr. Herpin's testing that you took issue with in
2 Section E of CIP2016?

3 A. Well, in August of 2016, regarding a
4 totally different litigation than the current
5 litigation, the information that's identified in
6 this expert report speaks to the issues at hand
7 regarding that litigation.

8 Q. Okay. And you also testified in your
9 second declaration about taking issue with some of
10 the things Dr. Herpin was testing?

11 A. Yes.

12 Q. So my question is, you've taken issue
13 in your second declaration with the viscosity --
14 the grade of -- the viscosity grade of HPMC that
15 Dr. Herpin used; is that right?

16 A. I have -- I have made note that he did
17 not reproduce Dr. Govindarajan's formulation
18 because he chose to use a different HPMC grade.

19 Q. Okay. And when you reviewed
20 Dr. Herpin's testing for the Apotex case, when you
21 were taking issue with that testing in 2016, did
22 you identify the -- the viscosity of the grade of

1 HPMC that Dr. Herpin used as an issue you wanted to
2 point out?

3 A. I was certainly aware of that. Whether
4 it's something that I pointed out in one of my
5 reports, I -- when I quickly glanced through the
6 one report you provided me, I don't recall a
7 paragraph that speaks directly to the viscosity
8 grade of the HPMC. But again, this was a different
9 litigation. It was a different set of patents that
10 were being discussed. So --

11 Q. Well, the '620 was at issue in both of
12 these litigations?

13 A. Again, parts of the '620. I don't
14 recall which. And it was a different litigation.
15 There would have been reasons that -- that
16 different arguments or characteristics would have
17 been noted, would have been included in a report.
18 Doesn't mean that I didn't note it. Doesn't mean
19 that it didn't exist at that time.

20 Q. And I guess at the time it just wasn't
21 a meaningful enough question to point out?

22 A. No. That's not the case. Just it

1 wasn't something that was -- was included in -- in
2 my expert reply report.

3 Q. Okay. So suffice it to say, it's not
4 in the reply report but it's something you're
5 taking issue with now? Is that --

6 A. It's something I noted when I first saw
7 Dr. Herpin's testing. It's something I still
8 believe -- or believed then is a factor, I believe
9 now is a factor. I included it in my second
10 declaration.

11 Q. Okay. So the -- it's -- it wasn't
12 there previously when you first looked at
13 Dr. Herpin's testing and now it is -- the viscosity
14 grade of HPMC is an issue now with your second
15 declaration?

16 A. The -- the discussion of the viscosity
17 difference or the HPMC differences was not included
18 in my expert reply report in the Apotex case.
19 There were other experts included in that case.
20 There were other issues in that case.

21 So whether I spoke to issues, whether
22 other experts spoke to issues, was -- it's a

1 different litigation. And so what's included in my
2 report for this litigation is what's included in my
3 report for this litigation.

4 Q. Okay. But you will admit that the
5 '620 -- portions of the '620 were involved in both
6 of these cases? There is that connection?

7 A. Yes, the '620 was at least one of the
8 patents-in-suit in the Apotex case.

9 Q. Okay. And in this case also?

10 A. Yes.

11 Q. Now, so you made note that Dr. -- the
12 grade of viscosity -- the viscosity grade of HPMC
13 used by Dr. Herpin was 3 centipoise?

14 A. One of the viscosity grades.

15 Q. One of the viscosity grades. But
16 Dr. Herpin used 6 centipoise grades of HPMC?

17 A. No, let's -- let's clarify that.

18 Q. So I was looking at paragraph 42 of
19 your second declaration.

20 A. And paragraph 42 indicates that
21 Dr. Herpin used an HPMC with viscosity grade of
22 3 centipoise. He also investigated another

1 viscosity grade that's not described in this
2 paragraph. And Dr. Govindarajan used a viscosity
3 grade of 6 centipoise.

4 Q. Excuse me. I thought it -- that was
5 what I mean to say.

6 Both 3 centipoise and 6 centipoise,
7 those grades of HPCM are both categorized as being
8 low viscosity HPMC grades, right?

9 A. It depends on sort of whose commercial
10 categorization schemes they are being used. I
11 guess I -- my preference would be to refer to the
12 handbook of pharmaceutical excipients and they have
13 I think probably a description of what's the --
14 what's a generalized classification scheme. But I
15 just don't remember what it is.

16 Q. Okay. So I'm going to hand you what's
17 been marked CIP2110. So is this the Handbook of
18 Pharmaceutical Excipients, Dr. Donovan, that you're
19 referring to?

20 A. Yes.

21 Q. And you're familiar with this exhibit?

22 A. Generally. In a general sense, yes.

1 Q. If we look at Table 2, it gives typical
2 viscosity values.

3 A. Okay.

4 Q. Are you with me so far?

5 A. Uh-huh.

6 Q. And the viscosity, the right-hand
7 column, those viscosities range from as low as
8 2.4 to as high as 120,000?

9 A. Yes.

10 Q. So if that's the spectrum of
11 viscosities that we're dealing with for -- and just
12 to clarify, these are all viscosity values of
13 commercial grades of HPMC, right?

14 A. The -- the methylcell grade as
15 indicated in the left-hand column are some of the
16 commercial labels for various HPMCs, yes.

17 Q. Are there grades of HPMC with different
18 viscosities that aren't listed on Table 2?

19 A. It's my suspicion that there are other
20 manufacturers of HPMC that don't use the
21 nomenclature K100 or K4MP or E50 or whatever in the
22 world. And they don't -- yeah, they're not

1 included in this table.

2 Q. But their viscosities would be within
3 the range of viscosities disclosed --

4 A. They would be at least within that
5 range.

6 Q. Okay. Yeah.

7 I mean, what I was trying to get at is,
8 you know, is there a viscosity out there of HPMC --
9 is there a grade of HPMC out there that has a
10 viscosity of 1 million, for example, that's not
11 included on Table 2?

12 A. I don't have any way of being aware of
13 that.

14 Q. So looking at Table 2, is it safe to
15 characterize both a viscosity grade of 3 and a
16 viscosity grade of 6 as both being low viscosity
17 HPMC grades?

18 MR. HOUSTON: Objection. Form.

19 THE WITNESS: You know, on an adjective
20 basis, if we want to call anything less than
21 10 low viscosity or less than 100 low
22 viscosity, I think we can define that however

1 we want. The -- the values of 3 and 6 are
2 certainly on the low spectrum of the broad
3 spectrum of possible molecular weights or
4 possible viscosities of hydroxypropyl
5 methylcellulose.

6 BY MR. LAROCK:

7 Q. So it's -- I mean, would a person of
8 ordinary skill be viewing a viscosity grade of 3
9 and a viscosity grade of 6 as being low grade
10 viscosity of HPMC?

11 MR. HOUSTON: Object to form.

12 BY MR. LAROCK:

13 Q. In 2002?

14 A. Well, it depends on what their -- what
15 their intended use is. I mean, the manufacturers
16 on -- have categorized HPMC to try to be helpful.
17 But just because it's a low viscosity grade doesn't
18 mean it's only capable of making low viscosity
19 systems.

20 Q. Okay. But in 2002 would -- if
21 hypothetically a person of ordinary skill was asked
22 to use a low grade viscosity HPMC to develop a

1 nasal spray, that's what their task was, and they
2 went to the shelf and they looked and they saw an
3 HPMC grade of viscosity of 3 and an HPMC grade with
4 a viscosity 6 and then an HPMC grade of viscosity
5 of 120,000. Those are the three choices that they
6 have in their stockroom.

7 Would they grab the 120,000 if they're
8 tasked with grabbing a low grade HPMC?

9 A. You know, I don't know because it seems
10 unusual that a formulator would initially be tasked
11 with that as a variable.

12 Q. Okay.

13 A. You know, unless they were trying to
14 follow a prescribed activity, there's no reason
15 that a formulator when they start out with a
16 formulation development activity only limits
17 themselves to using a particular subset of
18 materials that are available.

19 Q. So whatever the process that they're
20 going through, right, whether it's they're doing
21 their own formulation development or they're
22 following a prescribed methodology for whatever

1 reason, but their task was grabbing a low grade
2 viscosity HPMC, are they grabbing the 3 or the 6 or
3 are they grabbing the 120,000 grade HPMC?

4 MR. HOUSTON: Objection. Asked and
5 answered.

6 THE WITNESS: If they've been asked to
7 select a low viscosity grade as defined by
8 the manufacturers of a broad range of HPMCs,
9 they would be apt to pick some of the ones
10 that are viscosities at least below 50 and
11 below 100, somewhere in there.

12 BY MR. LAROCK:

13 Q. And that's because generally they would
14 be operating similarly those grades of viscosities?
15 Or why is it that -- why is it that we can lump
16 viscosity rates of 50 and below as being kind of
17 low grade?

18 MR. HOUSTON: Objection. Form.

19 THE WITNESS: Well, the -- the
20 viscosity of an HPMC system is due to the
21 polymer-polymer interactions of HPMC itself.
22 The bigger the polymer molecule, the higher

1 its molecular weight, the -- the more
2 interactions each individual molecule might
3 have in those solutions.

4 The smaller molecules, more flexible,
5 they have interactions, too, depending on
6 what you -- what the -- the characteristics
7 of your system are and how much methyl- -- or
8 how much hydroxypropyl methylcellulose from
9 an actual physical weight standpoint you want
10 to load into your system helps you determine
11 whether you would rather start with a low
12 molecular weight or low viscosity form of
13 HPMC or whether it's more beneficial to start
14 with a high molecular weight or high
15 viscosity form.

16 BY MR. LAROCK:

17 Q. So with a viscosity grade of the very
18 low end of methylcell HPMC to a viscosity grade of
19 50, are those -- you kind of classified those as
20 being lower grade?

21 A. Well, they're lower molecular weight.

22 Q. Okay. And that's kind of where the --

1 A. The measured viscosity results from.

2 Q. Yeah. And -- and the -- what's the
3 difference in the -- in whether you have a
4 viscosity grade of, say, 6 and 10, what's the
5 difference in the molecular weight between the two?

6 A. Depends on --

7 Q. That would change the viscosity?

8 A. Yeah, I mean, there's -- there's ways
9 of calculating that if I have the right parameters.
10 But I don't know. I would probably look at what
11 the manufacturers specify as what the monomer count
12 might be or the degree of substitution might be
13 that results in a particular viscosity.

14 But that's not something that we just
15 simply know, it's not a linear function of
16 increasing molecular weight in a polymer. It may
17 be that over small ranges. But I can't -- can't
18 tell you what the molecular difference between
19 viscosity grade of 4 made by one manufacturer and
20 viscosity grade of 6 or 3 or whatever made by a
21 different manufacturer. I have to go look at the
22 technical specs.

1 Q. Okay. And if you grabbed -- say we're
2 dealing with using HPMC as a thickening agent,
3 suspending agent, in an aqueous nasal spray
4 formulation. That's the -- what we're going to use
5 it for. And you made two formulations. One that
6 has a viscosity of 10 and one that has a
7 viscosity -- or one you're using an HPMC that has a
8 viscosity of 10 and the other formulation you make
9 you're using an HPMC that has a viscosity of 50.

10 A. Viscosity grade?

11 Q. Viscosity grade of 50.

12 A. Okay.

13 Q. And will there been a meaningful
14 difference in the -- in how those systems -- how
15 those compositions are operating?

16 MR. HOUSTON: Objection. Form.

17 THE WITNESS: It could be based on how
18 much of the agent you add and what other
19 things are in there and, again, what the --
20 the degree of substitution is.

21 Is it equivalent between those
22 viscosity grades or is it different?

1 BY MR. LAROCK:

2 Q. So say the same hypothetical where the
3 person of ordinary skill is adding whatever amount
4 of HPMC, whether it's the viscosity -- HPMC having
5 a viscosity grade of 10 or the HPMC having a
6 viscosity grade of 50, they're adding whatever
7 amount of viscosity into those formulations in
8 order to make, you know, a -- a uniform suspension.

9 A. Okay.

10 Q. Does that change -- are those two
11 formulations operating differently?

12 A. They can be, certainly.

13 Q. Okay. Is there a meaningful difference
14 between the two formulations that you've used two
15 different grades of viscosity?

16 A. Depends against what parameter you're
17 judging meaningful.

18 Q. Well, how would you -- if you wanted to
19 test whether those two -- whether that was a
20 meaningful difference between the two formulations,
21 what would you do?

22 A. Is it a meaningful difference in cost?

1 Is it a meaningful difference in appearance? Is it
2 a -- meaningful difference regarding what?

3 Q. A meaningful difference in how those
4 formulations are operating.

5 A. Potentially, yes.

6 Q. Okay. And what would be that
7 meaningful difference?

8 A. Could be a variety of things. Could be
9 the -- could be the network mesh formulation. It
10 could be the number of molecules able to complex
11 with the agents you used at the concentrations you
12 put in. It could be the final viscosity. Could be
13 a whole bunch of things.

14 Q. And how would you determine whether
15 those parameters that you were looking at, whether
16 those were -- whether you were getting a result
17 that was abnormal or something in any one of those
18 parameters that you were looking at?

19 A. Abnormal based on what? I mean, what's
20 my -- what's my goal? What am I doing? What am I
21 looking for? What do I want this -- these two
22 different viscosity grade HPMC in whatever system

1 I've put them in, what is it that I'm comparing
2 among them? What -- what am I doing? Then I can
3 tell you whether -- you know, what I might project
4 as differences might be.

5 Q. So you have one formulation that has --
6 they're both the same except one has an HPMC with a
7 viscosity grade of 10, the other one has a
8 viscosity grade of -- an HPMC with a viscosity
9 grade of 50. And the goal is to try to make a
10 uniform suspension.

11 Are those two formulations -- is the
12 difference in the viscosity grade a meaningful
13 difference between the two formulations?

14 A. It probably is. And I am -- if I have
15 a -- a goal for my formulation on -- on the
16 viscosity or something that's related to the
17 viscosity, I can use different amounts of each one
18 of those to likely get to a similar end point. But
19 again, I have very different amounts of polymer
20 doing that.

21 Q. And you would have to use a greater
22 amount of the lower grade viscosity compared to the

1 higher grade viscosity of HPMC in order to get a
2 uniform suspension?

3 A. I don't know that that's generalizable.
4 I don't know that I agree with that.

5 Q. If I wanted to see whether you were
6 comparing two formulations that had different
7 viscosity grades in them and you wanted to see
8 whether or not that viscosity was a difference of
9 viscosity between the two grades of HPMC that are
10 used as meaningful, what analyses or experiments
11 would you run?

12 A. Meaningful regarding what?

13 Q. The stability of the form- -- the
14 physical stability of the formulation?

15 A. And how is it that I'm defining the
16 physical stability of the formulation?

17 Q. Well, how do you define the physical
18 stability of the formulation?

19 A. I can define it as a multitude of
20 things depending on what my -- my product goal is.

21 Q. Okay.

22 A. Do I have a suspension that is

1 uniformly dispersed upon shaking? Do I have a
2 suspension that's uniformly dispersed after I shook
3 it and left it for a month? Very different outcome
4 parameters in whether the viscosity grade of HPMC
5 matters, and determines a difference in those. You
6 know, potentially. But I need to know more before
7 I can tell you that my -- that the absolute
8 parameter that's controlling any differences
9 observed might be only the HPMC viscosity.

10 Q. Or it could be something else
11 potentially but without more information you just
12 wouldn't know whether or not the difference in
13 viscosity grades of HPMC is what's causing
14 differences between the formulations?

15 A. Well, if there -- if there were
16 differences in what I was observing, I would
17 certainly not discount that it's a difference in
18 the viscosity grade that's causing that until I was
19 able to refute that. And there clearly must have
20 been other differences between the systems then if
21 it turns out that -- that it's -- it's not the
22 result of the HPMC grade.

1 Q. And how would you go about eliminating
2 whether it's some other parameter or it's the grade
3 of -- viscosity grade of HPMC?

4 A. Through a set of systematic
5 experiments, changing variables of amounts of
6 material or inclusion or exclusion of those
7 materials to determine. But I have to do that in
8 a -- in a -- in a fair sense of what I'm comparing.

9 But, you know, a well controlled set of
10 experiments that systematically evaluates
11 components would likely at least narrow down the
12 likely causative agents to certainly less than the
13 total number of agents that are in the system. And
14 the parameters that those agents then -- then
15 result in some pH, for example, versus the amount
16 of acid somebody added.

17 Q. So I take you back to your second
18 declaration, paragraph 43. I'm sorry. It would be
19 35 through 39. Are with me?

20 A. I found Section A there. I'm here.

21 Q. You didn't observe Dr. Govindarajan's
22 testing?

1 A. I wasn't aware that Dr. Govindarajan
2 was doing testing.

3 Q. Okay. And this was testing that
4 Dr. Govindarajan had done back in 2016 as part of
5 the Apotex case?

6 A. I don't even recall when he did it but
7 it was part of that case.

8 Q. Okay. So all you're basing your, I
9 guess, rehash of what Dr. Govindarajan had done,
10 you're just basing that on his notebook pages?

11 A. Yes.

12 Q. Not on your personal observations?

13 A. Like I said, I wasn't aware that he was
14 even doing these experiments. So yes, I read his
15 notebook summaries and wrote what I felt was a
16 reasonably -- reasonable excerpts that described
17 what he did.

18 Q. And if Dr. Govindarajan wrote that he
19 was easily able to redisperse a composition upon
20 gentle agitation, you wouldn't have an
21 understanding of how redispersed that formulation
22 was?

1 A. I -- you know, I read what
2 Dr. Govindarajan wrote and he described things as
3 being easily redispersed upon, you know, turning
4 the vial several times. And a typical POSA would
5 have -- if one's going to describe how many times
6 you inverted the vial to mix, if they saw a
7 gradation, they would have noted that also.

8 So in -- in sort of keeping with the
9 style, my expectation was that it was uniformly
10 redispersed along with being easily redispersed.
11 Otherwise, it would have been noted in the same
12 detail that other things about the methodologies
13 were noted.

14 Q. Okay. And that's just based on
15 convention or is that based on your experience with
16 Dr. Govindarajan?

17 A. It's certainly based on convention.
18 But I -- I mean, I know Dr. Govindarajan. And I
19 don't have any reason to not believe that
20 convention would hold in the methodologies he used
21 uses.

22 Q. So in paragraph 36 you say, "After

1 which Dr. Govindarajan identified a fine, settled
2 solid that was, quote, "'easily redispersed...'"
3 and then the sentence continues.

4 Do you see that in the middle of
5 paragraph 36?

6 A. Uh-huh.

7 Q. How easily redispersed was it?

8 A. He says it was easily redispersed.
9 That's what I have to believe. It took no special
10 efforts to redisperse.

11 Q. Okay. But you don't know how easily it
12 was -- how easily he was able to redisperse?

13 A. He clearly says he overturned the vials
14 three to four times with gentle agitation. That
15 gives me a general basis of behavior on which to --
16 to understand the amount of effort he put into
17 redispersing it. He said it was easily redispersed
18 and he said it was readily and uniformly
19 resuspended.

20 So with not much effort he was able to
21 readily and uniformly resuspend it is my summary of
22 my summary.

1 Q. And you don't know how gentle his
2 agitation was?

3 I mean, what might be gentle for one
4 person could be a different sense of general -- or
5 gentle for someone else, right?

6 A. I think in these kind of qualitative
7 descriptors there aren't 15 gradations of degree of
8 agitation that one would use. There's probably
9 three. There's probably gentle, moderate, and
10 vigorous. So gentle tells me sort of the area of
11 how much energy he expended in inverting that vial.

12 Q. And that's just based on the, again,
13 convention?

14 A. Based on convention, yes.

15 Q. And he continues on, or I guess you
16 continue on in paragraph 36 to say that "the solid
17 was readily and uniformly suspended."

18 Do you have an understanding of how
19 uniformly the resuspension was in paragraph -- that
20 he's referring to paragraph 36?

21 A. Again, I understand what he did based
22 on his laboratory notebook and that he was using

1 visual observation and that it appeared to be
2 uniformly resuspended.

3 Q. But there was no tests that were run to
4 determine whether or not it was uniform, it's just
5 a visual observation?

6 A. He was using visual observations on a
7 single formulation that he was approaching as a
8 POSA beginning a formulation development activity.

9 Q. So from your perspective, are you
10 saying that he was able to get a readily and
11 uniformly resuspended solution? Is that your
12 opinion of what he had done? Or is that just -- or
13 are you just simply restating what he had stated?

14 A. I had no reason to not believe that
15 Dr. Govindarajan, conducting the experiments he
16 did, described the way he described them in his lab
17 notebook, and redispersing the material the way he
18 claims he did, I believe he clearly -- he also
19 truthfully observed what he believed was a uniform
20 resuspension of the solids.

21 Q. So my question is a little bit
22 different. I understand that you're saying that he

1 truthfully believed that he got -- he was able to
2 readily and uniformly resuspend the solid.

3 But my question is, do you believe that
4 he readily and uniformly resuspended the solid?

5 A. I don't have any reason to --

6 Q. Based only on what he wrote.

7 A. I -- what he wrote is what he saw. I
8 am willing to believe that that is what he saw as
9 he described it.

10 Q. Now, is it typically -- strike that.

11 When you are coming up with an opinion
12 of whether or not someone made a uniform
13 suspension, do you typically base your opinion on
14 anything other than someone's notes saying that
15 they obtained uniform suspension?

16 MR. HOUSTON: Objection. Form.

17 THE WITNESS: If I'm provided other
18 information, I might be able to -- to
19 interpret that information in addition to
20 what was written and add in my opinion. But,
21 you know, I use whatever information I'm
22 provided and discern whether I think it makes

1 logical sense or a number of other issues.

2 I saw what Dr. Govindarajan reported in
3 his lab notebook. It was an entirely
4 consistent methodology with how I believe a
5 POSA would approach the problems he was
6 given. I have no reason to not believe the
7 notations he recorded. If he provided other
8 information, videos, photos, whatever, I
9 could take those into account also.

10 BY MR. LAROCK:

11 Q. So if Dr. Govindarajan said that he was
12 able to obtain a readily and uniformly resuspended
13 composition, and that was based on visual
14 observation, that doesn't foreclose the possibility
15 that the composition is not uniformly resuspended,
16 right?

17 A. I -- I -- there's -- yes, I mean,
18 visual observation is not a quantitative
19 observation. But this was not a formulation. This
20 was his first mixing of materials that were listed
21 as a composition. So -- so whether -- whether it
22 actually -- you know, if he went -- had gone to the

1 extent of -- of chemically analyzing it to see if
2 it was uniform, and we'd have to declare over what
3 time it was that we were going to allow that
4 suspension or we were going to -- going to stress
5 the suspension to see that it remained uniformly
6 dispersed, that's -- that's all fine. But that's
7 not what one does with the first formulation mixing
8 attempt that you undertake as a formulation
9 development scientist.

10 Q. So I think what you -- I think you
11 answered my question but -- actually, I don't think
12 so?

13 So -- so my question is, simply because
14 a person of ordinary skill in or in this case
15 Dr. Govindarajan was able to verbally come to the
16 conclusion that there was a uniform resuspension
17 does not foreclose the possibility that the
18 suspension is not actually a uniform -- uniformly
19 resuspended?

20 A. I mean, a qualitative visual
21 description versus a quantitative carefully carried
22 out scientifically designed sampling protocol are

1 not the same.

2 Q. Okay. So with visual observation, you
3 can come to one conclusion, but when you actually
4 test and undertake an analysis to see if you
5 actually obtained a uniformly suspension, you may
6 come to a different conclusion?

7 A. I guess there's the potential of that,
8 yes.

9 Q. So did Dr. Govindarajan, in your review
10 of what he had done, did he ever comment on the
11 rate of sedimentation of the settling?

12 A. I don't recall if he did. Let me read
13 my summary and then I might ask you for his report
14 to see whether he did or not.

15 Q. Let me ask this first. Is the rate of
16 sedimentation a meaningful parameter a person of
17 ordinary skill in 2002 looks to when assessing
18 whether they've -- they have a composition that is
19 physically stable?

20 A. Well, I mean, when assessing a
21 suspension, a person of ordinary skill anticipates
22 that there will be settling over some time period.

1 A person of ordinary skill decides what -- what
2 settling rate might be acceptable. And -- and they
3 have a number of ways of varying their formulation
4 to try to accomplish that settling. Or that --
5 that rate of settling, that lack of settling,
6 whatever.

7 And then on top of that, the ability to
8 re- -- to uniformly redisperse the system is -- is
9 another qualification criteria that -- you know,
10 while rate of settling is -- is potentially
11 meaningful, it can be potentially not meaningful.
12 It doesn't matter how fast it settles if as long as
13 when I shake it back up again it uniformly
14 redisperses. So it's a matter of -- a level of
15 concern with various parameters of my formulation.

16 Q. But wouldn't the rate of settling
17 affect how long you had a uniformly redispersed
18 drug in that formulation?

19 A. It may, but typically for short time
20 periods. You can easily adjust formulations to
21 accommodate uniformity for short time intervals.
22 It's the much longer time intervals that sometimes

1 become more complicated.

2 MR. LAROCK: Can we take a short break.

3 THE WITNESS: Sure.

4 (Whereupon, a recess was taken
5 from 2:52 p.m. to 3:01 p.m.)

6 BY MR. LAROCK:

7 Q. So Dr. Donovan, can you turn to
8 paragraph 68 of your second declaration there?

9 A. Yeah.

10 Q. And you say in -- you say halfway down,
11 "When preparing a suspension with MCC/CMC, a POSA
12 would avoid adding an additional" -- "adding any
13 additional electrolytes (e.g., sodium chloride) if
14 uncharged equivalents are available." Right?

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

16 Q. And the basis for that statement is the
17 fact that you're using that to say that the person
18 of ordinary skill would be motivated to avoid using
19 sodium chloride?

20 A. Well, they're motivated to limit the
21 number of extraneous electrolytes that are present
22 in the mixture. Sodium chloride acting as a

1 tonicity adjuster acts just as that, that there are
2 other nonelectrolyte equivalents. It's not
3 necessarily to use an electrolyte-based tonicity
4 adjuster. So the preference would be using one
5 that doesn't contribute to the electrolyte load in
6 the system.

7 Q. And that electrolyte load, the concern
8 being that electrolyte might have adverse effects
9 on the rest of the system?

10 A. Well, in particular the MCC/CMC reduces
11 the water activity.

12 Q. Would the impact of additional
13 electrolytes on an MCC/CMC, isn't that a reason --
14 a potential reason not to use MCC/CMC as the
15 thickening agent in this formulation if that's the
16 concern?

17 A. If -- if the suspending agent gives the
18 properties of the suspension that are desired,
19 it's -- there are -- there are more ways of finding
20 a nonelectrolyte tonicity adjusting agent to adjust
21 the tonicity than there are finding alternative
22 suspending agents that may give you as many

1 preferred properties to that suspension.

2 Q. But is it your opinion that the person
3 of ordinary skill would be able to find alternative
4 thickening agents to MCC/CMC that would give the
5 properties that they're looking for?

6 They would be able to do that, right,
7 in 2002?

8 A. There are certainly a number of
9 different thickening agents, viscosity enhancing
10 agents, suspending agents, whatever we want to call
11 them, that could have been evaluated or can be
12 evaluated to give -- to be combined to give the
13 properties of the suspension that are desired.

14 The adjusting of the tonicity is
15 somewhat of a second -- not secondary, but it -- it
16 happens later in the design because we know we have
17 a number of good alternatives for adjusting the
18 tonicity.

19 So a typical POSA would put priority on
20 selecting the suspending agent, developing the
21 suspension to give the properties they wanted,
22 having good confidence that they would be able to

1 adjust the tonicity with any number of different
2 agents to give them the final formulation with
3 the -- the tonicity that they desired.

4 So formulating around sodium chloride
5 as a tonicity adjuster as a priority is a -- is --
6 it would be hard for me to conceive that would
7 really be a starting point.

8 Q. So my question wasn't whether that was
9 a starting point or not. My question was, if you
10 anticipate that there's going to be a sodium
11 chloride MCC/CMC interaction, you have two
12 alternatives. You can either not use sodium
13 chloride, and that's what you're proposing here?

14 A. Uh-huh.

15 Q. Or you could use a different thickening
16 agent. And those -- those seem like -- I mean,
17 you're choosing one or the other. But I'm
18 saying -- but I'm having a more fundamental
19 question, which is both of those avenues are viable
20 avenues; whether the person of ordinary skill may
21 go down one or the other depends on a whole variety
22 of other things, but they're both viable avenues to

1 address this issue?

2 A. Changing formulation components early
3 on in a formulation development scheme happens
4 among all of the possible agents or could happen
5 among all the possible agents that are -- that
6 are -- are planned or desired for that formulation.

7 In this particular case, since Flonase
8 is a -- contains fluticasone propionate of the
9 concentration that was desired in the combination,
10 and it contained Avicel RC-591, using that same
11 suspending agent made the whole process or the
12 starting point for the process -- or preferred
13 starting point for the process just a faster
14 starting point.

15 And you could consider changing the
16 suspending agent. You could consider changing the
17 amount of Avicel 591 around the need to include
18 sodium chloride if you wanted. There's a number of
19 formulation variables, varieties that -- that a
20 POSA would be well familiar with and comfortable
21 with making.

22 Q. I think ultimately that was a "yes,"

1 that both of those avenues are viable?

2 A. Yes, they are.

3 Q. So we -- we spoke last time earlier
4 today about if a drug was FDA approved that it had
5 either passed a preservative challenge test or had
6 shown sufficiently to the FDA's liking that it was
7 able to control and inhibit microbial growth,
8 whatever preservatives were in the composition?

9 A. A drug product, for one thing.

10 Q. A drug product. Okay. So I'll ask the
11 question again.

12 So we spoke earlier that if the drug
13 product was FDA approved and it had either passed a
14 preservative challenge test so that we know that
15 whatever preservatives were in the system are
16 inhibiting -- sufficiently inhibiting bacterial
17 growth or had been shown by some other mechanism
18 sufficient to the FDA's liking that it had -- it
19 was not susceptible to unacceptable bacterial
20 growth. Right?

21 A. That's a reasonable, general statement,
22 yes.

1 Q. And both Astelin and Flonase were -- by
2 2002 they had been FDA approved, right?

3 A. Yes.

4 Q. And is it safe to assume that they --
5 either of them or both of them actually had passed
6 the preservative challenge test or had sufficiently
7 shown to the FDA that they inhibited bacterial
8 growth?

9 A. In their final packaging for the shelf
10 life that they claimed, yes.

11 Q. Okay. And that would have been known
12 by 2002, right?

13 A. That those -- yes.

14 Q. And it would have been known by 2002
15 what preservatives were in Astelin and what
16 preservatives were in Flonase?

17 A. Yeah, based on their labels.

18 Q. Based on the labels.

19 And so the person of ordinary skill
20 already had an idea of either the preservatives
21 that would be necessary to inhibit bacterial growth
22 or the preservatives and/or the concentrations to

1 inhibit bacterial growth that would be sufficient
2 to get a product so that it -- it wasn't
3 susceptible to unacceptable bacterial growth?

4 A. Well, formulators are aware of accepted
5 concentrations of many of the antimicrobial
6 preservatives, accepted concentrations for use in
7 particular dosage forms, and anticipated spectra of
8 coverage against particular microbial or fungal
9 specie. And so they're aware of all of those
10 characteristics of the antimicrobial preservatives.
11 And thus, if they are looking at somebody's label,
12 they can make a judgment likely about what microbes
13 are being -- are able to be killed or -- or
14 inhibited by the preservatives that are contained
15 in that particular -- in -- in -- using that set --
16 that preservative system.

17 Q. So my question was, given the fact that
18 Astelin and Flonase by 2002 had been FDA approved,
19 and given the fact that the labels of Astelin and
20 Flonase would tell the person of ordinary skill or
21 tell the public in 2002 what -- at least what
22 preservatives are in those products, if not the

1 preservatives and the concentrations, the person of
2 ordinary skill would have an idea of what -- the
3 person of ordinary skill would know that those
4 preservatives and those concentrations would be
5 able to pass a preservative challenge test or at
6 least gain FDA approval?

7 A. Yeah, at the time the test was
8 conducted.

9 Q. Okay. Right. And then -- okay.
10 You've had an opportunity to review the
11 Claims 42 and 44 of the '620 patent?

12 A. At some point in time I have.

13 Q. So paragraph 66 of your second
14 declaration you say that -- last sentence, "Claims
15 42 through 44 do not refer to unit dose
16 compositions or special systems that prevent
17 contamination."

18 Do you see that?

19 A. That's what the paragraph says, yes.

20 Q. How did you come to that?

21 A. Well, let me take a look at Claims 42
22 to 44.

1 Q. So handing you what's previously been
2 marked Exhibit 1001. Do you recognize this as the
3 '620 patent?

4 A. Yes, I do.

5 (Witness reviewed document.)

6 THE WITNESS: Okay. And the specific
7 question about --

8 BY MR. LAROCK:

9 Q. Are you -- I thought you were
10 familiarizing yourself with the patent.

11 A. I am. Okay.

12 Q. So my question was you stated in
13 paragraph 66 of your second declaration that Claims
14 42 to 44 do not refer to unit dose compositions.

15 My question is, how did you come to
16 that opinion?

17 A. Well, if a POSA were going to be
18 formulating a unit dose composition that was, you
19 know, an isolated system, there would be no need to
20 include a preservative in that -- or an
21 antimicrobial preservative in that system. The
22 unit dose device is designed such that microbial

1 ingress is -- is not possible until
2 post-administration.

3 Given that the Claims 42 through 44
4 describe the inclusion of antimicrobial
5 preservatives, the POSA would be led to believe
6 that this was intended for a multidose system.

7 Q. So if you were to have a composition
8 that had all of the components of Claim 42 through
9 44, which includes preservatives, that doesn't
10 foreclose them putting that formulation into a unit
11 dose device. Does it?

12 A. No, it doesn't.

13 Q. Okay. So I'm just trying to get at why
14 -- how you came to the conclusion that Claim 42
15 through 44 do not refer to unit dose compositions?

16 A. Well, again, the --

17 Q. Does it have anything to do with the
18 fact that besides the preservative point that you
19 already identified, is there any other basis for
20 that opinion?

21 A. The -- my opinion was formed based on
22 the knowledge that the overarching preference for

1 unit dose compositions is that they are -- they do
2 not contain antimicrobial preservatives. Many of
3 them are developed specifically to have the
4 antimicrobial preservatives removed from the
5 formulation.

6 And so given that 42, 43, and 44
7 contain antimicrobial preservatives, a POSA
8 would -- would likely not select those formulations
9 specifically for use in a unit dose, especially a
10 unit dose preservative-free composition, that is
11 Dr. Smyth, whom I'm quoting, had asserted would be
12 preferred.

13 Well, it's preferred or -- or at least
14 acknowledged that they exist. There are -- are
15 formulation strategies one would take for a unit of
16 use preservative-free system. There are
17 formulation strategies that a formulator would take
18 and materials that one would include for a multiuse
19 system. 42, 43, 44 speak to the materials that
20 would be included typically in a multidose system.

21 Q. So if you had that -- if you had a
22 formulation of 42, 43, or 44 and it was in a unit

1 dose system, would it be covered by Claim 42, 43,
2 and 44?

3 A. You know, I have a very difficult time
4 making a legal determination about what is covered
5 by certain claims. And not -- because I am not an
6 experienced claim reader nor writer. So I use
7 counsel to help me understand really what turns out
8 to be covered and what turns out to be not covered
9 given the wording of claims, dependent claims,
10 whatever. So I'm not -- I don't think I'm ready to
11 speak to what might be covered by a claim.

12 MR. LAROCK: No further questions.

13 MR. HOUSTON: We'll take a short break
14 and see if we have anything.

15 THE WITNESS: Okay.

16 (Whereupon, a recess was taken
17 from 3:21 p.m. to 3:49 p.m.)

18 MR. HOUSTON: No further questions.

19 (Said deposition was so concluded at
20 3:49 p.m.)

21

22

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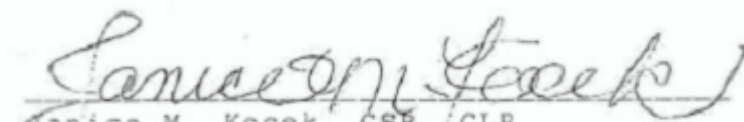
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5 Deponent: Maureen D. Donovan

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