

1 UNITED STATES DISTRICT COURT
2 NORTHERN DISTRICT OF WEST VIRGINIA

3 Regeneron Pharmaceuticals, Inc.

4 Plaintiff,

5 VS. CIVIL ACTION NO.

6 1:22-cv-61

7 Mylan Pharmaceuticals, Inc., and Volume 6

8 Biocon Biologics,

9 Defendants.

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11 Proceedings had in the bench trial of the above-styled
12 action on June 20, 2023, before Honorable Thomas S. Kleeh
District Judge, at Clarksburg, West Virginia.

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Proceedings recorded utilizing realtime translation.
Transcript produced by computer-aided transcription.

(Video deposition of Karen Chu)

Tuesday Morning Session,

June 20, 2023, 9:00 a.m.

- - -

THE COURT: We convene for day one, week two, of trial. Good morning, Counsel. Happy West Virginia Day to everybody.

Mylan may call its next witness.

MS. BODA: Good morning, Your Honor. Katie Boda.

Defendants' next witness will be Karen Chu by video deposition. Regeneron identified Ms. Chu in response to our 30(b)(6) topics identified in DTX 202, including conception and reduction to practice, the patent examples, and several issues relating to aflibercept development and associated clinical trials.

THE COURT: I'll note again Regeneron's objection to playing of the video in its entirety. Objection noted.

(Video deposition of Karen Chu.)

Q. Thank you. Good morning, Ms. Chu. My name is Deanne Mazzochi. Can you please state your full name and address for the record.

A. Yes. Karen Chu, and my home address is 73 Richbell Road, White Plains, New York 10605.

Q. And then what was your initial role and responsibilities at Regeneron?

A. So when I joined the company, I joined as a senior

(Video deposition of Karen Chu)

1 clinical trial manager. And then as is true, I think, for a
2 lot of small companies in that role, wore several different
3 hats and had a broad range of responsibilities as it related to
4 clinical development. And over the years moved into more of a
5 clinical project management role, and then finally into my
6 current role.

7 Q. Okay. And what -- was your initial title -- I think
8 it was -- what was it? -- director of therapeutic area project
9 management?

10 A. So that was not my first title at Regeneron.

11 Q. Okay. What was your first title?

12 A. I believe -- my recollection is that my first title
13 was senior clinical trial manager. But the director of
14 therapeutic area project management was promotion into a
15 broader clinical project management role.

16 Q. And then did you ever have any individuals who
17 reported to you in those roles?

18 A. At the time that I was a clinical trial manager I had
19 a group of people that reported to me who -- who were more
20 junior clinical trial managers and involved in the operations
21 of the clinical trials.

22 Q. Okay. How do you differentiate what your role was
23 versus what you call the operation of the clinical trials?

24 A. So within clinical research, there are several people
25 that contribute to any aspect of conducting a clinical trial.

(Video deposition of Karen Chu)

1 So the actual operations of the clinical trial, which includes
2 everything from ensuring that clinical study sites are
3 identified and trained appropriately to providing supplies for
4 the clinical study sites to deciding which laboratories to use
5 or how labs will be collected, that typically is considered
6 part of the operations role. So they're -- really, that -- you
7 know, they really oversee the actual execution of the clinical
8 trials.

9 Q. Let's focus on VEGF Trap. And if I call VEGF Trap
10 aflibercept, is that all right as well?

11 A. That is all right. I understand it to be the same
12 molecule.

13 So I can confirm that the document says "Plaintiff's
14 Rule 26(a) Initial Disclosures."

15 Q. Again, I'm trying to just get at what are identified
16 as alleged inventions in Defendants' Exhibit 4, the '601
17 patent. You said that in your role you participated in the
18 design of the studies, for example.

19 Can you tell me anything that you recall about
20 anything inventive or unique or new or different about those
21 particular trials that relate to the inventions set forth in
22 the '601 patent?

23 A. Certainly with every new molecule, the properties of
24 the molecule as well as considerations around its clinical use
25 go into the design of any trial. And Eylea represented a new

(Video deposition of Karen Chu)

1 anti-VEGF treatment that we felt had real potential advantages
2 and designed the trials in a way that we felt we could
3 demonstrate those unique properties to the best extent
4 possible.

5 Q. And is it fair to say that your clinical trials were
6 designed to try to optimize or maximize the chance of success?

7 A. So I think it's true that in clinical development
8 you're always trying to maximize your chances of success.

9 Q. Would Regeneron have followed or pursued a clinical
10 trial that it thought was going to fail?

11 A. So there's always a risk of failure. Clearly, you
12 know, the -- especially for Phase III trials, there is a
13 statistical threshold that you must meet. And there's always a
14 chance that you would not meet that for various reasons.

15 So I don't think it's true that Regeneron would not
16 have pursued a trial that had a chance of failure.

17 Q. Yeah. Maybe we can phrase it this way: Is it fair
18 to say that, in your time at Regeneron, if Regeneron was going
19 to pursue a clinical trial, they believed they would be able to
20 meet that -- the clinical end points they put in place? They
21 wouldn't have spent the money on a clinical trial if they
22 didn't?

23 A. So, again, every clinical trial, you know, we try to
24 design it for success. But there's always a risk that a
25 clinical trial would fail for one reason or another, whether

(Video deposition of Karen Chu)

1 that's safety or efficacy.

2 Q. When it comes to aflibercept, were there any clinical
3 trials you designed that led to failure as opposed to success
4 with regard to the ophthalmology category?

5 A. Can I ask for some limitations on the extent of my
6 answer? Is there a time frame that we're referring to?

7 Q. Sure. Let's say 2006 forward.

8 A. So, actually, most recently Regeneron has reported
9 two clinical trials with aflibercept that did not meet their
10 primary end point.

11 Q. And which were those?

12 A. Those are trials in the treatment of retinopathy of
13 prematurity.

14 Q. And what was the dosing regimen for those?

15 A. It's .4 milligrams either unilaterally or bilaterally
16 for up to three monthly doses.

17 Q. When you say "for up to three monthly doses," you
18 mean with three monthly doses or doses separated by three
19 months between them?

20 A. Sorry. In retinopathy of prematurity, physicians
21 treat initially with a single dose. If that does not regress
22 the retinopathy of prematurity sufficiently, they can give a
23 second dose a month later and a third dose a month later with
24 similar considerations.

25 Q. So besides this particular study that Regeneron

(Video deposition of Karen Chu)

1 conducted for the -- at the request of the FDA for pediatric
2 patients, are there any other studies that Regeneron has
3 pursued for aflibercept in the eye that have failed to meet
4 their clinical end points?

5 A. Not that I am aware of.

6 Q. All right. Ms. Chu, can you just confirm you have a
7 document before you marked DX 202 that is marked "Karen Chu
8 30(b)(6) Deposition Topics"?

9 A. Yes, the title of the document is "Karen Chu 30(b)(6)
10 Deposition Topics."

11 Q. Right. But who was the individual who ultimately
12 came up with the idea of dosing 2 milligrams approximately
13 every four weeks for the first three months and then the
14 2-milligram dose approximately once every eight weeks, or once
15 every two months, thereafter?

16 A. So, again, Regeneron operates in a -- you know,
17 cross-functional team environment; so there was input given by
18 many different functions and many different people. But George
19 Yancopoulos and Len Schleifer were definitely heavily involved
20 in these discussions, and any approval would have needed to
21 have been given by George to move ahead with the study design.

22 Q. Right. I understand they had to give approval, but
23 who actually came up with the idea of this particular regimen,
24 in Regeneron's view?

25 A. I don't recall.

(Video deposition of Karen Chu)

1 Q. All right. So, Ms. Chu, when it comes to Regeneron's
2 position with regard to the '601 patent, does Regeneron have a
3 position as to who was responsible for the conception of the
4 full claims set forth in Claim 1 of the '601 patent?

5 A. George Yancopoulos is the named inventor on the '601
6 patent.

7 Q. And why does Regeneron believe that George
8 Yancopoulos is the person who conceived of the methods set
9 forth in Claim 1 of the '601 patent?

10 A. George has always and continues to play a very
11 hands-on role in all research and development, including the
12 development of aflibercept. And he was personally involved in
13 many, many discussions related to the development of
14 aflibercept across all phases of clinical trials, including the
15 design of the Phase III studies.

16 Q. Okay. So is it Regeneron's position that the
17 reason -- that the reason for George Yancopoulos being the
18 named inventor is because he's the one who did the sign-off on
19 the Phase III clinical design study -- sorry -- Phase III
20 clinical study design?

21 A. So my knowledge is that George had tremendous input.
22 And ultimately it was his decision to move forward with the
23 final study design for the VIEW 1 and the VIEW 2 studies.

24 Q. Are there any documents that showed that it was
25 George Yancopoulos, as opposed to someone else, who

(Video deposition of Karen Chu)

1 specifically put together the 2-milligrams every four weeks for
2 the first six months followed by 2 milligrams once every eight
3 weeks, or every two months thereafter?

4 A. Off the top of my head, I don't recall specific
5 documents.

6 Q. Did you try to reach out to Dr. Cedarbaum to prepare
7 as a 30(b)(6) witness?

8 A. I did not reach out to Dr. Cedarbaum in preparation
9 for this deposition.

10 Q. What about Mr. Ingerman, Avner Ingerman?

11 A. Right. Avner Ingerman.

12 Q. Avner Ingerman, right. Wasn't he also one of the
13 individuals who was in favor of the eight-week interval?

14 A. My recollection of Dr. Ingerman's position at that
15 time is that he was lobbying for an as-needed or prn dosing
16 regimen, although he was part of many discussions about
17 alternative dosing regimens that could be employed.

18 Q. Such as?

19 A. Such as every eight weeks or other potential dosing
20 regimens.

21 Q. And what within the visual acuity data prompted
22 shortening the interval from 12 weeks to eight?

23 A. So within the visual acuity data, even though visual
24 acuity is a highly variable measure and this was a relatively
25 small study in that there were about 30 patients per group, we

(Video deposition of Karen Chu)

1 looked for trends to inform us of what's happening. And my
2 recollection is that the most important aspect of the visual
3 acuity was that the groups that were dosed with monthly
4 injections first overall had a greater gain in visual acuity.

5 Secondly, that when those patients were allowed to go
6 longer than four weeks without a dose, we saw some decline in
7 visual acuity over that period.

8 Q. Okay. And was the period a 12-week period, an
9 eight-week period, or was it a prn period?

10 A. So in this study, after Week 12, patients were dosed
11 prn. So the duration between that Week 12 dose and subsequent
12 doses was variable.

13 Q. Okay. Well, why go with eight weeks as opposed to
14 six weeks or just sticking with monthly?

15 A. So we did include two monthly dosing groups in the
16 VIEW 1 and the VIEW 2 study. We tested two separate
17 doses, .5 milligrams and 2 milligrams. As I mentioned before,
18 there were many considerations that went into the study design.
19 And some of those considerations have to do with the
20 constraints of a study conduct.

21 So one aspect of these studies is we must conduct
22 them as what we call double-masked studies. And we perform
23 sham injections at visits where patients are not receiving an
24 active injection. And it was impractical to include a group
25 where we had a six-week dosing interval because it would have

(Video deposition of Karen Chu)

1 necessitated visits essentially every two weeks for all
2 patients.

3 Q. Okay. So the every eight weeks just made the
4 clinical trial design easier in terms of maintaining the mask?

5 A. It was both a dosing interval that we felt was
6 supported by the data and also created a more practical way to
7 conduct the study.

8 Q. Now, in the '601 patent, Claim 10, we have the same
9 dosing regimen, but this time it's for a method of treating
10 diabetic macular edema in a patient in need thereof.

11 Who was the one -- what is Regeneron's position as to
12 who was the person who actually came up with the idea of
13 applying this regimen to the DME indication?

14 A. So this regimen is different in that it is for
15 2 milligrams given every four weeks for the first five
16 injections followed by approximately once every eight weeks, or
17 every two months.

18 And my recollection is that, again, there were
19 several discussions about the optimal study design for treating
20 diabetic macular edema. And those conversations would have
21 included both people from the clinical team as well as senior
22 management.

23 Q. Right. Who decided that the dosing was going to be
24 for the first five injections as opposed to three or four?

25 A. My recollection is that George Yancopoulos made that

(Video deposition of Karen Chu)

1 decision.

2 Q. Is that documented anywhere?

3 A. I don't recall if there is specific documentation of
4 that.

5 Q. If you can take a look at the '601 patent, is the
6 clinical trial protocol for the Phase III VIVID or VISTA
7 studies set forth in any of the patent examples?

8 A. To answer that question, I would have to go through
9 the entire patent. Is that something I should do?

10 Q. Sure. You can start with Example 1, which begins at
11 Column 8.

12 A. So in my review of the Patent '601, I do not see a
13 description -- or the VIVID and VISTA trials given as an
14 example, but I do see the Phase II clinical trial in diabetic
15 macular edema described as Example 5.

16 Q. And if I understand you, it was the data from this
17 Phase II study that justified the dosing regimen for the VIVID
18 and VISTA studies for diabetic retinopathy?

19 A. So data from this Phase II study did inform decisions
20 regarding the VIVID and VISTA study designs.

21 Q. And why is it that Regeneron believed that the DME
22 data could be transferred over to the diabetic retinopathy
23 indication?

24 A. So as I mentioned, data from the VIVID and VISTA
25 studies included a secondary end point of a proportion of

(Video deposition of Karen Chu)

1 patients with two or more step improvement in diabetic
2 retinopathy. Patients with diabetic macular edema do have
3 underlying diabetic retinopathy at various severities. And we
4 did see a statistically significant outcome of improvement in
5 patients that were treated with aflibercept in the VIVID and
6 VISTA studies -- oh, I'm sorry -- in the -- yes, in the VIVID
7 and VISTA studies. Sorry.

8 Q. Let me know when you have that exhibit before you.

9 A. I have Exhibit 204 in front of me.

10 Q. Okay. I'd like to take a look at Claim 6 of the '601
11 patent.

12 A. Okay. I see that.

13 Q. And -- yeah. So here again, I just have a question.
14 What can be done to the dosing regimen in Claim 1 to ensure
15 that a patient is going to be able to meet these requirements
16 of Claim 5 and Claim 6 and -- specifically using this
17 measurement technique that's set forth in Claim 6?

18 A. So I would respond the same way, that the response to
19 treatment is highly variable with individual patients.

20 Q. Okay. So how are we going to know, then, if an
21 individual patient actually meets the standard?

22 A. So in the treatment and monitoring of an individual
23 patient with neovascular age-related macular degeneration,
24 visual acuity would be assessed prior to treatment initiation
25 and at an interval deemed appropriate by the treating physician

(Video deposition of Karen Chu)

1 during the course of treatment.

2 Q. Ms. Chu, can you take a look at DX 205 and confirm
3 that it is the FDA-approved Eylea labeling?

4 A. So I have Exhibit 205 in front of me, and it
5 appears -- this appears to be the Eylea USPI revised as of
6 May 2019.

7 Q. Well, are you aware of any change to the formulation
8 description that appears here as compared to when the Eylea
9 product was first approved in 2011?

10 A. In my experience and knowledge, I am not aware of any
11 changes to the formulation as described here in the USPI.

12 Q. And then we've got George Yancopoulos, who is listed,
13 at least on this org chart, as the CSO. Is he still the CSO
14 today or does he have a better title?

15 A. My understanding is he still has the title chief
16 scientific officer.

17 Q. Okay. Anything, though, that would justify having
18 the longer dosing interval that you recall?

19 A. So I can't remember if this was specifically in
20 Neil's purview, but we did know that, based on the aflibercept
21 molecule comparing to Lucentis, that it did have a longer
22 half-life in the eye of animals. And so that gave us an
23 indication that potentially a longer dosing interval might be
24 possible. But certainly animal studies are only somewhat
25 translatable to human studies.

(Video deposition of Karen Chu)

1 Q. Okay. And then from Regeneron's perspective, which
2 clinical trial was it that allowed you to conclude that
3 aflibercept might have a longer half-life in the human eye that
4 might justify a longer dosing interval?

5 A. So we -- during the course of Eylea clinical
6 development, we did not measure half-life in the human eye.
7 That would have required sampling from ocular fluids, which, to
8 do serially in patients, is very difficult and causes
9 additional safety risk for patients. So the data from the
10 0508, or CLEAR-IT 2, study was really the clinical data that we
11 looked at in order to decide which dosing regimens to test in
12 Phase III.

13 Q. Okay. Can you confirm that Exhibit 207 is a Friday,
14 January 30th, 2004, email from Jesse Cedarbaum to you and
15 others involving what was described as draft VEGF Trap AMD
16 press and some thoughts for release on the start of an AMD
17 trial?

18 A. I see that the email is dated Friday, January 30th,
19 2004, and that I am one of the recipients of the email.

20 Q. Was it common for Regeneron to prepare press releases
21 when they were about to start clinical trials?

22 A. Regeneron was a small company back then; so the
23 initiation of a clinical development program would have been
24 something that we would have disclosed.

25 Q. Do you have Exhibit 209 in front of you?

(Video deposition of Karen Chu)

1 A. Yes, I have Exhibit 209 in front of me.

2 Q. All right. Can you confirm that the top email was
3 copied to you and others on Tuesday, August 31st, 2004?

4 A. Yes. I am on the cc line of this email dated -- just
5 to say dated August 31st, 2004.

6 Q. Macugen was dosing its product intravitreally,
7 correct?

8 A. That is correct.

9 Q. Did these results cause Regeneron to start thinking
10 more closely about doing an intravitreal injection?

11 A. I believe that the results from the Macugen trials
12 gave us more information about the safety and feasibility of
13 intravitreal injections given regularly to these -- to the --
14 to AMD patients over the course of a year of treatment.

15 Q. Did the Macugen results give you any sense that there
16 might be more willingness in the marketplace to accept an
17 intravitreal injection?

18 A. The Macugen results from these Phase III studies
19 definitely supported that intravitreal administration of a
20 product in wet AMD patients was possible.

21 Q. All right. And at this time it was known to
22 Regeneron that ranibizumab was also out there in Phase III
23 trials, right?

24 A. Yes. The Lucentis trials were being conducted
25 concurrently at this time.

(Video deposition of Karen Chu)

1 Q. And it also mentions at the end of the paragraph that
2 Regeneron's VEGF Trap was also currently in clinical and
3 preclinical trials, right?

4 A. Yes. The last sentence is "Other antiangiogenic
5 agents currently in clinical and preclinical trials are
6 Angstrom's A6, OXiGENE's CA4P, and Regeneron's VEGF Trap."

7 Q. At this point in time, were you looking at the
8 Lucentis dosing regimen as one that you might want to copy or
9 emulate?

10 A. I would say at this time we were monitoring the
11 Lucentis clinical development program closely from a
12 competitive intelligence perspective.

13 Q. Right. And certainly by the time we got to the 2010
14 time frame, at the time when you had submitted your Phase III
15 clinical trials, ranibizumab had been shown to produce some
16 consistent vision gain, right, when injected intravitreally?

17 A. So the pivotal Lucentis trials in neovascular AMD
18 were the ANCHOR and MARINA trials. And they demonstrated
19 vision gain with ranibizumab dosed every four weeks, or
20 monthly, for the -- for a year. So Week 52 was their primary
21 end point.

22 Q. Do you have that exhibit before you?

23 A. Yes, I have Exhibit 210.

24 Q. Okay. Can you confirm that Exhibit 210 contains an
25 email string including an email from Ilham Zoughi, Z-O-U-G-H-I,

(Video deposition of Karen Chu)

1 to you and others dated March 3rd, 2005?

2 A. Yes, I see that I am a recipient of this email from
3 Ilham Zoughi.

4 Q. If you look at the bottom line, the author there
5 said -- "We've been" -- the study clinician was quoted as
6 saying, "We've been injecting anti-VEGF drugs into the eye for
7 the past three years with very encouraging results."

8 Do you see that?

9 A. I do see that as part of the quote here.

10 Q. Right. And that quote is attributed to Philip J.
11 Rosenfeld, MD, PhD?

12 A. So this email just said Rosenfeld, which I assume to
13 mean Phil Rosenfeld.

14 Q. Right. Now, did Regeneron also reach out to get
15 input from Phil Rosenfeld in the context of this clinical trial
16 work?

17 A. Dr. Rosenfeld was a respected key opinion leader in
18 the retina community, and he is someone that we interacted with
19 occasionally to discuss aspects of the clinical development
20 program.

21 Q. Do you recall there being any impact within Regeneron
22 when it was reported that Avastin, a VEGF inhibitor, was
23 producing positive results in the eye?

24 A. I don't remember this study or the data from this
25 study having a specific impact at Regeneron.

(Video deposition of Karen Chu)

1 Q. All right. But what about Avastin generally, the
2 experience that clinicians were having with Avastin injecting
3 it into the eye to get -- to stop vision loss?

4 A. So this press release is referring to systemic
5 administration of Avastin.

6 Q. Right.

7 A. But Dr. Rosenfeld was involved in running his own
8 investigator-initiated studies with intravitreal Avastin.

9 Q. Right. Right. And he indicates, in this document at
10 least, that he had been doing that for at least three years?

11 A. That is what the document says.

12 Q. Right. So did the fact that someone like
13 Dr. Rosenfeld and others were injecting Avastin directly into
14 the eye, did that influence their thinking as to whether it
15 would be useful to dose VEGF Trap into the eye?

16 A. Dr. Rosenfeld, as well as other retina specialists in
17 the community, provided information that gave Regeneron more
18 confidence regarding the feasibility of moving forward with an
19 intravitreally delivered product.

20 Q. Okay.

21 A. So the study in Example 1 was referred to as the
22 CLEAR-IT 1 study; the study in Example 2 was the CLEAR-IT 2
23 study.

24 Q. Okay. Perfect. Thank you.

25 And then if we go on to the next column, Example 4,

(Video deposition of Karen Chu)

1 the Phase III clinical trials, was that the VIEW 1 study or
2 VIEW 2?

3 A. So this section under Example 4 refers to two
4 parallel Phase III clinical trials carried out to investigate
5 the use of VEGF-T to treat patients with neovascular -- with
6 the neovascular form of age-related macular degeneration. So
7 this section appears to be referring to both the VIEW 1 and the
8 VIEW 2 studies.

9 Q. Okay. And then if you can jump forward to Column 14,
10 there is an Example 5 provided there. Did that clinical study
11 also have a name?

12 A. Example 5 is the Phase II clinical trial of VEGF-T in
13 subjects with diabetic macular edema. This study was referred
14 to as the DA VINCI trial.

15 Q. Okay. And then Example 6, did that clinical trial
16 have a name?

17 A. So in Example 6, it's referring to a randomized
18 multicenter double-masked trial in treatment-naive patients
19 with macular edema secondary to CRVO. And I believe this is
20 referring to a study that we called the COPERNICUS study,
21 although there was a second CRVO trial conducted called the
22 GALILEO study.

23 Q. Can you confirm that this is a document, an email
24 string with the first one dated Sunday, January 8th, 2006,
25 regarding an AMD expert meeting, from Neil Stahl to Jesse

(Video deposition of Karen Chu)

1 Cedarbaum, you, and others?

2 A. I can confirm that the date of this email is Sunday,
3 January 8th, 2006, the subject is regarding AMD expert meeting,
4 it's from Neil Stahl, and I am one of the recipients of this
5 email.

6 Q. One of the other questions to ask these experts was
7 do they think that the PIER regimen of Lucentis will work?

8 Do you see that?

9 A. I do see that question.

10 Q. What was your understanding of PIER regimen for
11 Lucentis?

12 A. So the PIER study was an investigator-initiated study
13 conducted by Dr. Phil Rosenfeld that -- my understanding of
14 that regimen is that it was three initial monthly doses
15 of .5 milligrams of Lucentis followed by quarterly dosing; so
16 every-three-month dosing.

17 Q. Let me know when you have that.

18 Are you identified as one of the individuals who
19 participated in this advisory panel meeting?

20 A. Just give me a second to review this.

21 Okay. So I am listed as one of the Regeneron
22 attendees for this meeting.

23 Q. And one of the items listed here that Regeneron
24 wanted to get the consultant's impressions of was how will
25 Lucentis be used in practice: Monthly as in ANCHOR and MARINA,

(Video deposition of Karen Chu)

1 induction followed by quarterly maintenance as in PIER, or
2 induction followed by PIER and criteria-based dosing as in
3 SAILOR.

4 Do you see that?

5 A. I do see that under 3A.

6 Q. Now, the title of this was "CLEAR-IT 3 Advisory Panel
7 Meeting."

8 What was CLEAR-IT 3?

9 A. My recollection is that CLEAR-IT 3 was the initial
10 name that Dr. Cedarbaum wanted to give the Phase III AMD
11 studies.

12 Q. Okay. So CLEAR-IT 3 eventually became known as the
13 VIEW 1 and VIEW 2 studies?

14 A. The Phase III studies were eventually named VIEW 1
15 and VIEW 2, yes.

16 Q. Can you confirm it's dated Friday, February 10th,
17 2006, from Srilatha Vuthoori to you and many others at
18 Regeneron?

19 A. This email is dated Friday, February 10th, 2006. The
20 subject is "Actions and decisions VGT team meeting." And it's
21 from Sri Vuthoori, and I'm one of the recipients.

22 Q. Okay. Let me give you a document that has production
23 numbers NYLAF8703 through 8711, which I will mark as DX215.

24 A. Okay. I have Exhibit 215 in front of me.

25 Q. Okay. And do you see it says citation in the upper

(Video deposition of Karen Chu)

1 left-hand corner it says, "WHO drug information Volume 20,
2 Number 2, 2006"?

3 A. I see that the document is labeled in the upper
4 right-hand corner "WHO Drug Information Volume 20, Number 2,
5 2006."

6 Q. And then this was titled "International
7 Nonproprietary Names for Pharmaceutical Substances."

8 A. I see the document is titled "International
9 Nonproprietary Names for Pharmaceutical Substances."

10 Q. All right. Can you go ahead and turn to page 8706 as
11 the Bates number. It's page 118 within this volume. And do
12 you see a reference on this page to aflibercept?

13 A. Yes, I see on the second half of the page there is a
14 reference to aflibercept.

15 Q. In the context of your clinical work, did you ever
16 use the term "aflibercept" to refer to any chemical structure
17 other than VEGF Trap-Eye?

18 A. So the terms VEGF Trap, VGFT, VEGF Trap-Eye, and
19 aflibercept, depending on the time period, were used somewhat
20 synonymously. VEGF Trap-Eye was almost always used to
21 distinguish between the systemic formulation of aflibercept
22 versus the intravitreal formulation.

23 Q. Right. But the underlying structure of aflibercept,
24 the molecule, didn't change whether it was VEGF Trap-Eye or
25 VEGF Trap or aflibercept; is that fair?

(Video deposition of Karen Chu)

1 A. It is my understanding that the active ingredient was
2 the same in VEGF Trap-Eye and aflibercept whether that was
3 referring to the oncology product or the intravitreally
4 delivered product.

5 Q. I would like to mark as Defendant's Exhibit 218 a
6 document with production numbers RGN-EYLEA-MYLAN-553211 through
7 212.

8 And can you confirm this is a May 9th, 2006, email
9 from Jesse Cedarbaum to you and others discussing Rosenfeld's
10 Lucentis PrONTO press release?

11 A. This is an email dated Tuesday, May 9th, 2006, with
12 the subject "Rosenfeld's Lucentis PrONTO press release" from
13 Jesse Cedarbaum, and I am listed as one of the recipients.

14 Q. Okay. Now, according to this press release, it says,
15 "Open label on controlled study of Lucentis showed improvement
16 in vision with five to six doses at one year."

17 Do you see that?

18 A. I see that the title is "Open label on controlled
19 study of Lucentis showed improvement in vision with five to six
20 doses at one year."

21 Q. Do you recall whether anybody ever talked about a
22 dosing regimen that you thought might be superior to the
23 FDA-approved regimen for Lucentis?

24 A. We had -- we thought it was possible that aflibercept
25 could be superior to ranibizumab. And the design of the

(Video deposition of Karen Chu)

1 Phase III clinical trials was such that we did include a
2 2-milligram every-four-week dosing group as well as
3 a .5-milligram every-four-week dosing group with the ability,
4 if we met noninferiority in those groups, to then be able to
5 test for superiority.

6 I should just clarify that that would have been true
7 for all of the groups, including the third treatment group,
8 which was three initial monthly doses followed by a dosing
9 every eight weeks.

10 Q. During your time at Regeneron, has Regeneron
11 identified any head-to-head dosing regimen where it believes
12 aflibercept can demonstrate superiority to Lucentis in a manner
13 that the FDA or clinicians would accept?

14 A. In the protocol T study, which was a study conducted
15 by the Diabetic Retinopathy Clinical Research Network, with
16 aflibercept, ranibizumab, and bevacizumab dosed in the same
17 paradigm, which was a different paradigm than Regeneron has
18 tested in our trials, aflibercept was superior to both
19 ranibizumab and bevacizumab.

20 Q. Okay. And that particular dosing regimen of
21 aflibercept you just mentioned that was shown to be superior to
22 Lucentis, is that an FDA-approved dosing regimen or not?

23 A. That dosing regimen is not specifically reflected in
24 our labeling.

25 Q. Do you remember generally what was -- what they were

(Video deposition of Karen Chu)

1 doing in that one in terms of did it deviate from monthly
2 dosing? was it number of injections?

3 A. My recollection is that it was monthly dosing for a
4 certain number of doses and then criteria-based dosing based on
5 the protocol --

6 Q. Okay.

7 A. -- which allowed for a longer treatment interval.

8 Q. And can you confirm this is an email from Michael
9 Roosevelt to you, among others, dated Tuesday, May 9th, 2006?

10 A. Okay. I have Exhibit 219, and the date of the email
11 is Tuesday, May 9th, 2006, with the subject "Action Items -
12 May 9th, 2006," from Michael Roosevelt, and I am one of the
13 recipients of this email.

14 Q. Then we've got the 0508 study, and that was one of
15 the DME studies?

16 A. 0508 was the Phase II study in wet AMD with
17 intravitreal aflibercept.

18 Q. And what was the name of that trial?

19 A. We referred to that as the CLEAR-IT 2 trial.

20 Q. Do you recall any concerns expressed internally at
21 Regeneron about aflibercept's ability to achieve any efficacy
22 end points by the 12-week -- with a 12 weeks' high dosing
23 interval?

24 A. Are you referring to during the ongoing study?

25 Q. Yeah, either while the study was conducted or

(Video deposition of Karen Chu)

1 afterwards.

2 A. So once we had -- so this email is referring to a
3 time when the studies were ongoing. Once we received data from
4 the studies and analyzed it, we did have some concerns that,
5 based on the OCT data and an assessment of the visual acuity
6 data, that the 12-week interval was one where we were seeing
7 some loss of efficacy over that duration.

8 Q. And how were you defining loss of efficacy?

9 A. So, primarily, we were looking at the central retinal
10 lesion thickness measured by optical coherence tomography,
11 which was a very quantitative measure of the fluid in the
12 retina. And one aspect of that data is that we would see a
13 rapid reduction in retinal fluid after dosing with aflibercept,
14 and over the longer time period without treatment, we would see
15 some of that fluid begin to reaccumulate.

16 Q. And on this one I'd like to start with the email at
17 the end of the chain from George Yancopoulos to you and others
18 dated Tuesday, May 16th, 2006. So let me know when you're
19 there.

20 A. Yes, I have Exhibit 220 in front of me, and I see the
21 email from -- in the string from George Yancopoulos dated
22 Wednesday, May 17th, 2006, and I am one of the recipients.

23 Q. Okay. And they're also talking about the PrONTO
24 data, which was Dr. Rosenfeld's Lucentis study, right?

25 A. Yes, this email is referring to the PrONTO study.

(Video deposition of Karen Chu)

1 Q. It looks like Dr. Yancopoulos is saying, about the
2 PrONTO data, that Lucentis was not lasting for two months,
3 which could provide a major opportunity for VEGF Trap interval
4 advantage. Do you see that?

5 A. Yeah. So this is an email from the string dated
6 Tuesday, May 16th, 2006, subject, "PrONTO data."

7 Q. Okay. So was that -- was Dr. Yancopoulos's
8 assessment of the Lucentis PrONTO data something that caused
9 everybody to start saying, okay, we know Lucentis can't go for
10 more than two months?

11 A. So we were -- I don't recall specifically if this
12 data in any way translated to further discussions about the
13 dosing regimens planned for the VIEW 1 and VIEW 2 studies.

14 Q. Well, he says, "This indeed may provide us a major
15 opportunity for VEGF Trap interval advantage."

16 Did you look at that and get excited and say, yeah,
17 it will, or was it just more, like, whatever, you just
18 continued on your merry way?

19 A. We were excited about the possibility of aflibercept
20 having a longer treatment interval based on the properties of
21 the molecule itself as well as the emerging data from the
22 clinical development program.

23 I believe that Lucentis was approved in 2006 and was,
24 because of their clinical trial results, slated to become
25 standard of care. So I think that, you know, it wasn't

(Video deposition of Karen Chu)

1 specifically any outcome from Lucentis trials that made us
2 excited, but we were certainly monitoring the competitive
3 landscape closely.

4 Q. What was your -- to your recollection, what was
5 Regeneron's rationale for why the VEGF Trap aflibercept
6 molecule would be able to last longer as compared to Lucentis
7 ranibizumab?

8 A. So my understanding of Regeneron's rationale is that,
9 first, aflibercept is a larger molecule and, as a result, has a
10 longer half-life than Lucentis does, as well as the fact that
11 we have a much, much higher binding affinity and other kinetic
12 properties of binding to VEGF that we felt would be
13 advantageous for aflibercept and contribute to potentially a
14 longer duration of action.

15 Q. And to date, as far as you're aware, has Regeneron
16 ever validated that those two things, having a longer half-life
17 and increased binding affinity, actually is what's allowing
18 aflibercept to be dosed at these longer intervals as compared
19 to ranibizumab?

20 A. So the evidence we have of the longer duration of
21 action is from the clinical trial results based on outcome in
22 the clinical studies.

23 Q. Now, if we can go to the front page of Defendant's
24 Exhibit 220, you were also cc'd again on the email string, this
25 time on May 17th, 2006, from George Yancopoulos, about the

(Video deposition of Karen Chu)

1 PrONTO data, and he was responding to an email from Avner
2 Ingerman.

3 Do you see that?

4 A. I do see the email dated 17 May 2006 from George to
5 Avner and others where Avner is responding to an email from --
6 or sorry -- George is responding to an email from Avner.

7 Q. Now, Avner was discussing not just PrONTO but also
8 the MARINA and ANCHOR trials. Those were also -- those were
9 official Lucentis trials run by Genentech, right?

10 A. The MARINA and ANCHOR trials were the Phase III
11 studies sponsored by Genentech for Lucentis in neovascular AMD.

12 Q. Okay. In discussing those trials, he said, "It may
13 suggest that the so-called 'clinician prn practice' following
14 'induction dose' is as good as monthly injections for at least
15 the first year, and that is probably the take-home message that
16 the market will follow."

17 Do you see that?

18 A. I do see that sentence in the email.

19 Q. Do you know whether anybody agreed or disagreed with
20 Avner's assessment that that's how clinicians would likely
21 respond to this data?

22 A. Sorry. Can you just restate the question?

23 Q. Sure.

24 Do you recall within Regeneron whether people agreed
25 or disagreed with Dr. Ingerman's view that clinicians would

(Video deposition of Karen Chu)

1 probably perceive the clinician prn practice following
2 induction dose was as good as monthly injections for at least
3 the first year when it came to ranibizumab?

4 A. My recollection is that Dr. Yancopoulos strongly
5 disagreed with the concept that prn dosing was as good as
6 monthly dosing as studied in the ANCHOR and MARINA trials.

7 Q. So why did Dr. Yancopoulos agree to any type of
8 prn-type dosing in the later part of the VIEW studies if he was
9 adamant it wasn't going to work?

10 A. My recollection is that the most critical portion of
11 the study and the portion of the studies that defined our
12 initial dosing regimen in our application to the FDA was the
13 one-year data from the VIEW 1 and the VIEW 2 studies.

14 Q. Let me know when you have that.

15 A. Okay. I have Exhibit 222 in front of me.

16 Q. All right. And can you confirm that there's -- that
17 you were forwarded by Jesse Cedarbaum on or around
18 September 5th, 2006, a message -- an email message involving
19 Jesse Cedarbaum and Phil Rosenfeld, dated September 1st, 2006?

20 A. So I see the second sort of message in this string as
21 a forwarded message from Jesse Cedarbaum, dated the 5th of
22 September 2006. It was primarily to Len Schleifer, but I am
23 copied.

24 Q. Well, one of the things that Dr. Rosenfeld told Jesse
25 Cedarbaum which was passed on to you is he said, "You have a

(Video deposition of Karen Chu)

1 chance of use a 4-milligram dose, which is a fourfold molar
2 excess over Lucentis, with a good chance of better durability.
3 The more I thought about your dilemma, I would go with the
4 2-milligram and 4-milligram dose every two weeks or four weeks
5 for a fixed number of doses, then see the patients back every
6 four weeks and dose as needed. With the competition closing in
7 on you, I think your only choice is to go for the gold and
8 design a Phase III now."

9 Do you see that?

10 A. I do see where the email states that phrasing.

11 Q. Do you remember internally ever discussing the
12 possibility of using a 2-milligram dose in your Phase III
13 clinical trials before Jesse Cedarbaum got this feedback from
14 Dr. Rosenfeld?

15 A. I don't recall specifically the timing of the
16 discussions regarding dose selection for Phase III.

17 Q. All right. If you look at the top email, this is Len
18 Schleifer saying, "This is Phil Rosenfeld's view of our
19 diabetes opportunity." And then he says in the second line,
20 "Jesse showed him the four-week, five-patient DME data which
21 showed a nice response at four weeks and then a small loss by
22 six weeks."

23 Do you see that?

24 A. I do see where that sentence is.

25 Q. All right. Do you know which clinical trial data

(Video deposition of Karen Chu)

1 that was that was the four-week five-patient DME?

2 A. My assessment is that that is referring to the 0512
3 study, which was the Phase I study with intravitreal
4 aflibercept in DME.

5 Q. Is it possible that -- well, do you recall who was
6 responsible for designing the Phase II DME study that's
7 referred to here in Example 5 of the '601 patent?

8 A. So, again, I don't recall specifically who was
9 involved at that time, but it would have included members of
10 the clinical development group, including myself and Dr. Vitti.
11 Alyson Berliner, I believe was the study director. We
12 consulted with our regulatory colleagues as well as senior
13 management and others regarding the study design.

14 Q. I would like to mark as DX224 a document with
15 production numbers RGN-EYLEA-MYLAN-65438 through 449.

16 What was the purpose of the global project team?

17 A. The global project team was a cross-functional team
18 established as part of the Bayer collaboration to oversee
19 development for aflibercept with our codevelopment partner.

20 Q. And did the Bayer people have input into what your
21 Phase III clinical trial would look like in terms of dosing
22 regimens?

23 A. As part of the Bayer collaboration, they had input
24 into aspects of the clinical development planning, including
25 study designs, but the ultimate scientific decision-making

(Video deposition of Karen Chu)

1 remained with Regeneron.

2 Q. Can you confirm on the first page of DX226, there's
3 an email from you dated March 29th, 2007, to Jesse Cedarbaum
4 where you were forwarding the conversation on VEGF Trap
5 executive summary of scientific advice meeting with Swedish
6 MPA?

7 A. Yes. So I have Exhibit 226 in front of me, and I see
8 the second email in the string is a forwarded email from me to
9 Jesse Cedarbaum on the 29th of March 2007 with the subject
10 "VEGF Trap - Executive Summary of Scientific Advice meeting
11 with Swedish MPA on 28 March '07."

12 Q. If we take a look at Jesse Cedarbaum's responsive
13 email, can you confirm that that's dated March 29th, 2007, and
14 went to individuals such as Avner Ingerman and George
15 Yancopoulos?

16 A. Yes. So the first email in the string here is dated
17 Thursday, March 29th, 2007, forwarded VEGF Trap executive
18 summary of scientific advice meeting with Swedish MPA from
19 Jesse Cedarbaum to Peter Powchik, Avner Ingerman, and others.

20 Q. Sure. Is Regeneron aware of anyone who put together
21 for the Phase III VIEW 1-VIEW 2 clinical trial design a
22 2-milligram dose at an eight-week dosing interval before
23 Dr. Cedarbaum's email we're looking at here of March 29th,
24 2007?

25 A. I don't recall exactly the discussions around the

(Video deposition of Karen Chu)

1 eight-week interval or whether Dr. Cedarbaum, by virtue of this
2 email, was the first person to suggest the eight-week interval.

3 Q. Can Regeneron identify anybody who did it -- who put
4 those two pieces together -- 2-milligram dose, eight-week
5 interval -- before Dr. Cedarbaum did?

6 A. I can't speak on behalf of Regeneron. I can only
7 speak for myself, and I do not recall a person who specifically
8 put that together in this time frame.

9 Q. And, Ms. Chu, if you can confirm this is an email
10 from Kathleen Lawrence to you and others, dated Monday, April
11 2nd, 2007?

12 A. So I have Exhibit 227 in front of me with a date of
13 April 2nd, 2007, subject, "Decisions & Actions: AMD Phase III
14 Program Meeting, April 2, '07," from Kathleen Lawrence, and I
15 am a recipient of this email.

16 Q. Do you recall if you were a participant in this AMD
17 Phase III program meeting on April 2nd, 2007?

18 A. I don't recall this specific meeting, but in my role
19 I would have attended such meetings.

20 Q. Now, the third bullet point down says -- this is for
21 the first time we see this, "2 milligrams q8 weeks with PIER
22 lead-in (dose monthly for first three months)."

23 Do you see that?

24 A. I do see that the third bullet states, "2-milligram
25 q8 weeks with PIER lead-in (dose monthly for first three

(Video deposition of Karen Chu)

1 months)."

2 Q. All right. Who actually assembled that particular
3 regimen as one of the arms to consider for the VIEW 1 Phase III
4 clinical trial?

5 A. I don't recall specifically who proposed that dosing
6 regimen.

7 Q. Sure. In your capacity as Regeneron's 30(b)(6)
8 witness, what's the significance of this April 4, 2007, email
9 from George Yancopoulos to Darlene Jody?

10 A. So this email from George to Darlene Jody, who was a
11 senior executive responsible for the Bayer collaboration with
12 us, is communicating the Regeneron proposal and decisions
13 around the optimal designs for the VIEW 1 and the VIEW 2
14 trials.

15 Q. Is there anywhere in here where Dr. Yancopoulos is
16 advocating for starting off the regimen with three monthly
17 2-milligram doses and then going to the eight-week interval?

18 A. In my review of this email, I do not see that it
19 includes mention of the three initial monthly doses for the
20 q8-week group.

21 Q. And did you review this email in connection with
22 preparing for your deposition in this case?

23 A. I have Exhibit 229, date Tuesday, April 10th, 2007,
24 subject, "Forward: VEGF Trap-Eye GDP for REGN/Bayer" from
25 George Yancopoulos to Darlene Jody. And, no, I did not review

(Video deposition of Karen Chu)

1 this email in preparation for today's deposition.

2 Q. Right. And just to be clear, that dosing regimen of
3 VEGF Trap 2 milligrams every -- dosed every four weeks times
4 three, then q8 thereafter, that was a dosing regimen drafted by
5 Bob Terifay, right, in this email string?

6 A. My recollection of how decisions were made at
7 Regeneron at the time was that this proposal would not have
8 been discussed at the joint development committee meeting
9 unless George had had input and agreed that this was the
10 proposal for the Phase III studies.

11 Q. Well, if George Yancopoulos had signed off on that as
12 the dosing regimen, why is he actually arguing against that,
13 then, on April 10th, 2007, to Darlene Jody?

14 A. My read of the email didn't give me the impression
15 that George was arguing against it. If you can point to what
16 specifically you're referring to, I'd be happy to review it
17 again.

18 Q. Nowhere in this April 10th, 2007, email to Darlene
19 Jody is George Yancopoulos advocating for the dosing regimen
20 that Bob Terifay identified of an aflibercept dose of
21 2 milligrams dosed every four weeks three times followed by a
22 dosing every-eight-week regimen, true?

23 A. I can't speak to George's intent.

24 Q. It's not a question of intent. It's a question of
25 what's written here in the email.

(Video deposition of Karen Chu)

1 A. It is correct that that is what -- what is written in
2 this email is the sentence, "That is based on both U.S. and EU
3 regulatory interactions. Such a study will definitively
4 fulfill their requirements as one of the studies. While final
5 dose/interval for the fourth arm of the study are a bit
6 unsettled, we can use 2q8 for now as the most likely
7 dose/interval."

8 Q. I'd like you to take a look at the email from Robert
9 Terifay that is dated April 17th, 2007, to George Yancopoulos,
10 Len Schleifer, Peter Powchik, Avner Ingerman, and Neil Stahl,
11 subject, "U.S. commercial concerns regarding the Bayer
12 compromise."

13 Let me know when you're there.

14 A. I see that email beginning on page -- the second page
15 of this email -- the last three numbers are 333 -- from Robert
16 Terifay, dated 17th of April 2007, to George Yancopoulos with
17 others copied.

18 Q. Do you have an understanding as to why Robert Terifay
19 would have been involved in these discussions over selecting
20 the Phase III clinical trial regimen?

21 A. Bob Terifay was the head of our commercial group at
22 that time and, as such, would have had input on the clinical
23 development program as it related to commercial viability and
24 commercial considerations.

25 Q. Again, if we look in DX230, the top email, dated

(Video deposition of Karen Chu)

1 Wednesday, April 8th, 2007, from Robert Terifay to Peter
2 Powchik, Len Schleifer, and George Yancopoulos, Avner Ingerman,
3 Neil Stahl, and Laura Pologe, the second paragraph, he says,
4 "From an 0508 perspective, it appears that 2q8 (especially if
5 initiated as a 2q4 loading dose for the first three months) can
6 offer similar improvement in visual acuity and maintain that
7 level similarly to 2q4 and Lucentis q4. This would be a major
8 win for VT" -- referring to aflibercept -- "versus Ran" --
9 referring to ranibizumab -- "in Phase III," right?

10 A. I see the email dated Wednesday, April 18th, 2007,
11 from Bob Terifay to Peter Powchik and others with the first
12 bullet stating that "From an 0508 perspective, it appears that
13 2q8 (especially if initiated as a 2q4 loading dose for the
14 first three months) can offer similar improvement in visual
15 acuity and maintain that level similarly to 2q4 and Lucentis
16 q4."

17 Q. '601 patent, Claim 1.

18 A. So in patent '601, Claim 1, it's stated that a method
19 for treating age-related macular degeneration in a patient in
20 need thereof comprising intravitreally administering an
21 effective amount of aflibercept, which is 2 milligrams
22 approximately every four weeks for the first three months,
23 followed by 2 milligrams approximately once every eight weeks
24 or once every two months.

25 Q. Right. And that dosing regimen matches the one that

(Video deposition of Karen Chu)

1 Robert Terifay is advocating for in DX230, his April 8, 2007,
2 email, of 2q8 initiated as a 2q4 loading dose for the first
3 three months, right?

4 A. My interpretation of the email from Bob Terifay is
5 that he is describing the same dosing regimen.

6 Q. Ms. Chu, can you confirm that this document, DX231 is
7 an email to you and others from Avner Ingerman, dated Thursday,
8 August 2nd, 2007?

9 A. So I have Exhibit 231, which is an email dated
10 August 2nd, 2007. The subject is "Emailing: NCT00509795.htm"
11 from Avner Ingerman, and I am copied on this email.

12 Q. Okay. And in the text of this email, is he providing
13 the information that was published at ClinicalTrials.gov in
14 connection with ClinicalTrials.gov identifier NCT00509795?

15 A. So my review of this email this minute indicates that
16 this is Dr. Ingerman forwarding the ClinicalTrials.gov posting
17 of the VIEW 1 Phase III study.

18 Q. To your prior point, can you take a look at the last
19 page of Defendants' Exhibit 231. Can you confirm that, above
20 the last three lines, it says, "ClinicalTrials.gov processed
21 this record on August 1st, 2007."

22 A. I do see where it says, "ClinicalTrials.gov processed
23 this record on August 1st, 2007."

24 Q. And under the inclusion criteria, the signed informed
25 consent, were patients obligated to keep secret their

(Video deposition of Karen Chu)

1 participation in Regeneron's clinical trials?

2 A. No, patients were not obligated in any way to keep
3 their participation in the study secret.

4 Q. Do you have it now?

5 A. I have Exhibit 232 in front of me.

6 Q. Okay. And are you identified as a coauthor on this
7 presentation?

8 A. So this appears to be a poster, and I am listed as an
9 author.

10 Q. And why did Regeneron want to present its data
11 involving aflibercept and its clinical trial data at these
12 scientific conferences?

13 A. So it's scientific practice that we share our results
14 in the context of scientific congresses and publications, and
15 thus this was part of this scientific exchange that we were
16 contributing to.

17 Q. Could you try to find in your stack what they labeled
18 as Defense Exhibit 232.

19 A. Okay. I have Exhibit 232.

20 Q. Ms. Mazzochi had some questions for you about Defense
21 Exhibit 232. Do you know if this is a draft or final document?

22 A. I don't know if Exhibit 232 is draft or final.

23 Q. Okay. You can put that document aside.

24 If you could find in your stack Defense Exhibit 234.

25 A. Okay. I have 234.

(Video deposition of Karen Chu)

1 Q. On Defendants' Exhibit 234, do you have a habit of
2 letting people put your name on documents or scientific
3 presentations that you don't review and approve?

4 A. No. If I am an author, I definitely would have
5 reviewed and provided input into the content of the document.

6 Q. Right. And you would have made sure that any
7 statements, at least to the extent they were within your area
8 of operation, were truthful and accurate, right?

9 A. Yes. Part of my review would be for accuracy.

10 Q. And when you were assembling that information, that
11 was done with an understanding that the data would become
12 public, right?

13 A. Sure. So in assembling data for the purpose of a
14 presentation at a scientific congress, it was understood that
15 that data would become public.

16 (Video ends.)

17 MS. BODA: And for administrative purposes,
18 defendants move into evidence the following exhibits, which I
19 believe are all agreed to: DTX 200, DTX 202, DTX 204, DTX 205,
20 DTX 207, DTX 209, DTX 210, DTX 211, DTX 212, DTX 213, DTX 214,
21 DTX 215, DTX 218, DTX 219, DTX 220, DTX 222, DTX 224, DTX 226,
22 DTX 227, DTX 228, DTX 229, DTX 230, DTX 231, DTX 232, and
23 DTX 234.

24 MR. GREGORY: No objection.

25 THE COURT: No objection to those? Okay.

(Video deposition of Karen Chu)

1 That list, Counsel, is hereby deemed admitted.

2 Any exhibits from the plaintiff's perspective from
3 that deposition?

4 (DTX 200, DTX 202, DTX 204, DTX 205, DTX 207,
5 DTX 209, DTX 210, DTX 211, DTX 212, DTX 213, DTX 214, DTX 215,
6 DTX 218, DTX 219, DTX 220, DTX 222, DTX 224, DTX 226, DTX 227,
7 DTX 228, DTX 229, DTX 230, DTX 231, DTX 232, and DTX 234 were
8 admitted.)

9 MR. GREGORY: None from the plaintiff's perspective.

10 THE COURT: Understood. Why don't we go ahead and
11 take our morning break at this point. We'll take ten minutes,
12 then we'll proceed with Mylan's next witness.

13 (A recess was taken from 10:19 a.m. to
14 10:33 a.m.)

15 THE COURT: Mylan may call its next witness.

16 MS. MAZZOCHI: Thank you, Your Honor. The defendants
17 call Dr. Jay Stewart as part of their invalidity case in chief.
18 And Dr. Stewart's opinions specifically involve the issues
19 relating to the dosing patent claims in compliance with 35
20 U.S.C. Section 112.

21 Your Honor, during the break, I believe we made
22 efficient use of the binder distribution process; so hopefully
23 you have copies up there.

24 THE COURT: Outstanding. Thank you all. You may
25 proceed whenever you're ready, Counsel.

JAY M. STEWART, MD - DIRECT

1 MS. MAZZOCHI: Thank you, Your Honor.

2 **JAY M. STEWART, MD, DEFENDANTS' WITNESS, SWORN**

3 DIRECT EXAMINATION

4 BY MS. MAZZOCHI:

5 Q. Good morning, Dr. Stewart. Will you please state
6 your full name for the record.

7 A. Jay Stewart.

8 Q. Are you testifying on behalf of the defendants today?

9 A. Yes.

10 Q. Did you prepare demonstrative slides to assist the
11 Court with your testimony today?

12 A. Yes.

13 Q. All right. Let's go ahead and turn to those. Can
14 you briefly describe your educational background.

15 A. Yes. I received my undergraduate degree in
16 biochemical sciences at Harvard College, my medical degree at
17 Harvard Medical School. And I completed an internship at
18 Brigham and Women's hospital and then a residency in
19 ophthalmology at the University of California San Francisco,
20 which we call UCSF. After that I did a fellowship training in
21 vitreoretinal diseases and surgery at Doheny Retina Institute
22 at the University of Southern California.

23 Q. When did you begin your own full-time practice?

24 A. In 2005.

25 Q. And can you describe some of your clinical and

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1 academic positions, please.

2 A. Yes. So since 2005 I've been seeing patients at UCSF
3 Medical Center. And this is a practice where we have many
4 patients with age-related macular degeneration, or AMD, as well
5 as other retinal conditions.

6 From 2009 to 2014 I was the medical director of that
7 practice, in which capacity I oversaw decisions for the
8 clinical practice. And since 2020 I've been the subspecialty
9 medical director for the retina service.

10 Also since 2005 I've been seeing patients at San
11 Francisco General Hospital, which is a facility where we have
12 many patients with diabetes and diabetic retinopathy. I've
13 been the director of the vitreoretina service at that site
14 since 2006. And since 2014 I've been the chief of
15 ophthalmology at that site, where I am responsible for
16 overseeing all aspects of our department.

17 Q. Have you held any academic positions?

18 A. Yes. From 2005 to 2010 I was the assistant professor
19 of clinical ophthalmology. From 2010 to 2016 I was the
20 associate professor. And since 2016 I've been the professor of
21 clinical ophthalmology.

22 Q. Have you received any grants to support your
23 research?

24 A. Yes. I've had several grants from the National
25 Institutes of Health to support research, one of which was a

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1 study evaluating ultrasound for drug delivery into the eye.

2 Q. Do you currently serve as the editor of any medical
3 journals?

4 A. Yes. I'm the editor in chief of the *American Journal*
5 *of Ophthalmology Case Reports* and the associate editor in chief
6 of *Annals of Eye Science*.

7 Q. For how many years have you been working in the field
8 of ophthalmology?

9 A. Over 20 years.

10 Q. Approximately how many patients do you see each week?

11 A. About 75.

12 Q. And have you treated patients with age-related
13 macular degeneration, diabetic macular edema, and diabetic
14 retinopathy?

15 A. Yes.

16 Q. Prior to 2010 have you used any VEGF drugs to treat
17 AMD, DME, or diabetic retinopathy?

18 A. Yes. I was using Lucentis as well as Avastin
19 off-label.

20 Q. After Eylea came on the market, did you use that as
21 well?

22 A. Yes. I've been using Eylea since it came on the
23 market. And then more recently have also been using a new drug
24 called Vabysmo, which is spelled V-A-B-Y-S-M-O, which is also
25 approved for some of these indications.

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1 Q. What do you consider to be some of your areas of
2 expertise?

3 A. The diagnosis and treatment of vitreoretinal and
4 other ophthalmologic conditions.

5 Q. I'd like you to take a look at DTX 7100.

6 And we'll put that up on the screen as well.

7 What is this document?

8 A. It's a copy of my CV.

9 MS. MAZZOCHI: Your Honor, at this time Mylan and
10 Biocon proffer Dr. Stewart as an expert in the medical and
11 surgical treatment of vitreoretinal and ophthalmic diseases.

12 THE COURT: Any voir dire or objection?

13 MR. GREGORY: No objection, Your Honor.

14 THE COURT: Without objection, the witness is deemed
15 so qualified.

16 You may proceed, Counsel.

17 MS. MAZZOCHI: Thank you very much, Your Honor.

18 BY MS. MAZZOCHI:

19 Q. Dr. Stewart, have you heard the phrase "a person of
20 ordinary skill in the art"?

21 A. Yes.

22 Q. Does the next slide, DDX 7.5, have both parties'
23 definitions of a person of ordinary skill in the art displayed
24 on them?

25 A. Yes.

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1 Q. Do you qualify as a person of ordinary skill in the
2 art at least as early as of January 2011 under either
3 definition?

4 A. Yes.

5 Q. And have you applied that perspective of a person of
6 ordinary skill in the art here?

7 A. Yes.

8 Q. Do your opinions change whether Regeneron or
9 defendants' person of ordinary skill in the art definition
10 applies?

11 A. No.

12 Q. You have these in your binder. It's PTX 3, the '572
13 patent, and PTX 1, the '601 patent. Did you review both of
14 these patents in this case?

15 A. Yes.

16 Q. Can you summarize some of the issues that you
17 considered with regard to Claim 6 of the '572 patent?

18 A. Yes. So Claim 6 depends upon Claim 1, which
19 describes the method for treating an angiogenic eye disorder.
20 And I had concerns about the definition of angiogenic eye
21 disorder. It also describes a dosing regimen which I felt
22 lacked written description and enablement.

23 Q. And when it comes to the term "angiogenic eye
24 disorder," what are some of your concerns with the term
25 "angiogenic eye disorder"?

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1 A. I felt that the term was too broad and, therefore,
2 was not enabled and also lacked written description support.

3 Q. Do you have specific concerns with the dosing
4 information that's found in the patent?

5 A. Yes, that there is no limitation on the number of
6 doses given and, therefore, it's not enabled and also lacks
7 written description support.

8 Q. Thank you very much.

9 Can you summarize the issues that you looked at that
10 were specific for Claim 25 of the '572 patent as well as
11 Claims 11 and 19 of the '601 patent.

12 A. Yes. So Claim 25 depends upon Claim 15. Claim 11
13 depends upon Claim 10. And Claim 19 depends upon Claim 18.
14 And all of these refer to a regimen of dosing that involves
15 five loading doses. And I believe that there is no written
16 description support for this and that it lacks enablement.

17 Q. And are your enablement positions with regard to
18 these claims tied at least in part to some of the positions
19 that Regeneron and Dr. Csaky have taken in this case for
20 invalidity?

21 A. Yes.

22 Q. Have you also assessed the question of
23 indefiniteness?

24 A. Yes.

25 Q. Can you explain that, please.

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1 A. Yes. The term "approximately" is used at multiple
2 points throughout the claims, and I feel that terminology is
3 indefinite.

4 Q. Can you summarize some of the issues that you looked
5 at with regard to the disclosures and the specification's
6 related applications that may bear on the question of priority.

7 A. Yes. There were a series of applications that were
8 filed in which new information was added to the subsequent
9 filing.

10 Q. And did you consider whether that new matter
11 supported or enabled the claims as well?

12 A. Yes.

13 Q. All right. Let's start with some of your enablement
14 topics. And let's focus first on angiogenic eye disorder that
15 appears in Claim 6 of the '572 patent.

16 So, Dr. Stewart, in connection with your review of
17 the '572 patent's Claim 6, did you assess whether a person of
18 ordinary skill in the art at the time the patent applications
19 were filed would have been able to fully make and use the
20 claimed method to treat the full scope of angiogenic eye
21 disorders without undue experimentation?

22 A. Yes, I did.

23 Q. Did you also consider whether a person of ordinary
24 skill in the art at the time the various patent applications
25 were originally filed as well as amended, whether that person

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1 would believe the inventor actually invented and possessed the
2 particular dosing methods to treat the full scope of angiogenic
3 eye disorder conditions listed?

4 A. Yes.

5 Q. All right. Now, does the '572 patent specification
6 discuss eye disorders associated with angiogenesis?

7 A. Yes, it does.

8 Q. And is that in the '572 patent at Column 1, lines 40
9 to 65, and Column 5, lines 30 to 48?

10 A. Yes.

11 Q. In connection with your opinions in this case, have
12 you reviewed Dr. Yancopoulos's trial testimony, including
13 page 155, about what he called the common mechanism, that is,
14 VEGF driving abnormal blood vessel growth and leak, including a
15 statement that all these disorders shared a common mechanism?

16 A. Yes.

17 Q. In your opinion, can VEGF inhibitors driving
18 normal -- I'm sorry -- can VEGF inhibitors driving abnormal
19 blood vessel growth and leak be used today to treat some of the
20 diseases listed as angiogenic eye disorders in the patent?

21 A. Yes. And we do use them to treat some of these
22 disorders.

23 Q. Can you give a few examples of what those disorders
24 are.

25 A. Wet AMD, CRVO, DME, diabetic retinopathy.

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1 Q. Are there any other diseases on the '572 patent
2 specification list at Column 5 that the '572 patent calls an
3 angiogenic eye disorder where there is not so?

4 A. Yes. Several, including proliferative
5 vitreoretinopathy, also known as PVR; pannus; and pterygium.

6 Q. Dr. Stewart, in connection with your opinions, I'd
7 like you to assume that angiogenic eye disorders are associated
8 with the growth and proliferation of blood vessels, that
9 aflibercept is a VEGF inhibitor, and that a person of ordinary
10 skill in the art has all of the teachings and examples given in
11 the '572 patent.

12 With that understanding, would a person of ordinary
13 skill in the art believe that the inventor had invented a
14 method where the Claim 6 drug dose and schedule would apply for
15 intravitreal aflibercept to treat proliferative
16 vitreoretinopathy, pannus, and pterygium?

17 A. No.

18 Q. Can you explain why, please.

19 A. Because aflibercept, being a VEGF blocking agent,
20 would work to block VEGF, but these conditions have more
21 complex mechanisms of disease of which VEGF is only one
22 component.

23 Q. And how about today? Have those in the field found a
24 way to make intravitreal aflibercept work to treat
25 proliferative vitreoretinopathy -- PVR -- pannus, or pterygium

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1 using the dosing regimen set forth in Claim 6?

2 A. No.

3 Q. Can you explain why that is.

4 A. Well, I think through an understanding, again, of the
5 mechanism of -- action of the drug and the complex mechanism of
6 these diseases and clinical experience in the field.

7 Q. To support your opinions that the term "angiogenic
8 eye disorders" lacks written description and enablement across
9 the full scope of the term, did you find any support in the
10 medical literature?

11 A. Yes.

12 Q. Can you give the Court an example from the medical
13 literature that you believe supports your opinions that the
14 method of Claim 6 of the '572 patent does not work to treat the
15 full scope of conditions the specification lists as an
16 angiogenic eye disorder?

17 A. Yes. This publication from Shahlaee, et al.

18 Q. And is a copy of the Shahlaee publication in your
19 binder at DTX 5430?

20 A. Yes.

21 Q. Can you explain why you cited this Shahlaee paper.

22 A. This is a paper that reviewed several methods of
23 trying to treat proliferative vitreoretinopathy, and one of the
24 methods that they discussed was the use of anti-VEGF treatment.
25 And they presented the fact that several studies that looked at

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1 this method of treatment found no success.

2 Q. Do you have any other examples from the medical
3 literature?

4 A. Yes. This manuscript from Shahraki, et al.

5 Q. And is a copy of that publication in your binder at
6 DTX 5431?

7 A. Yes.

8 Q. Can you explain why you cited Shahraki?

9 A. Well, this was a --

10 MR. GREGORY: Your Honor, I'm sorry. I have to
11 object. This level of disclosures is not in his expert report
12 anywhere.

13 MS. MAZZOCHI: Your Honor, it's in his opening expert
14 report at paragraphs 76, 81, as well as --

15 THE COURT: Could I have the report?

16 MS. MAZZOCHI: It should be in your binder, Your
17 Honor.

18 THE COURT: There's a lot in here, Counsel. What tab
19 am I looking for?

20 MS. MAZZOCHI: Sure. DTX 7099, which is his opening
21 report.

22 THE COURT: Paragraphs for that again, Counsel? I'm
23 sorry.

24 MS. MAZZOCHI: Let's start at paragraph 81, where he
25 specifically cites these three references we've been reviewing

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1 for this very purpose, that a person of ordinary skill in the
2 art would not think they could be treated and are currently not
3 treated with aflibercept.

4 MR. GREGORY: I'm sorry. I think 7099 is his reply
5 report.

6 MS. MAZZOCHI: Oh, I apologize. 7098.

7 THE COURT: What paragraphs, then?

8 MS. MAZZOCHI: Paragraph 81. Oh, no. I'm sorry. My
9 apologies, Your Honor. Let me start that over.

10 In his reply report, paragraph 81 is -- Dr. Stewart
11 specifically cited these three references I've been reviewing
12 for this premise.

13 THE COURT: What's the objection, then, Counsel?

14 MR. GREGORY: The objection -- yes, Your Honor. My
15 objection is that -- I'm trying to find this here. In
16 paragraph 81 there is a very terse description -- or citation,
17 a string cite, "see e.g.," these three references, and no
18 description of the source that Dr. Stewart is offering now from
19 the discovery.

20 THE COURT: Was Dr. Stewart deposed?

21 MR. GREGORY: Dr. Stewart was deposed.

22 THE COURT: All right. Objection overruled.

23 You may continue, Counsel.

24 MS. MAZZOCHI: Thank you, Your Honor.

25

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1 BY MS. MAZZOCHI:

2 Q. So, Dr. Stewart, let's just circle back. Can you
3 just explain why you cited this publication, the Shahraki
4 publication.

5 A. Yes. This was a publication that reviewed treatment
6 approaches for the condition of pterygium.

7 Q. And did injecting the anti-VEGF drug improve the
8 outcomes for pterygium patients?

9 A. No. They described that one of the treatment options
10 that they were reviewing, which was the use of anti-VEGF
11 treatment, yielded inconclusive results.

12 Q. Now, I believe these two publications used
13 bevacizumab as the anti-VEGF inhibitor. Why did you choose to
14 rely on them to opine they wouldn't work with aflibercept?

15 A. Because they share a common mechanism of action,
16 which is to counteract VEGF. And so if we don't see efficacy
17 with bevacizumab, we also wouldn't expect that with
18 aflibercept.

19 Q. Do you have an example from the medical literature
20 that is specific to aflibercept that supports your opinions
21 that the method of Claim 6 of the '572 patent will not work to
22 treat one or more conditions the specification lists as an
23 angiogenic eye disorder?

24 A. Yes. This manuscript from Sella, et al.

25 Q. And is a copy of the Sella publication in your binder

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1 at DTX 5429?

2 A. Yes.

3 Q. Can you explain why you cited Sella in your report.

4 A. They used aflibercept for treatment of formed corneal
5 neovascularization and reported that it was ineffective.

6 Q. And is formed corneal neovascularization a subtype of
7 the more general description corneal neovascularization?

8 A. Yes.

9 Q. Are there any diseases in which formed corneal
10 neovascularization also plays a role?

11 A. Yes. One of the conditions we mentioned earlier,
12 which is pannus.

13 Q. Than what is pannus?

14 A. Pannus is a growth on the ocular surface that
15 contains corneal neovascularization as well as fibrotic tissue.

16 Q. And did the '572 patent offer any data beyond the
17 prior art pertaining to these specific diseases that you've
18 just identified: formed corneal neovascularization,
19 proliferative vitreoretinopathy, pannus, and pterygium?

20 A. No.

21 Q. How about a mechanism-of-action theory beyond
22 anti-VEGF?

23 A. No.

24 Q. Does the specification give any hint or suggestion
25 towards the appropriate dosing schedule that would be needed to

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1 treat diseases such as formed corneal neovascularization,
2 proliferative vitreoretinopathy, pannus, or pterygium?

3 A. No.

4 Q. And in response to your expert reports in this case,
5 did Dr. Csaky identify any data or test results, either in the
6 specification or the medical literature, showing that
7 intravitreal aflibercept actually will work using the Claim 6
8 method to treat each angiogenic eye disorder we see in the '572
9 patent?

10 A. No.

11 Q. In response to your expert report, did Dr. Csaky
12 identify any specific rationale in the specification or medical
13 literature beyond mere anti-VEGF behavior as to why a person of
14 ordinary skill in the art could expect aflibercept to work to
15 treat those diseases I just listed?

16 A. No.

17 Q. And to reach your conclusion that intravitreal
18 aflibercept does not work to treat these diseases at all, did
19 you rely on just the medical literature, or did you rely on
20 other things?

21 A. I relied on an understanding of the mechanism of
22 action of the drug as well as the complex mechanisms at issue
23 in these particular conditions and familiarity with the field.

24 Q. In terms of your own personal experience, have you
25 had to treat patients that have all four of these conditions?

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1 A. Yes, I have.

2 Q. And have you ever used aflibercept as part of their
3 care?

4 A. No.

5 Q. In your opinion, based on what we just discussed,
6 would a person of ordinary skill in the art reading the '572
7 patent specification believe that the inventor actually
8 possessed a method of treating the full scope of these
9 angiogenic eye disorders with aflibercept?

10 A. No.

11 Q. In your opinion, based on what we just discussed,
12 would a person of ordinary skill in the art reading the '572
13 patent specification in the relevant time frame believe that
14 the dosing method of aflibercept set forth in Claim 6 was
15 enabled to actually work to treat the full scope of angiogenic
16 eye disorders?

17 A. No.

18 Q. Now, for your nonenablement opinion, did you also
19 consider factors that are used to assess the question of
20 whether a person of ordinary skill in the art can practice the
21 full scope of the claims without undue experimentation?

22 A. Yes.

23 Q. All right. And on your Slide Number DDX 7.29, are
24 these eight factors listed here the undue experimentation
25 factors that you considered?

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1 A. Yes.

2 Q. Okay. Let's start with the first three of these
3 factors: quantity of experimentation, direction or guidance,
4 and presence or absence of working examples.

5 In your opinion, if a person of ordinary skill in the
6 art had the Claim 6 dosing regimen and a patient who presented
7 with formed corneal neovascularization, proliferative
8 vitreoretinopathy, pannus, or pterygium, would they find enough
9 in the specification to give treatment direction, guidance, or
10 working examples relevant to those disease states?

11 A. No.

12 Q. And can you explain why.

13 A. Because we don't receive any guidance or examples or
14 rationale shown in those specifications regarding those
15 conditions. And so they would need to perform an entirely new
16 research project to figure out whether it could be used.

17 Q. Now, in his pretrial opinions in this case, Dr. Csaky
18 suggested that, as long as you have the list of diseases, the
19 steps, and understanding of the VEGF mechanism and knowledge
20 that aflibercept worked well to treat wet AMD and other
21 diseases we see in the examples, that would be sufficient to
22 treat all of these other angiogenic eye disorders.

23 Do you agree?

24 A. No.

25 Q. Can you explain why.

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1 A. I think the issue is that some of these conditions
2 involve more than just VEGF as their mechanism of causing
3 pathogenesis in the eye. So that's one aspect which is the
4 complexity of the disease mechanism.

5 Another aspect is shown in this figure, which is a
6 picture of the eye where we see the ocular surface highlighted
7 in yellow where several of the conditions that we were just
8 discussing are located. And that's not proximal to the site of
9 intravitreal injections; so we wouldn't necessarily think that
10 administering intravitreally would be the most effective way to
11 treat those conditions.

12 Q. Let's talk about the next undue experimentation
13 factor, the predictability or unpredictability of the art.

14 Is there anything that a person of ordinary skill in
15 the art could use from the specification to predict that
16 aflibercept will perform well using the Claim 6 regimen in PVR,
17 pterygium, formed corneal neovascularization, or pannus in a
18 way that would let them achieve success?

19 A. No.

20 Q. And why is that?

21 A. Because there isn't any such guidance or examples
22 shown that would allow us to predict that it would work for
23 those conditions.

24 Q. And, also, if Regeneron argues that this art
25 generally is unpredictable for diseases such as DME or DR, even

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1 if you progressed to the Phase II clinical study phase, would
2 that increase or decrease the experimental burden on the person
3 of ordinary skill in the art for the specifications here in
4 your opinion?

5 A. That would increase the burden.

6 Q. And on this factor pertaining to the breadth of the
7 claims, what would a person of ordinary skill in the art
8 perceive about the breadth of the term "angiogenic eye
9 disorder"?

10 A. I think they would perceive that term to be
11 excessively broad.

12 Q. Now let's take a look at the factor relating to the
13 nature of the invention. Directing your attention to the '572
14 patent abstract, what does it describe as the nature of the
15 invention?

16 A. A method for treating angiogenic eye disorders by
17 administering VEGF antagonist.

18 Q. So in your opinion, is any failure of the claimed
19 methods to work to treat diseases such as pannus, pterygium,
20 formed corneal neovascularization, or PVR something that is
21 merely peripheral or more central to the invention?

22 A. It's central.

23 Q. For the factors involving the state of the art and
24 the level of ordinary skill in the art, will the state of the
25 art and high skill set of that person reduce the experimental

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1 burden?

2 A. No, because even knowing the state of the art and
3 even if they have a high level of skill, they would still, I
4 think, understand that there isn't information within the
5 specifications to guide them to be able to use this treatment
6 for those particular conditions.

7 Q. And we've had an issued patent out there for quite
8 some time. Since the patent has issued, to your knowledge, has
9 this become -- has aflibercept become the standard of care at
10 all or otherwise used for proliferative vitreoretinopathy,
11 pannus, or pterygium?

12 A. No.

13 Q. Let's turn, then, to your ultimate opinions when it
14 come to the angiogenic eye disorder for Claim 6.

15 Do you understand that, to satisfy the written
16 description requirement, the patent must describe an invention
17 understandable to a skilled artisan and show that the inventor
18 actually invented and possessed the invention claimed?

19 A. Yes.

20 Q. And in your opinion, based on what we've just
21 reviewed, would a person of ordinary skill in the art believe
22 that the inventor actually invented or possessed a working
23 intravitreal dosing regimen, as we see in Claim 6, to treat the
24 full scope of angiogenic eye disorders, including, for example,
25 proliferative vitreoretinopathy, pannus, and pterygium?

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1 A. No.

2 Q. In your opinion, based on what we just discussed,
3 would a person of ordinary skill in the art believe that the
4 specification enabled a person of ordinary skill in the art to
5 practice the full scope of angiogenic eye disorders covered by
6 Claim 6 without undue experimentation?

7 A. No.

8 Q. All right. Let's talk next about some of your
9 opinions relating to dosing.

10 MS. MAZZOCHI: And, Your Honor, I'm happy to have
11 Dr. Stewart go through and discuss the loading dose concept,
12 but if you're good with that, I don't need to repeat it.

13 THE COURT: I think I've got a good grasp of it at
14 this point.

15 MS. MAZZOCHI: I thought so, but I didn't want to
16 assume.

17 BY MS. MAZZOCHI:

18 Q. Dr. Stewart, directing your attention to the summary
19 of invention section of the '572 and '601 patents, did you find
20 anywhere in the specification that placed any emphasis on the
21 number of doses that should proceed the eight-week dosing
22 interval?

23 A. Yes. They referred to three doses.

24 Q. Did the specification illustrate what this type of
25 dosing regimen, the three doses at the start, would look like?

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1 A. Yes, in Figure 1.

2 Q. And in Figure 1 of the '572 and '601 patents, how
3 many total loading doses, spaced four weeks apart, are
4 illustrated before beginning the eight-week dosing regimen?

5 A. Three.

6 Q. Was there any figure that showed five?

7 A. No.

8 Q. Did you review the specification statements about
9 loading dose or secondary dose frequency?

10 A. Yes.

11 Q. And did you also review Dr. Yancopoulos's trial
12 testimony, including at transcript pages 235 to 236?

13 A. Yes.

14 Q. In your opinion, do the specifications for the '572
15 and '601 patents place any upper limit on the term "secondary"
16 or "tertiary" doses that we see in the claims?

17 A. No.

18 Q. Did the specification provide any rationale for why
19 you should stop with secondary dosing and switch to tertiary
20 dosing that was not already known in the prior art?

21 A. No.

22 Q. And can you explain why a little bit.

23 A. Well, because the language that's used here refers to
24 one or more secondary doses and then one or more -- so the --
25 there's no upper limit basically shown as to how many doses

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1 that you would use.

2 Q. And then when it comes to any adjustments that should
3 be made to the course of treatment by the physician as we see
4 in the -- in Column 4, does that column talk about or give any
5 guidance or recommendations to physicians for performing those
6 adjustments up or down or beyond what was known in the art?

7 A. No. It just says according to the needs of the
8 patient following clinical examination.

9 Q. And where would a person of ordinary skill in the art
10 have to go, then, for guidance or reasoning as to why they
11 should change their loading dose regimen?

12 A. I think it would be difficult, not having that
13 information provided here, to know when to do so.

14 Q. Separate and apart from what was known in the art?

15 A. Right.

16 Q. Does the specification provide any reason to expand
17 or limit the number of secondary or tertiary doses to use
18 beyond what the person of ordinary skill in the art had already
19 thought about and used for indications, such as DME or diabetic
20 retinopathy?

21 A. No.

22 Q. Did you see anything in the specification that
23 explains to a person of ordinary skill in the art that they
24 should not be concerned about risks or side effects of more
25 loading doses for the DME or DR regimen?

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1 A. No.

2 Q. Did the specification for the '572 and '601 patents
3 articulate for the person of ordinary skill in the art any
4 reason to choose or select four secondary doses or a total of
5 five monthly loading doses as opposed to the many other options
6 found in the specification, particularly in the context of a
7 DME or diabetic retinopathy indication?

8 A. No.

9 Q. All right. I'd like to direct your attention back to
10 Column 4, specifically lines 22 to 31 of the '572 patent,
11 because this is some text that Dr. Csaky pointed to to suggest
12 that the number four on this list is enough to pick or support
13 a dosing method with five monthly loading doses versus others.

14 In your opinion, is that enough?

15 A. No, it's not.

16 Q. And can you explain why.

17 A. Because it refers to two or more doses being shown.
18 And if we could go back to that slide, it -- in fact, it says,
19 for example, two, three, four, five, six, seven, eight, or more
20 secondary doses. And so there's no indication that four is
21 being differentiated or called out as compared to all the other
22 numbers that are there.

23 Q. And so then can you summarize some of the problems
24 that you identified regarding the specification when it comes
25 to the dosing regimens?

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1 A. Yes. Several. One was the fact that there were --
2 there was a preference for three doses, as we saw earlier, as
3 opposed to five, and there was no particular justification or
4 data as to why we would pull out five from the number of
5 loading doses that was presented.

6 There was also no guidance across the entire scope of
7 all the angiogenic eye disorders as to why we would choose a
8 particular secondary or tertiary dosing regimen for each of the
9 conditions.

10 There also wasn't any express guidance for DME and
11 diabetic retinopathy on, again, choosing the five loading
12 doses. And, in fact, there wasn't any clinical data at all
13 regarding diabetic retinopathy shown in the specification.

14 So just in general, I think that the fact that there
15 was no theory or rationale setting aside a lack of examples as
16 to why you would transition between dosing regimens.

17 Q. Okay. And let's take a look at Dr. Yancopoulos's
18 trial testimony at page 205. Does that testimony support or
19 refute your opinions here?

20 A. It supports it.

21 Q. Can you explain why?

22 A. Because it refers to the fact that there are -- there
23 wasn't any particular reasoning or rationale behind why you
24 would go between the loading doses and the eight-week dosing.

25 Q. Dr. Stewart, did you find any data or rationale in

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1 the '572 or '601 patent specification as a whole that was
2 identified or called out in a way that would provide a blaze
3 mark to a person of ordinary skill in the art to guide them
4 towards selecting a particular dosing regimen of five loading
5 doses followed by every-eight-week dosing for the specific
6 indications of DME or DR?

7 A. No.

8 Q. I'd also like to spend a little bit of time to
9 discuss Example 7 because that's another one of the things that
10 Dr. Csaky pointed to in support for the five loading doses in
11 response to your testimony.

12 Now, as a preliminary matter, did you also review, as
13 part of your opinions in this case, DTX 5330, Patent
14 Application Number 13/940,370 filed on July 12, 2013, as a
15 continuation-in-part application?

16 A. Yes.

17 Q. And did DTX 5330, this July 12, 2013,
18 continuation-in-part patent application, add anything new to
19 the existing specification?

20 A. Yes. Example 7.

21 Q. So focusing on Example 7, then, which was added to
22 the specification in July 12, 2013, did Example 7 contain any
23 new clinical data?

24 A. No.

25 Q. What did Example 7 contain?

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1 A. It contained, essentially, a laundry list of dosing
2 regimens that could be used for this treatment.

3 Q. Can you explain generally what this laundry list of
4 dosing regimens in Example 7 did include?

5 A. Yes. There were a variety of scenarios that were
6 presented. One of them was treating every four weeks with the
7 injection.

8 Another scenario involved treating every four weeks
9 for the first eight weeks, followed by several different
10 options, one of which was to give an injection every eight
11 weeks.

12 Another scenario was to give an injection on a less
13 frequent basis according to the physician's determination. And
14 another scenario was to give injections on an as-needed or pro
15 re nata, or prn, process.

16 There was another scenario in which injections were
17 given every four weeks for, essentially, a series of
18 durations -- 12, 16, 20, 24, et cetera, weeks -- followed by
19 injections every eight weeks.

20 And then finally there was one scenario where a
21 single injection was given in which all subsequent injections
22 would be given on an as-needed basis.

23 Q. And if we look, for example, at the one you have in
24 the upper right-hand corner where it says "once every four
25 weeks for the first 12 weeks followed," did that also include

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1 options for every eight weeks, physician assessments, prn
2 dosing as well?

3 A. Yes.

4 Q. Okay. And -- sorry -- then what was the last regimen
5 that we found in Example 7?

6 A. This is the single injection followed by an as-needed
7 schedule.

8 Q. And that was called prn dosing?

9 A. Yes.

10 Q. Have you reviewed Dr. Yancopoulos's trial testimony
11 at page 232?

12 A. Yes.

13 Q. Is Dr. Yancopoulos's testimony relevant to your
14 opinion that Example 7 does not have any statements of
15 preference?

16 A. Yes, it supports that.

17 Q. Okay. And why is that?

18 A. Because he said that we don't know which of these
19 regimens would be able to produce the best visual outcomes.

20 Q. What did Dr. Yancopoulos identify in trial testimony
21 you reviewed as needed to generate that guidance towards a
22 regimen that would produce the best visual outcomes?

23 A. Phase III clinical trial data.

24 Q. Is any Phase III clinical trial data in the
25 specification for DME?

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1 A. No.

2 Q. Is there any clinical data at all, whether Phase I,
3 II, or III, in the specification that is specific to a diabetic
4 retinopathy indication alone?

5 A. No.

6 Q. In your opinion, does Example 7 give the person of
7 ordinary skill in the art any added insight as to why or when
8 to stop monthly dosing or every-four-week dosing and switch to
9 a longer dosing interval?

10 A. No, it doesn't.

11 Q. In your opinion, does Example 7 give the person of
12 ordinary skill in the art any added insight as to why they
13 should select one of these particular regimens for any
14 particular disease without the need for more experimentation or
15 insight?

16 A. No.

17 Q. Did Example 7 include, though, a dosing regimen that
18 could be characterized as having five doses separated by four
19 weeks before transitioning to eight-week dosing?

20 A. Yes.

21 Q. Now, are there any blaze marks in either Example 7 or
22 the specification generally that, in your opinion, would
23 explicitly guide a person of ordinary skill in the art towards
24 that regimen with five monthly loading doses followed by
25 eight-week dosing?

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1 A. No.

2 Q. And directing your attention to Column 16, lines 35
3 to 51, of the '572 patent, is that section where there are
4 instances where you could have one loading dose followed by
5 four monthly doses for a total of five monthly loading doses?

6 A. Yes.

7 Q. And did the specification express, in your opinion,
8 any preference amongst these five loading dose different
9 regimens we see in Example 7, eight-week dosing versus the
10 other two listed, such as prn?

11 A. No.

12 Q. Now let's turn to some of the clinical indications
13 that follow Example 7.

14 Does the specification express any preference for
15 using one of these Example 7 regimens with five loading doses
16 or the one followed by the fixed eight-week dosing interval for
17 any particular clinical indication?

18 A. No, it doesn't.

19 Q. In your opinion, does Example 7 as a whole or
20 Example 7 in conjunction with the description of potential
21 diseases provide sufficient blaze marks to a person of ordinary
22 skill in the art to know which of these disease states might be
23 preferred or the best for a physician to use with a given
24 dosing regimen separate and apart from what was known in the
25 prior art?

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1 A. No.

2 Q. What diseases does the specification state these
3 Example 7 dosing methods can be used for?

4 A. It lists a variety of eye conditions.

5 Q. Is DME singled out in the list anywhere or listed as
6 preferred?

7 A. It does appear on the list, but it's not
8 differentiated or called out as being preferred.

9 Q. Is diabetic retinopathy provided as a standalone
10 indication?

11 A. No, it's not listed on this list.

12 Q. So if a person of ordinary skill in the art wanted to
13 make decisions about concluding secondary to move to tertiary
14 dosing or to select a fixed number of loading doses, in your
15 opinion, does the specification point to any test, measurement,
16 performance criteria they should use to make that decision that
17 is separate and apart from what was already known in the prior
18 art?

19 A. No, it doesn't.

20 Q. In your opinion, does the addition of Example 7 to
21 the continuation-in-part specification that was filed in July
22 2013, does that help convince a person of ordinary skill in the
23 art that the inventor possessed a method for treating all
24 angiogenic eye disorders with any number of secondary and
25 tertiary doses for all the diseases listed in the

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1 specification?

2 A. No, it doesn't.

3 Q. Now, based on what we've just discussed, is there
4 sufficient guidance in the specification to the person of
5 ordinary skill in the art to establish that the inventor
6 possessed the specific regimen of the method of Claim 19 of the
7 '601 patent that has five loading doses followed by eight-week
8 dosing specific to the diabetic retinopathy indication?

9 A. No.

10 Q. And can you give a brief explanation as to why.

11 A. Well, first of all, as I mentioned, diabetic
12 retinopathy, there was no clinical information or evidence
13 presented at all in the specification. And, again, there would
14 be no reason shown as to why we would choose a particular
15 regimen for that condition over any of the other regimens that
16 were also mentioned in the example.

17 Q. Now, one of the things that Dr. Csaky did point to is
18 that the original specification had Example 5 in it.

19 But what was the loading dose regimen and clinical
20 indication that was specified in Example 5 as the required
21 number of loading doses?

22 A. Three.

23 Q. Would a person of ordinary skill in the art accept,
24 then, that the inventor possessed the specific regimen of the
25 method of Claim 11 of the '601 patent that requires five

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1 loading doses followed by an eight-week dosing regimen for DME
2 if we accept Regeneron's view that the prior art taught away
3 from increasing the number of loading doses?

4 A. No.

5 Q. And can you explain why?

6 A. Well, again, because if the prior art was telling us
7 that we needed to not increase the number of doses out of the
8 concerns that were mentioned, that wouldn't naturally lead you
9 toward using five loading doses. And so that would be the
10 reason.

11 Q. And would your answer be the same for the '572
12 patent, Claim 25, which also requires DME and five loading
13 doses followed by an eight-week dosing regimen?

14 A. Yes.

15 Q. If the named inventor had discovered something
16 special or distinct about this species using a method with five
17 loading doses, what would you expect to see in the
18 specification?

19 A. I would expect to see examples or rationale
20 explaining that finding that would guide us to choose that
21 regimen.

22 Q. And Dr. Csaky has also alleged that the success of
23 the five loading doses for the treatment of DME and diabetic
24 retinopathy was unexpected.

25 Have you seen that opinion from him?

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1 A. Yes.

2 Q. And I believe Dr. Csaky said that it was subsequently
3 found after the VIEW 1 and VIEW 2 trials that the five loading
4 dose regimen for DME or DR worked, citing to publications from
5 Brown 2015 about the VISTA and VIVID studies and Brown 2021 for
6 the PANORAMA study.

7 Did you review those?

8 A. Yes.

9 Q. Did those change your opinions?

10 A. Well, no, because they came out in 2015 and 2021,
11 which was after the patent at issue here.

12 Q. And do the Brown 2015 and Brown 2021 articles support
13 the premise that the named inventor was in possession of a five
14 loading dose regimen back in 2011 or 2013?

15 A. No.

16 Q. In any event, did any of this Phase III data that
17 Dr. Csaky is relying on specific to DME and diabetic
18 retinopathy make it into the specification of the '572 or '601
19 patents?

20 A. No.

21 Q. All right. So based on what you had just discussed,
22 what did you ultimately conclude about the specification
23 disclosures and whether there is written description support
24 for choosing five loading doses followed by an eight-week
25 dosing regimen in the context of the DME or DR regimens within

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1 the specification?

2 A. I think, again, for diabetic retinopathy as its
3 diagnosis, there wasn't any data shown as to the treatment of
4 that condition. And when it comes to DME, the data that was
5 presented used three loading doses. And so there wasn't any
6 information -- there wasn't any guidance on why to expressly
7 choose the five loading dose regimen over any others.

8 Q. So when it comes to Claim 25 of the '572 patent and
9 Claims 11 and 19 of the '601 patent, in your ultimate opinion
10 based on what we've discussed today, is there sufficient
11 guidance in the specification to establish that the inventor
12 had possession of the claims to these specific dosing regimens
13 particularly with regard to the five monthly loading doses at
14 the time the applications were filed in 2011?

15 A. No.

16 Q. How about for 2013?

17 A. No.

18 Q. All right. Let's focus now again on enablement and
19 go back through those In Re: *Wands* factors. And let's start
20 again with the first three factors relating to quantity of
21 experimentation, direction or guidance, or the presence or
22 absence of working examples when it comes to the dosing.

23 So for Claim 6, does the '572 patent specification
24 give the person of ordinary skill in the art any guidance or
25 reason as to why he should stop secondary dosing and move to

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1 tertiary dosing beyond what was already known in the prior art?

2 A. No, it doesn't.

3 Q. And what kind of experimentation would a person of
4 ordinary skill in the art have to do to decide from the
5 specification the number of secondary doses that are needed
6 when treating the full scope of angiogenic disorders in
7 Claim 6, such as the ones we discussed earlier for PVR, pannus,
8 and pterygium?

9 A. They would need to conduct an entirely new research
10 project for each of those conditions to decide how and if the
11 treatment could be effective for it and what the dosing regimen
12 should be.

13 Q. Let's talk about one of the next factors,
14 predictability in the art. Would you be able to predict
15 whether or not any one of the numerous dosing regimens or
16 numerous secondary dosing options that the specification
17 permits would work for all of the disclosed angiogenic eye
18 disorders covered by Claim 6 of the '572 patent, including PVR,
19 pannus, and pterygium?

20 A. No.

21 Q. Let's take a look at the rest of the factors on your
22 chart.

23 Can you explain how you weighed the remaining
24 factors -- the breadth of the claims, nature of the invention,
25 state of the prior art, and relative skill -- for the full

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1 scope of the Claim 6 dosing regimens?

2 A. Yes. As I mentioned earlier, I think that the claim
3 is excessively broad and its inclusion of a variety of
4 diagnoses under the category of angiogenic eye disorders.
5 There wasn't any information presented in the prior art as to
6 why that particular treatment regimen should be used. And I
7 think that, even with a high level of skill, a person of
8 ordinary skill in the art would have a difficult time knowing
9 how they should proceed with that without conducting research
10 and experimentation.

11 Q. And in that context, you're referring to the pannus,
12 PVR, and pterygium, for example?

13 A. Correct.

14 Q. Now let's talk about the five loading dose claims.

15 If, as Dr. Yancopoulos suggested in his testimony,
16 and if Dr. Csaky testifies consistently with his opinions put
17 here on your slide that the Phase II DME data was not enough
18 for a person of ordinary skill in the art to reasonably expect
19 success in clinical practice that phase proof was needed, if we
20 accept those things, what would be the experimental burden on
21 the person of ordinary skill in the art when it comes to
22 clinical practice of the DME and DR claims with five loading
23 doses that we see in Claim 25 of the '572 patent and Claims 11
24 and 19 of the '601 patent?

25 A. They would be high if they have to conduct Phase III

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1 trials for each of those.

2 Q. And is there a working example or guidance or
3 reasoning why in the specification that expressly calls out any
4 benefit to having five doses for DME or DR beyond what was
5 already known in the prior art?

6 A. No.

7 Q. Again, does the specification give any working
8 examples specific to addressing diabetic retinopathy as a
9 standalone indication?

10 A. No.

11 Q. So for these five loading dose claims, if, as we
12 expect, Dr. Csaky is going to opine that the art taught away
13 from and discouraged the use of five loading doses for safety
14 reasons, in your opinion, does the specification resolve those
15 allegedly discouraging safety concerns when it comes to using
16 five loading doses in DME or DR patients?

17 A. No, it doesn't.

18 Q. And how do you know that?

19 A. Because we don't see any guidance about the safety
20 being assured that we should use a five-loading-dose regimen.

21 Q. On this question of examples and guidance and
22 direction, Dr. Csaky did point to Example 7 as containing a
23 dosing regimen with five monthly loading doses followed by
24 eight-week dosing, among others.

25 In your opinion, is that helpful here?

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1 A. It's not.

2 Q. And can you explain why.

3 A. I think the issue is simply that the
4 five-loading-dose regimen was one of many regimens that were
5 presented, and there was no differentiation of that regimen
6 over all the others. So we wouldn't know that that should be
7 the best one to use.

8 Q. And was there at least any attempt to tie increased
9 loading doses to a particular disease state such as DME or DR?

10 A. No.

11 Q. Now, in the relevant time period, did those of
12 ordinary skill in the art change their dosing strategies if
13 diabetic retinopathy was presented without DME?

14 A. Yes. I think diabetic retinopathy without DME has
15 different clinical end points, and the clinical decision-making
16 for injections is different. In fact, one might think that the
17 number of loading doses might be fewer or the frequency of
18 injections might be fewer if you're not trying to treat macular
19 edema but rather trying to treat other biomarkers and end
20 points in diabetic retinopathy.

21 Q. And either way, does the specification suggest to the
22 person of ordinary skill in the art that they should be varying
23 the number of loading doses depending on the type of diabetic
24 retinopathy that the patient has?

25 A. No.

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1 Q. So then in your opinion, and particularly if, as
2 Dr. Yancopoulos and Dr. Csaky have suggested, getting workable
3 dosing regimens are not routine and involve years of costly and
4 difficult advanced human Phase III clinical trial data before
5 someone can reasonably expect a regimen to work in their
6 clinical practice, will the person of ordinary skill in the art
7 have a high or low experimental burden when it comes to the DME
8 and DR claims with five loading doses we see in Claim 25 of the
9 '572 patent and Claims 11 and 19 of the '601 patent?

10 A. It would be high.

11 Q. And can you explain why.

12 A. Simply because, in order to carry out these studies,
13 it would be essentially a Phase III clinical trial for each of
14 these indications. And to be able to arrive at that
15 conclusion, it would be a high burden of experimentation.

16 Q. Now, again, in your opinion -- and, again, this is
17 qualified by if -- as Dr. Csaky suggests here, the art
18 suggested reducing loading doses to three or four or even less,
19 does the specification give a person of ordinary skill in the
20 art any type of express reason to buck that trend and pick five
21 loading doses instead for DME or DR with a belief that it would
22 work?

23 A. No.

24 Q. And that's true even if they have the specification
25 in hand?

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1 A. Correct.

2 Q. Can you explain how you weighed the remaining
3 factors, the breadth of the claims, the nature of the
4 invention, the state of the prior art, and the relative skill
5 for the '572 patent's Claim 25 and '601 patent Claims 11 and 19
6 pertaining to the five-loading-dose regimens?

7 A. I thought that these were more neutral with regard to
8 those claims.

9 Q. Okay. And can you explain why.

10 A. So why I felt they were more neutral? Is that what
11 you mean?

12 Q. Yes.

13 Actually, if we could go back one slide.

14 Yes, if you can explain briefly why.

15 A. Simply because these claims were narrower, and they
16 were not relying upon as broad of a terminology as was present
17 in the other claims. And that's primarily my thought process
18 here.

19 Q. So in view of the testimony that you've given, what
20 is your ultimate opinion regarding enablement for Claim 6 of
21 the '572 patent?

22 A. So my concern there is that, again, because there was
23 essentially an unlimited number of dosing regimens -- doses
24 that could be given and dosing regimens for -- even for
25 diseases that we wouldn't think it would be effective for, that

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1 that would cause problems for enablement. And, again, there
2 was no guidance or teaching to suggest why it should do so. So
3 this would lead to a need for excessive experimentation.

4 Q. In view of testimony that you've given, what is your
5 opinion regarding whether the five loading doses for the DME
6 claims found in Claim 25 of the '572 patent, Claim 11 of the
7 '601 patent, are enabled by the specification, again, with the
8 qualification if this Court were to accept Regeneron and
9 Dr. Csaky's opinions about the art?

10 A. Again, because there was no specific teaching or
11 guidance as to why that particular regimen should be chosen for
12 DME, that would, for me, cause concerns around enablement and
13 leading us to have to do experimentation to find that out.

14 Q. And likewise in view of the testimony that you've
15 given, what is your opinion regarding whether Claim 19 of the
16 '601 patent is enabled if -- and, again, this is if with a
17 qualification -- this Court were to accept Dr. Csaky and
18 Regeneron's view of the art?

19 A. I think similarly, because we don't see any guidance
20 or teaching regarding diabetic retinopathy and, in fact, no
21 clinical data at all about that condition save for the form
22 that has DME, we again would consider this to require
23 experimentation to determine if it could be effective or not.

24 Q. And, Dr. Stewart, in view of -- for all of those --
25 again, with the qualifications relating to what Regeneron's

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1 position has been and Dr. Csaky's opinions have been -- would
2 that experimentation be undue for a person of ordinary skill in
3 the art?

4 A. Yes.

5 Q. Dr. Stewart, in view of the testimony that you have
6 given, do you also have any opinions regarding the priority
7 date that should be given to Claim 25 of the '572 patent,
8 Claim 11 of the '601 patent, and Claim 19 of the '601 patent?

9 A. Yes.

10 Q. And can you summarize that for us briefly, please.

11 A. Essentially that the only scenario in which five
12 loading doses followed by an eight-week dosing regimen was
13 shown within the specification was in Example 7. And so that
14 was in July of 2013. So it wouldn't -- I wouldn't think that
15 it could go to a date earlier than that for that particular
16 regimen.

17 The previous submissions didn't include support for
18 that regimen. And none of the regimens that were -- there
19 wasn't express callout for why that regimen should be chosen,
20 and so there wasn't anything, I think, beyond what we already
21 knew as to why you would treat a patient in that fashion.

22 Q. But even though there was no dosing regimen with five
23 loading doses until the continuation-in-part application where
24 they added Example 7 in July 12th, 2013, even with Example 7,
25 is it still your opinion that the -- that there is no written

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1 description support or enablement for those claims?

2 A. Yes, it is.

3 Q. All right. Now, do you also understand that
4 Dr. Csaky has made some allegation that Regeneron may deserve
5 an earlier priority date perhaps based on some internal
6 documents from Regeneron?

7 A. Yes, I do.

8 Q. Did Dr. Csaky explain why he thought this was so?

9 A. No.

10 Q. Did you review these internal Regeneron documents?

11 A. Yes.

12 Q. And did your opinion regarding the priority date
13 change after your review?

14 A. No.

15 Q. And can you explain why.

16 A. Because, again, I didn't see any justification for
17 why those regimens should be called out for those particular
18 conditions even from review of those documents.

19 Q. All right. If you take a look at DTX 5329 in your
20 binder, can you confirm that this is U.S. Provisional Patent
21 Application Number 61/432,245 filed January 13, 2011?

22 A. Yes.

23 Q. And if you could take a look at DTX 5332 in your
24 binder, can you confirm that this is U.S. Provisional Patent
25 Application Number 61/561,957, filed November 21st, 2011.

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1 A. Yes.

2 Q. And are both of these applications in the chain of
3 applications that eventually issued as the '572 and '601
4 patents?

5 A. Yes.

6 Q. If you could take a look at DDX 572 in your binder.
7 And I think that's one of the spiral-bound ones
8 that's in the pocket, Your Honor. Did you prepare or have
9 prepared this demonstrative exhibit?

10 A. Yes.

11 Q. Can you explain what it shows?

12 A. It shows the information presented and the different
13 submissions being highlighted in different fashion. The
14 information from the January 2011 submission is in plain text.
15 The information added in the November 2011 submission is
16 highlighted in blue, and the information added in the July 2013
17 submission is highlighted in yellow.

18 Q. If you could take a look at DDX 601 in your binder.
19 Did you similarly prepare this demonstrative exhibit for the
20 same reasons and using the same color-coding?

21 A. Yes, I did.

22 MS. MAZZOCHI: So just to sum up for the record, Your
23 Honor --

24 BY MS. MAZZOCHI:

25 Q. And, Dr. Stewart, if you could confirm this.

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1 The highlighted copies of the patents DDX 572 and 601
2 put new material not found in the original provisional
3 application, DTX 5329, but found in DTX 5332 in the November
4 2011 application, Dr. Stewart, those are in blue highlights in
5 your DDX exhibits?

6 A. Yes.

7 Q. And the highlighted copies of the patents, DDX 572
8 and 601, included new material not found in the original
9 provisional application but which we do see in the July -- in
10 DTX 5330, the July 2013 continuation-in-part application in
11 yellow highlights?

12 A. Yes.

13 Q. Dr. Stewart, now let's move to our next major
14 category, which is indefiniteness. Do you understand that
15 patent claims are indefinite if they fail to inform a skilled
16 artisan with reasonable certainty about the scope of the
17 invention at the time the patent application was filed?

18 A. Yes.

19 Q. And do you understand that part of that analysis is
20 whether a person of ordinary skill in the art would be able to
21 determine with reasonable certainty what the claims do and do
22 not cover?

23 A. Yes.

24 Q. Did you identify claim terms that, in your opinion,
25 are indefinite?

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1 A. Yes. The use of the word "approximately" that
2 appears in multiple locations throughout the claims.

3 Q. And why, in your opinion, is the use of the word
4 "approximately" a problem in the context of these claims?

5 A. Because it creates uncertainty around what the dosing
6 regimen should be that would fall inside the scope of the
7 claims.

8 Q. Okay. Well, to illustrate this, let's focus on
9 Claims 10 and 11 of the '601 patent. What terms does
10 approximately modify in Claim 10?

11 A. In Claim 10 it modifies every four weeks and every
12 eight weeks.

13 Q. What terms does approximately modify in Claim 11?

14 A. In Claim 11 it modifies every four weeks, every
15 28 days, or monthly.

16 Q. Now, in the context of the '572 and '601 patent
17 claims, why can't we say that approximately every four weeks
18 means the same thing as approximately every 28 days or
19 approximately monthly?

20 A. Because each of those has a different unit of time
21 measure, and so it creates uncertainty around whether they mean
22 the same thing or not.

23 Q. Turning to your next slide, 77, can you explain what
24 you've shown on this slide.

25 A. This is a figure showing a calendar with a schedule

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1 of injections, with the first injection being given on
2 February 1st. The next injection four weeks later is on
3 March 1st. And four weeks after that would be March 29th. But
4 when we use the term "approximately every four weeks," it
5 creates some range of error on either side of those particular
6 injection dates.

7 Q. Okay. If we can turn to your next slide, 78. Can
8 you explain what you've shown on this slide.

9 A. Yes. This is also a schedule showing an initial
10 injection given on February 1st, 28 days later on March 1st,
11 and again 28 days later on March 29th. But when we have the
12 term "approximately every 28 days," this also creates
13 uncertainty with a range of error on either side of those
14 particular dates.

15 Q. Turning to your next slide, 79, can you explain what
16 you've shown on this slide.

17 A. Yes. Again, a schedule of injection, with the first
18 injection on February 1st, another injection four weeks later
19 on March 1st, and four weeks after that on March 29th. But
20 here if we think of this in the context of approximately
21 monthly, exactly monthly would be March 1st, but with
22 approximately monthly it creates a larger range of error around
23 when exactly that injection would fall.

24 And so we can see that even the injection on March
25 29th, which is actually the eight-week injection, conceivably

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1 could fall within an approximately monthly description.

2 Q. Does the specification use the term "approximately"
3 anywhere outside the claims?

4 A. It's used once to describe the number of subjects
5 enrolled in a clinical trial.

6 Q. Does that help give you any guidance as to the
7 appropriate range to be given the term "approximately" in the
8 claims we've been looking at here?

9 A. No.

10 Q. Did you see the term "approximately" applied to any
11 dosing interval in the specification where the dosing interval
12 was allowed to have some variability?

13 A. No.

14 Q. What did Dr. Csaky say about the definition of the
15 term "approximately"?

16 A. His response to provide clarification around this
17 topic used the word "approximate." So it didn't actually
18 clarify this further for me.

19 Q. Does Dr. Csaky's definition provide the person of
20 ordinary skill in the art with any more clarity, in your
21 opinion?

22 A. No.

23 Q. Did you also consider Dr. Csaky's comments that
24 approximately should be used merely to accommodate scheduling
25 issues?

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1 A. Yes.

2 Q. And he explains that the standard could be based on
3 scheduling issues involving both the physician or the patient.
4 Does that, in your view, help give the person of ordinary skill
5 in the art reasonable clarity --

6 A. No.

7 Q. -- as to the scope of the claims?

8 A. No.

9 Q. And why not?

10 A. Because the schedule of the physician and the
11 schedule of the patient might be subject to different
12 constraints. A patient might not be able to come on a
13 particular day depending on various factors. And that might
14 create a certain range of error as far as when the patient
15 could come back versus a doctor's schedule that might entail
16 only having appointments available on certain days of the week
17 and causing perhaps even a greater range of error around when
18 the schedule would resume.

19 Q. And do you understand that Regeneron has also
20 proposed that approximately should also take into account not
21 just the ability to return to the office but a whole new metric
22 which is a standard of retaining remarkable efficacy?

23 A. Yes.

24 Q. And does that standard of retaining remarkable
25 efficacy provide, in your opinion, more clarity regarding the

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1 term "approximately"?

2 A. It doesn't.

3 Q. And why not?

4 A. Because that would -- could potentially determine --
5 depend upon how we determine efficacy. We might determine
6 efficacy based upon vision or anatomic features of the eye, and
7 that might lead you to different strategies such as treat and
8 extend and other regimens that involve maintaining efficacy
9 over a certain period of time with a lesser frequency of
10 injection. And so having to retain efficacy doesn't actually
11 help guide us to know what the schedule should be.

12 Q. And could retaining efficacy also include a prn
13 regimen?

14 A. It could.

15 Q. All right. So if you're trying to perform the method
16 of Claim 11 of the '601 patent and want to be sure you're
17 inside the scope of the claims, what does the person of
18 ordinary skill in the art need to do?

19 A. I think the only way to be sure you're inside the
20 scope is to give the injection exactly every 28 days.

21 Q. And what if you wanted to dose aflibercept to a
22 patient and make sure that you were outside the scope of
23 Claim 11 of the '601 patent?

24 A. Well, I think that would be very challenging because
25 of what I showed earlier with the range of error around each

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1 scheduled injection. And so it would be hard to know whether a
2 particular date falls inside or outside of the approximate
3 schedule.

4 Q. And what if you were trying to apply the patient or
5 doctor's scheduling metric that Dr. Csaky proposed or the
6 efficacy metric that Regeneron has additionally proposed?
7 Would that help?

8 A. No, because, again, it would be difficult to know
9 whether a particular consideration would cause you to fall
10 inside or outside of the scope.

11 Q. Okay. And are these concerns that you've raised for
12 the term "approximately" equally applicable to the other
13 asserted claims -- Claim 6 of the '572 patent, Claim 19 of the
14 '601 patent, and Claim 25 of the '572 patent?

15 A. Yes.

16 Q. All right. So based on the testimony you've just
17 provided here, what is your ultimate opinion regarding the
18 indefiniteness of the term "approximately" that appears in
19 Claim 6 and Claim 25 of the '572 patent and Claims 11 and 19 of
20 the '601 patent?

21 A. That it creates uncertainty around what the treatment
22 schedule should be that would fall within the scope of the
23 claim, and so it's indefinite.

24 Q. And if a person of ordinary skill in the art has
25 multiple metric standards to choose from -- whether it's number

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1 of days, number of weeks, number of months, scheduling issues,
2 or efficacy issues -- does that complicate matters further or
3 does that clarify matters further?

4 A. It makes it more complicated.

5 Q. And, Dr. Stewart, let's go ahead and sum things up,
6 then. Can you summarize your opinions, please, for Claim 6 of
7 the '572 patent.

8 A. Yes. So in this claim my concern regarding the term
9 "angiogenic eye disorder" that I feel is too broad and
10 incorporates conditions for which this wouldn't be enabled and
11 lacks written description support.

12 The number of doses that's given was also unlimited,
13 as we discussed. And so I feel that this is also not enabled
14 and lacks written description support. And the use of the term
15 "approximately" is indefinite.

16 Q. All right. And, Dr. Stewart, can you sum up your
17 opinions, please, for Claim 25 of the '572 patent.

18 THE COURT: Just a smidge slower this time, Doctor.

19 THE WITNESS: I wasn't warned about that, but I'll
20 try.

21 Yes. For this claim, there were no blaze marks given
22 linking this particular condition, which is diabetic macular
23 edema, to this specific regimen of five loading doses. And,
24 again, that this was not enabled under Dr. Csaky's assessment
25 of the prior art teachings.

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1 I also again believe that the term "approximately" is
2 indefinite.

3 BY MS. MAZZOCHI:

4 Q. And, Dr. Stewart, can you also summarize your
5 opinions, please, for Claim 11 of the '601 patent.

6 A. Yes. Similarly, the absence of any blaze marks
7 guiding me to this -- link this particular disease with this
8 particular five-loading-dose schedule, it was also not enabled
9 under Dr. Csaky's assessment of the prior art. And, again, the
10 use of the word "approximately," which is indefinite.

11 Q. And then let's turn to the last claim, Dr. Stewart,
12 to wrap up. Can you summarize your opinions, please, for
13 Claim 19 of the '601 patent.

14 A. Yes. And similar to the others, there again were no
15 blaze marks linking this particular condition to the
16 five-loading-dose regimen. In fact, there wasn't any clinical
17 data at all in the specification about diabetic retinopathy,
18 the fact that it wasn't enabled again under Dr. Csaky's
19 assessment of the prior art, and the indefiniteness from the
20 term "approximately" being included.

21 MS. MAZZOCHI: And with that, Your Honor, unless you
22 have any questions, I'm happy to pass the witness.

23 And if you like, we can also move into evidence the
24 exhibits that we just discussed as an administrative matter.
25 Those would be DTX 7100, DTX 5430, DTX 5431, DTX 5429,

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1 DTX 5329, DTX 5330, and DTX 5332.

2 And I believe those are all not objected to.

3 THE COURT: Let's confirm. Any objection to any of
4 those?

5 MR. GREGORY: No objection, Your Honor.

6 THE COURT: Without objection, those exhibits are
7 hereby admitted.

8 Thank you, Counsel.

9 (DTX 7100, DTX 5430, DTX 5431, DTX 5429, DTX 5329,
10 DTX 5330, and DTX 5332 were admitted.)

11 MS. MAZZOCHI: Thank you, Your Honor.

12 THE COURT: You want to start and stop, Counsel, or
13 do you just want to take a break and start --

14 MR. GREGORY: Let's just go ahead, Your Honor, if
15 that's all right.

16 THE COURT: Go ahead. But you've probably got
17 about -- I'm going to say ten minutes before I've got to take a
18 break and meet a 7-year-old downstairs.

19 MR. GREGORY: In that case, Your Honor, I don't think
20 I have much, but I can't promise I'm going to be under ten
21 minutes. We could take a break.

22 THE COURT: Why don't we go ahead and do that. I
23 don't want to interrupt by exiting stage left -- going out that
24 door and from there.

25 Doctor, this is a little bit of a gift to you. You

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1 get to have lunch by yourself in the quiet. And I apologize.
2 I don't know if you've been here for any of the other days of
3 trial. If you have, you've heard me offer this caution or the
4 rules of this proceeding, of course, prevent anyone from
5 talking to you while you're midstream on your testimony.

6 So you're a man without a country, for lack of a
7 better term, over our lunch break. The lawyers are hereby
8 ordered to feed you, but they're ordered to not speak to you.
9 So you're welcome for this little break.

10 Why don't we go ahead and take 45 minutes at this
11 juncture, and we'll pick back up at 12:30 if that works for
12 everyone. We can proceed with cross at that point.

13 Thank you all. My apologies. It's a different Klee
14 kid's schedule this week than we're used to; so we'll see
15 everyone at 12:30.

16 Again, Doctor, no one is being rude or discourteous.
17 You're just sort of on your own.

18 Thank you all very much.

19 (A recess was taken from 11:44 a.m. to
20 12:37 p.m.)

21 THE COURT: Counsel, if you're ready, you may
22 proceed.

23 MR. GREGORY: Thank you, Your Honor.

24 CROSS-EXAMINATION

25

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1 BY MR. GREGORY:

2 Q. Good afternoon, Dr. Stewart. Nice to see you again.

3 You've offered opinions today about the '601 and the
4 '572 patent. Those are PTX 001 and 003 respectively, right?

5 A. Yes.

6 Q. And I think we may have a number of disagreements
7 between you and I about the legal implications of some of the
8 words in the patents, but I want to make sure that we can agree
9 about what the words actually are.

10 First, let me just be clear. You understand that the
11 specification of the '572 patent and the '601 patents, they're
12 effectively identical, correct?

13 A. I would need to compare them word for word to confirm
14 that, but I know they are largely similar.

15 Q. In your discussion with defense counsel earlier this
16 morning, you used, I believe, the '572 patent as your example
17 for the specification of both of them; is that right?

18 A. I believe so.

19 Q. So I'd like to do the same just to save a little bit
20 of time, if that's okay with you.

21 A. Okay.

22 Q. All right. So with that established, let's take a
23 look at the '572 patent. You can use defense counsel's binder
24 that they used this morning with you. Again, it's PTX 003.

25 Please let me know when you have it in front of you.

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1 A. I have it.

2 Q. So you studied this patent, right?

3 A. Yes.

4 Q. Closely?

5 A. Yes.

6 Q. Please take a look first at page 14, Column 2,
7 lines 42 to 46, if you would.

8 So one thing we can agree on, Dr. Stewart, is that
9 the specification does disclose that the methods of the present
10 invention can be used to treat any angiogenic eye disorder.

11 We can agree on that, right?

12 A. Can you say which lines you're referring to?

13 Q. Lines 42 to 46 of Column 2 of page 14.

14 A. I see that that's what is stated, yes.

15 Q. And we also can agree that the specification
16 describes more specifically that the methods of the present
17 invention can be used to treat age-related macular
18 degeneration, diabetic retinopathy, and diabetic macular edema.

19 You see those words, right?

20 A. I do.

21 Q. I want you now to turn to another document that I
22 believe is in the binder that defense counsel used with you
23 this morning. I believe it was DTX 5329. And that should be
24 the '245 provisional application.

25 Do you have that in front of you?

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1 A. Yes.

2 Q. I believe you testified this morning this is the
3 provisional application, dated January 13, 2011.

4 Do you recall that?

5 A. Yes, I do.

6 Q. I want to look at paragraph 6 on page 5 of this
7 provisional patent application.

8 Just let me know when you're there, and we'll put it
9 up on the screen for you as well.

10 A. I'm sorry. It has number two at the bottom of the
11 page. I see what you're referring to.

12 Q. You see paragraph 6?

13 A. Yes.

14 Q. Another thing we can agree on here is that the
15 provisional application includes the same disclosure that we
16 just saw from the '572 specification, right?

17 A. Yes.

18 Q. You'd agree that this provisional application here
19 discloses that the methods of the present invention can be used
20 to treat any angiogenic eye disorder.

21 We agree on that, right?

22 A. That's what it says.

23 Q. And just like the '572 specification, it discloses
24 that the methods of the present invention can be used to treat
25 age-related macular degeneration, diabetic retinopathy, and

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1 diabetic macular edema, correct?

2 A. Yes.

3 Q. Okay. Look back at the '572 patent, the one you
4 spent a lot of time on this morning. I specifically want to
5 direct your attention to page 16, Column 5, lines 30 to 48.
6 We're going to put it up on the screen for you as well.

7 Do you have that passage in front of you, Doctor?

8 A. Did you say Column 5? Oh, yes, I do. Yes, I do see
9 it in the middle of the column.

10 Q. And here this portion of the specification contains a
11 slightly longer list of angiogenic eye disorders, correct?

12 A. Yes.

13 Q. And you agree -- we can agree that the '572 patent
14 here again discloses that the method of the invention can be
15 used to treat angiogenic eye disorders, right?

16 A. It does say that.

17 Q. And we can again agree that here, the '572 patent
18 discloses that the methods of the invention can be used to
19 treat age-related macular degeneration, diabetic macular edema,
20 and diabetic retinopathies, right?

21 A. Yes.

22 Q. I want to do a little bit of comparison now between
23 the patent and the provisional. You're welcome to flip back
24 and forth in the binder, and I'll also put it on the screen for
25 you.

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1 First I want to look at Column 2, line 57 to 60, at
2 page 14 of the '572 patent. I want to compare it with
3 paragraph 8 of the '245 provisional.

4 We can agree, Doctor, that these passages that I've
5 just called out in both the '572 patent and the '245
6 provisional, they are identical, right?

7 A. Yes.

8 Q. We can agree that they both disclose topical or
9 intraocular administration, correct?

10 A. Yes.

11 Q. We can agree that they both single out intravitreal
12 administration, correct?

13 A. Yes, they cite that in the "for example" section.

14 Q. Okay. Another comparison.

15 Next, please let's look next at Column 3, line 66
16 over to Column 4, line 9, on page 15 of the '572 patent. I
17 also want you to look at paragraph 16 of the '245 provisional.
18 And, again, we'll put that on the screen for easy reference
19 there.

20 Do you have that before you?

21 A. Yes, I do.

22 Q. Again, we can agree that both of these passages in
23 the '572 patent and the '245 provisional, they're identical,
24 right?

25 A. Yes.

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1 Q. And we can agree that both of these passages disclose
2 an exemplary embodiment in which each secondary dose is
3 administered three to four weeks after the immediately
4 preceding dose, correct?

5 A. Yes.

6 Q. And, likewise, we can agree that both these passages
7 disclose an exemplary embodiment where each tertiary dose is
8 administered at least eight weeks after the immediately
9 preceding dose, right?

10 A. At least eight is listed as one of many choices up to
11 14 and a half or more.

12 Q. It reads, "Each tertiary dose is administered at
13 least" -- and then there's a parenthetical, and then -- "weeks
14 after the immediately preceding dose."

15 That's what it says, right?

16 A. Yes, it does.

17 Q. Eight is called out specifically, right?

18 A. Yes, it's the first in the series of numbers.

19 Q. Just a few more of these, Doctor.

20 Let's take a look next at Column 4, line 22, at
21 page 15 of the '572 patent -- so I think you can stay right
22 where you are -- and also paragraph 18 of the '245 provisional.
23 And it's up on the screen as well for ease of reference, sir.

24 Please let me know when you have it before you.

25 A. I have it.

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1 Q. We can again agree that these passages in the '572
2 patent and the '245 provisional, they're identical, right, sir?

3 A. Yes.

4 Q. And we can also agree that both the '572 patent and
5 the '245 provisional in these passages disclose methods wherein
6 two or more secondary doses are administered to a patient,
7 right?

8 A. Yes.

9 Q. And we can also agree that both the '245 provisional
10 and the '572 patent disclose methods wherein two secondary
11 doses are administered, right?

12 A. That is one of the examples given.

13 Q. It's set out right there in black and white, right?

14 A. Yes. It's the first of the numbers that are listed
15 in parentheses.

16 Q. And we can also agree that both the '572 patent and
17 the '245 provisional disclose methods wherein four secondary
18 doses are administered, correct?

19 A. Yes, it's also one of the many numbers that are
20 listed there.

21 Q. Well, to be clear, sir, how many numbers are listed
22 there? It's seven, right?

23 A. Well, it says "or more"; so that encompasses any
24 number beyond that point.

25 Q. And how many numbers are specifically called out by

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1 name?

2 A. Seven.

3 Q. And four is one of those seven that's listed,
4 correct?

5 A. Yes, it is.

6 Q. Let's take a look -- one more at least. Let's take a
7 look at Column 4, line 32, on page 15 of the '572 patent -- so
8 you don't have to turn far there -- and then paragraph 19 of
9 the '245 provisional.

10 Again, we can agree that these passages are
11 identical, right, sir?

12 A. Yes.

13 Q. And we can also agree, can't we, that both the '572
14 patent and the '245 provisional disclose, again, in these
15 passages administering secondary doses in four-week intervals,
16 right?

17 A. Yes.

18 Q. And we can also agree that both the patent and the
19 provisional application disclose in these passages
20 administering tertiary doses in eight-week intervals, correct?

21 A. Yes.

22 Q. I want to skip all the way down now to Example 7 of
23 the '572 patent, and that's going to be at page 21.

24 Would you take a look there?

25 A. Yes.

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1 Q. And you see that the '572 patent Example 1 --
2 Example 7, it's titled "Dosing Regimens," correct?

3 A. Yes.

4 Q. And Example 7 does, in fact, set forth various dosing
5 regimens?

6 A. Yes.

7 Q. I think on direct examination you referred to them as
8 a laundry list. Is that right?

9 A. Yes.

10 Q. To be clear, we may call them -- there's a specific
11 number there. There's 20; isn't that right?

12 A. There are 20 entries. I think that the reason that I
13 view it as going beyond that level is because some of these
14 encompass various permutations that can be considered.

15 Q. There are 20 entries, right, sir?

16 A. There are 20 entries on this example.

17 Q. And I want to look at Column 16, lines 35 to 38.
18 Column 16, for reference, is page 21.

19 Do you have that before you?

20 A. Yes.

21 Q. I believe you highlighted this particular exemplary
22 dosing regimen during your testimony this morning; is that
23 correct, Doctor?

24 A. Yes.

25 Q. We can agree, can we not, that this particular

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1 regimen includes the administration of 2 milligrams of
2 aflibercept by intravitreal injection once every four weeks for
3 the first 16 weeks followed by 2 milligrams of aflibercept via
4 intravitreal injection once every eight weeks.

5 That's what it says, right?

6 A. Yes.

7 Q. And you understand that intravitreal injections once
8 every four weeks for the first 16 weeks, that's five loading
9 doses, correct, sir?

10 A. Yes.

11 Q. So this particular exemplary dosing regimen set out
12 here in Column 16 includes monthly loading doses, right?

13 A. Yes.

14 Q. It includes fixed extended dosing -- or fixed
15 extended interval doses of every eight weeks as well, right?

16 A. Yes.

17 Q. It recites only one interval, time interval, for the
18 loading doses. That's four weeks, right?

19 A. Yes.

20 Q. It recites only one time interval for the fixed
21 extended doses. That's eight weeks, right?

22 A. Yes.

23 Q. It identifies the precise number of loading doses be
24 administered. That's five, right?

25 A. Yes.

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1 Q. And take a look now, if you will, at the bottom of
2 Column 15, which is right below -- at the bottom of Example 7.
3 Actually, I'm sorry. Column 15 at the top of Example 7, right
4 below the header.

5 Do you see that?

6 A. Yes.

7 Q. And it defines the exemplary dosing regimen we just
8 looked at as exactly that, a example of a dosing regimen,
9 quote, within the scope of the present invention, right?

10 A. Yes.

11 Q. Finally, let's take a look at the bottom of
12 Example 7. So this is going to be Column 17, and then into
13 Column 18 on page 22.

14 Do you have that before you?

15 A. Yes.

16 Q. And you agree with me, right, sir, that Example 7
17 discloses that that exemplary five loading dose method we just
18 talked about may be used for the treatment of diabetic macular
19 edema, right?

20 A. Yes. That is one of the conditions listed.

21 Q. And you agree with me, don't you, sir, that Example 7
22 discloses that this five loading dose exemplary regimen we just
23 talked about could be used for the treatment of vascular
24 retinopathy, right?

25 A. Yes. That's another of the conditions listed.

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1 Q. Okay. Now that we've established, I think, a little
2 bit more about what the patents actually say, let's talk about
3 how you reached some of your opinions in this case.

4 I believe you offered several opinions that various
5 patent claims at issue here lacked written description. Is
6 that right?

7 A. Yes.

8 Q. You offered an opinion that Claim 6 of the '572
9 patent lacks sufficient written description because the
10 specification of that patent does not disclose the inventor was
11 in possession of a method of treating angiogenic eye disorders.

12 That's one of the bases for your opinions, right?

13 A. Yes.

14 Q. And your understanding is that for this claim -- that
15 is, Claim 6 of the '572 patent -- to have written description
16 support, the specification must provide clinical data for a
17 substantial number of the exemplary angiogenic eye disorders
18 listed in the specification of the '572 patent, right?

19 A. No.

20 Q. Doctor, did you have your deposition taken in this
21 matter?

22 A. Yes, I did.

23 Q. And I actually took your deposition; is that right?

24 A. Yes.

25 Q. So we met a couple months ago, and we sat in a

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1 conference room and I asked you a series of questions, correct?

2 A. Yes.

3 Q. And you understood you were under oath during that
4 deposition?

5 A. Yes.

6 Q. You understood you had an obligation to tell the
7 truth?

8 A. Yes.

9 Q. To be accurate?

10 A. Yes.

11 Q. You were, in fact, truthful and accurate in that
12 deposition; is that right?

13 A. Yes.

14 Q. I want to put on the screen pages 111 to 112 of the
15 doctor's testimony.

16 Doctor, I'm going to read this, and I want you to
17 tell me if you were asked these questions and gave these
18 answers at your deposition:

19 "Q Okay. So then to cycle back to my
20 original question, is it your view that, to have
21 adequate written description support for Claim 1
22 of the '572 patent, there would need to be
23 disclosures in the relevant disclosure of
24 clinical data for at least the majority of the
25 listed angiogenic eye disorders?

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1 "A I think that the person of skill in the
2 art would need to believe that the inventor was
3 in possession of that information for a
4 substantial number of the listed disorders. And
5 to me, in my opinion, having it for only three of
6 the numerous is not sufficient.

7 "Q When you say that the person of
8 ordinary skill in the art would need to believe
9 that the inventor was in possession of that
10 information for the substantial number of listed
11 disorders, what do you mean by 'that
12 information'? Do you mean clinical data?

13 "A Yes."

14 Doctor, did you hear those questions and give those
15 answers at your deposition?

16 A. Yes, I did.

17 Q. You've also made various assumptions about the law to
18 reach your written description opinions, right?

19 A. I'm not sure which assumptions we're referring to.

20 Q. Any assumptions. You made assumptions about the law
21 to reach your written description opinions in this case,
22 correct?

23 A. Perhaps. I'm not sure which assumptions we're
24 referring to.

25 Q. Let me be more specific.

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1 In performing your written description analyses in
2 this case, one assumption you made was that the relevant
3 disclosure being assessed for written description needed to
4 include an example for every embodiment of the claimed
5 invention; isn't that right?

6 A. I may have said that during deposition, but I'm
7 pretty sure that I got some of my definitions mixed up when I
8 was speaking about written description and enablement. So I'm
9 not sure if that's what you're referring to in that moment.

10 Q. Let's take a look at the doctor's testimony from
11 page 36, so between lines 8 and 13.

12 Doctor, I want to read this, and you can tell me if
13 you were asked this question and gave this answer at your
14 deposition.

15 "Q In performing a written description
16 analyses in this case, you have assumed that the
17 relevant disclosure must include examples for
18 email embodiment, correct?

19 "A Yes."

20 Did you give that answer at your deposition, sir?

21 A. Yes.

22 MR. GREGORY: With the Court's permission, I'd like
23 to pass out one exhibit here.

24 THE COURT: Understood. You may.

25 MS. MAZZOCHI: Your Honor, I'll just object to this

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1 exhibit because it's outside the scope of the opinions that the
2 witness testified to, not only on direct but also in his
3 report.

4 MR. GREGORY: Your Honor, this is an expert
5 ophthalmologist who's been offered by defendants in this case.
6 He testified regarding this exhibit at his deposition. He's
7 familiar with this exhibit. At the very least for the sake of
8 efficiency, we'd rather do this now while he's currently on the
9 stand than either get a subpoena and bring him back in that
10 case or --

11 THE COURT: What is the relevance of DTX 3498?

12 MR. GREGORY: This is one of their core anticipation
13 pieces of prior art from the DME claim, sir.

14 THE COURT: Understood. Overruled.

15 BY MR. GREGORY:

16 Q. Doctor, do you recognize DTX 3198 which I've just
17 passed you?

18 A. Yes.

19 Q. And you saw this document actually before your
20 deposition, correct, sir?

21 A. Yes.

22 Q. You saw it again at your deposition, correct, sir?

23 A. Yes.

24 Q. Let's put it up on the screen.

25 You understand -- why don't you also take out the

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1 '601 patent while you're at it, and that is PTX 001.

2 THE COURT: Whereabouts in '601, Counsel?

3 MR. GREGORY: We're going to take a look at Claim 11
4 at the back of your packet.

5 THE COURT: For the record, that's on page 21 of
6 Column 22.

7 MR. GREGORY: Thank you, Your Honor.

8 THE COURT: Thank you. Go ahead.

9 BY MR. GREGORY:

10 Q. You're familiar with Claim 11, correct, Doctor?

11 A. Yes.

12 Q. You understand that Claim 11 depends from Claim 10?

13 A. Yes.

14 Q. And thus includes all of the elements or limitations
15 of Claim 10?

16 A. Yes.

17 Q. By the way, Doctor, I believe you testified earlier
18 today, you have the qualifications of the person of ordinary
19 skill in the art as to Claims 11 and 10 of the '601 patent,
20 right?

21 A. Yes.

22 Q. Taking a look now at the press release before you --
23 let me back up for a second.

24 You understand that this is a Regeneron press
25 release, DTX 3198, dated September 14th, 2009, right?

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1 A. Yes.

2 Q. It's titled "Enrollment Completed in Regeneron Bayer
3 Healthcare Phase 3 Studies of VEGF Trap-Eye in Neovascular
4 Age-Related Macular Degeneration (Wet AMD)," right?

5 A. Yes.

6 Q. You agree with me, don't you, Doctor, that this press
7 release, the September 14th, 2009, press release does not
8 disclose all of the limitations of Claim 11 of the '601 patent,
9 correct?

10 MS. MAZZOCHI: Again, Your Honor, here again I'd like
11 to object because Dr. Albini already testified about this
12 exhibit. The witness did not testify -- did not opine on this
13 at all in his expert reports. And when they brought this up at
14 his deposition, we likewise objected that it was outside the
15 scope of his expert reports.

16 THE COURT: Understood. It's relevant to his
17 methodology in reaching his opinions. Overruled.

18 BY MR. GREGORY:

19 Q. I'll repeat the question if you'd like, Doctor.

20 You agree that the September 14th, 2009, press
21 release does not disclose all the limitations of Claim 11 of
22 the '601 patent, correct?

23 A. When you say "all the limitations," where are you
24 referring to?

25 Q. I'm referring to the elements or the limitations of

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1 Claim 11 of the '601 patent.

2 Are you familiar with that claim?

3 A. Yes.

4 Q. Okay. And my question to you is whether the
5 September 14th, 2009, press release discloses all the
6 limitations of Claim 11 of the '601 patent.

7 A. The press release is about a study regarding wet
8 age-related macular degeneration, and this claim relates to
9 diabetic macular edema. So it's on a different topic.

10 Q. I'll direct your attention, sir, to the second page
11 of the press release, the second paragraph on the second page.

12 Nowhere there or anywhere else in the September 14th,
13 2009, press release is there a disclosure of all the
14 limitations of Claim 11 of the '601 patent, right?

15 A. It talks about diabetic macular edema and refers to
16 several treatment regimens, including monthly injection every
17 eight weeks after three monthly loading doses or as needed
18 after three monthly loading doses, and the claim here refers to
19 five loading doses.

20 Q. So is the answer to my question yes, sir?

21 A. Can you repeat the question?

22 Q. You agree with me, don't you, that nowhere in the
23 September 14th, 2009, press release is there a disclosure of
24 all the limitations of Claim 11 of the '601 patent?

25 A. The press release does not cite the specific dosing

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1 regimen that's listed in the claim.

2 Q. We can take that down.

3 You'd agree with me, sir, that in 2011 people --
4 ophthalmologists were exploring when and how to deviate from
5 monthly injection regimens, correct?

6 A. Yes.

7 Q. And the answer to that question was not as well as
8 established as in subsequent years when treat and extend became
9 more established, correct?

10 A. Correct.

11 Q. I want to shift gears one more time here.

12 You discussed your background a little bit earlier
13 today, your CV and some of the journals that you contribute to,
14 right?

15 A. Yes.

16 Q. You've published a number of papers, some of which
17 you mentioned?

18 A. Yes.

19 Q. And a number of those papers are in peer-reviewed
20 journals, correct?

21 A. That's correct.

22 Q. And the purpose of such publications is to present
23 replicable research, correct?

24 A. Sometimes they may be review articles describing
25 other people's research, or sometimes it might be primary

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1 research that you're reporting on.

2 Q. Sometimes they may be case reports, right?

3 A. Yes.

4 Q. But regardless of the use, you strive to be accurate
5 in your written submissions to medical journals, correct?

6 A. Yes.

7 Q. You strive to be clear in your written submissions to
8 medical journals, correct?

9 A. Yes.

10 Q. Now, you've offered an opinion earlier today that the
11 term "approximately" in the asserted claims of the '601 and the
12 '572 patents is indefinite, right?

13 A. Yes.

14 Q. You opine that ophthalmologists wouldn't understand
15 what that word meant, right?

16 A. No, I didn't opine that they wouldn't understand what
17 it meant. I stated that it provided uncertainty around the
18 specifics of a dosing schedule.

19 MR. GREGORY: Your Honor, with your permission, I'd
20 like to approach and pass out a few more exhibits.

21 THE COURT: Okay.

22 BY MR. GREGORY:

23 Q. So, Dr. Stewart, we've passed around now a folder
24 containing several exhibits. I'd like to talk about them each
25 very briefly, and I do promise to be brief.

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1 I want to first turn to PTX 626, which I believe
2 should be the first document in the stack. Do you have that
3 before you?

4 A. Yes, I do.

5 Q. And could you please take a look at the first page of
6 that document.

7 A. Yes.

8 Q. This is a paper you authored in the journal called
9 *Ophthalmology*, correct?

10 A. This was a journal *Ophthalmology Retina*, and I was a
11 coauthor on this paper.

12 Q. And I want you to turn to page 1040 of this paper. I
13 believe it's page 13 in the PDF or 13 in the printout.

14 Do you have that?

15 A. Yes.

16 Q. And in this paper in *Ophthalmology Retina* in a table
17 detailing patient examination and management guidelines, you
18 wrote, "Reattempting the refill exchange after
19 approximately" -- you instructed -- I'm sorry -- "reattempting
20 the refill exchange after approximately seven days."

21 Do you see those words?

22 A. Yes, I do.

23 Q. Let's look at the next paper in the stack. That's
24 PTX 3352. Do you have 3352 before you?

25 A. Yes.

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1 Q. This was another paper that you authored, correct?

2 A. Yes.

3 Q. It's in the journal *Investigative Ophthalmology &*
4 *Visual Sciences*, right?

5 A. Yes.

6 Q. This is from 2011?

7 A. Correct.

8 Q. Okay. I want you to turn to pages 9276 and 9277.

9 We'll put them up on the screen for ease of
10 reference.

11 Do you see that on those pages you wrote on the page
12 first 9276, "In some instances approximately 20 minutes into
13 the 30-minute measurement period, a single drop of bound salt
14 solution was placed on the cornea if the investigators judged
15 that the eye appeared dry." And then on the very next page,
16 you wrote, "In this study, corneal permeability was quantified
17 approximately three to six weeks after CXL."

18 Do you see that?

19 A. Yes.

20 Q. Those are your words?

21 A. Yes.

22 Q. There's a few more of these here, Doctor.

23 PTX 3350 should be the next one in the stack. Do you
24 have that before you?

25 A. Yes.

JAY M. STEWART, MD - CROSS

1 Q. This is another paper that you wrote, right?

2 A. Yes.

3 Q. This time in the journal *Retinal Cases and Brief*
4 *Reports*?

5 A. Yes.

6 Q. From a few years ago, 2017, right?

7 A. Yes.

8 Q. And on page 2 -- I believe it's page 2 of the
9 document -- sorry -- page 1 of the document -- I believe
10 actually the very first paragraph you write, "The patient had
11 been diagnosed with uveitis and had been treated for
12 approximately 18 months."

13 Those are your words, right, Doctor?

14 A. Yes.

15 Q. Turn to the next document in the stack. It's
16 PTX 3351. This is an abstract for an ARVO meeting that you
17 authored, correct?

18 A. Yes.

19 Q. ARVO stands for the Association for Research in
20 Vision and Ophthalmology; is that right?

21 A. Yes.

22 Q. You're a member of that association?

23 A. Yes.

24 Q. You submitted this abstract at their annual meeting,
25 correct?

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1 A. Yes.

2 Q. Let's take a look at the second page of this two-page
3 document. You write, "Postoperative intraocular pressures were
4 reported with a pneumatonometer at approximately 4, 8, and 11
5 hours and twice a day thereafter for five days."

6 Do you see that?

7 A. Yes.

8 Q. Other than my mispronunciation, those were your
9 words, correct, Doctor?

10 A. Yes.

11 THE COURT: Counsel, could we get a spelling of that
12 effort of that word for the court reporter's benefit.

13 MR. GREGORY: Understood. The spelling is
14 P-N-E-U-M-A-T-O-N-O-M-E-T-E-R.

15 THE COURT: Understood. Thank you.

16 BY MR. GREGORY:

17 Q. Look next at PTX 3348, if you would, Doctor. This is
18 another paper that you authored, right?

19 A. Yes.

20 Q. And it's in the *International Journal of Retina and*
21 *Vitreous*, right?

22 A. Yes.

23 Q. And this paper actually concerns, it looks like,
24 anti-VEGF therapy, right?

25 A. Yes.

JAY M. STEWART, MD - CROSS

1 Q. Can you take a look at the third page of the
2 document. Here, you don't use the word "approximately"; you
3 use the word "about," correct?

4 You say, "Patients received aflibercept injections
5 every six weeks on average and were then treated with
6 ranibizumab or bevacizumab about six weeks after their last
7 aflibercept injection."

8 Those are your words, right, Doctor?

9 A. Yes.

10 Q. One more of these. Take a look at PTX 3349.

11 Do you recognize this document, sir?

12 A. I do not. I recall being involved in this project
13 when I was a resident, but I actually didn't realize it had
14 gone forth to this level of submission.

15 Q. You don't have any reason to doubt that the Jay
16 Stewart there in the inventor and applicant line is yourself?

17 A. That's me.

18 Q. This is an international patent application --
19 publication?

20 A. It looks to be so, yes.

21 Q. And if we can turn to, I believe, the second page of
22 it, you'll see a heading called "Field of the Invention."

23 Do you see that?

24 A. Yes.

25 Q. And it recites that "The present invention generally

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1 regards the field of medicine; more particularly, it regards
2 the field of ophthalmology."

3 Do you see that?

4 A. Yes.

5 Q. And I want you to look at the claims in this patent
6 application publication and in particular Claims 45, 48, and
7 54, which should be on pages 53 and 54 of the printout.

8 Do you see that?

9 A. Yes.

10 Q. And in each of these you used the modifier "about"
11 before a measure of weeks or months. Do you see that?

12 A. I didn't use that modifier.

13 Q. This is your patent application publication, sir,
14 isn't it?

15 A. As I said, I remember working on this project as a
16 resident but didn't realize it had actually gone forward to
17 this level. I wasn't involved in the composing of the language
18 for this document.

19 Q. You didn't tell anybody that that word was too
20 imprecise?

21 A. I just stated that I wasn't involved in choosing the
22 language for this or writing it in any fashion.

23 Q. Okay. Shifting gears just a bit, Doctor, I want you
24 to look at what should be the next document in the stack.
25 That's PTX 628.

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1 Do you recognize this document?

2 A. Yes.

3 Q. It's the label for Eylea or a label for Eylea,
4 correct?

5 A. Yes.

6 Q. You've seen labels for Eylea before, right?

7 A. Yes, I have.

8 Q. In fact, you've reviewed them in your clinical
9 practice, right?

10 A. Yes.

11 Q. I want you to look at the highlights of the
12 prescribing information, the top part of the page that we have
13 called out right now on the screen. I want you to make sure
14 you have that in front of you as well.

15 Do you see that in the dosage and administration
16 section of the highlights of prescribing information the Eylea
17 label recites the recommended dose for Eylea is "2 milligrams
18 administered by intravitreal injection every four weeks" -- and
19 then there's a parenthetical -- "approximately every 28 days,
20 monthly, for the first three months."

21 Do you see that?

22 A. Yes.

23 Q. Do you see that, similarly, at the very next bullet
24 it says that "Although Eylea may be dosed as frequently as
25 2 milligrams every four weeks (approximately every 25 days),

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1 monthly, additional efficacy was not demonstrated in most
2 patients when Eylea was dosed every four weeks compared to
3 every eight weeks"?

4 Do you see that?

5 A. Yes.

6 Q. Then do you see there are, I think, three more uses
7 of the word "approximately" on this first page of the Eylea
8 label modifying measures of time in either days or months.

9 Do you see that?

10 A. Yes.

11 Q. I want you to look at another document which I think
12 you may be familiar with, PTX 0472. It should be the next one
13 up in the stack.

14 Have you seen this document before, sir?

15 A. Yes.

16 Q. This is the Yesafili label, right, or a proposed
17 Yesafili label?

18 A. Yes.

19 Q. You understand that Yesafili is Mylan and Biocon's
20 proposed aflibercept biosimilar product, correct?

21 A. Yes.

22 Q. And you see the same uses of "approximately" to
23 modify measures of time in either days or months as we just saw
24 in the Eylea label here in the Yesafili label, correct?

25 A. It looks very similar.

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1 Q. Have you told Mylan or Biocon that they should amend
2 this language because it's unclear?

3 A. No.

4 Q. I want you to look at one more label for me. It's
5 the last one, I believe, in the stack. It's PTX 1617.

6 This is a label for Lucentis, right?

7 A. Yes.

8 Q. The active ingredient is ranibizumab?

9 A. That's correct.

10 Q. And this is a label from June 2010, correct?

11 A. Yes, it is.

12 Q. This is before priority dates that you assessed in
13 performing your various analyses in this case, right?

14 A. Yes.

15 Q. And you see again that the word "approximately" is
16 used multiple times in the first page of the highlights of
17 prescribing information to modify measures of time and days.

18 Do you see that?

19 A. Yes.

20 Q. You're familiar with Dr. Karl Csaky, right, sir?

21 A. I'm familiar with him as someone in the field. And
22 as I mentioned at my deposition, I have seen him give one or
23 more presentations at conferences in the past.

24 Q. You consider Dr. Csaky an expert in vitreoretinal
25 diseases?

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1 A. Yes.

2 Q. You consider him an expert in wet age-related macular
3 degeneration?

4 A. Yes.

5 Q. You consider him an expert in diabetic macular edema?

6 A. Yes.

7 Q. And you consider him an expert in diabetic
8 retinopathy, right?

9 A. Yes.

10 Q. And you would agree that Dr. Csaky is well respected
11 in the fields of wet AMD, DME, DR, and vitreoretinal diseases
12 generally, correct, sir?

13 A. I believe so.

14 MR. GREGORY: No further questions at this time.

15 THE COURT: Redirect, Counsel?

16 MS. MAZZOCHI: You knew there would be, Your Honor.
17 I apologize.

18 THE COURT: It makes the record look cleaner when I
19 ask.

20 MS. MAZZOCHI: I do appreciate that.

21 REDIRECT EXAMINATION

22 BY MS. MAZZOCHI:

23 Q. Dr. Stewart, for all of these references that
24 Mr. Gregory took you through, did any of them use the term
25 "approximately" in the same inconsistent manner that the claims

JAY M. STEWART, MD - REDIRECT

1 you discussed did from the '572 and '601 patents?

2 A. No, not that I could tell.

3 Q. Can you expand on that a little bit?

4 A. I think the issue in the patent claims that we were
5 discussing earlier was that there were several different means
6 of -- measures of time being modified. And in the case of a
7 patent claim, my understanding is that we want to be able to
8 determine if a particular schedule falls in or outside the
9 scope of that claim; so having that uncertainty in so many
10 units of time makes it hard to know if a particular dosing
11 schedule does fall in or outside of that claim.

12 Q. And if you can pull from that stack of papers that
13 Mr. Gregory gave you. Let's start, for example, at PTX 3348.

14 A. Yes.

15 THE COURT: Which article is that, Counsel? I'm
16 sorry.

17 MS. MAZZOCHI: 3348. This one is one of
18 Dr. Stewart's articles titled "Conversion back to bevacizumab
19 or ranibizumab for recurrent neovascular activity with
20 aflibercept in age-related macular degeneration: a case
21 series."

22 THE COURT: Okay. A thrilling title.

23 Sorry. Sorry, Doctor. Couldn't resist.

24 BY MS. MAZZOCHI:

25 Q. Dr. Stewart, if you could turn to the third page of

JAY M. STEWART, MD - REDIRECT

1 the exhibit, Table 1, where it talks about patient
2 characteristics. Did you actually put a specific range or
3 standard deviation that was permitted for the approximate
4 interval?

5 A. Yes. We included the mean and the standard
6 deviation.

7 Q. Does the '572 or '601 patent have that same degree of
8 specificity or definition?

9 A. No.

10 Q. If you could take a look at the -- let's start with
11 the Eylea labeling. And I believe that one was PTX 628. And
12 we can go ahead and look at the dosage and administration
13 section on the first page.

14 In the context of the labeling, did they apply the
15 term "approximately" to two different types of units, as in
16 approximately every 28 days and approximately monthly, as we
17 see in the '572 and '601 patent claims?

18 A. I think it's only modifying days in these instances.

19 Q. Sure.

20 Does the label apply the term "approximately monthly"
21 in addition to "approximately every 28 days"?

22 A. No.

23 Q. Does that change the scope, in your opinion?

24 A. Yes.

25 Q. Can you explain why.

JAY M. STEWART, MD - REDIRECT

1 A. Because monthly is a much larger unit of measurement.
2 And so if you're approximating that, then you're going to have
3 a wider error bar on your side of that timeline.

4 Q. But if you're looking in the context of the labeling
5 where it says "approximately every 28 days, monthly," without
6 the term "approximately" modifying the term "monthly," is the
7 term "monthly" narrow in your opinion, or is it broad?

8 A. It's narrow.

9 Q. If you -- and would your answer be the same, for
10 example, for the Yesafili labeling that you were directed to?

11 A. Yes.

12 Q. And, likewise, do you know whether the Lucentis
13 labeling has any of that same problem that you saw in the
14 claims of the '572 or '601 patent?

15 A. I think the Lucentis label is only using
16 approximately to modify 28 days.

17 Q. So no worry about the scope of range on units?

18 A. Only one type of unit is used here.

19 Q. All right. Let's go back to a couple of things that
20 Mr. Gregory asked you.

21 Now, Dr. Stewart, when Mr. Gregory asked you if
22 things were disclosed on a page or disclosed in the press
23 release, were you using the term "disclosed" in an ordinary
24 sense or in a legal sense?

25 A. To me, that would be an ordinary sense.

JAY M. STEWART, MD - REDIRECT

1 Q. As in just what's written on the page?

2 A. Yes, meaning do I see it on the page.

3 Q. Okay. Let's go back to Example 7, which I believe is
4 in PTX 3, exhibit page 21.

5 And let's highlight that first set of language on the
6 bottom of Column 15 that runs from around line 61 to 67.

7 Do you have that, sir?

8 A. Yes.

9 Q. Now, Mr. Gregory pointed you to only one little
10 snippet of the first two lines under Example 7. Can you read
11 the whole thing into the record.

12 A. "Example 7: Dosing Regimens. Specific, nonlimiting
13 examples of dosing regimens within the scope of the present
14 invention are as follows: VEGFT 2 milligrams (0.05
15 milliliters) administered by intravitreal injection once every
16 four weeks (monthly)."

17 Q. Now, would the person of ordinary skill in the art
18 read those first two lines that you read referring to specific
19 nonlimiting examples, would the person of ordinary skill in the
20 art view that language as limiting the number of regimens to 20
21 or not limiting the number of regimens to 20?

22 A. Not limiting because it says nonlimiting.

23 Q. And then, likewise, to the extent -- I think
24 Mr. Gregory asked you if all of these regimens could be used.
25 Is there anything that a person of ordinary skill in the art

JAY M. STEWART, MD - REDIRECT

1 would find in the specification that says any one of these
2 regimens should be used or called out to be used with DME or
3 diabetic retinopathy?

4 A. No.

5 Q. When it came to your testimony that you provided here
6 in court today, did you assume that you had to find an example
7 in order to find enablement or written description?

8 A. No, I didn't.

9 Q. Let's go back, then, to the press release, which was
10 DTX 3198. And let's go to the second page of the exhibit.

11 And let's call up the description of the VEGF
12 Trap-Eye in Phase II development paragraph.

13 Now, I believe you indicated that what was written on
14 the page for the first indication that involved an eight-week
15 dosing regimen was what? 2 milligrams every eight weeks after
16 three monthly loading doses?

17 A. The first one was 2 milligram monthly and then
18 2 milligram every eight weeks after three monthly loading doses
19 was the second option.

20 Q. Now, even if there's no express recitation of the
21 number five there, does the prn dosing regimen permit dosing
22 that would include five monthly loading doses in the context of
23 this regimen?

24 A. You could happen upon a scenario where five loading
25 doses are given through the course of using a prn approach.

JAY M. STEWART, MD - REDIRECT

1 Q. And would that prn regimen also permit, then, those
2 five loading doses being followed by an eight-week dosing
3 regimen?

4 A. It could be if that's how circumstances played out
5 for that particular patient.

6 MS. MAZZOCHI: Nothing further, Your Honor. Thank
7 you.

8 THE COURT: Recross?

9 MR. GREGORY: Nothing further, Your Honor.

10 THE COURT: Any exhibits we need to tidy up with the
11 doctor?

12 MR. GREGORY: None from us, sir.

13 THE COURT: Are the stack that was in the binder part
14 of the record, or are you satisfied just --

15 MR. GREGORY: We are satisfied. We don't need to
16 move them into evidence.

17 THE COURT: All right. Understood.

18 Any other exhibits from defense standpoint, then.

19 MS. MAZZOCHI: Your Honor, because so many of what
20 was in the stack I've never seen before, let me -- can I just
21 have -- to see if I need to put them in the record for this
22 witness just to make sure that the Court has context and
23 completeness. But, otherwise, we don't have anything further.
24 But we'll clean that up tomorrow morning if that's all right.

25 THE COURT: Understood.

GREGORY MACMICHAEL, PhD - DIRECT

1 MS. MAZZOCHI: Thank you.

2 THE COURT: Doctor, thank you. You can step down.
3 You can leave all the documents up there. Someone will tidy
4 those up. Thank you, sir.

5 If I could ask counsel to grab whatever's up here,
6 whomever it belongs to.

7 While we're doing that, Mylan may call its next
8 witness.

9 If everyone has finished rotating and whatnot,
10 Counsel, you may call your next witness.

11 MR. SALMEN: Thank you, Your Honor. Heinz Salmen on
12 behalf of defendants Mylan and Biocon. We call Dr. Gregory
13 MacMichael as our next witness.

14 THE COURT: Doctor, if you would come all the way to
15 the front.

16 You may proceed, Counsel.

17 MR. SALMEN: Thank you, Your Honor.

18 **GREGORY MACMICHAEL, PhD, DEFENDANTS' WITNESS, SWORN**

19 DIRECT EXAMINATION

20 BY MR. SALMEN:

21 Q. Good afternoon, Dr. MacMichael.

22 A. Good afternoon.

23 Q. Would you please introduce yourself to the Court.

24 THE WITNESS: Your Honor, my name is Greg MacMichael.

25 THE COURT: Good afternoon, sir.

GREGORY MACMICHAEL, PhD - DIRECT

1 BY MR. SALMEN:

2 Q. Dr. MacMichael, are you here testifying on behalf of
3 Mylan and Biocon?

4 A. Yes, I am.

5 Q. And did you prepare a set of demonstrative slides to
6 assist with your testimony today?

7 A. Yes, I did.

8 Q. Okay.

9 If we could pull up DDX 8 on the screen.

10 And I believe you've been provided a binder and a
11 printout of these slides. Dr. MacMichael, are these the slides
12 that you prepared?

13 A. Yes, they are.

14 Q. Dr. MacMichael, where are you from?

15 A. I'm from New Jersey.

16 Q. And turning to your demonstrative slide, DDX 2, on
17 the screen, will you please provide the Court with a summary of
18 your educational background.

19 A. Yes. I went to Penn State to get a bachelor's degree
20 in microbiology. Subsequent to that, I went to North Carolina
21 State University to get a master's degree in microbiology and
22 biochemistry focusing on the use of -- I went to North Carolina
23 State to get my master's degree in microbiology and
24 biochemistry with a focus on the use of bacteria to break down
25 hazardous wastes and degrade oil spills.

GREGORY MACMICHAEL, PhD - DIRECT

1 Q. What was your doctoral thesis in?

2 A. Yes. I got my PhD in microbiology and biochemistry
3 at Mississippi State University, again working on the use of
4 bacteria for the cleanup of hazardous waste and oil spills.

5 Q. After receiving your doctorate from Mississippi State
6 University in 1984, where did you begin your career?

7 A. Yeah. My first job after college was working at a
8 company called Techne.

9 Q. And will you please summarize for the Court your
10 professional experience at Techne.

11 A. Yes. At Techne I was working with an individual
12 named Norman Burney, who also was a famous innovator. And
13 together we worked on the development of bioreactors for
14 growing up animal cells to produce therapeutic proteins.

15 Q. How many years were you at Techne?

16 A. Six years.

17 Q. After your six years at Techne, where did you
18 continue your career?

19 A. I moved over to Centocor and was the assistant
20 director of cell culture research and development.

21 Q. What was the focus of your work at Centocor?

22 A. It was focused on developing high-cell-density,
23 high-volumetric productivity processes for making monoclonal
24 antibodies.

25 Q. Will you please explain to the Court what a

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1 monoclonal antibody is.

2 A. Yes. As you're developing a therapeutic, you will
3 basically genetically modify numerous cells, and then you will
4 look to see which one was the highest level of productivity.
5 You will then pick that specific clone that was obtained from
6 that one cell, and thus the term "monoclonal antibody."

7 Q. Did you have any notable achievements during your
8 time at Centocor?

9 A. Yes, I did.

10 Q. And can you describe for the Court, please.

11 A. Yes. I developed the high-density upstream processes
12 for Centoxin, the first monoclonal ever approved, Remicade, and
13 ReoPro.

14 Q. And were those FDA-approved medications?

15 A. They were all FDA-approved medications.

16 Q. And what type of drug product is Centoxin?

17 A. Centoxin is a immunoglobulin M for the treatment of
18 sepsis.

19 Q. What were your primary contributions to the
20 development of Centoxin?

21 A. Developing the high cell density processes, doing the
22 tech transfer into manufacturing, and supporting the
23 manufacturing efforts.

24 Q. What type of drug product is Remicade?

25 A. Remicade is an IgG monoclonal antibody for the

GREGORY MACMICHAEL, PhD - DIRECT

1 treatment of autoimmune disorder.

2 Q. What were your primary contributions to the
3 development of the Remicade product?

4 A. Again, developing high cell density, high volumetric
5 productivity processes for the manufacturing of Remicade.

6 Q. And turning to the ReoPro product, what type of drug
7 product is ReoPro?

8 A. ReoPro is a subclass of a monoclonal. It's a
9 fragment, called Fab -- fragment of an antibody is called a
10 Fab -- and it was actually a fusion protein. It was part
11 human, part mouse.

12 Q. Can you describe to the Court what your primary
13 contributions were to the development of ReoPro?

14 A. Again, my focus was on the upstream processes to
15 develop high productivity to be able to meet market demand.

16 Q. After your time at Centocor, I see you moved on to
17 Chiron. Why did you make the move to Chiron?

18 A. Yes. My supervisor, the head of development at
19 Centocor, moved over to Chiron to be the senior vice president
20 of development and manufacturing. He asked if I would join him
21 at Chiron, and I became the director of production in vaccines
22 development in St. Louis.

23 Q. What was the focus of your work at Chiron?

24 A. It was developing subunit vaccines in a cell line
25 called Chinese hamster ovarian cells.

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1 Q. Will you please explain to the Court what a Chinese
2 hamster ovarian, or CHO, cell is.

3 A. Yes. In the production of various therapeutic
4 proteins, they use animal cells. A Chinese hamster ovarian
5 cell was proved to be a very robust cell line, reached high
6 levels of cell density and productivity, and also had more
7 favorable what we call glycosylation patterns.

8 Q. Can you expand on that? What is a glycosylation
9 pattern?

10 A. Yes. Inside each of our cells, there's a whole set
11 of machinery that synthesizes proteins. And after the primary
12 protein is synthesized, the cells then can further -- what's
13 called posttranslational modification. They can modify those
14 cells by putting sugars on those cells to change the
15 performance in the bloodstream.

16 Q. Dr. MacMichael, did you invent the glycosylation
17 pattern for the proteins you were working on?

18 A. No. Every cell in the human body has the ability to
19 glycosylate proteins.

20 Q. And what notable achievements did you have at Chiron?

21 A. At Chiron we produced -- we developed multiple
22 vaccines, but one of most interest would be hepatitis B vaccine
23 where I led the global team, which included a clinical,
24 regulatory, and manufacturing and development, and basically
25 developed a new formulation for that vaccine.

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1 Q. Let me follow up on that, Dr. MacMichael. Were you
2 overseeing the formulation activities during that development?

3 A. Yes, I was.

4 Q. After Chiron, I see you moved over to Eli Lilly in
5 1997. Why did you make the move to Lilly?

6 A. Yes. Eli Lilly was trying to develop a product
7 called Xigris, activated protein C produced in HEK293 cell
8 line, but they lacked the internal experience of how to grow
9 those cells at high cell density. So they recruited me in to
10 help them develop the process.

11 Q. What was your title at Lilly?

12 A. Senior director of development.

13 Q. What type of drug products were you working on at
14 Lilly? What was your focus?

15 A. The focus was on therapeutic proteins.

16 Q. Will you please describe to the Court some of your
17 notable achievements at Lilly.

18 A. Yes. Probably the two more notable achievements was
19 the successful development and registration of Xigris,
20 activated protein C for the treatment of sepsis; and
21 additionally the development of truncated parathyroid hormone,
22 known as Forteo, for the treatment of osteoporosis.

23 Q. Were those drugs approved by any regulatory
24 authorities?

25 A. They were approved by the FDA and the EMA.

GREGORY MACMICHAEL, PhD - DIRECT

1 Q. I see you continued your career at Wyeth. What was
2 your title at Wyeth?

3 A. At Wyeth I was vice president of vaccines
4 development.

5 Q. And I see you have a couple drug names listed here on
6 Slide 3 of DDX 8. What are those drugs that you were referring
7 to?

8 A. They're probably two of my more notable
9 accomplishments while at Wyeth. Prevnar 13 is a pneumococcal
10 vaccine that vaccinates against 13 different types of
11 pneumococcal pneumonia.

12 Q. Let me ask a follow-up to that, Dr. MacMichael. What
13 was your contribution to the development of the Prevnar 13
14 formulation?

15 A. Yes. I had responsibilities from cell line
16 development through upstream process development, purification
17 and final formulation and the development of the analytical --
18 of the assays required for in process and release testing.

19 Q. Did you contribute to the stable formulation for the
20 Prevnar 13?

21 A. Yes.

22 Q. And how did you achieve a stable formulation in
23 Prevnar 13?

24 A. Yes. Initially, we found that, heading into Phase I
25 clinical trials, the vials -- just vibration in the

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1 refrigerators was sufficient agitation to cause some undesired
2 aggregation. We addressed that by adding Pluronic -- by adding
3 polysorbate 80 to prevent the aggregation.

4 Q. The second product on your list at Wyeth is FluMist.
5 What type of drug product is FluMist?

6 A. FluMist is a more advanced version of the annual flu
7 vaccine that many of us get. The difference with FluMist is
8 it's -- actually, the virus is not inactivated; so it elicits a
9 better immune response. It's sprayed up the nose, and it
10 cannot grow in the lungs. So it gets a very good immune
11 response protecting the recipient against the flu.

12 Q. Dr. MacMichael, what was the general time frame for
13 your work on the Prevnar 13 and FluMist formulation?

14 A. 2002 through 2008.

15 Q. I see you next were the senior vice president of
16 development and manufacturing at Cook Pharmica in 2008.

17 What was the focus of your work at Cook?

18 A. Cook was a contract development and manufacturing
19 organization. That is, we didn't have our own products; we
20 developed and manufactured the products for our clients.

21 Q. And then in 2010 you moved on to Novartis as global
22 head of biologics. What was the focus of your work at
23 Novartis?

24 A. My focus at Novartis was the development activities
25 required to bring the biologic pipeline in Novartis, which

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1 included cell line development, upstream process development,
2 purification, final formulation development, and the analytics
3 required for all of those activities.

4 Q. Thank you, Dr. MacMichael.

5 If we turn to Slide 4 of DDX 8, can you describe to
6 the Court what you have illustrated here on Slide 4.

7 A. This is a summary of some of the products that we
8 touched on. These are eight products that I successfully
9 developed and supported the registration and the interactions
10 with the FDA and EMA.

11 Q. Let me ask about that, Dr. MacMichael. In your over
12 30 years of industry experience, did you gain experience on the
13 regulatory side of product development?

14 A. Yes, I did.

15 Q. Can you describe that experience briefly.

16 A. Yes. To bring these types of molecules successfully
17 forward, you have numerous interactions with the FDA and the
18 EMA. It also requires an understanding of how to construct the
19 various submissions that are required for successful
20 registration.

21 Q. Dr. MacMichael, are you still active in the
22 pharmaceutical industry?

23 A. Yes, I am. I founded my own consultancy called
24 CMC Bioservices.

25 Q. And what types of companies do you generally consult

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1 for?

2 A. I consult in the pharmaceutical industry everything
3 from a large pharma company down to small startups.

4 Q. What technical areas do you generally consult in?

5 A. My focus is on therapeutic proteins, vaccines, and
6 cell and gene therapies, from development of cell lines all the
7 way down through the final drug product.

8 Q. Last question on your background Dr. MacMichael.
9 Using your own words, how would you describe your areas of
10 expertise?

11 A. Yeah. My expertise -- CMC stands for chemistry
12 manufacturing control is the term we used for doing process
13 development and manufacturing. My expertise starts with cell
14 line development, and the cell lines that produce therapeutic
15 proteins are put down in vials called cell banks. We do a cell
16 line selection for the highest producer.

17 Subsequent to that, we develop across the upstream
18 process, grow the cells up, and produce the desired protein.
19 We then need to purify it. And then subsequent to having it
20 purified in what we call bulk. It is then formulated into the
21 final vial.

22 So in many ways, I have responsibilities from vial to
23 vial, is one way to put it.

24 Q. Is that vial to vial illustrated on Slide 6 of DDX 8?

25 A. Yes, it is.

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1 Q. Dr. MacMichael, I see you've cited DTX 7087, pages 1
2 through 6. There's a copy of it in your binder, but we could
3 also show that on the screen for you.

4 Is this a copy of your current CV?

5 A. Yes, it is.

6 MR. SALMEN: Your Honor, we move to admit DTX 7087
7 into evidence.

8 THE COURT: Any objection?

9 MR. BERL: No objection.

10 THE COURT: Without objection, so admitted.

11 (DTX 7087 was admitted.)

12 MR. SALMEN: And at this time, Your Honor, we proffer
13 Dr. Gregory MacMichael as an expert in the formulation and
14 development of therapeutic proteins.

15 THE COURT: Any voir dire or objection?

16 MR. BERL: No, Your Honor.

17 THE COURT: Without objection then, motion granted.
18 The doctor is deemed so qualified.

19 You may proceed, Counsel.

20 MR. SALMEN: Thank you, Your Honor.

21 BY MR. SALMEN:

22 Q. Dr. MacMichael, if we turn to Slide 7 of your slide
23 presentation, DDX 8, let's talk about the opinions that you
24 plan to provide to the Court today.

25 If I could first direct your attention to PTX 2, we

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1 have the first page of PTX 2 here on Slide 8.

2 What is PTX 2?

3 A. PTX 2 is the '865 patent.

4 Q. And did you review and analyze the '865 patent,
5 PTX 2, in forming your opinions?

6 A. Yes, I did.

7 Q. And let's also put DTX 0030 on the screen.

8 Dr. MacMichael, did you review and consider the
9 document known as the prosecution history for the '865 patent
10 in forming your opinions?

11 A. Yes, I did.

12 Q. Turning to slide -- back to Slide 8 of DDX 8,
13 Dr. MacMichael, before we go through your opinions, let's just
14 set the stage a little.

15 Did you conduct your analysis in this case from the
16 perspective of a person of ordinary skill in the art?

17 A. Yes.

18 Q. And if we look at Slide 8, top callout, citing
19 DDX 2679, pages 19 to 20, MacMichael opening report, is this
20 the definition for the person of ordinary skill in the art that
21 you applied in forming your opinions?

22 A. Yes, it is.

23 Q. And I'll read that definition into the record for
24 you, Dr. MacMichael.

25 "A POSA during the relevant time period would have a

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1 fairly high level of education and skill. Here, a POSA would
2 have at least a PhD in chemistry, chemical engineering,
3 biochemistry, pharmacology, or a related field, along with one
4 to two years of experience in the development and manufacture
5 of formulations of therapeutic proteins or a lower degree with
6 more practical industrial experience. A POSA would have access
7 to biologists, biochemists, physicians, pharmaceutical
8 formulators, and the like with knowledge and experience in
9 fields such as drug discovery and development and the treatment
10 of ophthalmologic conditions."

11 Dr. MacMichael, is this the definition of a person of
12 ordinary skill in the art that you applied in forming your
13 opinions?

14 A. Yes, it is.

15 Q. Dr. MacMichael, did Dr. Trout also offer for a person
16 of ordinary skill in the art?

17 A. Yes, he did.

18 Q. Do you have Dr. Trout's definition illustrated at the
19 bottom right-hand side of Slide 8 of DTX 8, citing DTX 2251,
20 page 11?

21 A. Yes, I did.

22 Q. How did Dr. Trout's definition compare to yours?

23 A. Relatively similar. Dr. Trout just had a master's
24 degree where I had suggested a PhD for the POSA. Other than
25 that, the two definitions were relatively similar.

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1 Q. Dr. MacMichael, would your opinions regarding the
2 '865 patent change at all if the Court were to adopt
3 Dr. Trout's definition?

4 A. No, they would not.

5 Q. Now, let's move on to our second foundational point,
6 Dr. MacMichael. Turning to Slide 9 of DDX 8, are you aware
7 that the Court issued a claim construction order regarding
8 certain terms of the '865 patent that are relevant to your
9 opinions?

10 A. Yes, I am.

11 Q. And if we look here on Slide 9, we have the Court's
12 claim construction order marked for identification at DTX 6439
13 here at page 20. I'll read this for you, Dr. MacMichael.

14 "The Court adopts Mylan's definition of 'cosolvent.'
15 It is an organic substance added to the primary solvent to
16 increase the solubility of the solute, here a VEGF antagonist."

17 Dr. MacMichael, is this the construction of the claim
18 term "cosolvent" that you applied to your analysis regarding
19 infringement and validity of the '865 patent?

20 A. Yes, it is.

21 Q. If we turn to Slide 10, please.

22 Dr. MacMichael, will you explain to the Court what
23 you have illustrated here in the bubble at the center of
24 Slide 10, DDX 8, citing DTX 6439, page 20.

25 A. Yes. I took the Court's construction for an organic

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1 cosolvent and edited Claim 1. And as you see in the
2 highlighted yellow -- excuse me -- red is the insertion of the
3 Court's construct.

4 Q. And, Dr. MacMichael, is that the version of Claim 1
5 that you applied in your analysis regarding the infringement
6 inquiry?

7 A. Yes, it is.

8 Q. If we turn to Slide 11, please, of DDX 11.

9 Dr. MacMichael, will you please summarize for the
10 Court the opinions you plan to offer today regarding the
11 alleged infringement of the '865 patent against Mylan and
12 Biocon's Yesafili product.

13 A. Yes. Applying the Court's claim construction order,
14 Yesafili does not infringe on the asserted Claims 4, 7, 9, 11,
15 and 14 through 17 of the '865 patent.

16 Q. And did you form an opinion regarding whether
17 polysorbate 20 at 0.03 percent in Yesafili is an organic
18 cosolvent?

19 A. Yes, I did.

20 Q. And what was your conclusion?

21 A. My conclusion is that polysorbate 20 at 0.03 percent
22 in Yesafili is not an organic cosolvent.

23 Q. And did you form an opinion regarding whether
24 polysorbate 20 at 0.03 percent in Yesafili is increasing
25 solubility of the solute aflibercept in the Yesafili product?

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1 A. Yes, I did evaluate.

2 Q. And what was your conclusion in that regard?

3 A. My conclusion was that polysorbate 20 at 0.03 percent
4 in Yesafili does not increase solubility of the solute
5 aflibercept.

6 Q. Dr. MacMichael, I understand that you were unable to
7 attend Dr. Trout's testimony in person. Were you nonetheless
8 able to review Dr. Trout's trial testimony as well as his
9 associated demonstratives?

10 A. Yes, I was.

11 Q. Was there any portion of Dr. Trout's testimony that
12 you want to respond to specifically during your testimony
13 today?

14 A. There's two points where I believe we disagree.

15 Q. Can you explain to the Court those two points of
16 Dr. Trout's testimony that you would like to respond to.

17 A. Yes.

18 Q. First point, please.

19 A. The first point, Dr. Trout defined inhibiting
20 aggregation as equal to increasing solubility.

21 Q. Do you agree or disagree with that testimony?

22 A. I disagree.

23 Q. And your second point, Dr. MacMichael?

24 A. The second point where I differ is reducing
25 insolubility is equivalent to increasing solubility. I

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1 disagree.

2 Q. Dr. MacMichael, I would next like to talk about some
3 of the technology relevant to your opinions in this case. If
4 we could turn to Slide 13. Here on Slide 13 of DDX 8 we have
5 DTX 5172, the Bontempo reference. Dr. MacMichael, did you
6 review and consider the Bontempo reference in forming your
7 opinion?

8 A. Yes, I did.

9 Q. Will you please explain to the Court the information
10 you have identified here in Slide 13 from Bontempo that's
11 relevant to your opinions and testimony in this case.

12 A. Yes. I pulled a list of potential buffers that could
13 be used in a protein formulation.

14 Q. And that information -- does that information come
15 from page 7 of DTX 5172, Bontempo?

16 A. Yes, it does.

17 Q. If we turn to the next slide, Slide 14 -- actually,
18 I'm sorry. I forgot to ask a question.

19 Could we go back one.

20 Dr. MacMichael, can you please explain the relevance
21 of the information that you provided in the parentheses
22 following each of the listed buffers?

23 A. Yeah. The parentheses are showing the pH ranges
24 where each of these buffers would -- each one of these moieties
25 would be effective as a buffer.

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1 Q. And, for example, if we look at succinate, what would
2 be the buffering range for that buffer?

3 A. A pH of 3.2 to 6.6.

4 Q. And for citrate, what would be the known buffering
5 range for a citrate buffer?

6 A. 2.1 to 6.2.

7 Q. For histidine, what would be the known buffering
8 range for a histidine buffer?

9 A. 5.5 to 6.5.

10 Q. If we turn to Slide 14, please, of DDX 8.

11 Here, Dr. MacMichael, we have Exhibit DTX 5196. This
12 is the Strickley reference. Dr. MacMichael, did you review and
13 rely on the Strickley reference?

14 A. Yes, I did.

15 Q. And please explain to the Court the teaching in
16 Strickley that you have highlighted here on Slide 14 from
17 page 2 of DTX 5196.

18 A. Yes. I pulled out Strickley's definition of a
19 cosolvent.

20 Q. And is that identified in the yellow highlighted
21 language there?

22 A. Yes, it is.

23 Q. I'll read that for you, Dr. MacMichael.

24 "Cosolvents are mixtures of miscible solvents and are
25 often used to solubilize water-insoluble drugs."

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1 Is that part of the information from Strickley that
2 you relied upon?

3 A. Yes, it is.

4 Q. And is this disclosure in Strickley consistent with
5 how a person of ordinary skill in the art would understand the
6 use of cosolvents in pharmaceutical formulations?

7 A. Yes.

8 Q. Could we turn to Slide 15, please.

9 Here on Slide 15 we have another passage from the
10 Strickley reference, DTX 5196. This time we're on page 1.

11 Dr. MacMichael, will you please explain to the Court
12 the information in Strickley that you have identified here to
13 help inform your testimony.

14 A. Yes. What's pulled out in the paragraph that's being
15 shown is examples of water-soluble organic solvents. Some of
16 the examples would be polyethylene glycol 300, polyethylene
17 glycol 400.

18 Q. And with regard to the nonionic surfactants that you
19 have highlighted there, does Strickley provide examples of
20 nonionic surfactants?

21 A. Yes, they do.

22 Q. What are a couple of the examples of nonionic
23 surfactants that you've highlighted here on Slide 15, DDX 8?

24 A. For today's discussion I highlighted polysorbate 20
25 and polysorbate 80.

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1 Q. Dr. MacMichael, are these descriptions from Strickley
2 of polysorbate 20, polysorbate 80, and polyethylene glycol
3 consistent with how a person of ordinary skill in the art would
4 understand and characterize those excipients?

5 A. Yes.

6 Q. If we turn to Slide 16, please.

7 Here, Dr. MacMichael, we have DTX 5011. This is the
8 Akers reference. Did you review and consider the Akers
9 reference, DTX 5011?

10 A. Yes.

11 Q. And will you please explain to the Court the
12 information from Akers here on page 3, DTX 5011, that you've
13 identified to help inform your testimony.

14 A. Yes. Again, it defines a cosolvent and then gives
15 additional information on how a cosolvent works in water.

16 Q. Let's break that down with the first highlighted
17 language. I'll read that for you, Dr. MacMichael.

18 "Cosolvents are used to increase the solubility of a
19 poorly soluble drug in water."

20 Is that part of the disclosure from Akers that you
21 reviewed and considered?

22 A. Yes, it is.

23 Q. And can you describe for the Court the importance of
24 the second passage from Strickley that you have here.

25 A. Yes. The second passage is showing how a cosolvent

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1 changes the overall physical chemistry of the solution. And
2 the way that Akers defines it is a water-miscible cosolvent
3 operates on the principle of lowering the dielectric constant
4 property of water, thereby increasing the aqueous solubility of
5 a poorly water-soluble drug.

6 Q. If we turn to the next slide, please, Slide 17.

7 Here, Dr. MacMichael, we have DTX 5012, what's known
8 as the Ansel reference, *Ansel's Pharmaceutical Dosage Forms and*
9 *Drug Delivery Systems*. Dr. MacMichael, did you review and
10 consider DTX 5012 in forming your opinions?

11 A. Yes, I did.

12 Q. I see you have two callouts here, Dr. MacMichael,
13 both from page 12 of DTX 5012. Will you please explain to the
14 Court the information from Ansel that you've identified here to
15 help inform your testimony.

16 A. There's two things I wanted to accomplish. One was
17 the definitions of a solvent and a surfactant. Then secondly
18 to give a list of examples of potential solvents and
19 surfactants.

20 Q. Let's start with the first definition applied here
21 for solvent. I'll read that for you, Dr. MacMichael.

22 "Used to dissolve another substance in preparation of
23 a solution."

24 Dr. MacMichael, is that definition for solvent
25 consistent with how a person of ordinary skill in the art would

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1 understand that excipient?

2 A. Yes, it is.

3 Q. And the second definition you've highlighted here is
4 for surfactant. I'll read that for you as well.

5 "Substances that absorb to surfaces or interfaces to
6 reduce surface or interfacial tension."

7 Dr. MacMichael, is that definition consistent with
8 how a person of ordinary skill in the art would define and
9 characterize a surfactant?

10 A. Yes, it is.

11 Q. We turn now to Slide 18, please.

12 Here on Slide 18 of DDX 8, we have what's already
13 been admitted as PTX 1817. This is the Randolph and Jones
14 reference, Dr. MacMichael.

15 Did you review and consider the Randolph and Jones
16 reference to help inform your opinions and testimony?

17 A. Yes, I did.

18 Q. And will you please explain to the Court the
19 information from Randolph and Jones that you have identified
20 here to help inform your testimony.

21 A. Yes. Again, I used the Randolph and Jones to
22 further -- give further support of the definition of a
23 surfactant as being used as a stabilizing agent in a protein
24 formulation, and they're typically nonionic.

25 Q. And let me ask you, Dr. MacMichael, what subject

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1 matter did Randolph and Jones direct their focus on in this
2 chapter?

3 A. It focused on the interaction of nonionic surfactants
4 and proteins with respect to developing formulations.

5 Q. Thank you.

6 We move to just the next slide, please, Slide 19.

7 MR. SALMEN: Your Honor, if I may, at this point in
8 time I am going to have to ask to have the courtroom sealed
9 pursuant to Your Honor's previous order. We are going to be
10 getting into the details of Mylan and Biocon's Yesafili
11 product.

12 THE COURT: Understood.

13 Any objection to that from Regeneron?

14 MR. BERL: No objection.

15 THE COURT: Ladies and gentlemen, consistent with our
16 prior -- I meant to turn that off.

17 Ladies and gentlemen, consistent with our prior
18 practice, anyone who's not permitted to be in the courtroom
19 consistent with this Court's protective order entered in this
20 case, I would kindly ask you to step out, please. Thank you.

21 I would continue to ask counsel to assist the Court
22 in policing enforcement of that requirement just with a quick
23 look around.

24 THE COURT: Seeing no further objections, I'll ask
25 court security to please seal our courtroom, sir. Thank you.

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1 Go right ahead, Counsel.

2 MR. SALMEN: Thank you, Your Honor.

3 (The following proceedings (1384/3 to 1416/2) were
4 had under seal, and are filed under separate cover.)

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1 (Record unsealed.)

2 THE COURT: Counsel, if you're ready, you may
3 proceed.

4 MR. SALMEN: Thank you, Your Honor.

5 BY MR. SALMEN:

6 Q. Ready, Dr. MacMichael?

7 A. Yes, I am.

8 Q. Dr. MacMichael, have you been asked to offer an
9 opinion regarding the validity of the asserted claims of the
10 '865 patent?

11 A. Yes, I have.

12 MR. SALMEN: I just wanted to make sure we unsealed
13 the courtroom, Your Honor.

14 THE COURT: We have.

15 MR. SALMEN: Just double-checking.

16 BY MR. SALMEN:

17 Q. And, Dr. MacMichael, if we turn to Slide 41 of your
18 presentation here.

19 Will you please provide the Court with a brief
20 summary of your opinions that you plan to provide today.

21 A. Yeah. This slide shows three of my opinions.

22 Q. If we address them one at a time, have you formed an
23 opinion regarding the enablement of the '865 patent?

24 A. Yes. My first opinion was it lacks enablement. The
25 breadth of the asserted claims is not enabled by the '865

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1 patent specifications.

2 Q. Will you please summarize for the Court your opinion
3 regarding the written description of the '865 patent.

4 A. My opinion is the asserted claims do not have
5 sufficient written description. The '865 patent specification
6 fails to inform the skilled person that the named inventors
7 possessed anything but a phosphate-buffered sucrose-stabilized
8 formulation.

9 Q. And then lastly, Dr. MacMichael, will you please
10 provide a summary of your opinion regarding the indefiniteness
11 inquiry of the '865 patent.

12 A. Yes. The patent's indefinite because the '865 patent
13 specification fails to inform the skilled person what suitable
14 for intravitreal administration means. That term is subjective
15 and prone to multiple interpretations.

16 Q. If we turn to Slide 42, please.

17 Here on Slide 42, Dr. MacMichael, I see you have the
18 enablement legal standard. And I'll read that for you.

19 "A claimed invention is not enabled and, therefore,
20 is not patentable when the specification does not provide a
21 sufficient description to a person of ordinary skill in the art
22 how to make and use the full scope of the claimed invention
23 without undue experimentation."

24 Dr. MacMichael, is this the standard you applied in
25 your assessment of whether the '865 patent specification

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1 enables the asserted claims?

2 A. Yes, it is.

3 Q. If we turn to the next slide, Slide 43, please. Here
4 on Slide 43, Dr. MacMichael, I see you have a graphic that
5 looks like an upside-down pyramid. Can you please explain to
6 the Court what information you are trying to convey with this
7 graphic.

8 A. Yes. This graphic is showing that, as you build on
9 the -- the claims build upon one another, there should be a
10 narrowing in scope of the invention.

11 Q. And I see on the left-hand side of this Slide 43 you
12 have identified claims of the '865 patent, the referenced
13 Claims 2, 5, and 10, followed by the asserted Claims 4, 7, 9,
14 11, 14, 15, 16, and 17.

15 Let me ask, Dr. MacMichael, does this graphic on
16 Slide 43 illustrate the breadth of the asserted '865 --
17 asserted claims of the '865 patent?

18 A. No, it doesn't.

19 Q. If we turn to Slide 44, please, please explain to the
20 Court what you have illustrated here in Slide 44.

21 A. Yes. What we are seeing here, the way these claims
22 are constructed, rather than narrowing -- rather than narrowing
23 the overall claims of the invention, it actually broadens them.

24 Q. Let's break that down, Dr. MacMichael.

25 Here from Claim 5 to Claim 7 can you explain how the

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1 claims compare in scope?

2 A. Yeah. All the claims that are being highlighted with
3 the word "compromises," [sic] as we know just means includes,
4 polysorbate; so it gives various examples of components that
5 could be used and potential concentrations and ranges of -- for
6 example, ranges of pH. So there's an extraordinary -- not
7 extraordinary number, but there's a large number of variables
8 that have to be worked through. And that's not clearly defined
9 within the scope of this claim.

10 Q. Thank you, Dr. MacMichael. Let's turn to your
11 enablement analysis.

12 If we turn to Slide 45.

13 Dr. MacMichael, did you apply each -- here on
14 Slide 45 we have identified the *Wands* factor. Did you apply
15 each of the *Wands* factors in forming your opinion regarding the
16 enablement of the '865 patent claims?

17 A. Yes, I did.

18 Q. And let's walk through these. If we turn to
19 Slide 46, I'd like to start at the bottom of this list with
20 *Wands* Factor 8, the breadth of the claims.

21 Dr. MacMichael, did you form an opinion regarding the
22 breadth of the '865 patent asserted claims?

23 A. Yes, I did.

24 Q. And Dr. MacMichael, will you please explain to the
25 Court the conclusions you reached regarding the breadth of the

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1 claims?

2 A. Yes.

3 THE COURT: One second, Doctor.

4 Yes, Counsel?

5 MR. BERL: Objection, Your Honor. This is leading.

6 I mean, we haven't been sticklers about this, but this is
7 basically having the answers on a screen and asking him to read
8 them. That doesn't seem like an appropriate question.

9 THE COURT: Overruled at this point.

10 But it is direct examination, Counsel. Go ahead.

11 BY MR. SALMEN:

12 Q. Dr. MacMichael, let me ask the question again.

13 Will you please explain to the Court the conclusions
14 you've reached regarding the breadth of the claims.

15 A. Yes. There's different types of formulations that
16 are being cited. There's various types and concentrations of
17 the buffers. Examples are given -- citrate, succinate,
18 phosphate, histidine. However, that claim uses the word
19 "comprise." So those are examples. Multiple other buffers
20 could be, in fact, used.

21 Secondly, various types and concentrations of
22 stabilizing agents are suggested. And then various types and
23 concentrations of the organic cosolvent are also being
24 suggested. But they use the word "comprises," which leaves it
25 open-ended.

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1 Q. And let me ask, Dr. MacMichael, would a skilled
2 person understand that combinations of different buffers could
3 be used as well?

4 A. Yes. You could use more than one specific buffer.
5 You can use a combination, which is actually practiced to
6 achieve a desired pH.

7 Q. And under the claim language here, could combinations
8 of different stabilizing agents be used as well?

9 A. Yes, they could.

10 Q. And same question for cosolvents, could combination
11 of organic cosolvents be used here under the claim language?

12 A. Yes. In fact, we were going to use cosolvents --
13 various cosolvents could be used and examples were highlighted.

14 Q. Last question for this part, Dr. MacMichael. Now
15 that you've identified the variables in the claims with respect
16 to each of the required components of Claim 1, do the asserted
17 dependent claims sufficiently narrow this universe of
18 formulations that would lessen the burden on the person of
19 ordinary skill in the art practicing these claims?

20 A. No, they would not.

21 Q. If we turn to Slide 47, please.

22 Did you also consider and apply *Wands* Factors 4, 5,
23 6, and 7 listed here on Slide 47 on the left-hand side?

24 A. Yes, I did.

25 Q. I'll read those for you, Dr. MacMichael. *Wands*

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1 Factor 4, the nature of the invention. Factor 5, the state of
2 the prior art. Factor 6, the relative skill of the art. And
3 Factor 7, the predictability or unpredictability of the art.

4 Dr. MacMichael, what conclusion did you reach with
5 respect to the amount of experimentation a person of ordinary
6 skill in the art would need to practice the full scope of the
7 claims?

8 A. There would need to be a significant amount of
9 experimentation.

10 Q. Dr. MacMichael, did you identify any evidence in the
11 record that supports your opinion that the skilled person would
12 require a significant amount of experimentation?

13 A. Yes. I cite two examples that are highlighted in
14 yellow.

15 Q. So let's take those one at a time. DTX 5053, this is
16 at page 17. This is Regeneron's response to an office action.

17 Dr. MacMichael, did you review and consider this
18 document?

19 A. Yes, I did.

20 Q. And I'll read that for you.

21 "Thus, one of ordinary skill in the art, upon reading
22 Remington's, would expect to engage in significant nonroutine
23 experimentation to develop a successful formulation as claimed
24 herein."

25 Dr. MacMichael, was that some of the evidence that

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1 you identified --

2 A. Yes, it is.

3 Q. -- as support for your opinion that the skilled
4 person would require additional -- undue experimentation?

5 A. Yes, it is.

6 Q. If we look at the bottom callout, DTX 4430, at
7 page 3, that's a declaration of named inventor Daniel Dix.

8 Dr. MacMichael, did you review and consider DTX 4430
9 with regard to your opinions?

10 A. Yes, I did.

11 Q. And I'll read that statement for you.

12 "Formulation of pharmaceutical preparations and
13 achieving a stable composition is not a simple or routine
14 matter."

15 Dr. MacMichael, do you agree with that statement from
16 Dr. Daniel Dix?

17 A. Yes.

18 Q. And is this part of the evidence that you reviewed
19 and considered to support your opinion that the skilled person
20 would require undue experimentation practicing the asserted
21 claims of the '865 patent?

22 A. Yes.

23 Q. And, Dr. MacMichael, if we move to our next slide,
24 Slide 48, did you form an opinion regarding the amount of
25 direct -- I'm sorry.

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1 Did you form an opinion regarding the amount of
2 direction or guidance presented in the '865 patent
3 specification?

4 A. Yes, I did.

5 Q. And did you form an opinion regarding the presence of
6 working examples in the '865 patent specification?

7 A. Yes, I did.

8 Q. Let's start with *Wands* Factor Number 3. What
9 conclusions did you reach regarding the presence or absence of
10 working examples in the '865 patent specification?

11 A. Yeah. There were examples given from the
12 phosphate-buffered sucrose-stabilized formulations. However,
13 for the other examples -- the other areas where the term
14 "comprised" was used, there were no examples given.

15 Q. Were there any examples provided in the '865 patent
16 specification of using any other type of buffer or stabilizer
17 in a stable formulation?

18 A. I'm trying to recall. I believe it was glycol or
19 glycerol. I'm sorry.

20 Q. Let me ask a more direct question, Dr. MacMichael.
21 Does the '865 patent specification provide any
22 example that is not a phosphate-buffered solution?

23 A. No.

24 Q. Let's now look at *Wands* Factor 2, the amount of
25 direction or guidance presented.

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1 Dr. MacMichael, what conclusions did you reach
2 regarding the amount of direction or guidance presented in the
3 '865 patent specification?

4 A. That there was insufficient guidance.

5 Q. And here on Slide 48 of DDX 8, I see you have a
6 callout from the patent, PTX 2, page 4, Column 2, lines 39 to
7 48. Will you please explain to the Court the information that
8 you've highlighted here from the patent.

9 A. Yeah. I wanted to highlight the fact that there was
10 multiple examples that are being given for some of the various
11 constituents for both -- for the stabilizing agents as well as
12 the organic cosolvent.

13 Q. And what was the purpose of highlighting the language
14 in this passage "for example, for example, or a combination of,
15 maybe," then "maybe, for example."

16 A. Because it's not specific. It's open-ended, and it
17 allows numerous components to be considered at various
18 concentrations.

19 Q. Let's turn to Slide 49.

20 Dr. MacMichael, did you form an opinion regarding the
21 final *Wands* factor listed here, *Wands* Factor Number 1, the
22 quantity of experimentation necessary?

23 A. Yes, I did.

24 Q. And what was your conclusion with respect to *Wands*
25 Factor Number 1, the quantity of experimentation necessary?

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1 A. Although there would be a significant amount of
2 experimentation that would be needed, and the screen -- the
3 screening can be significant and the screening can be complex.

4 Q. Let's move on to Slide 50, please.

5 Dr. MacMichael, were you asked to provide an opinion
6 regarding the written description requirement as it applies to
7 the '865 patent?

8 A. Yes, I was.

9 Q. If we turn to Slide 51, I see here you have the legal
10 standard for a written description. I'll read that for you,
11 Dr. MacMichael.

12 "The patent must convey with reasonable clarity to
13 persons of ordinary skill in the art that, as of the filing
14 date, the inventor was in possession of the entire claimed
15 genus, not just a species of the genus."

16 Dr. MacMichael, is this the legal standard that you
17 applied in forming your opinion?

18 A. Yes, it is.

19 Q. Let me ask you the first question, Dr. MacMichael.

20 Does the '865 patent disclose a representative number
21 of species that fall within the scope of the claimed genus of
22 formulations covered by the '865 asserted claims?

23 A. No, it does not.

24 Q. How many species of the claimed genus are disclosed
25 in the '865 patent?

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1 A. I'm sorry. Please repeat your question.

2 Q. Sure.

3 How many species of the claimed genus are actually
4 disclosed in the '865 patent?

5 A. I'm trying to recall. The names are given, but not
6 the structural -- structure. So maybe if you could be a little
7 more precise with your question.

8 Q. Does the patent disclose a phosphate-buffered
9 sucrose-stabilized species?

10 A. Yes, it does.

11 Q. And does the patent disclose any other formulation
12 that does not use a phosphate buffer?

13 A. No, it does not.

14 Q. And I'll ask you the second question of the written
15 description legal inquiry.

16 Quote -- excuse me.

17 Does the '865 patent disclose structural features
18 common to the members of the genus so that a person of ordinary
19 skill in the art can visualize or recognize the members of the
20 genus of formulations?

21 A. No, it does not.

22 Q. If we turn to Slide 52 of slide deck DDX 8,
23 Dr. MacMichael, will you please provide the Court with a
24 summary of your opinions with regard to the written description
25 inquiry.

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1 A. My summaries are -- there's three points I'd like to
2 make.

3 One is every example has phosphate buffer or sucrose
4 stabilizer -- excuse me -- every example has phosphate buffer
5 and a sucrose stabilizer.

6 Q. And how many embodiments are within the possession of
7 the inventors of the '865 patent according to the '865
8 specification?

9 A. There's only one embodiment.

10 Q. And in your opinion, Dr. MacMichael, would a person
11 of ordinary skill in the art be able to visualize or recognize
12 any other members of the genus of formulations that's claimed
13 by the '865 patent?

14 A. No.

15 Q. If we turn to Slide 54, please.

16 THE COURT: Yes, counsel?

17 MR. BERL: I just want to note for the record that we
18 did not receive that slide that he just presented.

19 THE COURT: I'm sorry. Say that again.

20 MR. BERL: We did not receive the slide that he just
21 presented. The parties have been exchanging demonstratives,
22 objecting. We've all been playing by the rules, and I've never
23 seen that slide before.

24 MR. SALMEN: Your Honor, I can explain that.

25 Counsel for Regeneron objected to our original slides

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1 there; so we tried to pare those down in response to their
2 objections. And then we submitted them today.

3 THE COURT: Is the objection, Mr. Berl, to Slide 54?

4 MR. BERL: No. 52.

5 THE COURT: 52.

6 MR. BERL: They pared it down, I suppose, but they
7 had information there that wasn't on the slide originally, and
8 then they didn't send it to us after they changed it.

9 THE COURT: Understood.

10 We've run afoul of any number of agreements in the
11 parties' joint memo. With y'all going forward from here, it is
12 this Court's rule we're going to convene and conduct this trial
13 pursuant to the rules of civil procedure, rules of evidence.
14 Y'all can deal with the fallout of failing to comply and abide
15 by the agreements you reached and the trial had been.

16 The Court will overrule the objection and the
17 presentation of the slide with that noted.

18 MR. SALMEN: Thank you, Your Honor.

19 BY MR. SALMEN:

20 Q. If we turn to Slide 54, please.

21 Dr. MacMichael, were you asked to evaluate whether
22 the patent passes the test for indefiniteness?

23 A. Yes.

24 Q. And here on Slide 54, I see you have the
25 indefiniteness legal standard. I'll read that for you.

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1 "A patent is invalid for indefiniteness if it
2 claims -- if its claims" -- I'm sorry. Let me start over.

3 "A patent is invalid for indefiniteness if its claims
4 read in the light of the specification and the prosecution
5 history fail to inform with reasonable certainty those skilled
6 in the art about the scope of the invention."

7 Dr. MacMichael, is this the legal standard you
8 applied in evaluating the indefiniteness inquiry?

9 A. Yes.

10 Q. If we turn to Slide 54, please, Dr. MacMichael, what
11 conclusion did you reach regarding whether the asserted claims
12 of the '865 patent passed the test for indefiniteness?

13 A. Yes. They weren't -- the claims are indefinite.

14 Q. And what part of the asserted claims, in your
15 opinion, are indefinite?

16 A. Well, there's the term "suitable for intravitreal
17 administration." However, what's suitable for intravitreal
18 administration is undefined.

19 Q. Dr. MacMichael, does the patent specification provide
20 any guidance to a skilled person to understand what is
21 considered suitable for intravitreal administration under the
22 asserted patent claims?

23 A. No. There's no information on suitability.

24 Q. And, Dr. MacMichael, because the term is not defined,
25 would persons of ordinary skill in the art be able to identify

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1 a single interpretation of what it means to be suitable -- a
2 suitable formulation under the '865 patent?

3 A. Different POSAs approaching this could have
4 potentially different interpretations of what suitable means
5 and what's acceptable for the eye.

6 Q. Let's turn to Slide 57, please.

7 Dr. MacMichael, were you asked to evaluate the
8 written description requirement of the '572 patent? That's the
9 additional dosing patent that's been asserted against Mylan and
10 Biocon's BLA product.

11 A. Yes.

12 Q. And what conclusions did you reach regarding the
13 written description requirement of the dosing patent?

14 A. Yes. I highlight that it's an aqueous media for
15 injection. There are, for example, physiological saline and
16 isotonic solution.

17 Q. Dr. MacMichael, does the '572 patent disclose a
18 representative number of species falling within the scope of
19 the genus of isotonic solutions covered by Claim 6 which we
20 have at the top here as PTX 3?

21 A. No. It only gives one mention of isotonic solution.

22 Q. What is that one mention of an isotonic solution?

23 A. Yes. It's given on the physiological saline. And as
24 this paragraph shows, physiological saline is the isotonic
25 solution that's being highlighted.

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1 Q. Dr. MacMichael, does the '572 patent disclose
2 structural features common to the members of the genus of
3 isotonic solutions covered by Claim 6 so that a person of
4 ordinary skill in the art can visualize or recognize all of the
5 members of the genus of isotonic solutions?

6 A. No, it does not.

7 Q. If we turn to Slide 58, please.

8 Dr. MacMichael, were you asked to review and evaluate
9 certain Regeneron aflibercept patents?

10 A. Yes, I was.

11 Q. If we turn to Slide 59, please. Dr. MacMichael, I
12 see you have a table here on DDX 8, Slide 59. Will you please
13 identify the information that you're going to provide in these
14 columns.

15 A. Yes. I'll go across the headers. The first column
16 is the U.S. patent number. The second header is publication
17 date. The third is issue date. The fourth is expiration date,
18 and the fifth is summary of claims/disclosures.

19 Q. And, Dr. MacMichael, did you review and consider all
20 of the patents and corresponding publications listed in this
21 table?

22 A. Yes, I did.

23 Q. Let's go through these one by one, please. First, in
24 Row 1, the '959 patent, did you review that patent?

25 A. Yes, I did.

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1 Q. And did you form an opinion regarding -- excuse me.

2 Did you reach a conclusion as to when the information
3 provided in the '959 patent was first published?

4 A. Yes, I did.

5 Q. And what was that publication date?

6 A. December 14th, 2000.

7 Q. And did you obtain that information from the document
8 here, DTX 3619?

9 A. Yes.

10 Q. Did you review and consider that document?

11 A. Yes.

12 Q. And what was the summary of your review and analysis
13 of the '959 patent disclosures?

14 A. Yes. The '959 was -- pertained to the isolation of
15 the nucleic acids that actually coded for aflibercept. The
16 expression vectors used helped to assist with that expression
17 and met this for producing the VEGF Trap-Eye aflibercept.

18 Q. And based on your review and analysis of the '959
19 patent and its corresponding publication, would skilled persons
20 have been aware of the isolated nucleic acids expression
21 vectors and methods of producing VEGF Trap-Eye aflibercept as
22 of December 14th, 2000?

23 A. Yes.

24 Q. Moving on to the next one, Dr. MacMichael, the '746
25 patent, did you review and analyze the '746 patent?

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1 A. Yes, I did.

2 Q. And did you reach a conclusion as to when the
3 information provided in the '746 patent was first published?

4 A. Yes, I did.

5 Q. And did you obtain that information from DTX 4229?

6 A. Yes.

7 Q. What was the publication date of the information
8 provided in the '746 patent?

9 A. August 11th, 2005.

10 Q. Based on your review and analysis of the '746 patent
11 and its corresponding publication, what disclosures would have
12 been available to the skilled person as of August 11, 2005?

13 A. I'm sorry. Could you please repeat that. I didn't
14 track.

15 Q. Sure.

16 Did you provide a summary of the disclosures from the
17 '746 patent and its corresponding publication?

18 A. Yes.

19 Q. And what was the summary of the disclosures that you
20 concluded?

21 A. That the patent was a method of treating retinal
22 neovascularization.

23 Q. And did that method include the use and
24 administration of aflibercept?

25 A. Yes, it did.

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1 Q. So based on your review and analysis of the '746
2 patent and its corresponding publication, would a person of
3 ordinary skill in the art have known as of August 11th, 2005,
4 the method of treating retinal neovascularization with
5 aflibercept?

6 A. Yes.

7 Q. And turning to the next row on the table in Slide 59,
8 DDX 8, this is the '747 patent, Dr. MacMichael. Did you review
9 and analyze the '747 patent?

10 A. Yes, I did.

11 Q. And did you form a conclusion as to when the
12 information provided in the '747 patent was first published?

13 A. Yes, I did.

14 Q. What was that date?

15 A. February 9th, 2006.

16 Q. And did you obtain that information from DTX 8209?

17 A. Yes, I did.

18 Q. Did you review and analyze that document?

19 A. Yes, I did.

20 Q. And what summary did you reach with regard to the
21 disclosures of the '747 patent that would have been available
22 as of that publication?

23 A. It was a therapeutic method for treating an eye
24 disorder.

25 Q. And did that therapeutic method for treating an eye

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1 disorder disclosure include the use of aflibercept?

2 A. Yes, it did.

3 Q. Turning to the next row, the '799 patent, did you
4 review the '799 patent?

5 A. Yes, I did.

6 Q. Did you reach a conclusion as to when the information
7 disclosed in the '799 patent was first published?

8 A. Yes, I did.

9 Q. What was that date?

10 A. November 24th, 2005.

11 Q. Did you obtain that information from DTX 8208?

12 A. Yes.

13 Q. Did you review and analyze that document?

14 A. Yes, I did.

15 Q. And what summary did you reach regarding the
16 disclosures of the '799 patent and its corresponding
17 publication?

18 A. That it was a therapeutic method for treating an eye
19 disorder, including with aflibercept.

20 Q. If we turn to the next row, the '757 patent, did you
21 review and analyze the '757 patent?

22 A. Yes, I did.

23 Q. Did you reach a conclusion as to when the information
24 available in the '757 patent was first published?

25 A. Yes, I did.

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1 Q. What was that date?

2 A. July 28th, 2005.

3 Q. Did you obtain that information from DTX 8206?

4 A. Yes, I did.

5 Q. Did you review and analyze that document as well?

6 A. Yes, I did.

7 Q. And what conclusion did you reach regarding the
8 disclosure that was available via the '757 patent and its
9 corresponding publication as of July 28th, 2005?

10 A. Yes. The patent focuses on the VEGF Trap-Eye
11 aflibercept molecule and the nucleotide amino acid sequences
12 that produced the aflibercept product.

13 Q. Two more, Dr. MacMichael.

14 Looking at the second-to-last row, the '758 patent,
15 did you review and analyze that patent?

16 A. Yes, I did.

17 Q. And did you reach a conclusion as to when the
18 information available -- I'm sorry. Did you reach a conclusion
19 as to when the information provided in the '758 patent was
20 first published?

21 A. Yes.

22 Q. And what was that date?

23 A. November 3rd, 2005.

24 Q. And did you obtain that information from the
25 documents cited here, DTX 8207?

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1 A. Yes, I did.

2 Q. Did you review and analyze that document as well?

3 A. Yes, I did.

4 Q. And what conclusion did you reach regarding the scope
5 of the disclosure of the '758 patent and its corresponding 2005
6 publication?

7 A. That it was a method for inhibiting VEGF activity in
8 a mammal.

9 Q. Did that method of inhibiting VEGF activity in a
10 mammal include a disclosure of the aflibercept molecule?

11 A. Yes, it did.

12 Q. Last one, last row, the '173 patent, Dr. MacMichael,
13 did you review and analyze the '173 patent?

14 A. Yes, I did.

15 Q. And did you reach a conclusion as to when the
16 information provided in the '173 patent was first published?

17 A. Yes, I did.

18 Q. What was that date?

19 A. April 10th, 2008.

20 Q. And what conclusion did you reach regarding the
21 disclosures that were available to a skilled person as of
22 April 10th, 2008, based on the '173 patent?

23 A. Yes. It was a patent focused on the composition
24 comprising the VEGF Trap-Eye aflibercept molecule.

25 Q. Dr. MacMichael, one final point I wanted to ask, did

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1 you have an opportunity to review the animations and other
2 demonstratives that Dr. Trout presented to the Court during his
3 direct examination?

4 A. Yes, I did.

5 Q. And have you provided your own version of those
6 animations?

7 A. Yes, I did.

8 Q. Have you prepared a version of those animations?

9 A. Yes.

10 Q. Can you explain to the Court why you wanted to
11 provide your own version of those animations.

12 A. Yes. Though Dr. Trout's animation was helpful, I
13 thought it could be -- should be a little more realistic and
14 show a little more detail with respect to the overall size of
15 polysorbate with respect to the aflibercept molecule, and the
16 fact that the polysorbate acting as a surface-active agent
17 would have also coated the walls of the vial as well as the
18 exposed portion of the stopper that faces the liquid.

19 Q. Here on the screen?

20 A. I'm sorry. I misstated that. It would also coat the
21 stopper, but it would also protect inactivation at the
22 air-water interface. And that was not shown in the diagram
23 either.

24 Q. And I think we'll cover that in your version of the
25 animation, Dr. MacMichael. Can you please identify for the

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1 Court what we have on the screen here.

2 A. Yes. What we have on the screen is this is an
3 illustration of a vial containing aflibercept and
4 polysorbate 80.

5 Q. Is this Dr. Trout's version?

6 THE COURT: 20, Doctor? Polysorbate 20.

7 THE WITNESS: I'm sorry. Polysorbate 20. My
8 apologies.

9 THE COURT: Okay. Just making sure. Thank you.

10 BY MR. SALMEN:

11 Q. And if we proceed through this -- turn to the next
12 slide -- what do we have here?

13 A. Yes. We have illustrated the representations of a
14 polysorbate 20 molecule and an aflibercept molecule.

15 Q. Is the polysorbate 20 -- again, this is Dr. Trout's
16 characterization of the polysorbate 20 in the aflibercept?

17 A. Yes. And what Dr. Trout did was he showed where the
18 hydrophobic patches would be shown on the molecule itself are
19 highlighted in red as well as the hydrophobic tail of the
20 polysorbate is highlighted in red.

21 Q. And how did you want to modify this presentation that
22 Dr. Trout gave to the Court?

23 A. Just to show a little more realistic representation
24 of the size of the molecules and some of the additional
25 functionality of the surface-active agent of polysorbate 20.

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1 Q. And here on DDX 10, Slide Number 3, is this a
2 replication of one of Dr. Trout's slides, PDX 5004?

3 A. Yes, it is.

4 Q. Is this where you obtained the proportionality
5 between the polysorbate 20 and the aflibercept?

6 A. Yes, it is.

7 Q. And if we carry on to the next slide here, DDX 10-4,
8 can you please explain to the Court how you modified
9 Dr. Trout's explanation?

10 A. Yes. We replaced the original illustrations with the
11 previous -- the one from the previous slide which actually show
12 the molecular spinal structure of aflibercept.

13 Q. And we also have the molecular structure of
14 polysorbate here?

15 A. As well as polysorbate 20.

16 Q. And then how did we modify the animation in the box?

17 A. We basically replaced the illustrations of the
18 aflibercept and the polysorbate with the more representative
19 and more realistic size ratio using the electron cloud
20 structures of the aflibercept and polysorbate 20.

21 Q. Dr. MacMichael, did you review Dr. Trout's testimony
22 regarding these presentations?

23 A. Yes, I did.

24 Q. And what clarification did you want to make with
25 regard to the animated portion of Dr. Trout's presentation?

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1 A. Well, there's two things. One is these -- in
2 chemistry there can be chemical bonds that are called covalent
3 bonds, and it takes energy to break them. What we have here is
4 not a covalent interaction. It's called a hydrophobic
5 interaction. So the light likes to dissolve light. So the
6 hydrophobic portions of the molecule of the polysorbate are
7 being attracted to the hydrophobic portions of the aflibercept.

8 Q. Okay.

9 If we run the animation here, Mr. Gibson.

10 Can you explain to the Court what you've illustrated
11 here, Dr. MacMichael.

12 A. Yes. What we're showing is, though the aflibercept
13 binds hydrophobically to the hydrophobic patches -- I'm
14 sorry -- the polysorbate 20 binds to the hydrophobic patches of
15 the aflibercept, it can disassociate from those -- and then
16 reassociate to those hydrophobic patches of the aflibercept.

17 Q. Would you describe this as a static or a dynamic
18 environment?

19 A. It's dynamic.

20 Q. If we turn to the next slide here, were there any
21 additional clarifications that you wanted to make?

22 A. Yeah. I wanted to show that, in fact, the
23 polysorbate 20 puts a layer on the surface of the vial as well
24 as the surface of the stopper and at the surface area
25 interface.

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1 Q. And if we could run the animation here,
2 Dr. MacMichael, would you please explain to the Court.

3 A. Yes. What we're seeing here is that, by polysorbate
4 adhering to the walls of the vessel and at the air interface,
5 the hydrophobic portions of the polysorbate are interacting
6 with the surface of the vial and the hydrophilic -- or loves
7 water is what hydrophilic means -- is facing out into the
8 aqueous environment.

9 But the polysorbate is coating the walls of the
10 vessel and the stopper, preventing the aflibercept from
11 adhering to the wall. Though it's not absolute, some
12 aflibercept may -- the polysorbate can disassociate from the
13 wall and reassociate to the wall -- I'm sorry -- the
14 polysorbate can disassociate from the wall and reassociate to
15 the wall.

16 Q. And this is on Slide 15 and 16 of DDX 10.

17 Dr. MacMichael, any last clarifications to the
18 animations here?

19 A. Just that you also can see that it's protecting the
20 aflibercept from denaturation by putting a layer of polysorbate
21 at the air-liquid interface.

22 MR. SALMEN: Thank you, Dr. MacMichael.

23 Your Honor, at this time I pass the witness.

24 THE COURT: Understood.

25 Cross. Go right ahead, Counsel.

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1 CROSS-EXAMINATION

2 BY MR. BERL:

3 Q. Good afternoon, Dr. MacMichael.

4 A. Good afternoon, Mr. Berl.

5 Q. First of all, I hope you're having a speedy recovery
6 from your surgery.

7 A. Yes. Thank you.

8 Q. Doctor, you're not Mylan-Biocon's only formulation
9 expert on the '865 patent in this case, are you?

10 A. No.

11 Q. Dr. Rabinow also testified, correct?

12 A. Yes.

13 Q. And you've read Dr. Rabinow's expert report in this
14 case?

15 A. Yes.

16 Q. There's a section of your report entitled "State of
17 the Art," right?

18 A. Yes.

19 Q. And in that section you undertake an analysis of
20 scores of references, correct?

21 A. Correct.

22 Q. Including some of the references you discussed today,
23 right?

24 A. I'd have to -- yes.

25 Q. Now, Doctor, if we go to the first slide, there's a

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1 section of Dr. Rabinow's report that's also about the state of
2 the art, right?

3 A. Yes.

4 Q. And if we look here on the screen, page 12 of your
5 report is identical, virtually word for word, to page 19 of
6 Dr. Rabinow's report, right?

7 A. I would have to read through them and do a
8 comparative analysis; but for sake of time, I'll assume you're
9 making an accurate statement.

10 Q. Let's go to the next page. Page 13 of your report is
11 identical, word for word, with page 20 of Dr. Rabinow's report,
12 right?

13 A. I would have to read through them; but for today,
14 I'll assume that you're correct.

15 Q. Looks like it, right?

16 A. There seem to be similarities as I'm taking a very
17 quick look at it.

18 Q. And page 21 of Dr. Rabinow's report, if we go to the
19 next, is essentially identical to page 14 of your report,
20 right?

21 A. Again, I would have to read through it. High level,
22 just taking a quick look, there seems to be similarity.

23 Q. And, Doctor, the entire section, page after page
24 after page after page of your report, is identical word for
25 word with Dr. Rabinow's report, right?

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1 THE COURT: One second, Doctor.

2 Yes, Counsel?

3 MR. SALMEN: Object to that question, Your Honor.

4 He's already stated he would need to do a comparison of this.

5 That's quite a generalization to present to the doctor at this
6 time.

7 THE COURT: Why don't we go one at a time, Mr. Berl,
8 given that limitation. I mean, I don't have all the reports.
9 I've made that abundantly clear, but I understand the point
10 thus far. But I'm going to sustain the objection.

11 Ask your next question, sir.

12 BY MR. BERL:

13 Q. Doctor, are you aware of any differences of any words
14 of that long substantive section of your report compared to
15 Dr. Rabinow's?

16 MR. SALMEN: Same objection, Your Honor.

17 THE COURT: Overruled.

18 THE WITNESS: I would have to read through both
19 documents and do a comparative analysis.

20 BY MR. BERL:

21 Q. You don't deny, Dr. MacMichael, that there are other
22 substantive sections of your report that are identical to the
23 sections of Dr. Rabinow's report, right?

24 A. I would have to look at both reports and look at the
25 various sections. You just asked me I don't deny that they're

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1 identical. I would have to look at both reports.

2 Q. You read his report, right, Dr. MacMichael?

3 A. Yes.

4 Q. And you have no basis to tell me right now that there
5 are -- or to deny that there are large sections of the
6 report -- multiple sections of your report that are identical
7 to Dr. Rabinow's report, right?

8 A. I would have to read both reports and do a cross -- a
9 cross comparison of the two reports.

10 Q. Doctor, the first draft of your expert reports was
11 generated by the lawyers at RMMS, right?

12 A. No, it wasn't.

13 Q. The first draft of your expert report was not
14 generated by RMMS?

15 A. RMMS, using my opinions and my information, helped
16 write the report.

17 Q. Okay. So my question is really simple.

18 The first draft of your expert report was generated
19 by RMMS, correct?

20 A. They took my opinions and put them into the report.

21 Q. The final report was written by the RMMS attorneys
22 too, right?

23 A. With my opinions and input.

24 Q. But they wrote it, right?

25 A. If you mean wrote it by actually typing it up into

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1 the document, then the answer would be yes.

2 Q. The actual writing of your reports was performed by
3 an RMMS attorney actually writing the report, right?

4 A. With strong input from myself.

5 Q. Well, Doctor, all of the materials considered in
6 preparing your reports were provided for you by the lawyers at
7 RMMS, correct?

8 A. All the citations that are in these various documents
9 that were cited were also provided in our reading room.

10 Q. In fact, Doctor, at your deposition you weren't able
11 to point to a single section, paragraph, or even sentence of
12 your expert reports that you yourself wrote. Isn't that true?

13 A. During my deposition I can't recall that conversation
14 occurring.

15 Q. Do you deny that at your deposition you were unable
16 to point to a single section, paragraph, or even sentence of
17 your expert reports that you wrote?

18 A. I'll repeat it. That conversation, I don't recall.
19 So I can't deny it.

20 Q. Let's take a look at your deposition, Doctor, on
21 page 21. You recall that I deposed you just a few months ago,
22 right?

23 A. Yes.

24 Q. In Chicago. It was already spring and warm, right?

25 A. It was Easter.

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1 Q. Okay.

2 THE COURT: Doctor, if I could ask you -- I know
3 you're relying on that screen there, but if you wouldn't mind
4 adjusting that mic just to make sure everyone can hear you, in
5 particular Madam Court Reporter.

6 Thank you so much, sir.

7 I'm sorry, Mr. Berl. I think we were discussing the
8 weather in Chicago.

9 MR. BERL: Yes.

10 BY MR. BERL:

11 Q. We had a nice day inside while the sun was shining in
12 Chicago; is that right?

13 A. We had a day inside.

14 Q. I enjoyed a day inside.

15 THE COURT: It sounds like a lovely day. Let's get
16 to the substance of the matter.

17 MR. BERL: The court reporter did not enjoy it.

18 BY MR. BERL:

19 Q. Doctor, you were under oath through that day,
20 correct?

21 A. Yes, I was.

22 Q. And you were testifying truthfully that day?

23 A. Yes, I was.

24 Q. And let's put up page 21 of your deposition starting
25 on line 10 to page -- to line 16.

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1 Doctor, I asked you, "Can you point to any section,
2 paragraph, even sentence of your report and say that's my
3 writing? I wrote those words?"

4 "A No. But if given time, I'll walk
5 through here and show you the sections that are
6 in here that were my concepts that were then put
7 down by the RMMS attorneys into the document."

8 Did I ask you that question, and did you give that
9 answer, Doctor?

10 THE COURT: One second, Doctor.

11 Yes, Counsel?

12 Will you repeat that, Mr. Berl.

13 BY MR. BERL:

14 Q. Did I ask you that question and did you provide that
15 answer?

16 A. Well, if this is the written deposition, then I'm
17 going to have to say yes.

18 MR. SALMEN: I would just object to that as improper
19 impeachment. He stated in response to the first answer that he
20 didn't recall.

21 THE COURT: Understood. Overruled.

22 Mr. Berl.

23 MR. BERL: I'm moving to infringement now. I don't
24 think I'm going to get in for a while into the -- what's been
25 considered by Mylan to be highly confidential material. But I

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1 don't know what the witness is going to say in response to my
2 questions; so I'm not sure what to do. I'm fine proceeding
3 open. But if they want to close it, I have no objection.

4 THE COURT: Fair enough. But given the interest of a
5 free flow of exchange on cross, it seems that if -- we should
6 seal the courtroom out of abundance of caution unless Mylan has
7 an objection to that.

8 MR. SALMEN: No objection. That would be our
9 preference, Your Honor.

10 THE COURT: Understood.

11 Ladies and gentlemen, those of you who have been kind
12 enough to come and go, if I could ask you to go once again
13 given that we may get into some of the subject matter subject
14 to this Court's protective order. So if you're not permitted
15 to be here pursuant to that order, if I could ask you to step
16 out. Thank you all so very much.

17 I'll ask court security to seal our courtroom again.
18 Thank you.

19 (The following proceedings (1451/19 to 1480/8) were
20 had under seal, and are filed under separate cover.)
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(Record unsealed.)

THE COURT: Apologies. With my 7-year-old here, there was a line to my private restroom; so it took me longer to get here than I expected.

Mr. Berl, go right ahead.

BY MR. BERL:

Q. Doctor, I would like to discuss the effect of the word "comprising" in the claims which you addressed on direct, right?

A. Yes, I did.

Q. You're not a legal expert on the effect of the word "comprising," correct?

A. No, but I'm getting a lot smarter. You guys are advising me on this stuff.

Q. Someone is.

Doctor, in your view, because of the use of the word "comprising," there are a litany of compounds that could be added to the formulation, right?

A. That's the way I understand it.

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1 Q. For example, you could add hydrochloric acid which
2 would denature the protein?

3 A. Well, if you look at the claims, there's broad
4 categories that are being proposed and examples given for
5 comprised. There was no example of adding an acid to it.

6 Q. But your view is, as an example, you could add
7 hydrochloric acid in these claims and denature the protein,
8 right?

9 A. If you're adjusting the pH, you could, yeah.

10 Q. Okay. And in your view, the patent doesn't exclude
11 those kinds of inoperative embodiments, right?

12 A. Well, when you use the word "comprise," which then
13 opens -- very broadly opens up multiple potential compounds
14 that can be used, without experimentation, you could wind up
15 with a formulation that would be detrimental to the protein.

16 Q. Right. And you think the patent is not enabled
17 because it doesn't exclude those kinds of embodiments that will
18 work, right?

19 A. What I'm saying is that the claims using the term
20 "comprised" -- and they give examples, four, five, six examples
21 in each of the comprises -- that there's an inordinate number
22 of potential possible formulations. It would require
23 experimentation to determine the ideal formulation.

24 Q. Okay. Doctor, your enablement analysis is premised
25 on the scope or breadth of the claims as shown in Slide 44 that

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1 you showed, right?

2 A. I'm sorry.

3 Yes.

4 Q. And your Slide 44 suggests that the claims that are
5 asserted like Claim 4 are no narrower than Claim 1, right?

6 A. That's what we're graphically trying to show.

7 Q. Okay. But Claim 1 doesn't require 40 mg/mL of
8 aflibercept and Claim 4 does, right?

9 A. Claim 1 -- I'm sorry. Yeah. Claim 2 is dependent on
10 Claim 1, but -- yeah, you're right.

11 Q. And, likewise, Claim 1 doesn't require .03
12 to .1 percent polysorbate but Claim 4 does, right?

13 A. Yeah, I don't have Claim 1 memorized and it's not on
14 this graphic; so I don't want to answer from memory.

15 Q. Okay. But you understand that Claim 2 adds the
16 comprises polysorbate limitation, right?

17 A. Yes. But, again, I'd have to see the entirety, and
18 we're missing Claim 1. I apologize.

19 Q. Doctor, you know that Dr. Rabinow testified on
20 Friday, right?

21 A. That's what I was told, yes.

22 Q. And let's take a look at some of what he said if we
23 go to page 1164 of the transcript.

24 He was asked, "As of 2006, in your opinion,
25 optimizing the stability of a protein formulation was routine

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1 for the POSA?"

2 And he answered, "Yes."

3 Do you see that?

4 A. It's routine. Yes, I see it.

5 Q. Do you agree with Dr. Rabinow?

6 A. Routine in the fact that an organization -- a
7 biotechnology company or a biopharmaceutical company engaged in
8 developing multiple proteins would have a routine for how they
9 screen those products.

10 Q. So do you agree or do you not with Dr. Rabinow,
11 Doctor?

12 A. In general.

13 Q. In general yes?

14 A. Yes.

15 Q. And let's take a look at the next thing he said on
16 page 1168.

17 He was asked, "And it wouldn't require undue
18 experimentation to make formulations falling within the scope
19 of the asserted claims, right?"

20 And he answered, "Correct."

21 Do you agree with him?

22 A. "Undue" is a relative term. It would take a
23 significant amount of experimentation looking at all the
24 possible variables that are proposed in the claims to come up
25 with a formulation that is satisfactory; so I would say

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1 significant experimentation.

2 Q. Do you agree with Dr. Rabinow or do you disagree?

3 A. I'm saying it requires significant experimentation.

4 So undue experimentation, meaning that it's impossible? No.

5 But significant experimentation. So I guess with that nuance,

6 I'll agree with Dr. Rabinow.

7 Q. Okay. Well, I want to make sure I understand your

8 opinion.

9 You don't have an opinion in this case that making
10 the formulations to practice the claims that are asserted of
11 the '865 patent would be undue experimentation, right?

12 A. What I've said all along is it would take a
13 significant amount of experimentation.

14 Q. So you don't have an opinion -- you're not telling
15 the Court as an expert that it would require undue
16 experimentation, right?

17 A. Well, like I said, "undue" is a relative term. My
18 term "significant" really means a significant amount of work.

19 Q. I have a single question, Doctor. It's a yes or no.

20 Are you telling the Court that practicing claim --
21 the claims that are asserted in the '865 patent would require
22 undue experimentation, or are you not telling the Court that?

23 A. It would require undue experimentation. It would
24 require a significant amount of experimentation. That's my
25 testimony.

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1 Q. That's as far as you'll go, right?

2 A. Well, undue means an inordinate number of
3 experiments. But every organization that works in therapeutic
4 proteins has staff and equipment on board with the proper
5 resources to do that significant amount of work to develop the
6 formulations. So undue would mean something that is beyond the
7 realm of being able to be achieved.

8 Q. In your view, undue experimentation is a very
9 amorphous term, right?

10 A. It's left open to interpretation.

11 Q. Undue experimentation, as you've applied the phrase
12 in this case, depends on whether you're a big company or a
13 small company?

14 A. That's not what I said.

15 Q. Okay. Let's take a look at your deposition,
16 page 233, line 1. We'll go to line 11.

17 "Q Right. And why the experimentation to
18 fill in any gaps between the examples would not
19 be undue experimentation, that burden was on
20 Regeneron to show that?

21 "A Undue experimentation depends -- is a
22 very amorphous term. If I'm a little company,
23 undue; and if I'm a big company, it might not be
24 a big deal to run an inordinate number of
25 experiments. So the word "undue," let's take

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1 that out of it. Additional experiments."

2 Was that my question and was that your answer,
3 Doctor?

4 A. Yes. And I believe that you're citing this on this
5 slide. I believe that it agrees with the statement I just
6 made.

7 Q. Okay. Now, Doctor, you understand that the Court
8 here may have to decide whether the experimentation to practice
9 the claims is routine experimentation or undue experimentation,
10 right?

11 A. Yes. So what we're saying is that the patent fails
12 to give sufficient information on how to make the formulation;
13 so the patent in itself is indefinite. You have to go out and
14 do experiments to determine which of these various comprises,
15 various stabilizing agents, et cetera, would be acceptable in a
16 final formulation.

17 So as we've been saying for the last two or three
18 minutes, undue versus significant, these are relative terms.
19 It would take work.

20 Q. Okay. So it would take work, but you're not taking a
21 position on the question of whether that work would be undue or
22 routine, right?

23 A. The term "undue" is being -- you know, the term
24 "undue" means if the patent had been properly constructed and
25 gave information to the reader of how to actually develop the

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1 cited product in the patent, then it wouldn't require
2 significant experimentation. But the patent fails to do that.
3 And, therefore, significant experimentation would be required.

4 Q. Okay. Let me -- I'll give you one more chance to
5 answer the question, and then I'm going to move on.

6 If the Court has to decide between routine
7 experimentation and undue experimentation, you're not putting
8 your finger on the scale of undue experimentation, right?
9 You're not giving an opinion?

10 A. I'm saying -- you can use the word "undue," but
11 I'm -- it's undue because the patent wasn't properly
12 constructed. But a significant amount of work would have to be
13 done to do that work.

14 Q. Now, Doctor, your opinion is that "protein
15 formulations are routinely optimized to improve stability of
16 their active ingredients"?

17 A. Protein -- can you show me that quote.

18 Q. Sure. I'll read it again.

19 "Protein formulations are routinely optimized to
20 improve stability of their active ingredients."

21 A. Is that from one of my depositions or one article I
22 wrote?

23 Q. I'm asking whether you agree with that statement,
24 Doctor.

25 A. Could you repeat it one more time.

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1 Q. Sure.

2 "Protein formulations are routinely optimized to
3 improve stability of their active ingredients."

4 A. Yes.

5 Q. Okay. Now, you and Dr. Rabinow both relied on the
6 Kaisheva reference; isn't that right?

7 A. Yes. I read the Rabinow testimony, but I can't pull
8 out off the top of my head if he, in fact, looked at that
9 document.

10 Q. Okay. Let's take a look at what Dr. Rabinow said
11 about it. And that's on page 1020 of the transcript from last
12 week.

13 And he says, "Kaisheva provides a recipe for how you
14 go about developing protein formulations in terms of a
15 three-step process."

16 Is that right?

17 A. That's what it says.

18 Q. And you said essentially the same thing in your
19 expert report if we pull up paragraph 63 of your first expert
20 report. And you cite Kaisheva at the end of that paragraph.

21 Do you see that?

22 A. Yes.

23 Q. And it says, "The optimization process further
24 involves combining a therapeutic protein with excipients and
25 then varying the concentrations of the excipients. The

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1 formulation development approach is as follows: Selecting the
2 optimum solution pH, selecting buffer type and concentration,
3 evaluating the effect of various excipients of the liquid and
4 lyophilized stability, and optimizing the concentration of the
5 screened excipients."

6 That's your opinion, correct?

7 A. Yes. If I had a new protein coming over from
8 discovery that had not been properly formulated and we were
9 needing to get into animal studies and clinical trials, it
10 would require a series of activities to get that into a
11 successful formulation.

12 Q. But if you know the optimum pH, then you can take
13 that linear approach to select a buffer type and concentration,
14 then various other excipients, then optimize the concentration,
15 right?

16 A. And what -- these two sentences in this paragraph are
17 talking about is a significant amount of work. Now, that work
18 may be routine, meaning the formulation organization does that
19 work on a repeated basis, thus the term "routine." Let's not
20 take away the fact that it's a significant amount of work.

21 Q. Okay. In this case, Doctor, the patent already
22 discloses the optimum pH for aflibercept, 6.2 to 6.3, right?

23 A. So that's one point of the overall formulation. We
24 have the pH.

25 Q. You agree with me, right?

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1 A. I'd have to go back to the patent, but I do recall
2 that one of the formulations was at pH 6.2. But I don't want
3 to make a sweeping statement.

4 Q. Now, that information, as far as you know, was not
5 known before the '865 patent, correct?

6 A. The optimum -- the pI of aflibercept.

7 Q. The optimum pH formulations for aflibercept for
8 ophthalmologic administration, right?

9 A. I'd have to look at the sequence, go back and look at
10 the literature, but the pI, where the protein's neutral,
11 meaning it has the same positive and negative charge and there
12 it's neutral, that pI dictate what pH you want to hold it at.
13 And if I was to go back and search the literature, you're
14 asking me was there any previous art that showed aflibercept
15 had a pI that was acceptable at pH 6.2. I just don't have that
16 information in front of me.

17 Q. Okay. Doctor, in choosing excipients in that process
18 that we've just described from Kaisheva, the POSA would narrow
19 down choices on the basis of their knowledge from the
20 literature, right?

21 A. If they had a new novel protein coming in, this is
22 how they would approach it. But if they had a protein that had
23 a patent on it, one would expect that there would be more
24 guidance in that patent on how to actually do it without having
25 to go back and de novo do additional experiments to get to that

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1 final point.

2 Q. Okay. Doctor, you can't imagine a scenario where
3 someone would be working on products for helping with diseases
4 of the eye without referring to the previous literature, right?

5 A. I've never met a scientist that's developing
6 something that doesn't look at the previous literature.

7 Q. That would actually be irresponsible not to look at
8 the previous literature, including the prior products that have
9 been approved, right?

10 A. Well, yeah. I think the hypothetical, if one of my
11 formulation people came to me and said, hey, I didn't look at
12 anything; I'm just going to go ahead and start formulating, I'd
13 be a little uncomfortable with that answer. Well, have you
14 looked at other similar molecules and gotten some guidance on
15 what may be successful?

16 Q. And included within that literature that the POSA
17 would consult is information about what excipients have been
18 used in intravitreal products, right?

19 A. Yes.

20 Q. But in conducting your analysis in this case, you
21 didn't look at all the intravitreal products that FDA had
22 approved and look at all the formulations, right?

23 A. I looked at a majority of them. I can't recall if I
24 looked at every approved intravitreal eye formulation. I
25 cannot tell you that I have.

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1 Q. Doctor, in fact, other than Lucentis, you couldn't
2 identify any FDA-approved formulation that you looked at in
3 connection with your expert reports in this case, right?

4 A. I looked at Regeneron's product Eylea. I looked at
5 Lucentis.

6 Q. That's it, right?

7 A. Those were two that I looked at, yes.

8 Q. And neither one of those was approved as of the
9 priority date in the middle of 2006, right?

10 A. I'd have to go back and look at the approval dates,
11 et cetera.

12 Q. Doctor, the POSA engaging in experimentation to
13 practice the claim would not make formulations at random,
14 right?

15 A. Any good formulation scientist would be a POSA,
16 according to either Dr. Trout's or my definition, would have --
17 you know, in either of our definitions, such a POSA that would
18 be working in your formulation group would at least have some
19 sense of what excipients to use.

20 I believe that was your question.

21 Q. And they wouldn't make formulations at random, right?

22 A. They would do it in a logical manner.

23 Q. And if you've worked in proteins, you'll have a good
24 understanding of what excipients have been used successfully
25 and what buffers have been used successfully, right?

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1 A. Yes. Yes.

2 Q. Doctor, in the patent, the '865 patent, there are no
3 new classes of excipients, right?

4 A. Everything in that patent is -- all the compounds
5 cited in the patent are known molecules. There's no novel new
6 molecule being introduced.

7 Is that your question? I'm not sure.

8 Q. Yeah, they're pretty much all household names in
9 excipients and stabilizers, right?

10 A. Yes, they are.

11 Q. Now, I'd like to talk about choosing a buffer, which
12 you address.

13 Another consideration for formulating to avoid
14 aggregation is the choice of a buffer to keep the formulation
15 within the narrow pH range to keep your formulation stable,
16 right?

17 A. Ideally you want to keep it in a narrow pH range. If
18 you go too basic or too acidic, you can get undesirable changes
19 in the charge of the molecule and undesirable interactions.

20 Q. And various buffers are available to adjust the pH
21 of protein formulations?

22 A. There's multiple compounds out there that can be used
23 as a buffering agent.

24 Q. And, typically, you pick a range for a buffer that's
25 applicable to the pH you're trying to achieve?

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1 A. Yes. What you look at, again, is what they call the
2 pI. That's where the neutral pH of a protein is. Where is
3 it neutral? And from that, you pick a candidate buffer that
4 would then be where the pI of that protein would fall within
5 the range of that buffer.

6 Q. And the POSA reading the claims and the specification
7 would have considered four buffers as suitable for formulations
8 of the asserted claims: succinate, citrate, phosphate, and
9 histidine. Right?

10 A. There's other buffers out there that could have been
11 considered.

12 Q. But those are the ones that the person of skill
13 reading the patent would want to use, correct?

14 A. You can pull up the claims so I can read it because
15 it comprised those, but I believe it was open-ended.

16 Q. My question is those are the four buffers that the
17 POSA practicing the claim would want to use, correct?

18 A. Those were examples that were given by the author.
19 They are buffers that could potentially be used.

20 Q. Those are the ones that the POSA would want to use,
21 correct?

22 A. Those are four examples that were used by the authors
23 to give examples of the other potential buffers that could be
24 used. The word "comprised" means that many other buffers could
25 be considered as well.

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1 Q. To choose a buffer, you would look at the prior art
2 for which buffers were used successfully in previous products
3 for injection into the eye, right?

4 A. That would be a useful guidepost.

5 Q. And that can narrow down the overall number of
6 candidates you need to screen?

7 A. It can if you say such and such buffer was used in an
8 approved product by the FDA; therefore, there's precedent for
9 that buffer being previously used in an intravitreal
10 application.

11 Q. But you never undertook that analysis to look at
12 prior products, correct?

13 A. I didn't look at all the prior products.

14 Q. And with respect to a stabilizing agent, Doctor,
15 considerations for formulating a protein to avoid aggregation
16 typically include a choice of a stabilizing agent, right?

17 A. Yeah, if you're reading off of a document, it would
18 be very helpful if you could share it up on the screen. Is
19 that possible?

20 Q. Doctor, I'm asking you a question whether you agree
21 or not. Considerations for formulating a protein to avoid
22 aggregation typically include a choice of a stabilizing agent,
23 right?

24 A. Is that a quote from my deposition?

25 Q. I just want an answer to my question, Doctor.

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1 A. Say it again, please.

2 Q. Yes.

3 Considerations for formulating a protein to avoid
4 aggregation typically include a choice of a stabilizing agent,
5 right?

6 A. It can require a stabilizing agent. Depending on
7 whether it's a liquid or a lyophilized formulation, you may use
8 certain sugars that you might not use in a liquid formulation.

9 Q. The patent says the stabilizing agent may be sucrose,
10 sorbitol, glycerol, trehalose, or mannitol, right?

11 A. That's not what it says. It says "comprises," and it
12 gives examples of those sugars.

13 Q. Doctor, those are the examples of sugars -- or of
14 stabilizing agents provided in the patent, right?

15 A. Those were examples that were provided in the patent
16 under the word "comprises," meaning that any other sugar could
17 be considered as well as a stabilizing agent.

18 Q. Doctor, all five of those options were well-known
19 stabilizing agents?

20 A. They were known to be stabilizing agents.

21 Q. If one was developing a formulation, one would screen
22 those stabilizing agents and see which one gave the overall
23 satisfactory performance, right?

24 A. If those were the five I wanted to look at, I would
25 screen those five.

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1 Q. Now, you also reference in your slides -- so I don't
2 think you actually talked about it today -- something called
3 formulation design systems, right?

4 A. Are you talking about factorial design?

5 Q. A formulation design system. You know, something
6 called DOE or --

7 A. Design of -- yes, there's a book out there that I
8 wrote for cell gene therapy called *Aging* that describes the use
9 and the design of experiments.

10 Q. Through the design of experiments, or DOE, the whole
11 purpose is to minimize the amount of testing you have to do,
12 right?

13 A. Yes. Because if we were to run the hypothetical
14 amount of experiments that would have to be ran if you were to
15 make each individual formulation, it would be an inordinate
16 number.

17 Q. You yourself have either done or supervised design of
18 experiments going all the way back to 1990, right?

19 A. Yes.

20 Q. And the bottom line for design of experiments is you
21 look at multiple variables, like what excipients and what
22 buffers, and using various software out there, you can actually
23 achieve a screening of what is successful and not successful,
24 correct?

25 A. Yes. If I could explain to the Court what a design

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1 of experiment is and how it's used, it might be helpful.

2 THE COURT: Go ahead, doctor.

3 THE WITNESS: Yes. A design of experiment you have,
4 Your Honor, have you in a numerous number of variables. And in
5 a traditional manner, you would only -- you would hold
6 everything constant but one variable and then change that
7 variable to see how it influences the outcome.

8 In a design of experiment, you can change multiple
9 variables, two or three, and then look at the results. And
10 there's software out there. There's one very popular one
11 called JNT, J-N-T, that lets you look at the results. And,
12 therefore, you can then sift through more results quicker and
13 have more variables in play rather than looking at one at a
14 time.

15 I believe, Mr. Berl, that's what you're referring to.

16 BY MR. BERL:

17 Q. Yes, it is. Thank you for the explanation,
18 Dr. MacMichael.

19 DOE is an intelligent technique to use to minimize
20 the amount of screening that's necessary?

21 A. Yes. It reduces -- it doesn't reduce the number of
22 candidates; it reduces the amount of work.

23 Q. It will exclude things that don't work?

24 A. Yes. The results will show which variables are not
25 getting you to the desired outcome.

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1 Q. And so using design of experiments, you wouldn't have
2 to make every formulation, right?

3 A. That's correct.

4 Q. And anybody in the street knows that DOE is what
5 everybody does?

6 A. Everybody on the street -- I don't know about
7 everybody; but yes, scientists would know that a DOE can be
8 used to effectively reduce the number of variables that have to
9 be looked at in an actual physical wet chemistry lab.

10 Q. The POSA would conduct the design of experiments,
11 right?

12 A. The POSA could do a design of experiment.

13 Q. And, Doctor, you couldn't tell me at your deposition
14 how many formulations the POSA would have to make to practice
15 the claim using design of experiments, correct?

16 A. Yeah, because you -- and I couldn't answer that
17 today. I'd have to sit down, design the experiments, and look
18 at the number of components -- both the stabilizing agent, the
19 surfactants, et cetera -- and design that and look at which
20 variables I wanted to look at and how I wanted to vary those
21 variables.

22 Q. All you could say at your deposition was that with
23 design of experiments, the POSA would have to conduct multiple
24 experiments. You couldn't give any more specificity than that,
25 right?

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1 A. And I just gave a little more specificity, yes.

2 Q. Not much, right? You don't have a number for me, do
3 you, in terms of how many experiments the POSA would have to
4 conduct?

5 THE COURT: One second, Doctor.

6 Yes, Counsel?

7 MR. SALMEN: Objection, Your Honor. He answered the
8 question, and it was consistent with his testimony at his
9 deposition.

10 THE COURT: Overruled.

11 Ask your question again, Mr. Berl.

12 BY MR. BERL:

13 Q. You don't have a number for me or for the Court today
14 about how many experiments a POSA would have to conduct to
15 practice the claims using a design of experiments, do you?

16 A. It's a large number. If I took six to seven
17 stabilizers and I took three to five surfactants, et cetera,
18 and I moved that down and multiplied it through, very quickly
19 you get to a very large number.

20 Q. With design of experiments you don't have a number of
21 how many experiments the POSA would have to conduct to practice
22 the claims, do you?

23 A. Well, I just explained to you, you're asking me to,
24 off the top of my head, tell you I was going to design a
25 complex experiment with five to six variables with multiple

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1 candidates in each variable and that you would have to sit down
2 and intelligently design that experiment to determine which
3 variables you wanted to change in each experiment.

4 Q. You haven't undertaken that analysis in this case,
5 right?

6 A. We've looked at some hypotheticals. I was just going
7 to say, hypothetically, you would come to a very large number.

8 Q. But with design of experiments, the number is
9 smaller, and you have not provided a number about how many
10 experiments the POSA would have to conduct with design of
11 experiments, correct?

12 A. As I've explained three times -- I'll explain
13 again -- I would have to sit down and look -- remember, they
14 say comprised; so it isn't just glucose, sucrose, and mannitol;
15 it could be glucose, sucrose, mannitol, galactose, et cetera,
16 because it says "comprises." So the question is how broad am I
17 going on all the various claims that use the term "comprised"?
18 I could -- not just the examples given. Those are just
19 examples. I could wind up with an inordinate number.

20 Q. Doctor, you didn't consider any studies Regeneron did
21 other than those described in the '865 patent, right?

22 A. I did not have access to all the experiments that
23 Regeneron did.

24 Q. You never asked your counsel whether there was SEC
25 data for formulations that met requirements of the claim that

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1 you didn't have already in the patent, right?

2 A. I don't recall.

3 Q. Doctor, you did look instead, when you talked today,
4 about various statements and file histories, correct?

5 A. Various statements and file histories?

6 Q. Do you remember you presented that earlier today?

7 A. Yes.

8 Q. Okay. Let's look at your Slide 47. You relied there
9 on a statement from --

10 THE COURT: One second, Mr. Berl.

11 Go ahead.

12 BY MR. BERL:

13 Q. You relied here, Doctor, in DTX 5053 on a statement
14 from a different file history, not the file history of the
15 '865 patent, right?

16 A. These are two documents that were cited on the --
17 looking at the *Wands* factors and looking on whether or not it
18 would take undue experimentation. And there's two citations
19 here.

20 Q. My question is, Doctor, that first citation, 5053, is
21 from the prosecution history of a different patent, not the
22 '865 patent, right?

23 A. I'll take your word for it.

24 Q. Okay. It's not even in the same family as the '865
25 patent, right?

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1 A. I don't understand where you're heading with the
2 question. I'd love to answer it, but I'm not quite sure what
3 you're looking for.

4 Q. Okay. Doctor, you showed a statement on the screen
5 here that one of ordinary skill upon reading Remington's would
6 expect to engage -- would expect to engage in significant
7 nonroutine experimentation to develop a successful formulation
8 as claimed herein.

9 Is that what you showed?

10 A. That's what I showed.

11 Q. Now, Remington's is not the '865 patent, right?

12 A. No, it's not the '865 patent.

13 Q. Remington's does not disclose ophthalmologic
14 formulations of aflibercept, right?

15 A. I can't recall all the content of the Remington
16 article.

17 Q. As far as you know, Remington's does not disclose the
18 optimal pH range for ophthalmologic formulations of
19 aflibercept, right?

20 A. Off the top of my head, I can't recall that that
21 document cites that, no.

22 Q. Now, Doctor, you also cite in the second part of this
23 slide a statement from DTX 4430 that formulations of
24 pharmaceutical preparations and achieving a stable composition
25 is not a simple or routine matter. Is that right?

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1 A. That's what it says.

2 Q. And you cited that from paragraph 10 of 4430, right?

3 A. 4430, page 003. I'm not sure -- it's enumerated 10,
4 yes.

5 Q. Okay.

6 Can we pull up the entirety of paragraph 10 rather
7 than the expurgated version that was presented by
8 Dr. MacMichael.

9 Do you see -- you showed the Court the first sentence
10 of paragraph 10; is that right?

11 A. I showed the first sentence of that paragraph.

12 Q. And in the last sentence it says, "I am familiar with
13 these literature articles, all in peer-review journals, which
14 indicate that arriving at a stable formulation is not a
15 straightforward matter, and it is not, for instance, possible
16 to apply a formulation for one drug to another."

17 Do you see that?

18 A. Yes.

19 Q. And in practicing the '865 patent, the POSA wouldn't
20 have to go from one drug in the specification to another in the
21 claims. It's aflibercept in the specification and aflibercept
22 in the claims, right?

23 A. Yes. But I'm not quite sure what the question is.

24 Q. Okay. You answered it.

25 Doctor, you understand that Mylan conducted research

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1 in connection with its 40 mg/mL aflibercept formulation, right?

2 A. Yes.

3 Q. And you never investigated how much research was
4 required for Mylan with the '865 patent in hand to make
5 formulations within the scope of the claim, right?

6 A. I read through their formulation development history
7 report. It was a significant amount of work that was required.

8 Q. Well, you never had any conversation with Mylan
9 personnel about the research, correct?

10 A. I did not interact with Mylan personnel.

11 Q. You never had conversations with the RMMS attorneys
12 about Mylan's research, correct?

13 A. No. We reviewed the development and history report
14 together and went through the content and discussed the
15 meanings of the results.

16 Q. Well, you never asked the attorneys to show you the
17 experimentation performed by Mylan, did you?

18 THE COURT: One second.

19 Yes, Counsel?

20 MR. SALMEN: I would object that this is getting into
21 attorney work product. I mean, I don't understand the basis
22 for this question.

23 THE COURT: I think --

24 MR. SALMEN: What information he's asking of his
25 attorneys.

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1 THE COURT: Understood.

2 Mr. Berl?

3 MR. BERL: First of all, it's not privileged. But
4 second of all, if it were, it's waived because this is right
5 from his deposition.

6 THE COURT: Yeah, I don't believe there is any
7 privilege. He's already testified about it here today, and
8 we've heard from the deposition. I believe it's relevant, as
9 it probes the bases for the doctor's opinions in this case.

10 Objection overruled.

11 BY MR. BERL:

12 Q. Doctor, you never asked the attorneys to show you the
13 experimentation performed by Mylan, correct?

14 A. I was given the Mylan development history report; I
15 didn't have to ask for it. And I read through it, and we had
16 extensive discussions with the attorneys on the content and how
17 the results could be interpreted.

18 Q. Doctor, you assumed that the Mylan attorneys would
19 have access to additional information that you didn't have,
20 right?

21 A. My assumption is yes, they have additional
22 information I'm not privy to.

23 Q. And you believe that the Mylan -- that the research
24 Mylan conducted to obtain its proposed aflibercept formulation
25 was relevant to the analysis you were conducting in this case,

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1 right?

2 A. It had some relevancy to it, yes.

3 Q. And you agree that it would be useful?

4 A. The data would be useful.

5 Q. And in retrospect, it would have been beneficial to
6 look at that, right?

7 A. I'm sorry. I did look at it. I don't understand
8 what you're saying. I did look at it.

9 Q. Okay.

10 Let's take a look at the doctor's deposition again.
11 And let's take a look at page 335. Let's start at line 6, go
12 to line 14.

13 "Q Yeah, the research that Mylan conducted
14 to obtain its proposed aflibercept formulation of
15 40 mg/mL, did you think that was relevant to the
16 analysis you were conducting in this case or not
17 relevant?

18 "A It has relevancy. It would be useful.

19 "Q It would be --

20 "A In retrospect, would it be beneficial
21 to take a look at that? Sure."

22 Were those my questions and were those your answers,
23 Doctor?

24 A. They look familiar, yes, they do, Mr. Berl.

25 Q. If you could go back in time and ask Mylan's

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1 attorneys whether they had additional information about Mylan's
2 research that led to their proposed aflibercept formulation,
3 maybe you would do that, right?

4 A. I have done that, and I have read through the
5 development history report multiple times and discussed it at
6 length with the RMMS attorneys.

7 Q. Doctor, turning to a separate topic, you didn't
8 identify today any particular formulation that would require
9 undue experimentation to make, correct?

10 A. As opposed to what? With respect to aflibercept or
11 any hypothetical protein or --

12 Q. Within the claims. You didn't identify a formulation
13 that has the ingredients of the claim that would require undue
14 experimentation to make, did you?

15 A. All of those examples are examples. So what we have
16 is maybe 12 recipes making a cake, but you're not telling me
17 how to go about making that cake.

18 Q. Okay. I have a simple question, Doctor.

19 Did you identify -- because I didn't hear it, but
20 tell me if I missed it.

21 Did you identify any particular formulation that has
22 the ingredients required by the claims that, in your view,
23 would require undue experimentation to make?

24 A. If you're asking me just to make that formulation?
25 Is that the question?

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1 Q. Yes, Doctor.

2 A. Well, how -- making it and how -- ensuring its
3 stability takes experimentation. I'm not following you.

4 Q. Okay. Doctor, Claim 1 requires a buffer, correct?

5 A. Claim 1 requires a buffer.

6 Is it possible to put the claims up on the screen?

7 Q. Sure. Let me put up the claim that has 1, 2, and 4
8 together.

9 There you go, Doctor.

10 A. Yes. Thank you.

11 Q. Claim 1 requires a buffer, correct?

12 A. Yes.

13 Q. And buffers refer to a known set of structures,
14 right?

15 A. There's various types of buffers out there, and
16 there's various categories of buffers. There's not one
17 specific category of buffers.

18 Q. Let me try it again.

19 Buffers refers to a known set of structures, right,
20 Doctor?

21 A. No. There's multiple -- there's various types of
22 molecules out there that can function as buffers.

23 Q. Okay. Let's go to the doctor's deposition again at
24 page 428, line 20. Go into 429, line 3.

25 Doctor, I asked you:

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1 "Q And I think we've talked about these
2 before, but that was a known set of structures,
3 buffers, right?

4 "A Uh-huh.

5 "Q Yes?

6 "A Yes."

7 Were those my questions and were those your answers,
8 Doctor?

9 A. Yes, they were.

10 Q. Okay. And Claim 1 requires a stabilizing agent,
11 correct?

12 A. Are we going to put the claims back up on the screen?

13 Q. We'll try to do that.

14 You know that Claim 1 requires -- the claims require
15 a stabilizing agent, right, Doctor?

16 A. It states that Claim 1 requires a stabilizing agent.

17 Q. And that's a known set of structures too, right?

18 A. When you say a known set of structures, when you give
19 a specific example, a POSA would know the structure that --
20 when you start talking about various categories, you have to
21 give examples of what those might be.

22 So your question was a buffer is a known set of
23 structures. A buffer is a term that can encompass multiple
24 types of molecules; so maybe -- does the word "buffer" give me
25 the structures? The answer is no.

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1 Q. Doctor, I'm asking about the stabilizing agent now.
2 We're past buffers. My question is simple.

3 Stabilizing agent is a known set of structures,
4 right?

5 A. There's multiple molecules that can be used as
6 stabilizing agent. Stabilizing agent is very broad. Sugars
7 are stabilizing agents. Surfactants are stabilizing agents.

8 Q. Is that a known set of structures, Doctor, or not?

9 A. There's multiple sets of structures.

10 Q. So no or yes?

11 A. What I'm saying is this patent fails to define what
12 all the potential structures are.

13 Q. Okay.

14 Let's take a look at the doctor's deposition again,
15 right after where we were, page 429, line 4 down to line 11.

16 "Q Claim 1 requires a stabilizing agent,
17 correct?

18 "A Yes, it does.

19 "Q That's a known set of structures too?

20 "A Well -- I'm going down looking at
21 dependent claims. Yes, it does."

22 Were those my questions and were those your answers?

23 A. Those were my answers.

24 Q. Doctor, Claim 1 recites various structural
25 requirements with respect to both the active ingredient and

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1 with respect to excipients.

2 A. I'm sorry. Where are we --

3 Q. Claim 1, Doctor, recites various structural
4 requirements with respect to both the active ingredient and
5 with respect to the excipients, correct?

6 A. I'm getting lost in your question, Mr. Berl.

7 Q. Okay. Here it is. I'll try to do it slow.

8 Claim 1 recites various structural requirements with
9 respect to both the active ingredient and with respect to the
10 excipients, right?

11 A. Are you reading the claims or is this your statement?

12 Q. That's my question.

13 A. Could you repeat it, please.

14 Q. Yes.

15 Claim 1 recites various structural requirements with
16 respect to both the active ingredient and with respect to the
17 excipients?

18 A. Does it require -- yes.

19 Q. If those structural requirements are met, one is --
20 well, sorry.

21 If those structural requirements are not met, one is
22 not within the scope of the claims, right?

23 A. I'm not aware, but that's my understanding.

24 Q. Okay. So each formulation, to your understanding, in
25 order to be within the genus of formulations of Claim 1, must

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1 meet every structural requirement of Claim 1, the organic
2 cosolvent, the buffer, the stabilizing agent, and the VEGF
3 antagonist fusion protein with a particular sequence, right?

4 A. Your question was it has to meet all of the criteria
5 in Claim 1? Was that your question?

6 Q. Yes.

7 A. The answer is yes.

8 Q. So all of the formulations within Claim 1 have those
9 structural features, correct?

10 A. No.

11 Q. Okay. Doctor, you talked about the '572 patent for a
12 moment. You have one slide on that, I believe. It's Slide 57.

13 Can we put that up.

14 Now, you understand that the '572 patent priority
15 date is several years after the priority date of the '865
16 patent, right?

17 A. Yes, I do.

18 Q. And the POSA practicing the claims of the '572 patent
19 would not make a new formulation, right; they'd use an existing
20 formulation?

21 A. I cannot read the minds of the inventors, but I'll
22 follow your train of thought.

23 Q. By 2011 many aflibercept formulations were known,
24 right?

25 A. Yes. But you're referring to a patent that obviously

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1 had done some variations; so I'm not quite sure where you're
2 heading.

3 Q. You think the '572 patent had made new formulations?

4 A. No. I'd have to pull up the '572 patent and look at
5 it to be able to follow your question.

6 Q. Okay. Doctor, you agree that as of 2011 there were
7 formulations of aflibercept known that the person of skill
8 practicing the '572 patent would use, right?

9 A. As of?

10 Q. 2011 or 2013.

11 A. And if they did have to use what? The '865 patent or
12 the '572?

13 Q. Sure. They could use the '865 patent.

14 A. The '865 is patent is not enabled; so they wouldn't
15 know how to make those buffers.

16 Q. So you don't think that the person of skill could
17 have used the formulations from the '865 patent in practicing
18 the '572 patent?

19 A. They could with a significant amount of work and
20 effort and studies and screening.

21 Q. You haven't asserted that the Dix patent is not
22 enabled, have you?

23 A. Well, let's pull -- I'm not sure -- which Dix patent
24 are you referring to? Doesn't Dix have multiple patents?

25 Q. The Dix '226 patent that you addressed thoroughly in

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1 your expert report. You don't think that's not enabled, do
2 you?

3 THE COURT: One second.

4 Yes, Counsel?

5 MR. SALMEN: Objection, Your Honor. It's outside the
6 scope of his direct examination.

7 THE COURT: How is this now -- Mr. Berl, how are we
8 within the scope of his direct?

9 MR. BERL: Because he opined about how the person of
10 skill would practice this -- the Claim 6 of the '572 patent.
11 And he says it would be really hard. It doesn't disclose
12 anything. And I'm exploring what the person of skill actually
13 would have done.

14 THE COURT: Overruled.

15 THE WITNESS: I don't have the '572 patent in front
16 of me; so I'm not going to address the specific detailed
17 content unless we can -- if you have specifics you want to pull
18 up.

19 Can you rephrase your question again.

20 BY MR. BERL:

21 Q. Sure.

22 A. I'm trying to answer your question, but I just want
23 to get a little more --

24 Q. I think I asked you whether the person of skill
25 practicing the '572 patent would use the '865 patent

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1 formulations which have been published by that point. And you
2 said no because they're not enabled.

3 Are we with each other so far?

4 A. What I said is -- you said, well, they can just use
5 one of the buffers in the '865 patent. And I said no, they're
6 not enabled.

7 Q. That's not what I said, but let me try it again to
8 make sure we're on the same page.

9 A. Let's try it again.

10 Q. In your view, would the person of skill practicing
11 the '572 patent in 2011 or 2013 use as an ophthalmologic
12 formulation the formulations disclosed in the '865 patent which
13 had published by that time?

14 A. They may have. I don't know that they would have,
15 but they would certainly -- especially because the patents were
16 issued to the same company, one would expect that they were
17 using it at least as a reference document.

18 Q. And they could use the Dix patent too which was also
19 issued to the same company, Regeneron, correct?

20 A. Yeah. One would expect, with the normal business
21 practice, to be referring to your own internal prior art.

22 Q. And it's not your view that the POSA would have had a
23 preference for one of those formulations from the '865 patent
24 or the Dix patent over the others in practicing the '865
25 patent, right?

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1 A. I would expect that Regeneron personnel might have
2 had some preferences. But you're asking me to ask if a
3 hypothetical POSA would have a preferred buffer? I can't
4 answer what the hypothetical POSA would want.

5 Q. So you have no -- as someone who opined on the '572
6 patent as to what formulation in 2011 the POSA would have
7 wanted to use for treating ophthalmic diseases using
8 aflibercept, right?

9 A. Well, yes. What we're highlighting here is one of --
10 they're called the quantity attributes of the final product.
11 One of the characteristics. Yes, you'd want an isotonic
12 solution that's physiological with respect to the eye.

13 Q. Let me try that question again.

14 Do you have an opinion about whether the POSA would
15 prefer one formulation in the prior art, such as Dix, or a
16 different formulation, such as one of the '865 formulations?

17 THE COURT: One second.

18 Yes?

19 MR. SALMEN: Your Honor, I'd just renew my objection.
20 This goes to the obviousness analysis. And Dr. MacMichael had
21 testified here with regard to a written description of the '572
22 patent, but we're going way far afield of any opinion that was
23 disclosed in his reports or during direct examination.

24 MR. BERL: I disagree. He's talking about how the
25 person of skill would practice this. He says basically the

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1 person of skill could practice this. I don't see how they
2 would.

3 THE COURT: And I disagree.

4 Sustained.

5 BY MR. BERL:

6 Q. Now, Doctor, let me ask you about one final topic,
7 which is indefiniteness.

8 A. May I correct your inaccurate quote of what I said?

9 Q. No.

10 THE COURT: No. I sustained the objection, Doctor.
11 So moving forward.

12 BY MR. BERL:

13 Q. Finally, I want to address indefiniteness.

14 You're not an expert about the medical aspect of
15 whether something is suitable for intravitreal administration,
16 correct?

17 A. I am a development and manufacturing expert. I do
18 work very closely with colleagues that are physicians. And so
19 I do have an understanding of what's acceptable from working
20 with physicians and regulatory and quality members. You're
21 never an individual working alone; you're working with a team.

22 Q. Right. But you on your own don't have that knowledge
23 of what excipients or what formulations would be suitable for
24 intravitreal administration, right?

25 A. I am not an ophthalmologist.

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1 Q. And you on your own don't have that knowledge of what
2 excipients or what formulations would be suitable for
3 intravitreal administration, right?

4 A. I have a working knowledge of what excipients and
5 which buffers, et cetera, are acceptable in the human body from
6 all the multiple products I've developed over my career.

7 Q. I'm asking about intravitreal formulations, Doctor.
8 Let me try it one more time.

9 You on your own don't have that knowledge of what
10 excipients or what formulations would be suitable for
11 intravitreal administration, right?

12 A. It's available in the literature.

13 Q. But you would -- you said at your deposition you
14 would consult other people on a team who have that expertise,
15 like ophthalmologists?

16 A. Yes. That's what I just said.

17 Q. Okay. But you didn't consult with an ophthalmologist
18 in preparing your expert reports as to the '865 patent, right?

19 A. No, I didn't consult with an ophthalmologist.

20 Q. And you didn't consult with a toxicologist?

21 A. No, I did not consult with a toxicologist.

22 Q. You didn't interact or consult with anyone other than
23 the attorneys in connection with your opinions in this case,
24 right?

25 A. I was asked questions that were related to my

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1 background and expertise in how to manufacture and formulate
2 drug products.

3 Q. You understand, Doctor, that the issue of
4 indefiniteness is whether the POSA would understand the scope
5 of the claims, right?

6 A. Yes.

7 Q. And the POSA would understand the scope of the '865
8 patent claims, right?

9 A. They would understand that they're very broad and
10 open, using the term "comprised" in multiple claims.

11 Q. But they would understand the scope of the claims,
12 right, Doctor?

13 A. No, they wouldn't, because the scope of the claims is
14 extremely broad and they're open-ended.

15 Q. Doctor, you're a POSA and you understand the scope of
16 the claims, right?

17 A. No. I believe the scope of many of the claims is --
18 because it uses the term "comprises" and gives several examples
19 but it's open-ended. So it's not narrow. It's very broad.

20 Q. Okay.

21 Let's take a look at the doctor's deposition
22 hopefully one last time, page 486, line 21, through 487,
23 line 1.

24 Doctor, I asked:

25 "Q And the POSA would understand the scope

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1 of the claims?

2 "A Well, I am a POSA, and I understand
3 this."

4 Was that my question and was that your answer?

5 A. Yes. The scope of the claims is open-ended and
6 broad.

7 Q. Thank you.

8 MR. BERL: No further questions at this time.

9 THE COURT: Thank you.

10 Counsel, I assume redirect would be longer than five
11 minutes?

12 MR. SALMEN: Unfortunately, yes, Your Honor.

13 THE COURT: Well, I wasn't going to put an adjective
14 on it.

15 Doctor, we're going to break for the day. You remain
16 midstream in your testimony; so that means you get through the
17 evening without anyone bothering you.

18 THE WITNESS: Being a lonely guy.

19 THE COURT: You do. You are alone. Whether you
20 prefer that or not, I'll leave to you. I won't ask. But just
21 so you understand, no one can talk to you about your testimony
22 because you remain midstream.

23 We'll resume at 9:00 tomorrow.

24 You can go ahead and step down, sir.

25 THE WITNESS: Thank you, Your Honor.

1 THE COURT: Thank you.

2 It was my understanding this was Mylan's last witness
3 in this phase of the case; is that correct?

4 MS. MAZZOCHI: Yes, Your Honor. This is going to be
5 Mylan's last witness as part of its invalidity/infringement
6 response. We do have one live witness for sure, Dr. Hofmann,
7 who is going to be responding to their witness on commercial
8 success.

9 Whether we need to bring Dr. Albini or Dr. Stewart
10 back after we hear from Dr. Csaky, for example, or any of the
11 other witnesses, particularly on the issue of secondary
12 considerations, we don't know. We're hoping we don't have to.
13 But one of the things that I certainly would say, though, Your
14 Honor, in terms of timing, again, we're very concerned that
15 Regeneron has been really stacking up a lot --

16 THE COURT: The timekeepers are keeping track of it,
17 Counsel. We are where we are. I've told you guys how much
18 time you have.

19 MS. MAZZOCHI: We're on track. I just don't want to
20 get stuck.

21 There are a couple things, though, Your Honor, that
22 have come up, and I did want to preview them for you because
23 I'd like to get some guidance.

24 THE COURT: I don't need a preview at this point,
25 Counsel. We're going to break for the day. I'm just trying to

1 get a good feel for where we're headed. We can take those
2 issues up at 9:00 tomorrow morning just before the doctor
3 resumes his testimony.

4 MS. MAZZOCHI: That's fine. Thank you, Your Honor.

5 THE COURT: Is Regeneron's plan still the same,
6 Ms. Chu, Dr. Csaky, Dr. Trout. And if Mr. Graham and
7 Mr. Manning are doctors, I apologize to those witnesses.

8 MR. BERL: Dr. Graham will be after Dr. Chu.

9 THE COURT: The order was --

10 MR. BERL: The order was not --

11 THE COURT: Okay.

12 MR. BERL: But we're calling those people.

13 THE COURT: Understood.

14 All right. We're going to break for the day. I'll
15 see everyone at 9:00 tomorrow.

16 (Proceedings concluded at 5:22 p.m.)

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CERTIFICATE

I, Cindy L. Knecht, Registered Professional Reporter and Official Reporter of the United States District Court for the Northern District of West Virginia, do hereby certify that the foregoing is a true and correct transcript of the proceedings had in the above-styled action on June 20, 2023, as reported by me in stenotypy.

I certify that the transcript fees and format comply with those prescribed by the Court and the Judicial Conference of the United States.

Given under my hand this 20th day of June 2023.

/s/Cindy L. Knecht

Cindy L. Knecht, RMR/CRR
Official reporter, United States
District Court for the Northern
District of West Virginia