

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 2  
8 Biocon Biologics,  
9 Defendants.  
10 - - -  
11 Proceedings had in the bench trial of the above-styled  
12 action on June 13, 2023, before Honorable Thomas S. Kleeh  
13 District Judge, at Clarksburg, West Virginia.  
14 - - -  
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Transcript produced by computer-aided transcription.  
  
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1 Tuesday Morning Session,  
2 June 13, 2023, 9:30 a.m.  
3 - - -  
4 THE COURT: Convene for day two of trial. Plaintiff  
5 may call its next witness.  
6 MS. OBERWETTER: Your Honor, if I may, Ellen  
7 Oberwetter for Regeneron. A brief housekeeping matter from  
8 yesterday relating to the admission of exhibits used in  
9 Dr. Yancopoulos's direct and redirect testimony.  
10 I'm happy to handle this however you would prefer. I  
11 can either read the list into the record. We've had an  
12 opportunity to make sure our list conforms to what Ms. Kinsey  
13 had yesterday so that those are moved into the record as  
14 evidence.  
15 THE COURT: Let's go ahead. If you'll read that  
16 slowly for Madam Court Reporter's benefit. Go right ahead.  
17 MS. OBERWETTER: I'm happy to do that, Your Honor.  
18 PTX 0001, PTX 0003, PTX 3333, DTX 212, PTX 0419.  
19 THE COURT: Is that 19 or 91?  
20 MS. OBERWETTER: My list says 19.  
21 THE COURT: Okay.  
22 MS. OBERWETTER: Your list is correct, Your Honor.  
23 THE COURT: As is Mr. Ruby's.  
24 MS. OBERWETTER: PTX 491, DTX 228, PTX 0311,  
25 PTX 0304, PTX 3216, PTX 3187, PTX 3188, PTX 0080, PTX 1028-C,  
  
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1 PTX 1170, PTX 0932.  
2 THE COURT: I've got two others a little further down  
3 my list.  
4 MS. OBERWETTER: Yes.  
5 THE COURT: DTX 4070.  
6 MS. OBERWETTER: That was the Nguyen 2006 reference.  
7 That's correct, Your Honor.  
8 THE COURT: And PTX 0311?  
9 MS. OBERWETTER: Yes.  
10 THE COURT: That's the Heier article on wet  
11 age-related macular degeneration.  
12 MS. OBERWETTER: Yes, Your Honor. That one was  
13 further up in my list. That's correct.  
14 THE COURT: Any objection to any of those, Counsel?  
15 MS. MAZZOCHI: No. But, again, as long we -- I know  
16 you instructed we are going to be doing the issue of whether  
17 they are allowed to use their conception surveys --  
18 THE COURT: Try it again.  
19 MS. MAZZOCHI: Yesterday the Court indicated -- my  
20 understanding is that the Court indicated that, to the extent  
21 we had an objection as to whether Regeneron can use any of  
22 these exhibits in connection with, for example, its conception  
23 or reduction practice theories or other theories not disclosed  
24 in their interrogatory responses, we will have the opportunity  
25 to raise that in posttrial briefing. Thank you.  
  
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1 that we were working on.

2 A second, similar sized part was to really understand

3 what happens in animals, in humans, and to be able to measure

4 those things and prepare drugs to get ready to move into the

5 clinic.

6 Q. When did you begin working on the VEGF Trap or a VEGF

7 Trap?

8 A. I would say approximately a year after I was there,

9 maybe 2003.

10 Q. And what was the result of that project?

11 A. The biggest thing that came out of it was Eylea.

12 Q. Now, I'm going to place on the screen what's been

13 marked as PTX 2 in this case.

14 Dr. Furfine, is this the patent that describes and

15 claims your inventions working on the project on aflibercept?

16 A. Yes, it is.

17 Q. We've highlighted various people who are listed as

18 inventors. The first one, Eric Furfine, we know.

19 Who is Daniel Dix?

20 A. Daniel Dix was the head of the formulation group that

21 reported to me.

22 Q. How about Kenneth Graham? Who is he?

23 A. Kenneth was a scientist in the formulation group, and

24 he reported to Dan.

25 Q. And Kelly Frye, who is that?

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1 Q. Now, we've been talking in this case about

2 aflibercept. What is aflibercept?

3 A. Aflibercept is a man-made, humanly devised protein

4 where you take two receptors that are normally on the surface

5 of the cell and you genetically engineer them to be on an

6 antibody part. We call that the FC domain.

7 So you make this construct of receptor domains fused

8 to an antibody part, and that creates a drug.

9 Q. And when you say they're fused, does that make them

10 what we've heard of called as a fusion protein?

11 A. Correct. It's referred to commonly as a fusion

12 protein.

13 Q. And was aflibercept the only VEGF blocker known at

14 the time that you were working on the project?

15 A. No, it was not.

16 Q. Were there any prominent VEGF blockers that you were

17 knowing about and following at the time?

18 A. Two of the most prominent VEGF blockers were Avastin,

19 or bevacizumab is the genetic name, and Lucentis, or it was

20 ranibizumab at that time because it wasn't approved when we

21 first started working on it.

22 Q. Who was developing those molecules?

23 A. Genentech was the company that was doing that.

24 Q. And at the time you were working on your project, who

25 was Genentech in the field of biotechnology and in the field of

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1 A. Kelly Frye was also a formulation scientist that

2 reported to Dan.

3 Q. Dr. Yancopoulos, from whom the Court heard yesterday,

4 is not listed as an inventor on the patent.

5 What was his role vis-a-vis the project that you were

6 working on with aflibercept?

7 A. Yeah. I mean, as a senior leader in the company,

8 George was very intimately involved in all the things that were

9 required to move a drug into the clinic and follow it

10 throughout the clinic. And he stayed abreast of the work that

11 we were doing to prepare drugs to be ready to go into clinical

12 trials and to be able to maintain them in clinical trials.

13 Q. Did you meet with Dr. Yancopoulos during this period?

14 A. Absolutely. Yes, on a regular basis.

15 Q. Now, we've highlighted under Number 73 there

16 "Assignee: Regeneron Pharmaceuticals."

17 What is your understanding about how Regeneron

18 Pharmaceuticals is the assignee of the patent that you helped

19 invent?

20 A. All employees of Regeneron were required to assign

21 their inventions to the company. That was a condition of your

22 employment.

23 Q. Was that true throughout the time that you were at

24 Regeneron?

25 A. Yes, it was, absolutely.

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1 VEGF?

2 A. Genentech were really leaders in both of those

3 spaces. They were probably the premier company in protein

4 therapeutics, and they were arguably the premier company in

5 understanding VEGF biology and pursuing drugs that modulate or

6 inhibit VEGF.

7 Q. Who did you understand to be leading their VEGF

8 development?

9 A. A lot of the scientific leadership came from a man

10 named Napoleon Ferrara, who is arguably the father of VEGF and

11 Avastin.

12 Q. How did Regeneron compare to Genentech at the time?

13 A. Analogous to us being David in the David and Goliath.

14 Q. Was aflibercept initially being pursued by Regeneron

15 to treat eye diseases?

16 A. Not originally, no. It was treating cancer.

17 Q. Did you participate in that work?

18 A. I did, yes.

19 Q. Did there come time when Regeneron considered using

20 aflibercept to treat eye diseases?

21 A. Yes, we did.

22 Q. And at the time you began the project, did you

23 consider the project of formulating aflibercept to treat eye

24 diseases easy or hard?

25 A. We considered that it would be a challenging,

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1 difficult problem.

2 Q. Why is that?

3 A. First of all, aflibercept itself being a fusion

4 protein was a challenge because there just wasn't that much

5 knowledge on how to formulate and what the behaviors of those

6 types of molecules, of fusion proteins general.

7 And the second reason was there just wasn't a lot of

8 experience in the industry in developing formulations that were

9 going to be injected intravitreally.

10 Q. Did the fact that aflibercept Trap VEGF mean that it

11 could be used to treat diseases in the retina?

12 A. No. It had to reach the retina in order to be able

13 to do that, both block VEGF and reach the site of action.

14 Q. Now, you mentioned ranibizumab, which was one of the

15 two molecules that Genentech was developing.

16 What was your understanding about for what diseases

17 Genentech was pursuing ranibizumab?

18 A. My understanding was they were only pursuing retinal

19 diseases with ranibizumab.

20 Q. Did you consider aflibercept to be like ranibizumab

21 for purposes of treating eye diseases?

22 A. It was similar in a very high-level sense in that

23 they're both protein therapeutics, but the chemical nature of

24 these two drugs was very, very different, and they were

25 different classes of proteins.

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1 up more space.

2 Q. And so was aflibercept more like the wide receiver or

3 like the fullback?

4 A. More like the wide receiver and, therefore, more

5 similar to an antibody in size, despite its actual weight being

6 somewhat less.

7 Q. And was aflibercept in the same class of molecules as

8 ranibizumab?

9 A. No. As I mentioned, ranibizumab was an antibody or

10 considered an antibody as it was part of an antibody, and

11 aflibercept was a receptor fusion protein. It had receptor

12 domains on it that were previously in a normal setting on the

13 surface of a cell and bore no resemblance to the structures of

14 an antibody.

15 Q. Based on your understanding at the time, does a

16 formulation that works to stabilize one protein in a class work

17 to stabilize a separate protein in a class?

18 A. No, not necessarily.

19 Q. Why not?

20 A. The chemical nature of even two antibodies can be

21 very different, and it's the chemical nature of those

22 antibodies, how charged they are, hydrophobic they are --

23 hydrophobic meaning kind of a dislike of water, if you will.

24 Depending on the nature, they could be very different things

25 that are required to maintain their stability in solution.

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1 Q. Did they have any other differences that you

2 considered to be important for purposes of your project?

3 A. Yes. Aflibercept was considerably larger than

4 ranibizumab was.

5 Q. What do you mean by larger or smaller in the context

6 of molecules or proteins?

7 A. So what we mean by larger is molecular weight, kind

8 of the space a molecule takes up. And the ranibizumab molecule

9 was about a third the size of a full antibody. So it's an

10 antibody part. It's in some ways considered an antibody, but

11 it's really a part of an antibody, the FAB domain. And that's

12 about a third of the size of a total antibody.

13 And the VEGF Trap or aflibercept is much more similar

14 in size to an antibody than it is to ranibizumab.

15 Q. Was a molecular weight or the weight the only thing

16 you considered in terms of the size?

17 A. No. So the molecular weight of aflibercept was a

18 little bit smaller than an antibody, but we felt like it

19 behaved more like the size of an antibody. It's kind of like

20 if you -- could make a football analogy where you get somebody

21 who's a fullback might be or a running back might be, this

22 relatively heavy, relatively dense, small, compact person; and

23 then you have a wide receiver who might weigh even maybe a

24 little bit less but be much bigger, might have more trouble

25 fitting in an airplane seat because of their -- they just take

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1 Q. Did you understand that a formulation that stabilizes

2 an antibody could be used to stabilize a fusion protein?

3 A. Definitely not. The differences between a fusion

4 protein's chemical nature is even more different than an

5 antibody to an antibody.

6 Q. And I should have asked you this before. When you

7 came to Regeneron in 2002, did you start working on protein

8 formulations immediately?

9 A. Yes.

10 Q. Was it your understanding, Dr. Furfine, that you

11 could take an existing antibody formulation, take out the

12 antibody, and put in a different molecule such as a fusion

13 protein?

14 A. No. That's not how we do formulation discovery. We

15 have a path where we do things that are fit for purpose. You

16 decide what's going to be used for, you decide the nature of

17 the molecule you're formulating, and you design the formulation

18 for that.

19 Q. Would it even be allowed to make that kind of

20 substitution to make your product that way?

21 A. Absolutely not. It's a cardinal rule of formulation

22 science and drug discovery generally that you only put things

23 in that you need. You have to actually go through the process

24 of showing that you need something and figuring out exactly not

25 only that you need it but how much to put in, and that includes

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1 the drug itself.

2 Q. Now, you said a moment ago that you had to get into

3 the proper areas of the eye. I just want to put up a figure on

4 the screen from Exhibit 579. That's PTX 579.

5 When you were working on the project on aflibercept,

6 what was your understanding about where the molecule had to go

7 to treat the diseases you were targeting?

8 A. It would help if I had --

9 MR. BERL: May I approach, Your Honor?

10 THE COURT: You may.

11 THE WITNESS: So you see the word "choroid" here.

12 This is the -- roughly the place in the eyeball where you would

13 stick the needle, and it would go through the sclera here and

14 into this kind of like peach-colored area. That's called the

15 vitreous. So you would directly inject the drug right into the

16 vitreous.

17 Now, the drug will freely over time, maybe about a

18 day, diffuse throughout the vitreous, but the key is you see

19 this lighter yellow-colored part that abuts the vitreous here,

20 that goes here, that's the retina. So it has to be able to get

21 out of the vitreous and into the retina.

22 It also needs to be able to get past the retina into

23 this next darker red color next to the light yellow. That's

24 called the choroid. Those are the two places where the disease

25 happens, the choroid and the retina. So the drug needs to get

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1 Can you explain what Genentech was conveying and what

2 you understood about it when you were working on your project?

3 A. Right. So you can see right here they point out the

4 difference in molecular weight or the size. So you can see

5 it's 150 versus about 50. So it's a third the size; so that's

6 essentially consistent with what I was saying. And that the

7 antibody, the bigger molecule, did not penetrate the retinal

8 tissues whereas the ranibizumab, or the FAB fragment of the

9 antibody, was able to penetrate the tissues in this study.

10 Q. What was the principle of this -- what was the

11 relevance of this principle to your work on aflibercept at the

12 time?

13 A. Well, as I mentioned before, because aflibercept was

14 more similar in size to an antibody, we were concerned that we

15 could see the same thing and that, if we gave an intravitreal

16 injection of aflibercept, it might not get to the place where

17 we needed it to go to affect the disease. So we were concerned

18 about that.

19 Q. Did you understand this issue of size to be relevant

20 to Genentech's development of ranibizumab?

21 A. Absolutely. I think that's partly why they published

22 this paper too. And they clearly thought that this smaller

23 molecule was the better way to go, and that's what they pushed

24 forward with.

25 Q. When you read this when you were working at

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1 out of the vitreous, needs to penetrate these two tissues in

2 order to work.

3 BY MR. BERL:

4 Q. And what was your understanding at the time about

5 what kind of molecules would be most likely to get in

6 significant amounts into the retina and choroid?

7 A. So there was evidence from our colleagues,

8 competitors at Genentech that said that larger molecules,

9 antibody-sized molecules, essentially stayed mostly in the

10 vitreous and did not penetrate the retina; but smaller

11 molecules, like ranibizumab, which is a third of the size of an

12 antibody, was able to actually get into those tissues where the

13 disease biology happens.

14 Q. Let's take a look -- it's in your binder as well --

15 at Exhibit 1848. Can you identify this document for the Court?

16 A. Yes. This is the paper that I was referring to from

17 Genentech that compared the antibody to the ranibizumab.

18 Q. And did you read this article when you were working

19 on your aflibercept project at Regeneron?

20 A. Yes, I did.

21 Q. And you mentioned Dr. Ferrara earlier. Is he one of

22 the authors of this article?

23 A. Yes, he is, right here.

24 Q. Let's take a look at the abstract, and we've

25 highlighted part of the abstract on the first page.

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1 Regeneron, were you certain that Genentech was correct about

2 what it was saying?

3 A. I wasn't. I was skeptical of this article. As a

4 scientist, we're often skeptical of articles and not that they

5 think of everything. And I didn't -- I wasn't sure that this

6 was right.

7 Q. What did you do in view of your skepticism?

8 A. Usually what scientists do when they're skeptical is

9 they do their own experiment, and we did a study in rabbits.

10 Q. We'll get to that in a moment.

11 This issue of getting into the retina and the

12 choroid, is it all or none like a light switch, Dr. Furfine?

13 A. No. I think there are degrees of penetration, and

14 there can be examples sometimes where there is a sharp cutoff,

15 but I don't think that was the case here. This is a gradient,

16 if you will.

17 Q. Did Regeneron only have aflibercept to block VEGF, or

18 did it have smaller molecules too?

19 A. We had small molecules. Well, we had something

20 called a Mini-Trap. Kind of like what the FAB or the

21 ranibizumab was a part of the antibody, we had the Mini-Trap

22 that was a part of aflibercept that, in case I was wrong, then

23 we would have the smaller molecule to move forward with as

24 well.

25 Q. Just so it's clear, why did Regeneron create the

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1 A. This is a summary of a lot of the nonclinical work  
2 that we did, including the formulation development to support  
3 clinical studies.

4 Q. You've been using the term "nonclinical" or  
5 "preclinical." Is that experimentation done before you  
6 actually administer something to human beings?

7 A. Yes.

8 Q. Now, let's turn to the Bates number ending in 262  
9 which is on page 10 of the document. And this is under -- at  
10 the top of the page we can see here 1.3. It's a little faded,  
11 but it says "Summary of Formulation Development." And then  
12 there's a Table 3.

13 Can you explain what's shown in Table 3.

14 A. Yes. This shows four formulations. Two of them are  
15 intravitreal formulations, and then the other two are what was  
16 used in the cancer programs for systemic, either IV or  
17 subcutaneous is SC.

18 The intravitreal formulation 1 there was the first  
19 formulation that we moved forward with into clinical studies.

20 Q. Why did you start with this formulation, labeled  
21 ITV-1?

22 A. So as I mentioned, you don't want to have anything in  
23 your formulation that is, you know, more than what you need or  
24 have a reason for having it there. So this was a minimalist  
25 approach that we took to this formulation. And we wanted to

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1 make sure that we were using things that we thought had a high  
2 probability of success in the eye because there wasn't a lot of  
3 experience with eye formulations.

4 And so we focused on mostly excipients that we knew  
5 actually were there already. Sodium phosphate, of course, is  
6 in the eye; sodium chloride, saline, same thing is in the eye.  
7 So we used ingredients here that we thought would be reasonably  
8 well-tolerated. It was kind of a minimalist approach, if you  
9 will.

10 Q. Didn't you already have formulations of aflibercept  
11 that had been developed for systemic treatment of cancer?

12 A. Yes. The two furthest to the right, IV and SC, were  
13 already developed.

14 Q. Did you consider starting with those in your research  
15 on an ophthalmic formulation?

16 A. That didn't occur to us. That's not how you do  
17 science.

18 When you make a formulation, when you make a drug or  
19 a drug product, there's this idea of fit for purpose. You have  
20 to decide what you're going to do with the drug, what's it  
21 going to be used for, and what are you stabilizing.

22 And so you don't start with something that was made  
23 for something else to use it for something completely  
24 different. You have to start over again and ask your question:  
25 What's the right thing to do in this situation?

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1 And so that's what we did. We started over.

2 Q. Are there considerations that are relevant for  
3 intravitreal formulations that are less important for  
4 intravenous or subcutaneous formulations?

5 A. Absolutely. One big one, and maybe one of the  
6 biggest ones, was that there's a stress that happens in  
7 intravitreal formulations that wouldn't happen in systemic  
8 formulations.

9 So when you do an injection in the eye, you can  
10 imagine you want to use the smallest needle you can because who  
11 wants a big needle in their eye?

12 THE COURT: That is well established.

13 THE WITNESS: See, I don't have to do too many more  
14 studies on that. It's already known.

15 So what you do is you use these really narrow-bore  
16 needles. It's a very thin hull. What happens is, when you  
17 force solutions, protein solutions especially, through a  
18 narrow-bore needle, you create what's called shear stress.  
19 It's like a pressure, and that creates a stress that can cause  
20 a protein to come out of solution.

21 So you need to add agents into your formulation,  
22 ingredients that stabilize the solution and keep the drug in  
23 solution under these kinds of stressful situations. That would  
24 not happen for IV and SC.

25 THE COURT: When you say "in solution," I assume you

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1 mean still floating in the carrying liquid, for lack of any  
2 scientific term.

3 THE WITNESS: That's exactly right. That's perfectly  
4 scientific.

5 And what happens here, in fact, is if you don't  
6 survive shear stress, you see particles that are clearly -- by  
7 definition, a particle is not in solution. So, in fact, it's  
8 black and white. They're either in solution or they're not.

9 THE COURT: And in this form, again, because we're  
10 using a needle and a syringe, particles might be attached to  
11 the syringe itself or --

12 THE WITNESS: No. The manufacturer of syringe  
13 needles and the like has them clear of, really, any detectable  
14 particles. And so if you saw particles after shooting the drug  
15 through it, it would be solely the result of the protein coming  
16 out of the solution.

17 MR. BERL: I think what Your Honor -- what the Court  
18 may have been asking is do the particles get stuck in the  
19 needle? Is what you're asking, Your Honor?

20 THE COURT: Yeah. You're talking about shear stress  
21 which I'm envisioning sort of three lanes of traffic merging as  
22 one, right?

23 THE WITNESS: That's right. That's right. That's  
24 right.

25 THE COURT: You have all that there. So when that

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1 A. Moderate to severe inflammation -- repeated moderate  
2 to severe inflammation might cause vision loss.

3 Q. So your view is that moderate to severe vision loss  
4 that could resolve in a week would be enough to stop  
5 development of a drug that can prevent vision loss. That's  
6 your testimony?

7 A. My testimony is not exactly that. It's that a  
8 repeated moderate to severe inflammation could have  
9 consequences that might result in vision loss. You would have  
10 to do the experiments.

11 Q. But that inflammation, that transient inflammation  
12 that resolved in a week or two, was not enough to prevent  
13 Lucentis development or Eylea development, correct?

14 A. It prevented -- well, by inference, because they did  
15 not develop the 40 mg/mL formulation, it would suggest that  
16 they were concerned about the same thing because they stuck  
17 with 10, which didn't have that finding in that study.

18 Q. The Gaudreault paper concluded that all the doses  
19 they tested had transient inflammation that resolved.

20 A. The degree. It's a severity. You have to include  
21 the severity when you make your judgment of what you want to  
22 do.

23 Q. All right. Let's actually -- I forgot to mention  
24 something in your patent. Let's toggle back to your patent.

25 A. Okay. Remind me.

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1 Q. PTX 2. If we go to page 2. And I'm going to  
2 focus -- and I'll put it on the screen -- on the application  
3 number and date.

4 A. Yes.

5 Q. And you see that the --

6 If we could go down, Mr. Gibson, to the application  
7 number in the middle.

8 You see this patent issued from Application  
9 Number 16 --

10 A. -- 739 --

11 Q. -- 739,559, filed January 20 -- let me back up. Let  
12 me strike that. I'll start over.

13 Your '865 patent issued from Application Number  
14 16/739,559 filed January 10, 2020; is that right?

15 A. That's correct.

16 Q. I want to look further down on this same page to the  
17 related U.S. application data.

18 A. Yes.

19 Q. You see that section?

20 A. I do.

21 Q. And I want to focus on paragraph 60 where it says  
22 "Provisional Application."

23 Do you see that?

24 A. I do.

25 Q. And so the provisional application, number 60/814,484

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1 was filed on January 16, 2006, correct?

2 A. Say that number again, which one you were...

3 Q. Yes. So it's highlighted on the screen.

4 A. Sorry.

5 Q. The U.S. Provisional Application Number 60/814 --

6 A. Right.

7 Q. -- 484 was filed on June 16, 2006, correct?

8 A. That's correct, yes.

9 Q. Are you okay if I refer to that as the provisional  
10 application just for short?

11 A. Yes.

12 Q. Now, let's look at PTX 8. I'm sorry. Strike that.

13 Let's look at PTX 3249, which is in the small binder  
14 right in front of you.

15 A. Sorry. It's not another tab on here?

16 Q. No. The small binder right there. Go to PTX 3249.  
17 If we go to page 8, please.

18 A. Okay.

19 Q. You see this is the provisional application for  
20 patent. Do you see that?

21 A. I do.

22 Q. And you're listed as an inventor right there. Do you  
23 see that?

24 A. Yes, I do.

25 Q. And you see the title is "VEGF Antagonist Formulation

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1 Suitable for Intravitreal Administration," correct?

2 A. Yes, I do.

3 Q. And if you go to the bottom of this page, you see  
4 dated June 16, 2006, correct?

5 A. Yes.

6 Q. Did you review this provisional application before it  
7 was filed on June 16, 2006?

8 A. I presume that I did, but, honestly, I don't remember  
9 that far ago. That was, like, 20 years ago or something.

10 Q. How about before your testimony yesterday? Did you  
11 review this provisional application before yesterday?

12 A. I reviewed the patent application, but I'm trying to  
13 remember if I reviewed the first -- I think I might have  
14 reviewed the provisional, but I can't remember for certain.

15 Q. So do you remember doing a side-by-side comparison of  
16 this provisional application with your issued '865 patent  
17 before your testimony yesterday?

18 A. I don't recall doing a side-by-side comparison, no.

19 Q. Let's look at page 11 of your provisional  
20 application. So that's PTX 32 --

21 A. It doesn't mean that I didn't. I just don't recall.

22 Q. I'm asking, before your testimony yesterday, did you  
23 do a line-by-line comparison?

24 A. No, not that I remember, no.

25 Q. So let's look at page 11 of your provisional

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BERNHARDT TROUT - DIRECT

1 troubling manifestation of protein instability encountered in  
2 almost all stages of protein drug development."

3 Can you explain what Wang is conveying here?

4 A. Yes. This is the first sentence of the abstract, so  
5 really the first sentence in the paper. And it talks about,  
6 right here, protein aggregation. That's the protein molecules  
7 coming together, which we don't want. That's a manifestation  
8 of the instability. And it's omnipresent is what Wang is  
9 saying here.

10 Q. Let's go to page 3 of the article. And we have blown  
11 up a paragraph that begins with "protein aggregation has been  
12 observed frequently."

13 Can you explain what Wang is saying here?

14 A. Yes. Well, again, Wang is talking about protein  
15 aggregation, as I just mentioned from the abstract.

16 And specifically I've highlighted, Your Honor, two  
17 places, shearing/shaking. So that's an example of a pressure  
18 or pressure disturbance which is going to be omnipresent in --

19 THE COURT: And shearing would refer to the  
20 propulsion, if you will, of the solution through the needle.

21 THE WITNESS: Yes, sir, that can be it. But also  
22 during shipping, for example, during usage when the doctor or  
23 the medical professional takes it out, it can slosh around, to  
24 use a better term. So certainly that's the case. And then  
25 also just during storage, to name two examples.

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1 solution?

2 A. Well, there are several problems. One problem is  
3 that, if it comes out of solution, it's typically inactivated  
4 so it's not going to be useful to the pharmaceutical or at  
5 least the material that comes out of solution.

6 But above and beyond that, it can cause serious  
7 reactions. We talked about inflammation even earlier today,  
8 but then even the most serious one is immune response, which  
9 means that the body's immune system can actually attack the  
10 molecule which is meant to be a therapeutic.

11 Q. Let's take a look further down on page 3 of Wang,  
12 under the Subsection 2 in the paper "Protein aggregation and  
13 its influencing factors."

14 What is Wang writing here?

15 A. Well, Wang is just talking about two categories of  
16 aggregation, which I've highlighted in yellow. The first  
17 category is physical aggregation. So that's molecules coming  
18 together, for example, through hydrophobic, hydrophobic  
19 effects. I'll have some pictures of that shortly. But that  
20 does not involve the breaking of formation of chemical bonds.

21 And the second is the chemical aggregation, which can  
22 involve the breaking or formation of chemical bonds, for  
23 example, sulfur-sulfur bond forming.

24 Q. Doctor, in terms of assessing or determining the  
25 solubility of a protein, does it make any difference which of

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1 BY MR. BERL:

2 Q. Are there particular conditions that scientists would  
3 think about in assessing intravitreal formulations?

4 A. Yes. So, again, for intravitreal we want the needle  
5 to be as thin as possible, typically, a 30-gauge needle, which  
6 has a very thin bore, which means that the solution has to get  
7 through that bore. And it can -- it is -- the bore exerts  
8 significant shear, a great amount of shear, because of the very  
9 small diameter.

10 Q. Doctor, what is the connection between this protein  
11 aggregation that Wang is discussing on the one hand and the  
12 concept of solubility that you discussed a moment ago?

13 A. Well, protein aggregation is, first of all, the first  
14 stage of solubility, and then it also -- or first stage towards  
15 insolubility I should say, and it also describes the insoluble  
16 particles which can be called insoluble aggregates.

17 Q. Can a protein come out of solution without  
18 aggregation?

19 A. No.

20 Q. What does it mean for a protein to stay in solution?

21 A. Well, it means that it is in solution. It is  
22 surrounded by the solvent molecules, primarily water molecules,  
23 and it doesn't aggregate and eventually come out of solution  
24 and precipitate.

25 Q. What's the problem with a protein not staying in

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1 these mechanisms that Wang is describing caused the protein to  
2 come out of the formulation?

3 A. No. It just matters the degree to which it's soluble  
4 or not soluble; it comes out of solution.

5 Q. How does a scientist know how much of a protein stays  
6 in solution under a particular set of conditions?

7 A. Well, in the extreme case, a scientist can, for  
8 example, experiment or do experiments under certain conditions;  
9 and if the solution gets cloudy, which one can see visually,  
10 then it's come out of solution, it's insoluble, that part  
11 that's cloudy.

12 But that's really an extreme case. Long before one  
13 can visually see the cloudiness, we can use analytical  
14 techniques, such as probing it with lasers and whatnot to  
15 determine the degree of insolubility.

16 Q. What kinds of conditions are used in these tests of  
17 solubility?

18 A. Well, the kind of conditions at which the protein  
19 might be subjected to during its lifetime as a pharmaceutical  
20 product, conditions such as shear, shaking, going through the  
21 needle as we just talked about, and potential temperature  
22 excursions.

23 MR. BERL: Your Honor, at this point I'm going to  
24 start getting into the claims and Mylan's product. I think  
25 Mylan has requested that the balance of the examination have a

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THOMAS A. ALBINI, MD - VOIR DIRE 821

1 for a discussion of this testimony? It was an IPR proceeding,  
2 I believe.

3 MR. McLAUGHLIN: No.  
4 THE COURT: Okay. All right.  
5 So, Ms. Oberwetter, my apologies for trusting but  
6 verifying. Go right ahead.

7 MS. OBERWETTER: Always appreciated, Your Honor.  
8 BY MS. OBERWETTER:  
9 Q. If we take a look at page 125 of this transcript.  
10 And you recall you were being questioned in that deposition by  
11 another attorney for Regeneron, correct?  
12 A. That is correct. I do recall that.  
13 Q. And you were asked in that proceeding a question  
14 about whether the composition of an intravitreally administered  
15 drug, including its osmolality and excipients, can affect the  
16 half-life of the drug in the vitreous, correct?  
17 Do you see that question?  
18 A. Let me just take a second to digest that. Hold on  
19 one second.  
20 Okay. I've read the question.  
21 Q. And your answer was you're getting into some very  
22 technical issues, correct?  
23 A. That is correct.  
24 Q. And then if we scroll down to the next several lines,  
25 you said, "It happens that, as I sit here before you today, I

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THOMAS A. ALBINI, MD - DIRECT 823

1 BY MR. McLAUGHLIN:  
2 Q. So I will resume my direct, but in the meantime I  
3 just want to ask you, Dr. Albin, a few questions about your  
4 background. I understand that you don't consider yourself an  
5 expert in the design of therapeutics, but would you consider  
6 yourself to be knowledgeable about the impact of the injection  
7 of an isotonic or nonisotonic solution into the eyes of one of  
8 your patients?  
9 A. I would consider myself being an expert in the use of  
10 these drugs. The question of the importance of the isotonicity  
11 and various options for choosing different osmolarity of  
12 agents, I'm not an expert in those issues, but I certainly feel  
13 myself confident to describe the use of drugs with formulations  
14 that have been approved.  
15 Q. In the course of your work and your research, have  
16 you published -- did you publish an article in 2014 called "Ziv  
17 Aflibercept as a Possible Alternative to Aflibercept"?  
18 A. Yes, I did.  
19 Q. Do you recall publishing that article?  
20 A. I do.  
21 Q. Do you recall who you published that article with,  
22 who your coauthors were?  
23 A. I think my coauthors, as I recollect, were Andrew  
24 Moshfeghi, and Jonathan Chang.  
25 Q. If you can recall -- but we can also put the article

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THOMAS A. ALBINI, MD - VOIR DIRE 822

1 think off the top of my head that osmolality would not affect  
2 half-life, although it would have many effects. But I could be  
3 wrong on that. And, again, I am not an expert in the design of  
4 therapeutics."  
5 Do you see that?  
6 A. That is correct.  
7 Q. And then you said, "But as a clinician that uses  
8 angiogenic drugs and that has written these declarations, I  
9 don't think that sounds reasonable. But I don't really have a  
10 strong opinion or a lot of experience in that area."  
11 Correct?  
12 A. That is what I said.  
13 Q. And those are answers that you gave with respect to  
14 the osmolality of the drug you were being asked about, correct?  
15 A. I don't recall if this was in reference to a specific  
16 drug.  
17 Q. Okay.  
18 MS. OBERWETTER: Thank you, Your Honor. That is the  
19 extent of my questions on this topic.  
20 THE COURT: Understood. Thank you.  
21 The Court's ruling with respect to the objection  
22 remains.  
23 Counsel, you may resume your direct.  
24 MR. McLAUGHLIN: Thank you, Your Honor.  
25 DIRECT EXAMINATION (Resumed)

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THOMAS A. ALBINI, MD - DIRECT 824

1 up for you, if you'd like, but can you recall what the subject  
2 matter of that article was?  
3 A. The subject matter was that there was some early  
4 interest, particularly in Brazil as I recall, for using  
5 Regeneron's product ziv-aflibercept, which is designed for  
6 intravenous use as a cancer therapeutic, to aliquot it in a  
7 very analogous fashion as bevacizumab is aliquoted for  
8 intravitreal use, to use ziv-aflibercept off-label, again with  
9 the goal being of obtaining the -- being able to use the  
10 VEGF Trap molecule at a reduced price for patients that could  
11 not meet the price point for aflibercept.  
12 Q. And is this a copy of your article shown here?  
13 A. That's correct.  
14 Q. And if we could turn to the second page, I don't know  
15 if there's a way to -- is there a way to zoom that in?  
16 So in this top paragraph in the upper left of page 68  
17 of that article, do you discuss the osmolality of  
18 ziv-aflibercept versus aflibercept?  
19 A. That is correct.  
20 Q. What did you conclude about the osmolality of the two  
21 different formulations?  
22 A. I haven't actually read this whole thing in a while,  
23 but as I recollect, I remember having a concern that the higher  
24 osmolarity of ziv-aflibercept relative to aflibercept that's  
25 injected in the eye, I think the numbers are there,

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1 815 milliosmoles relative to 260 -- or compared to  
2 260 milliosmoles, that this higher osmolarity may cause a  
3 clinical problem in that I had been familiar with work that was  
4 done by Dr. Marmor in the 1970s -- and, honestly, right now  
5 sitting here, I can't remember what the point of this paper  
6 was.

7 But I remember that the higher osmolarity of  
8 intravitreal injections given by Dr. Marmor in -- I think it  
9 was a monkey study, I want to say; it's been many, many years  
10 since I've read this paper -- that in that -- with that higher  
11 osmolarity, there was a risk, a very high risk, for retinal  
12 detachment.

13 And I remember that some of us who were pondering  
14 this issue, including me and my coauthors here, were wondering  
15 whether ziv-aflibercept was produced with higher osmolarity  
16 just to avoid the possibility of intravitreal injection.

17 So that's my recollections on this issue, but I think  
18 I was concerned in this particular case about higher osmolarity  
19 given my prior familiarity with work done by Dr. Marmor, as was  
20 cited in this article.

21 Q. Okay. Now, a few minutes ago you said you couldn't  
22 remember what this article was about.

23 You were referring to Dr. Marmor's 1979 article, not  
24 the one in front of you here?

25 A. Thank you for the clarification. Absolutely, yes.

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THOMAS A. ALBINI, MD - DIRECT

1 when formulating your opinions in this case?

2 A. That's correct.

3 Q. And is this a snapshot of that Eylea label, DTX 3316?

4 A. Yes, it is.

5 Q. And what's this say about Eylea in DTX 3316?

6 A. It says that it is formulated as an iso-osmotic  
7 solution.

8 Q. And in your opinion as an ophthalmologist, is the  
9 FDA-approved formulation typically the one that was used in the  
10 pivotal Phase III trials that were responsible for that FDA  
11 approval?

12 MS. OBERWETTER: Objection, Your Honor. That's a  
13 fact question, not an opinion question if he's asking about  
14 this trial.

15 THE COURT: Repeat that question, Counsel, please.

16 BY MR. McLAUGHLIN:

17 Q. In your opinion as a treating physician, is the  
18 FDA-approved formulation typically the one that's used in a  
19 drug's pivotal Phase III clinical trials?

20 A. That's my --

21 THE COURT: One second, Doctor. Sorry.

22 Objection overruled.

23 Now you can answer. Thank you.

24 THE WITNESS: That's my opinion and would be the  
25 opinion of the POSA.

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1 The Marmor article that -- I have not read that in -- probably  
2 since this article was published.

3 MR. McLAUGHLIN: Okay. With that, with Your Honor's  
4 permission, I'm going to resume my direct. See if I can recall  
5 where we left off.

6 BY MR. McLAUGHLIN:

7 Q. So Slide 121, we were talking about Dr. Rabinow's  
8 opinion. This is his opinion that you relied upon in  
9 formulating your opinions with respect to Claim 6?

10 A. That's exactly right.

11 Q. Okay. And this passage that he cites from Dixon,  
12 that comes from DTX 0204?

13 A. That's correct.

14 Q. If we could pull that up so we can show the Court  
15 this language.

16 This comes -- this is language from Dixon. That's  
17 that 2009 article regarding VEGF Trap-Eye; is that correct?

18 A. That's correct.

19 Q. What does Dixon say about VEGF Trap-Eye and its  
20 formulation?

21 A. He teaches that it is formulated with different  
22 buffers at different concentrations suitable for the  
23 comfortable, nonirritating direct injection into the eye.

24 Q. Going back to the slide deck here, turning to the  
25 next slide, Slide 122, did you also rely on the Eylea label

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1 BY MR. McLAUGHLIN:

2 Q. Did you review Dr. Csaky's rebuttal expert report?

3 A. Yes, I did.

4 Q. And did you review the portion in which he was  
5 rebutting -- he was providing his rebuttal opinions with  
6 respect to Claim 6 of the '572 patent?

7 A. Yes, I did.

8 Q. Did Dr. Csaky provide any rebuttal opinion indicating  
9 that the FDA-approved formulation of aflibercept was not the  
10 one used in the Phase III clinical trial?

11 A. No, he did not.

12 Q. Now proceeding forward and now relying upon what you  
13 learned from Dr. Barrett Rabinow, the formulation expert that's  
14 going to be offered by Mylan, can you provide a summary of your  
15 final opinion with respect to Claim 6 of the '572 patent?

16 A. Yeah. I believe that Claim 6 is anticipated by  
17 Dixon, given that a suitable, comfortable, nonirritating direct  
18 injection of the eye would inherently be isotonic, as taught to  
19 me by Dr. Rabinow.

20 Q. And now we're going to shift focus a little bit and  
21 talk about obviousness of Claim 6 of the '572 patent.

22 So turning to the Slide 126, can you briefly  
23 summarize the opinions you're going to provide in this section  
24 of your testimony?

25 A. Given the text that we've discussed and the Dixon

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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 5  
8 Biocon Biologics,  
9 Defendants.  
10 - - -  
11 Proceedings had in the bench trial of the above-styled  
12 action on June 16, 2023, before Honorable Thomas S. Kleeh  
13 District Judge, at Clarksburg, West Virginia.  
14 - - -  
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1 Friday Morning Session,  
2 June 16, 2023, 9:30 a.m.  
3 - - -  
4 THE COURT: We convene for day five then -- it's a  
5 casino in here some days -- of trial counsels presence. Had a  
6 chance to skim, but I certainly wouldn't say I've read  
7 Regeneron's second motion to exclude undisclosed expert  
8 opinion.  
9 Would it be fair to characterize that motion as  
10 largely based on similar issues as the motion we addressed  
11 yesterday?  
12 MR. BERL: Yes, Your Honor.  
13 THE COURT: All right. I need to see Dr. Rabinow's  
14 report where this combination of prior art was disclosed and  
15 the explanation as to why it would be obvious, then.  
16 MR. HUNT: Your Honor, we will have copies for you  
17 here shortly. If I may.  
18 THE COURT: I have -- I do have his report.  
19 MR. HUNT: Very good. Then I would like to take you  
20 to paragraph 290 of Dr. Rabinow's opening expert report. There  
21 are a number of combinations listed in paragraph 290 of both  
22 Dr. Rabinow's opening report, Your Honor. For the Court's  
23 benefit and certainly the benefit of everyone's time, we have  
24 simplified things a bit for trial today.  
25 Dr. Rabinow, in Number 1, is testifying today

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1 regarding the combination of Fraser with Liu. And in addition  
2 to that combination, he will separately be offering opinions  
3 today with regard to Number 4, the prior art Lucentis  
4 formulations, as evidenced by the Shams and Gaudreault  
5 articles, in combination with Fraser.  
6 Now, I expect, Your Honor, that counsel for plaintiff  
7 is concerned that, the way that Dr. Rabinow's demonstratives  
8 have been organized, that he, they suspect, is going to offer  
9 opinions regarding the combination of Lucentis and Liu.  
10 I have assured counsel for plaintiff that that is not  
11 Dr. Rabinow's intent, that is not a combination, as we  
12 discussed, that is disclosed in his opening report. However,  
13 it is important for the Court to keep in mind -- and I think  
14 plaintiff may have a response to this -- that prior art needs  
15 to be considered in the context of the knowledge of the person  
16 of ordinary skill in the art as a whole.  
17 And I suspect that may be where the issue is here,  
18 Your Honor. There are certain disclosures in the Lucentis  
19 prior art, and there are certain disclosures in Fraser. And  
20 the person of ordinary skill in the art, as of June 16, 2006,  
21 would have an understanding and a body of knowledge based upon  
22 the prior art as a whole that would inform their reading of  
23 those references.  
24 So while Dr. Rabinow is not offering opinions as to  
25 the combination of anything more than Lucentis and Fraser,

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BARRETT E. RABINOW, PhD - DIRECT 1035

1 Q. And did you rely on DTX 0726 in connection with your  
2 opinions?  
3 A. I did.  
4 Q. Moving to the next slide, what would the person of  
5 ordinary skill in the art find significant about Shams?  
6 A. Shams is disclosed to be an example of a VEGF  
7 antagonist. Its name is ranibizumab. It referred to its brand  
8 name, Lucentis. It is described as a humanized antihuman VEGF  
9 Fab fragment for intravitreal administration.  
10 It is supplied in a liquid-filled vial. The  
11 concentration is 10 mg/mL for the .5-milligram dose level. And  
12 if you divide those two numbers, you learn that the intended  
13 volume for intravitreal injection is .05 milliliters; and that  
14 the formulation contains a histidine buffer, a trehalose sugar  
15 stabilizer, and polysorbate 20; and that the study drug is  
16 stored at 2 to 8 degrees.  
17 Q. And that disclosure, Dr. Rabinow, is at DTX 726,  
18 page 32; is that right?  
19 A. That's correct.  
20 Q. And if we look at the top of the callout that you  
21 have here, again, as of May 4th, 2006, the date of the Shams  
22 reference, would the person of ordinary skill in the art have  
23 an understanding that ranibizumab and Lucentis are synonymous?  
24 A. Yes, they would.  
25 Q. If you could please turn to Slide 45. What is shown

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BARRETT E. RABINOW, PhD - DIRECT 1037

1 Q. Thank you, Dr. Rabinow.  
2 If we could turn to the next slide, Slide 47, would  
3 the person of ordinary skill in the art have had a particular  
4 understanding relating to FDA-approved protein formulations in  
5 or around June 16th, 2006?  
6 A. He would. He would be amazed by the apparent routine  
7 nature of the ability to formulate all these different antibody  
8 formulations with surprisingly few formulation alternatives.  
9 So as we see here, there are half a dozen different  
10 antibodies. Some of them -- many of them are fusion proteins.  
11 Some of them are not. They all involve a buffer, a surfactant,  
12 and a stabilizer for either a liquid or a lyophilized  
13 formulation. And within each category of buffer, surfactant,  
14 or stabilizer, there are, as indicated here, only two  
15 alternatives that are -- that were used.  
16 You could -- for the buffer you can use either  
17 histidine or phosphate. For the surfactant you can choose  
18 either polysorbate 20 or polysorbate 80. For the stabilizer,  
19 you can use either trehalose or sucrose. It reads like a menu  
20 in terms of what do you want for soup, salad, appetizer in  
21 terms of limited choices here.  
22 Q. And with apologies, Dr. Rabinow, I need to walk  
23 through a few exhibits that are referenced on your Slide 47  
24 just for the record.  
25 So is DTX 5036 the Remicade prescribing information

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BARRETT E. RABINOW, PhD - DIRECT 1036

1 here, Dr. Rabinow?  
2 A. This is the Lucentis prescribing information dating  
3 from 2006 from Genentech.  
4 Q. And DTX 3040 is the Lucentis prescribing information,  
5 correct?  
6 A. Yes.  
7 Q. Did you rely on DTX 3040 in connection with your  
8 opinions?  
9 A. I did.  
10 Q. Now, why did you include DTX 3040 in your analysis?  
11 A. I included it to show that it essentially confirmed  
12 what we learned from Shams that was published earlier.  
13 Q. But you're not asserting that the Lucentis  
14 prescribing information from 2006 is prior art; is that right?  
15 A. That is correct.  
16 Q. Looking at Slide 46, what did you find relevant about  
17 the Lucentis prescribing information?  
18 A. So on page 4 it states that Lucentis --  
19 ranibizumab -- injection is a monoclonal antibody fragment and  
20 that, furthermore, it is provided in a vial and that it is  
21 designed to deliver 0.05 mL of a 10-mg/mL Lucentis solution.  
22 And, furthermore, it's disclosed that the formulation comprises  
23 a histidine buffer, a trehalose sugar stabilizer, and a  
24 polysorbate 20 formulation component as well. This is at  
25 DTX 3040, page 4.

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BARRETT E. RABINOW, PhD - DIRECT 1038

1 reflected here?  
2 A. It is.  
3 Q. Did you rely on DTX 5036 in connection with your  
4 opinions?  
5 A. I did.  
6 Q. Similarly, is DTX 5037 the Xolair prescribing  
7 information reflected here?  
8 A. It is.  
9 Q. Did you rely on DTX 5037 in connection with your  
10 opinions?  
11 A. I did.  
12 Q. Is DTX 5038 the Raptiva prescribing information?  
13 A. Yes.  
14 Q. And did you rely on DTX 5038 in connection with your  
15 opinions?  
16 A. I did.  
17 Q. And, finally -- and there, I believe, is a  
18 typographical error on this slide, but DTX 5040, is that the  
19 Xolair -- I'm sorry -- is that the Herceptin prescribing  
20 information reference reflected in your Slide 47?  
21 A. Yes.  
22 Q. And did you rely on DTX 5040 in connection with your  
23 opinions?  
24 A. Yes.  
25 Q. Overall, Dr. Rabinow, what is your opinion regarding

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BARRETT E. RABINOW, PhD - CROSS 1171

1 A. Yes.

2 Q. We'll take that down.

3 The POSA would view a hypertonic formulation as

4 suitable for intravitreal administration, right, based on the

5 literature?

6 A. Would view a hypertonic solution? No. I wouldn't

7 agree with that.

8 Q. Okay.

9 Can we put up the doctor's transcript at 136,

10 line 19, through 137, line 2.

11 Doctor, at your deposition I asked:

12 "Q And when you say he wouldn't find it

13 strange, you mean the POSA would view a

14 hypertonic formulation as suitable for

15 intravitreal administration, right, based on the

16 literature?

17 "A Yes."

18 Did I read that correctly?

19 A. You read it correctly. This was taken out of

20 context. You had shown me a document purportedly for an

21 intravitreal dosage form that was at an extraordinarily high

22 osmolarity. And I wasn't sure where this came from, and I was

23 trying to think through the issues.

24 And I recall that it was said at some places that the

25 eye is remarkably tolerant to hyperosmolar situations, but that

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BARRETT E. RABINOW, PhD - CROSS 1173

1 A. No.

2 Q. Doctor, is it your position that something

3 850 milliosmoles or higher would be a good idea to administer

4 intravitreally?

5 A. No.

6 Q. But you said remarkably -- that the eye is remarkably

7 tolerant to hypertonic solutions, right?

8 A. Yes, but one should exercise a good degree of caution

9 and not -- and be extremely conservative with designing a

10 dosage form that is designed to go into the eye. Just because

11 the eye may be tolerant in some individuals is no reason to try

12 to seek approval for something that could very well be

13 injurious to some fraction of the patient population.

14 Q. So you agree, then, Doctor, that something that is

15 just slightly outside the range of isotonicity would be okay to

16 administer intravitreally, but you wouldn't want to administer

17 something as high as 850 milliosmoles, right?

18 A. I didn't say that.

19 Q. The eye is remarkably tolerant to hypertonic

20 formulations, right?

21 A. There's a difference between asking the question --

22 what would happen if I injected something into somebody's

23 eyeball that had a tonicity of 600 milliosmoles? What would

24 happen to that person? That's one question.

25 Another question is should I go out and intentionally

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BARRETT E. RABINOW, PhD - CROSS 1172

1 doesn't mean that one should take liberties to intentionally

2 develop a hyperosmolar solution based upon that. One should

3 always err on the side of being conservative.

4 Q. So your position, Doctor, is that you wouldn't

5 administer a formulation that is too high in terms of its

6 hypertonicity, right?

7 A. Certainly.

8 Q. So something over 850 milliosmoles would not be a

9 good idea to inject intravitreally, right?

10 A. Right. And that doesn't mean that I would find it

11 acceptable to administer something under that but well above

12 what is normally considered iso-osmotic.

13 Q. So your testimony is that you could administer

14 something that's hypertonic, not isotonic, but not something

15 that's too high in terms of its hypertonicity, right?

16 A. The line of questions that you had put me through --

17 THE COURT: Doctor, that's what redirect examination

18 is for. If you could just answer counsel's question.

19 THE WITNESS: Okay.

20 Repeat, please.

21 BY MR. TRASK:

22 Q. Your testimony is that it wouldn't be a good idea to

23 inject a formulation that is too high in terms of its

24 hypertonicity, but something that is somewhat hypertonic would

25 be okay to administer?

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BARRETT E. RABINOW, PhD - CROSS 1174

1 develop a drug that is going to be administered to potentially

2 millions of people with that degree of osmolarity? There's a

3 difference there. There's a risk-benefit equation that your

4 question does not recognize.

5 Q. Doctor, my question was simpler.

6 The eye is remarkably tolerant to hypertonic

7 solutions, correct?

8 A. Yes. I said that.

9 Q. Let's turn to the Saishin reference. This is

10 Defendants' Exhibit 2751. I believe this is one in both

11 binders.

12 Can you put up 2751, please.

13 Doctor, you've relied on the Saishin reference during

14 your direct testimony?

15 A. Yes.

16 Q. And you said it provided a motivation to administer

17 VEGF Trap intravitreally, right?

18 A. Yes.

19 Q. Saishin was a study in mice, right?

20 A. Yes.

21 Q. And it involved administration of VEGF Trap?

22 A. Yes.

23 Q. And the authors were comparing two routes of

24 administration for the VEGF Trap, subcutaneous and

25 intravitreal, right?

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1223

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.

10 - - -

11 Proceedings had in the bench trial of the above-styled

12 action on June 20, 2023, before Honorable Thomas S. Kleeh

13 District Judge, at Clarksburg, West Virginia.

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1225

(Video deposition of Karen Chu)

1 Tuesday Morning Session,

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

3 - - -

4 THE COURT: We convene for day one, week two, of

5 trial. Good morning, Counsel. Happy West Virginia Day to

6 everybody.

7 Mylan may call its next witness.

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

9 Defendants' next witness will be Karen Chu by video

10 deposition. Regeneron identified Ms. Chu in response to our

11 30(b)(6) topics identified in DTX 202, including conception and

12 reduction to practice, the patent examples, and several issues

13 relating to aflibercept development and associated clinical

14 trials.

15 THE COURT: I'll note again Regeneron's objection to

16 playing of the video in its entirety. Objection noted.

17 (Video deposition of Karen Chu.)

18 Q. Thank you. Good morning, Ms. Chu. My name is Deanne

19 Mazzochi. Can you please state your full name and address for

20 the record.

21 A. Yes. Karen Chu, and my home address is 73 Richbell

22 Road, White Plains, New York 10605.

23 Q. And then what was your initial role and

24 responsibilities at Regeneron?

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

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1226

(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.

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1494

GREGORY MACMICHAEL, MD - CROSS

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.

1496

GREGORY MACMICHAEL, MD - CROSS

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.

1495

GREGORY MACMICHAEL, MD - CROSS

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.

1497

GREGORY MACMICHAEL, MD - CROSS

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

1525

1

2 UNITED STATES DISTRICT COURT

3 NORTHERN DISTRICT OF WEST VIRGINIA

4 Regeneron Pharmaceuticals, Inc.

5 Plaintiff,

6 VS. CIVIL ACTION NO.

7 1:22-cv-61

8 Mylan Pharmaceuticals, Inc., and

9 Biocon Biologics, Volume 7

10 Defendants.

11 - - -

12 Proceedings had in the bench trial of the above-styled

13 action on June 21, 2023, before Honorable Thomas S. Klee

14 District Judge, at Clarksburg, West Virginia.

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1527

1 Wednesday Afternoon Session,

2 June 21, 2023, 9:00 a.m.

3 - - -

4 THE COURT: Day seven, I think, we convene for trial.

5 Counsel is present. Dr. MacMichael is on the stand. I believe

6 we're ready for redirect.

7 Is that correct, Counsel?

8 Madam Court Reporter is ready. You may proceed.

9 MR. SALMEN: Yes, Your Honor. For the first portion

10 of my redirect, I'm probably going to have to get into some

11 information that has been designated confidential. So pursuant

12 to your previous order, we ask for a sealed courtroom.

13 THE COURT: Understood.

14 In an effort to get everyone their steps in early

15 this morning, those of you not permitted to be here under the

16 Court's protective order, if I could ask you to step out. We

17 would certainly appreciate it.

18 We'll also ask the court security, once those folks

19 have vacated the premises, to seal our courtroom, please.

20 Thank you so much.

21 (The following proceedings (1527/23 to 1533/12) were

22 had under seal, and are filed under separate cover.)

23

24

25

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1526

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1533

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12 (Courtroom unsealed.)

13 THE COURT: Welcome back, everybody.

14 Counsel, you may proceed.

15 MR. SALMEN: Thank you, Your Honor.

16 BY MR. SALMEN:

17 Q. Dr. MacMichael, do you recall Mr. Berl asking you the

18 question "Polysorbate in Claim 1 is being used as a

19 surface-active agent to prevent aggregation and denaturation?"

20 A. I don't recall the specific question.

21 Q. That appears at trial transcript page 1455. Why

22 don't we put that on the screen to refresh your recollection.

23 I'll give you a moment to read that.

24 A. Yes.

25 Q. Do you recall this question?

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1679

KENNETH S. GRAHAM, PhD - DIRECT

1 done so I could understand the types of things that had been

2 tested, what the results were. So I went through and reviewed

3 the previous stability studies and things that we had conducted

4 and in formulation development.

5 Q. Were all of the prior aflibercept formulations

6 intravitreal formulations?

7 A. No.

8 Q. What were some of the others used for?

9 A. So aflibercept was originally developed to treat

10 cancer. So it was -- the idea was it would stop tumors from

11 growing. So we had looked at IV, maybe some subcu routes, but

12 the predominant work was focused on IV.

13 Q. And when you were tasked with developing an

14 intravitreal formulation of aflibercept, did you consider using

15 the prior formulation for cancer for that purpose?

16 A. No. So the cancer formulation was designed to be a

17 concentrate that you would put into an IV bag, dilute out, and

18 give to a patient through an IV. So it had a really high

19 osmolality, like 1100, 1160 milliosmoles. It had a lot of

20 sucrose in it, 20 percent sucrose. And there was concerns that

21 sucrose can be toxic to the eye. Different buffer system.

22 Q. Now, when was it that you first attempted to develop

23 an improved intravitreal formulation of aflibercept?

24 A. Well, the improved version came after our first

25 version started to fail. And this was -- I'm sorry. I was

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1681

KENNETH S. GRAHAM, PhD - DIRECT

1 that point.

2 Q. Were the objectives of having a formulation that

3 was -- had high stability and a high concentration, were those

4 compatible or in contention with one another?

5 A. Well, to put it simply, they're like opposites. So

6 if you have a lower concentration formulation, they tend to be

7 more stable. As you make the concentration higher, the

8 stability goes down. And this is because, at least with

9 aflibercept, the primary degradation pathway is molecules

10 coming together.

11 So it's just -- the more concentrated, the more

12 molecules, the greater the chance that they'll come together

13 and aggregate. You know, if you want to put it in an equation,

14 it goes up as the square of the concentration. So, you know,

15 you double the concentration, you go from 10 to 20, it's the

16 difference between a rate of 100 and a rate of 400 if I can

17 still do math.

18 Q. Why was it that you were aiming to develop a

19 formulation with a high concentration of aflibercept?

20 A. So this is for an injection into the eye. Based on

21 my experience when my mother was treated for AMD, an injection

22 into the eye is really traumatic. You know, even if you go

23 once a month, it takes a couple days out of the person's life.

24 There's a lot of risk associated with it. A lot of bad things

25 can happen. And we wanted to be able to have as long an

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1680

KENNETH S. GRAHAM, PhD - DIRECT

1 going to say oh, crap, you know, now what do we do? because

2 everything is falling apart.

3 And it was pretty much, all right, we have to have

4 this trial -- these clinical trials to keep running. We have

5 to be able to dose the patients. What do we do?

6 So we started looking at the cause of what was

7 happening with the first formulation. We figured out -- or I

8 figured out that exposure to the shear stress going through the

9 tiny needle that's used for intravitreal injections was likely

10 causing the particles to form. And we began working on that,

11 really, mid of 2005, May time frame, I would say.

12 Q. Now, when you set out to develop an improved

13 intravitreal formulation of aflibercept, did you have any

14 objectives in mind relating to the stability of the

15 formulation?

16 A. So we wanted to ensure that the product had a minimum

17 two-year shelf life. We were looking to make the most stable

18 product possible; so we were concerned about having very pure

19 aflibercept to start with. That was a focus in the pilot

20 manufacturing, and then we wanted to sustain that.

21 Q. Did you have any objectives in mind regarding the

22 concentration of aflibercept in the intravitreal formulation?

23 A. So the desire was to have a -- I'm going to use the

24 words "high-concentration formulation." And we tested a range

25 of concentrations, but we didn't have a specific one in mind at

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1 efficacious range as possible.

2 Q. Now, if the goal was to get more drug into the

3 patient's eye, why couldn't we just use a lower concentration

4 formulation and inject more of it?

5 A. Well, the eye is a closed thing. It's kind of

6 like -- I don't know -- a ping-pong ball. You just have that

7 much volume in there. And when you go to inject it, you run

8 the risk of increasing the pressure. So you can't put a lot of

9 volume in it.

10 Based on what I understand to be the limits, you

11 know, you certainly don't want to inject more than 100

12 microliters. You know, 50 microliters is considered to be an

13 optimal injection.

14 MR. RAKOCZY: Objection, Your Honor. This witness

15 has not been qualified as an expert in ophthalmology or

16 intravitreal injections.

17 THE COURT: Understood. Sustained.

18 But you can continue. I recognize it's background

19 information.

20 MR. TRASK: Thank you, Your Honor.

21 BY MR. TRASK:

22 Q. So about -- can you just give the Court a sense for

23 how much is the volume that we're talking about here in these

24 formulations that would be injected.

25 A. So I don't know if you've ever played with the

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1 A. Yes, I was.

2 Q. What was your involvement?

3 A. So I supplied data and data tables to the attorney

4 who drafted the document.

5 Q. Were those the same data tables that appear in the

6 '865 patent itself?

7 A. The data is the same that appears in the patent, yes.

8 Q. And did you also review the provisional application

9 before it was filed on June 16th, 2006?

10 A. Yes, I did.

11 Q. And you're familiar with the contents of that

12 provisional application?

13 A. Yes, I am.

14 Q. All right. I'd like to ask you about some of the

15 internal work you did at Regeneron leading and relating to your

16 invention.

17 So first let's take a look at PTX 2293.

18 What is this document, Dr. Graham?

19 A. It's one of Regeneron's laboratory notebooks. It

20 looks like it belonged to Kelly Frye.

21 Q. And remind us. Who's Kelly Frye?

22 A. So she was one you of my colleagues. She worked in

23 the lab alongside of me.

24 Q. Does she have a PhD as well?

25 A. She does.

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1 and check how it is.

2 Q. So if we look at the second paragraph shown on this

3 page of the exhibit, can you make out what's written there

4 highlighted in yellow?

5 A. It's getting to be a stretch; but yes, it says,

6 "There is a problem with the physical stability of VEGF Trap in

7 the current IVT formulation above 10 mg/mL, VEGF Trap.

8 Specifically, particulate is seen after high-concentration

9 formulations are pulled into a syringe and ejected into vials

10 or into a vial. Therefore, a more stable ITV formulation is

11 essential."

12 Q. Does this help explain why your group was researching

13 more stable intravitreal formulations of aflibercept?

14 A. Yes.

15 Q. What are the types of stress conditions that were

16 used in the stability studies your group ran?

17 A. It was dependent on the study. But, typically, we

18 would look at agitation stress. Agitation stress is you take

19 the container of the formulation and you put it on a lab scale

20 vortexer, which is like a paint shaker. And it just shakes it

21 up.

22 We would do thermal stress. So we would look at it

23 at a range of temperatures. Sometimes we would just use

24 accelerate and stress temperatures like 25, 37, and 45 to kind

25 of get an early read on what's going on.

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1 Q. And she's your coinventor on the '865 patent?

2 A. Yes, she is.

3 Q. Did you review this lab notebook, PTX 2293, as part

4 of your role in Regeneron's formulation development group?

5 A. Yes, I did.

6 Q. You're familiar with its contents?

7 A. Yes.

8 Q. Let's turn to page 58 of this document. What's shown

9 on this page of the laboratory notebook?

10 A. So this is a protocol for a stability study. This is

11 Protocol Number 195.

12 Q. What is a stability study, Dr. Graham?

13 A. So a stability study is a collection of tests and

14 formulations or formulations containers and tests that we

15 assemble and conduct to look at the stability of a formulation.

16 The protocol's kind of like a contract in that it tells you

17 what you're going to test, what tests you're going to do, and

18 when you're going to do them.

19 Q. And what other types of documentation would be

20 associated with a stability study?

21 A. So typically we create what's called a pull schedule.

22 And the pull schedule outlines when we're going to do specific

23 thermal tests. So thermal tests basically put the formulation

24 in a refrigerator or a freezer, an oven. And, you know, you

25 say I'm going to come back three days, one month, six months,

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1 We'd also do freeze/thaw, is another one that we

2 would use.

3 Q. Let's take a look at the formulations that you tested

4 in this SS195 stability study. This is under the heading

5 "Procedure" on page 58 of PTX 2293.

6 Doctor, how many different formulations did you test

7 in this study?

8 A. There were five.

9 Q. And can you make out what is the makeup of the

10 Formulation Number 2 in the study?

11 A. Okay. So what we would do is we had a base

12 formulation which was common to all the formulations that are

13 being tested in the study. That's in the little snippet out

14 above. And that says that we used 10 millimolar

15 phosphate, .03 percent polysorbate 20, 40 mg/mL of VEGF Trap,

16 and the pH was 6.25.

17 In addition, that formulation also contained

18 40-millimolar sodium chloride and 5 percent sucrose.

19 Q. And does that Formulation Number 2 stand out to you

20 today, Dr. Graham?

21 A. It does.

22 Q. Why is that?

23 A. It's what ultimately became the commercial Eylea

24 formulation.

25 Q. And does this laboratory notebook also indicate when

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1 that formulation was first made?

2 A. Yes, it does.

3 Q. Let's turn to page 60 of PTX 2293.

4 What's shown here, Dr. Graham?

5 A. So this is the compounding record; so the mixing of

6 the formulation. And it's for Formulation Number 2 with a

7 specific lot number. And it was conducted on September 30th of

8 2005.

9 Q. To your knowledge, is this the very first time that

10 the formulation was made that is known today as the Eylea

11 formulation?

12 A. I believe it is, yes.

13 Q. And who made this formulation?

14 A. This was done by Kelly.

15 Q. Okay. And what was the date?

16 A. September 30th, 2005.

17 Q. Did your group test the stability of this formulation

18 that was run as part of Stability Study SS195?

19 A. Yes, we did.

20 Q. And what did you find?

21 A. We found it to be a very good stable formulation.

22 Q. Is there stability data for this same composition in

23 the '865 patent?

24 A. For the same composition in terms of the excipients,

25 yes, there is. It's for a different lot of material.

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1 A. Yes, I am.

2 Q. How is it that you're familiar with this notebook?

3 A. I reviewed its contents when I joined the VEGF Trap

4 team.

5 Q. Let's turn to page 34 of the notebook.

6 What's shown on this page, Dr. Graham?

7 A. It says that the protocol for stability VEGF

8 Trap 065.

9 Q. And is there a date on this stability study protocol?

10 A. Yes, there is.

11 Q. Can you make out the date?

12 A. It was signed by Kelly on December 4th of 2003. I

13 can't make out the other signature.

14 Q. That's okay.

15 Let's look at the procedures section of this protocol

16 on page 34. What types of things were varied with respect to

17 the formulations studied in this stability study?

18 A. So a couple things. There were different buffers

19 used. We changed the concentration of sodium chloride. We

20 tested 50 and 100 millimolar. We tested polysorbate. We

21 tested PEG. We tested a couple of different concentrations of

22 sucrose.

23 Q. And what is Formulation Number 2 in this study?

24 A. Formulation Number 2 was a 50 mg/mL VEGF Trap

25 formulation with 10-millimolar phosphate, 50-millimolar sodium

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1 Q. Do you recall which example in the '865 patent this

2 is?

3 A. So it's Stability Study 207, and I think it is

4 Example 3.

5 Q. And so as of September 30th, 2005, had you and your

6 coinventors made and tested the stability of the formulation

7 that eventually became the commercial Eylea formulation?

8 A. Yes, we did.

9 Q. Let's look at Example 1 of the '865 patent. You see

10 that on the screen, Doctor?

11 A. Yes, I do.

12 Q. Do you see that the formulation in Example 1 is

13 highlighted in yellow?

14 A. Yes, I do.

15 Q. What's the term VGFT-SS065 that's shown as part of

16 Example 1?

17 A. So that's our stability study number. The VGFT

18 identified the product. 065 is it's the 65th study we put up.

19 Q. Was there a protocol associated with this stability

20 study?

21 A. Yes, there was.

22 Q. Let's look at PTX 2292.

23 What's this document, Doctor?

24 A. It's one of Kelly Frye's notebooks.

25 Q. And are you familiar with that document?

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1 chloride, .1 percent polysorbate 20, and 5 percent sucrose.

2 Q. Let's compare this formulation, Formulation Number 2

3 in Stability Study SS065, with the formulation in Example 1 of

4 the '865 patent.

5 Do you see those both on the screen?

6 A. Yes, I do.

7 Q. Can you confirm whether or not the same formulation

8 is used in both of these documents?

9 A. They're identical.

10 Q. Does this formulation have a buffer?

11 A. Yes, it does.

12 Q. What's that?

13 A. 10-millimolar phosphate.

14 Q. Does it have an organic cosolvent?

15 A. Yes, it does.

16 Q. What's that?

17 A. Polysorbate 20.

18 Q. Can that also be called a stabilizer?

19 A. Yes, it can.

20 Q. Does it also have a stabilizing agent?

21 A. That would be 5 percent sucrose.

22 Q. Is the VEGF Trap referenced here in these

23 formulations aflibercept?

24 A. It is.

25 Q. And what's the concentration of VEGF Trap in this

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1 formulation?

2 A. 50 mg/mL.

3 Q. Did you do size-exclusion chromatography analysis on

4 this study?

5 A. Yes, we did.

6 Q. Let's look at PTX 1921.

7 Is this the SEC data for SS065?

8 A. Yes, it is.

9 Q. For Formulation Number 2 stored at 5 degrees C, what

10 was the starting percent native VEGF Trap percent?

11 A. It was 98.8 percent.

12 Q. And what was the value at three months stored at 5C?

13 A. 98.7 percent.

14 Q. And what about at six months?

15 A. 98.3 percent.

16 Q. What does that tell you about the percent native

17 conformation of this sample at two months at 5 degrees Celsius?

18 A. I would expect it to be greater than 98.7 percent.

19 Q. Why is that?

20 A. So when a protein aggregates, it's like rolling a

21 ball downhill. It goes -- the level of purity goes down. It

22 doesn't roll back up.

23 Q. Let's look at the bottom of this spreadsheet,

24 PTX 1921. Does this information tell you when the six-month

25 pull sample in Stability Study 065 was analyzed by SEC?

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1 opinion.

2 THE COURT: It is, Counsel. You need to reword that

3 question, please.

4 BY MR. TRASK:

5 Q. Okay. Doctor, what did you understand the percent

6 native conformation at 50 mg/mL reported in this table would

7 tell you about the percent native conformation of a 40 mg/mL

8 formulation of aflibercept at 5C for two months?

9 MR. RAKOCZY: Objection, Your Honor. It's the exact

10 same question.

11 THE COURT: It's not exact. It's close.

12 But I assume, Counsel, this is part of the work in

13 developing the ultimate formulation that results in the patent

14 at issue, correct?

15 MR. TRASK: Absolutely, Your Honor.

16 THE COURT: With that understanding, objection

17 overruled. Would you repeat your question, Counsel.

18 BY MR. TRASK:

19 Q. Dr. Graham, for the third time, I suppose, what did

20 you understand the percent native conformation at 50 mg/mL, as

21 reported in this data sheet, tell you about the percent native

22 conformation of a 40 mg/mL formulation of aflibercept stored at

23 5 degrees Celsius for two months?

24 A. Okay. So as the concentration of a formulation

25 increases -- at least as the concentration of aflibercept

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1 A. Yes, it does. It says it was May 24th, 2004.

2 Q. Let's look back up at the Formulation Number 2 in

3 this spreadsheet. Now, you've said that this formulation

4 involved aflibercept at 50 mg/mL, right?

5 A. Yes, it does.

6 Q. What did this tell you about the percent native

7 conformation of 40 mg/mL formulation of aflibercept stored at

8 5 degrees Celsius for two months?

9 MR. RAKOCZY: Objection, Your Honor. Again, the

10 witness has not been qualified as an expert.

11 MR. TRASK: Your Honor, if I may, this is data from

12 his group that he would -- he testified he routinely relied

13 upon in performing the studies that led to the claimed

14 invention, and he testified that he's run over 100,000

15 size-exclusion chromatography analyses during his time at

16 Regeneron. He has personal knowledge of this data and relied

17 upon it in the course of developing the inventions.

18 THE COURT: Understood.

19 Counsel.

20 MR. RAKOCZY: Your Honor, that didn't have anything

21 to do with my objection. My objection is -- let me back up.

22 I'm not objecting that this formulation tested a

23 50 mg/mL. That's the whole point. That's what this is. The

24 question was asking for an opinion on how does that bear on a

25 40 mg/mL, a different formulation. That's asking for an expert

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1 formulation increases, generally the rate of -- the rate of

2 aggregation goes up. So it's more concentrated, more crowded,

3 faster aggregation.

4 If you got a rate at 50 mg/mL, you can predict

5 reliably that the rate at 40 mg/mL is going to be less in the

6 same formulation.

7 MR. RAKOCZY: Objection, Your Honor. Again, that's

8 pure expert opinion predicting what would and would not happen.

9 That's for the experts.

10 MR. TRASK: I disagree, Your Honor. He's a scientist

11 talking about the work he did leading to the inventions claimed

12 in that patent being asserted in the suit. This is routine

13 testimony at patent trials.

14 THE COURT: I don't believe the word "routine" shows

15 up in the rules of evidence, but I understand the background

16 involved here. Objection overruled.

17 BY MR. TRASK:

18 Q. Did you view the results of this study as promising,

19 Dr. Graham?

20 A. Yes.

21 Q. Let's turn to Example 3 of your '865 patent, Doctor.

22 You see Example 3 on the screen?

23 A. I do.

24 Q. You see the formulation used in this study is

25 highlighted in yellow?

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KENNETH S. GRAHAM, PhD - DIRECT 1711

1 A. Yes, it is.

2 Q. What is the term there, VGFT-SS207?

3 A. That is Stability Study 207, 207th study.

4 Q. That's another stability study you performed?

5 A. Yes.

6 Q. Let's look at PTX 1825, and I want to see page 85 of

7 this document.

8 Now, is this the protocol for Stability Study

9 VGFT-SS207?

10 A. Yes.

11 Q. This stability study is part of a larger document

12 that was produced in this case, all of which appeared to relate

13 to SS207.

14 Is this how the documentation for stability studies

15 was kept in the ordinary course of Regeneron's business?

16 A. So yes, it was. We kept what was called a study

17 file, and that collected all the paper. We also kept lab

18 notebooks as well.

19 Q. Okay. Let's turn to page 92 of this exhibit. Is

20 this the approval page for the stability study we just

21 discussed?

22 A. Yes, it is.

23 Q. Is that your signature on the page, Doctor?

24 A. It is.

25 Q. What does this page indicate your role was with

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KENNETH S. GRAHAM, PhD - DIRECT 1713

1 Q. Does this formulation have a buffer?

2 A. Yes.

3 Q. What's that?

4 A. 10-millimolar phosphate.

5 Q. Does it have an organic cosolvent?

6 A. Yes, it does.

7 Q. What's that?

8 A. .03 percent polysorbate 20.

9 Q. Is there a stabilizing agent?

10 A. Yes, there is.

11 Q. What's that?

12 A. 5 percent sucrose.

13 Q. And the VEGF Trap here is aflibercept?

14 A. Yes, it is.

15 Q. And what's the concentration?

16 A. 40 mg/mL.

17 Q. Let's turn to Table 1 of the SS207 protocol. This is

18 PTX 1825 at page 86.

19 You see that table on the screen?

20 A. I do, yes.

21 Q. Did this study involve testing the formulation

22 stability in different containers?

23 A. It did.

24 Q. Was a glass vial one of those containers?

25 A. So the glass vial was what's listed as Device

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KENNETH S. GRAHAM, PhD - DIRECT 1712

1 respect to SS207?

2 A. It says that I was the study director.

3 Q. And what does the role of study director entail?

4 A. Well, that meant I was the responsible party. So I

5 had to ensure pulls were done as scheduled, make sure there was

6 staff assigned to do the analysis, do some of the analysis

7 myself, summarize the data, interpret the data, give readouts

8 to management in terms of what we had, prepare presentations.

9 Pretty much name it.

10 Q. And when did you sign this protocol, Dr. Graham?

11 A. On the 16th of January 2006.

12 Q. And so had you made the formulation that was tested

13 in SS207 prior to January 2006?

14 A. Yes. It actually was made the previous year, I think

15 in October of 2005.

16 Q. I'd like you to compare the formulation identified in

17 the study protocol for SS207 -- that's PTX 1825, page 85 --

18 with the formulation in Example 3 of the '865 patent. That's

19 PTX 2, page 8, Column 9.

20 Do you see those on the screen?

21 A. I do.

22 Q. Is the formulation that you studied in Stability

23 Study 207 the same as the one disclosed in Example 3 of the

24 '865 patent?

25 A. They're identical, yes.

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KENNETH S. GRAHAM, PhD - DIRECT 1714

1 Number 7.

2 Q. Okay. Was there a pull schedule for this stability

3 study as well?

4 A. Absolutely.

5 Q. Let's look at that. Page 172 of PTX 1825.

6 Is this the pull schedule for SS207?

7 A. Yes, it is.

8 Q. What was the two-month pull date for this study?

9 A. March 21st of 2006.

10 Q. And so what does that mean? What happened on that

11 date?

12 A. So this is for a 5-degree C condition. That meant on

13 the 21st analysts went in, removed the samples from the

14 5-degree, and began performing the tests that were outlined in

15 the protocol.

16 Q. And was size-exclusion chromatography one of the

17 tests performed on these samples?

18 A. Yes, it was.

19 Q. Let's look at PTX 2277 at page 15. This is a

20 spreadsheet produced in native format.

21 Does the spreadsheet shown in this document report

22 the SEC data for the glass vial Device Number 7?

23 A. It does.

24 Q. What did the SEC data show after two months' storage

25 at 5C?

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1 THE COURT: Well, let's stick to those actual  
2 documents as opposed to what's his interpretation thereof.  
3 Otherwise, sustained.  
4 MR. TRASK: Thank you, Your Honor.  
5 BY MR. TRASK:  
6 Q. Let's look at PTX 672.  
7 What is this document, Doctor?  
8 A. So this is the pharmaceutical development section  
9 that I wrote for Eylea.  
10 Q. Section of what?  
11 A. The BLA.  
12 Q. Is this the Eylea BLA?  
13 A. Yes.  
14 Q. Okay. And you're familiar with this document?  
15 A. Yes.  
16 Q. It's a long document, 483 pages. What was your  
17 specific involvement with this document?  
18 A. I wrote it.  
19 Q. The whole thing?  
20 A. Yes.  
21 Q. Okay. If we turn to page --  
22 A. Sorry.  
23 THE COURT: Understood, Doctor.  
24 BY MR. TRASK:  
25 Q. If we turn to page 26 of this document, Dr. Graham,

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1 intravitreal formulations of aflibercept, were you aware of  
2 public information about other existing protein formulations?  
3 A. Some, yes.  
4 Q. And in the course of your work, did you ever consider  
5 taking the aflibercept and just plugging it into a formulation  
6 that had been used to stabilize a different protein?  
7 A. No.  
8 Q. Why not?  
9 A. All right. So proteins are individuals. No two  
10 proteins really behave exactly the same. They have different  
11 likes and dislikes. So a formulation that works well for one  
12 protein may not work well for another one. Things like pH  
13 are critical. Choice of stabilizer can be critical.  
14 MR. RAKOCZY: Again, objection, Your Honor. Again,  
15 that's expert opinion testimony. He can testify about his  
16 personal experience with aflibercept, but now he's venturing  
17 into other proteins and what would and would not work.  
18 THE COURT: That's sustained.  
19 BY MR. TRASK:  
20 Q. Moving on, when developing your invention, was  
21 tonicity a consideration for you, Doctor?  
22 A. To a degree.  
23 Q. Okay. Can you explain that?  
24 A. So we knew that we -- or thought that we did not want  
25 to inject something that was 1,000 milliosmoles. We thought

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KENNETH S. GRAHAM, PhD - DIRECT 1740

1 did you write this section of the document as well?  
2 A. I did.  
3 Q. And what is this section of the document?  
4 A. It is describing the choice of organic cosolvent and  
5 the selection of the concentration for the formulation.  
6 Q. If we look at the last paragraph on page 26 of  
7 Exhibit PTX 672, do you see where it says polysorbate 20 was  
8 selected as the organic cosolvent?  
9 A. Yes. It says polysorbate 20 was selected as the  
10 organic cosolvent because a lower concentration was required to  
11 stabilize the VEGF Trap when subjected to agitation stress.  
12 Q. Why did you call polysorbate 20 an organic cosolvent  
13 in this document?  
14 A. Because that's what I was using it for in the  
15 formulation.  
16 Q. And you understood, when you wrote this document,  
17 that it would be submitted to the FDA?  
18 A. Yes.  
19 Q. And was it, in fact, submitted to the FDA?  
20 A. Yes, it was.  
21 Q. And this is an accurate statement?  
22 A. Yes, it is.  
23 Q. Okay.  
24 We can take that down.  
25 Now, when you were working to develop more stable

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1 that could potentially be bad. But we weren't necessarily  
2 concerned that we had to be exactly isotonic with the  
3 environment. We figured we had wiggle room.  
4 Q. And you testified earlier that Example 5 of your '865  
5 patent was not an isotonic formulation; is that right?  
6 A. That is correct.  
7 Q. Did you nonetheless consider the formulation of  
8 Example 5 to be a candidate formulation for intravitreal  
9 injection?  
10 A. Yes.  
11 Q. Now, does -- the '865 patent on which you're named as  
12 an inventor, does that identify which of the formulations it  
13 discloses is the one that corresponds to Regeneron's Eylea  
14 formulation?  
15 A. No, it does not.  
16 Q. Does it indicate anything about whether Regeneron  
17 preferred one of those formulations over another?  
18 A. Not that I've seen in the document, no.  
19 Q. Were you permitted as a Regeneron employee to  
20 publicly identify the formulation for Eylea before the Eylea  
21 product was released onto the market?  
22 A. I was not.  
23 Q. And to your knowledge, prior to Eylea's launch, was  
24 the formulation that you invented that eventually became the  
25 commercial Eylea formulation ever publicly identified as

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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 8  
8 Biocon Biologics,  
9 Defendants.  
10 - - -  
11 Proceedings had in the bench trial of the above-styled  
12 action on June 22, 2023, before Honorable Thomas S. Kleeh  
13 District Judge, at Clarksburg, West Virginia.  
14 - - -  
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33 Transcript produced by computer-aided transcription.  
  
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1 Thursday morning session,  
2 June 22, 2023, 9:00 a.m.  
3 - - -  
4 THE COURT: This Thursday we convene for day eight of  
5 trial. Counsel is present. The Court did see the joint  
6 stipulation the parties filed. The Court's digital signature  
7 is being affixed to that as we speak and will be entered  
8 forthwith.  
9 Anything else we need to take up before we hear from  
10 Mylan's next witness, then?  
11 MS. OBERWETTER: No, Your Honor. We're ready to call  
12 our next witness.  
13 THE COURT: Okay.  
14 From the defense standpoint, anything else?  
15 MS. MAZZOCHI: No, not right now, Your Honor.  
16 THE COURT: All right. Regeneron may call its next  
17 witness, then.  
18 MS. OBERWETTER: Yes, Your Honor. Regeneron calls  
19 its next witness, Dr. Karl Csaky.  
20 THE COURT: Hello, again, Dr. Csaky.  
21 If you wouldn't mind repeating the drill. Come all  
22 the way to the front. We'll have you sworn in and ask you to  
23 take the witness stand. Thank you, sir.  
24 **KARL CSAKY, MD, PHD, PLAINTIFF'S WITNESS, SWORN**  
25 MS. OBERWETTER: Before we start, Your Honor, I

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1 KARL CSAKY, MD, PHD - DIRECT  
2 believe everyone should have their advance copies of the binder  
3 and slides.  
4 THE COURT: I believe I do. Thank you all very much.  
5 Good morning again, Doctor. If you wouldn't mind  
6 adjusting that mic. Stay close to that for us.  
7 Counsel, you may proceed.  
8 DIRECT EXAMINATION  
9 BY MS. OBERWETTER:  
10 Q. Good morning, Dr. Csaky. Can you please reintroduce  
11 yourself to the Court.  
12 A. Yes. My name is Karl Csaky. I'm a retina specialist  
13 from Dallas, Texas.  
14 Q. And we're going to cover -- since you were here with  
15 us last week, we're going to cover some material today that  
16 relates some other of your opinions besides those bearing on  
17 infringement. I'd like to start first with your definition of  
18 the POSA.  
19 If we can please pull that up onto the screen.  
20 For the record, that's PDX 8.002.  
21 Can you please read for us your definition of the  
22 POSA.  
23 A. Yes. So this is the definition that I used during my  
24 opinions.  
25 A person of ordinary skill in the art relevant to the  
claims is an ophthalmologist with experience in treating

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2012

BERNHARDT TROUT, PHD - DIRECT

1 Q. Do you understand Mylan's definition of the POSA to

2 differ substantially from yours?

3 A. No, not much.

4 Q. Would any of your opinions be different if Mylan's

5 definition were used instead of yours?

6 A. No.

7 Q. And did you apply the Court's claim constructions in

8 your validity analysis?

9 A. Yes, I did.

10 Q. I'd like to ask about some background issues before

11 we get into the prior art itself.

12 What is aflibercept?

13 A. Well, aflibercept, as we've heard for the past couple

14 weeks, is what's known as a fusion protein. So it's made up of

15 three different pieces of three different proteins. And we

16 could call it a Frankenstein molecule because it's a nonnatural

17 molecule.

18 Q. Let's look at PTX 1826, the Aruffo article. Did you

19 review this article in connection with your work in the case?

20 A. Yes, I did.

21 Q. And if we look at page 1 and blow up one excerpt,

22 beginning with "fusion proteins" and "these proteins consist,"

23 can you explain what Aruffo is telling us.

24 A. Yes. And I guess just to be clear, it continues,

25 "These proteins consist of the constant regions of

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2014

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1 protein formulations?

2 A. Yes, I do.

3 Q. Did Dr. Rabinow identify any fusion protein drug

4 products on this slide?

5 A. No. And as a matter of fact, each of those is

6 highlighted because they're all antibody, noting that

7 ranibizumab is an antibody fragment, a piece of an antibody.

8 Q. And the next one in the chart, that's bevacizumab, is

9 that also called Avastin?

10 A. Yes. That's correct.

11 Q. And is that a fusion protein or an antibody?

12 A. No. That's an antibody.

13 Q. Now, do fusion proteins and antibodies have the same

14 properties?

15 A. No.

16 Q. Okay.

17 Let's bring up the Fast reference. That's PTX 1835.

18 Did you review this article in connection with your

19 work on the case?

20 A. Yes, I did.

21 Q. And if we go to page 15. And we'll also show an

22 excerpt from page 19 below it, beginning in the paragraph that

23 starts "intact antibodies."

24 Can you explain the relevance of the Fast disclosure?

25 A. Yes. And I've highlighted, I think, the relevant

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2013

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1 immunoglobulin, typically mouse or human, fused to an unrelated

2 protein or protein fragment."

3 So basically what I said, they're nonnatural proteins

4 that are made by fusing various parts of other proteins.

5 Q. And what are the parts of the aflibercept fusion

6 protein?

7 A. So one of the parts is what's called the constant

8 domain of an antibody, so a piece of an antibody. And then

9 there are two other parts from two different receptor proteins.

10 Q. You heard Dr. Rabinow testify last week about a

11 fusion protein and an antibody being largely the same thing.

12 Do you agree?

13 A. No, I don't agree.

14 Q. How are fusion proteins different from antibodies?

15 A. Well, as I've been emphasizing, fusion protein is

16 made of different pieces of other proteins. It's not natural.

17 Antibodies have evolved over time or are part of nature.

18 Q. Were fusion proteins known as of 2006?

19 A. Yes.

20 Q. Were any commercially available?

21 A. Yes.

22 Q. Let's look at one of the slides shown by Dr. Rabinow.

23 It was his Slide 47.

24 Let's put that on the screen.

25 Do you remember this chart you put up of stable

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2015

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1 pieces of that section.

2 "In comparison with native IgG proteins" -- like the

3 ones on the previous slide -- "wherein interdomain interactions

4 presumably here evolved to provide mutual stabilization, fusion

5 proteins may lack such stabilizing interdomain stabilization."

6 And then a little skip there, but goes on to say,

7 "This has been seen in other artificial fusion proteins as

8 well."

9 And this referenced the Souillac, which is a bit more

10 of a technical article.

11 Q. What is this conveying with respect to the relative

12 expected stability of antibodies on the one hand compared to

13 fusion proteins on the other?

14 A. Well, this is conveying that the skilled person or

15 the person of ordinary skill in the art would expect that

16 fusion proteins could be less stable than antibodies.

17 Q. And the Souillac reference that's cited for this

18 proposition, in what year was that published?

19 A. That was published, as highlighted here, in 2005.

20 Q. And the proposition about the expected relative

21 stability of fusion proteins compared to antibodies, would that

22 have been consistent or inconsistent with the POSA's thinking

23 as of 2006?

24 A. That would have been consistent. This is

25 illustrative of what the POSA would expect.

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2016

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1 Q. Now, I'd like to turn to obviousness and invalidity

2 over the prior art now, Doctor.

3 Do you understand that Dr. Rabinow testified that the

4 asserted claims of the '865 patent are invalid on three bases:

5 Fraser plus Lucentis; Fraser plus Liu; and, thirdly, Dix?

6 A. Yes.

7 Q. Do you agree with Dr. Rabinow's opinions?

8 A. No, I do not.

9 Q. Let's take them one at a time. And let's start with

10 Lucentis plus Fraser.

11 Let's take a look at 2.13.47.

12 Now, you heard Dr. Rabinow -- or did you hear

13 Dr. Rabinow testify first about Claim 1 and then about the

14 asserted claims?

15 A. Yes, I did.

16 Q. Is that how you conducted your anticipation and

17 obviousness analyses?

18 A. No, that is not. I started with the asserted

19 claims -- for example, Claim 4 here -- noting that Claim 4

20 depends on Claim 2. Claim 2 depends on Claim 1. And I looked

21 at all of that together.

22 Q. Now, in order to reference Dr. Rabinow's testimony

23 and demonstratives, I'm going to go back to his demonstratives

24 even though they address Claim 1 and the dependent claims

25 separately.

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2018

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1 specifically say otherwise, I'd like you to assume for the rest

2 of your testimony about this combination that the POSA would

3 have combined Fraser with Lucentis as Dr. Rabinow urges.

4 Can you make that assumption?

5 A. Okay.

6 Q. Now, let's go back to Claim 1 for a moment.

7 What does Claim 1 recite with respect to the claimed

8 VEGF antagonist?

9 A. Well, it's what's highlighted here. It's a VEGF

10 antagonist. But it's not just any; it's a specific one. It's

11 got to be glycosylated. And it comprises a specific sequence

12 of amino acids that is specifically defined and described in

13 the patent.

14 Q. Let's go to Dr. Rabinow's Demonstrative 51.

15 And what did Dr. Rabinow rely on to meet those

16 limitations in his Fraser plus Lucentis combination?

17 A. Well, Dr. Rabinow relied on this disclosure in Fraser

18 which says VEGF Trap R1R2.

19 Q. And does Fraser disclose the limitations that we're

20 discussing relating to the VEGF antagonist in Claim 1?

21 A. No, it doesn't. It doesn't disclose this sequence.

22 Q. Do you recall that Dr. Rabinow relied on Holash as

23 somehow being incorporated into Fraser?

24 A. Yes.

25 Q. And if we look at the next -- does Fraser incorporate

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2017

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1 Is that okay?

2 A. Okay.

3 Q. Before we get into the various limitations of the

4 claims and the details of these references, do you think a POSA

5 looking to make a formulation to treat eye diseases would have

6 selected Fraser and the Lucentis references from all of the

7 available prior art?

8 A. No.

9 Q. Why not?

10 A. Well, there was quite a bit of prior art. And

11 there's no particular reason why the POSA would be pointed to

12 those two references.

13 Q. Do you think the POSA would have any reason to choose

14 to combine Fraser and the Lucentis references of Gaudreault and

15 Shams?

16 A. No. There's no reason.

17 Q. Is that how formulation research is done, to take a

18 formulation form from one molecule and combine it with another

19 and put them together?

20 A. No, it is not.

21 Q. Is there any reason that Dr. Rabinow provided that

22 you heard to choose these references from amongst all of the

23 prior art?

24 A. No.

25 Q. Now, Doctor, I understand your opinions, but unless I

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2019

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1 Holash?

2 A. No. Holash is just one of the many references in

3 Fraser.

4 Q. Now, I understand your opinion there, but I'd like to

5 look at Holash nevertheless. That's DTX 3549. And we've shown

6 part of page 2 of the Holash reference.

7 Does that disclose the amino acid sequence recited in

8 Claim 1 of the '865 patent?

9 A. No, sir, it does not. It just discloses this

10 schematic here which does not disclose or relate the sequence.

11 Q. Are these disclosures from -- are these the

12 disclosures from Fraser and Holash that Dr. Rabinow relied on

13 to meet these claim limitations about the amino acid sequence

14 of aflibercept?

15 A. Yes.

16 Q. And to be clear, do either disclose the claimed amino

17 acid sequence?

18 A. No, neither do.

19 Q. And did you highlight in red boxes for the

20 disclosures that don't meet the claim limitations in

21 Dr. Rabinow's demonstrative?

22 A. Yes, I did, right here on the screen.

23 Q. Now, do you recall Dr. Rabinow discussing the

24 Papadopoulos reference, DTX 3619?

25 A. Yes, I do.

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BERNHARDT TROUT, PHD - DIRECT 2020

1 Q. Do you understand Papadopoulos to be part of either  
2 of Dr. Rabinow's obviousness combinations?

3 A. It is not.

4 Q. Do any of the references in Dr. Rabinow's obviousness  
5 combinations cite or discuss Papadopoulos?

6 A. No.

7 Q. Now, Doctor, did you prepare a demonstrative exhibit  
8 summarizing the fusion proteins disclosed by Papadopoulos?

9 A. Yes, I did.

10 Q. And were those sequences voluminous in Papadopoulos?

11 A. Yes.

12 And the summary, Your Honor, is here in this table,  
13 all the different -- I just have the names here. You can  
14 imagine each of those sequences is about a page or longer. But  
15 the Papadopoulos discloses all of those.

16 MR. BERL: And for the record, this is marked as  
17 DTX 3619A.

18 BY MR. BERL:

19 Q. Doctor, can you explain what is shown here.

20 A. Yes.

21 So this is a list that I've prepared. On the right  
22 side are different names as disclosed in Papadopoulos. On the  
23 left side are the figures that are in Papadopoulos. Those  
24 figures actually contain the sequences listed out.

25 Q. Doctor, there are a lot of letters on this table.

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BERNHARDT TROUT, PHD - DIRECT 2022

1 page 60 of DTX 3619, the Papadopoulos reference on about  
2 lines 4 to 5?

3 A. Yes. That's correct.

4 Q. Do these two fusion proteins that are denoted R1R2  
5 have the same sequence or different sequences?

6 A. They have different sequences.

7 Q. How do you know?

8 A. Well, I did a comparison. I talked about a different  
9 comparison last week that I did. But I did a comparison here  
10 using the same National Institute of Health software. And I  
11 showed that the sequences, as we say, do not align. In other  
12 words, they're different.

13 Q. How would the POSA interpret the references to VEGF  
14 Trap R1R2 in the literature such as Fraser?

15 A. Well, the POSA would interpret them as meaning a  
16 multiplicity of different sequences.

17 Q. Now, the claims also require that the VEGF antagonist  
18 is glycosylated; is that right?

19 A. Yes. Correct.

20 Q. Very briefly, Dr. Trout, what is glycosylation again?

21 A. Very briefly, it's the addition of carbohydrate  
22 groups, or kind of extended sugar groups, to various sites in  
23 the protein.

24 Q. And why does glycosylation matter?

25 A. Well, I think it could be a number of reasons. But

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BERNHARDT TROUT, PHD - DIRECT 2021

1 I'd like to discuss a couple of them with you. What is Flt1,  
2 or Flt1?

3 A. Yes.

4 So that, Your Honor, might be new in terms of the  
5 abbreviation, but all it means is the same as this VEGF1.  
6 Biologists may have a certain sense of humor in naming  
7 different proteins, but that's just the VEGF R1.

8 Q. So that's VEGF Receptor 1?

9 A. Yes. Correct.

10 Q. And there's also something in here that's referenced  
11 as Flk1. What's Flk1?

12 A. Well, again, Flk1 is just another name for the VEGF  
13 Receptor R2. So the Flt and the Flk together are the R1R2.

14 Q. And we saw earlier that there was a description in  
15 the references that Dr. Rabinow testified about to VEGF R1R2.

16 Do you remember that?

17 A. Yes.

18 Q. And how many fusion proteins does Papadopoulos  
19 describe that fall within that categorization?

20 A. Well, it describes these two. I've just highlighted  
21 in the table, the small reproduction of the table, the two that  
22 I just mentioned. And here on the upper right side is where  
23 they are in the text. And, again, it tells you that R1R2 are  
24 just the Flt1 and the Flk1.

25 Q. And are you showing on the right-hand side part of

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BERNHARDT TROUT, PHD - DIRECT 2023

1 for the standpoint here, I think it matters because, if a  
2 molecule is glycosylated, it makes it bigger, more voluminous.

3 Q. You said that proteins can be glycosylated at certain  
4 sites; is that right?

5 A. Correct.

6 Q. Now, if those sites are present, if those amino acids  
7 are present, will the protein always be glycosylated?

8 A. Not necessarily, no. Not always, I should say.

9 Q. And let's look at the Sinclair reference. That's  
10 PTX 1773. Did you review this reference?

11 A. Yes, I did.

12 Q. And let's look at page 2 of that reference beginning  
13 with the sentence that says, "Most naturally occurring  
14 consensus sequences in secreted proteins are not glycosylated."

15 What is this conveying as relevant to your opinions?

16 A. Well, it's conveying, again, what a POSA would know  
17 and what I just stated, which is that not all proteins are  
18 glycosylated.

19 Q. And is that true even if they have the sites that  
20 would potentially permit glycosylation?

21 A. Yes. That's correct.

22 Q. Let's turn back now to Dr. Rabinow's slides and focus  
23 on the glycosylated requirement.

24 Now, does Fraser teach that VEGF R1R2 is  
25 glycosylated?

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2024

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1 A. No, it does not.

2 Q. Does Fraser say anything about glycosylation?

3 A. No, it does not.

4 Q. Did you hear Dr. Rabinow refer to Papadopoulos with

5 respect to glycosylation?

6 A. Yes.

7 Q. Did Papadopoulos describe glycosylation of the

8 sequence recited in the '865 patent claims?

9 A. No.

10 Q. Is that disclosed anywhere in the prior art, as far

11 as you know?

12 A. Not as far as I know. Not as far as I've seen.

13 Q. Now, if we go back to Papadopoulos at page 82 of the

14 reference, what sequence did Papadopoulos disclose the

15 glycosylation of?

16 A. Well, as I've showed here in this excerpt that there

17 are five possible glycosylation sites. And it describes a

18 different molecule or different fusion protein than the one in

19 the '865 patent.

20 Q. So to be clear, what we have here at line 20 in

21 Papadopoulos at page 82 of the exhibit, is -- that protein

22 that's identified with the glycosylation sites, is that

23 aflibercept or is that a different protein?

24 A. No. That's different protein. Again, I did a

25 comparison between that and aflibercept. And this one is not

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2026

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1 A. Okay.

2 Q. Based on the prior art as a whole, what kind of

3 molecule would the POSA have wanted to use for intravitreal

4 injection?

5 A. Well, the POSA would have wanted to use a relatively

6 small molecule relative to aflibercept, for example, because of

7 the limit of going through the various membranes to reach the

8 retina.

9 Q. Now, Mylan's combination of Lucentis and Fraser

10 relies on the Gaudreault reference as one of the Lucentis

11 references, correct?

12 A. Yes.

13 Q. Okay. We've placed on the screen part of page 6 of

14 the Gaudreault reference. That's Exhibit PTX 1839.

15 What does Gaudreault teach with respect to retinal

16 penetration?

17 A. Well, it teaches what I've basically just said,

18 highlighted here, "Notably, penetration of ranibizumab into the

19 retina is critical for its clinical use. Retinal penetration

20 suggests the availability of ranibizumab to inactivate VEGF at

21 the site of AMD."

22 Q. Now, let's go back to page 1 of Gaudreault,

23 Exhibit 1839 and beginning with this paragraph that starts

24 "ranibizumab."

25 Can you explain what Gaudreault is teaching a person

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2025

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1 the same.

2 Q. Would you know from the glycosylation of a different

3 protein that the protein in the claims of the '865 patent,

4 aflibercept, would be glycosylated?

5 A. No, you would not.

6 Q. Now, let's look at the claims of the '865 patent

7 again and, in particular, if we could look to Claim 14 on

8 page 13 of the reference.

9 Doctor, what does Claim 14 require?

10 A. Well, it requires glycosylation at these specific

11 sites. There are five sites in sequence ID Number 4. These

12 are asparagine sites, and they're numbered right here.

13 Q. Does Papadopoulos teach the glycosylation of

14 aflibercept at those sites recited in Claim 14 of the '865

15 patent?

16 A. No, it does not.

17 Q. As far as you're aware, is that disclosed in any

18 prior art that's been advanced by Dr. Rabinow?

19 A. No, it does not.

20 Q. Does Holash -- also I recognize not part of the

21 obviousness combination -- teach glycosylation at these

22 residues?

23 A. No, it does not.

24 Q. I'd like to shift to a different topic, Dr. Trout.

25 I'd like to talk about retinal penetration and aflibercept.

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2027

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1 of ordinary skill as it relates to retinal penetration?

2 A. Yes. So, again, with respect to ranibizumab, I'll

3 just focus on that larger highlighted portion of this excerpt.

4 "Ranibizumab has also been shown to penetrate all

5 layers of the rabbit retina, the first demonstration of retinal

6 penetration of an anti-VEGF therapy intended for AMD."

7 Q. And was it the understanding -- what did the POSA

8 understand about why ranibizumab was being developed by

9 Genentech? For what kinds of diseases was it being developed?

10 A. Well, for anti-VEGF diseases; in other words,

11 diseases of angiogenesis.

12 Q. Where in particular?

13 A. In the eye, of course, yes.

14 Q. Now, if we go further down on page 1 of the

15 reference, Gaudreault, 1839, was the size of ranibizumab

16 disclosed to be relevant for that purpose?

17 A. Yes. Extremely relevant.

18 Q. What is Gaudreault saying in that regard?

19 A. Well, again, just right below what I had read before,

20 the "ability" -- that is, for retinal penetration -- "has been

21 attributed to the small molecular size (48 kilodaltons) because

22 a full-length antibody, trastuzumab (148 kilodaltons) was not

23 able to penetrate all the retinal layers of rhesus monkeys."

24 It continues, "The small molecular weight of

25 ranibizumab probably also contributes to its demonstrated

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2028

BERNHARDT TROUT, PHD - DIRECT

1 ability to penetrate the retina."

2 Q. What is that conveying?

3 A. Okay. All that sort of technical terms basically

4 says if you have a relatively small molecule, 48 kilodaltons --

5 I understand that's a weight, but it can also be reflected in

6 the volume. So it's a small molecule. That can penetrate the

7 retina -- or layers to get to the retina, I should say; whereas

8 larger molecules, like antibodies or aflibercept, were thought

9 not to be able to get through to the retina.

10 Q. What is molecular radius that's being described here

11 by Gaudreault?

12 A. Okay. So that is the important term here. That's

13 basically the size of the molecule. So it's related to the

14 molecular weight in kilodaltons, but it's the size. And that's

15 what's, at the end of the day, most important.

16 Q. Does glycosylation affect a protein size?

17 A. Yes, it does.

18 Q. And in what way?

19 A. Well, again, glycosylation means that carbohydrates

20 are added, they're extended carbohydrates. So they're going to

21 be added to these sites, extend out, and increase the effective

22 volume.

23 Q. Was ranibizumab glycosylated?

24 A. No.

25 Q. Now, Gaudreault was a Genentech paper. Did

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1 And let's put up the Jackson reference. That's

2 PTX 1842.

3 Did you rely on Jackson in connection with your

4 opinions?

5 A. Yes, I did.

6 Q. Okay.

7 And if we can put up page 1 of Jackson in the

8 conclusion.

9 What is it disclosing?

10 A. Well, sort of the beginning of the conclusion here,

11 "In humans, the inner and outer plexiform layers are sites of

12 high resistance to the diffusion of large molecules, resulting

13 in an REL of" -- about 76, 77 kilodaltons -- it says 76.5.

14 And REL is the retina exclusion limit.

15 Q. And did you prepare a demonstrative to help show the

16 relative sizes of aflibercept compared to ranibizumab?

17 A. Yes, I did.

18 Q. Okay. And if we take a look at that, that's

19 Demonstrative 4 on the screen.

20 Can you explain how these compare.

21 A. Yes.

22 And, Your Honor, I'll just focus on the middle and

23 the right one.

24 So this is the aflibercept that we've been talking

25 about. It's about 115 kilodaltons, remembering that the

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1 literature from other researchers inform your opinions as to

2 the issue of size and retinal penetration?

3 A. Yes.

4 Q. And let's look at the Gbate reference. That's

5 PTX 576. Did you review this article?

6 A. Yes, I did.

7 Q. And what did it disclose with respect to retinal

8 penetration?

9 A. Well, here I've just highlighted an excerpt. It

10 says, "The internal limiting membrane" -- that's the membrane

11 to get from the vitreous to the retina, "that membrane is

12 impermeable to" -- and then it talks about linear molecules,

13 which aren't so important for this situation.

14 But what it also talks about are globular molecules

15 greater than 70 kilodaltons. So the larger macromolecules

16 would have a longer retention time, possibly weeks, but their

17 effect on the retina after an intravitreal injection is

18 limited.

19 Q. Did you look at other references as well?

20 By the way, was that pages 8 and 9 of

21 Exhibit PTX 576?

22 A. Yes.

23 Q. Did you look at other references as well?

24 A. Yes.

25 Q. Okay.

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1 retinal exclusion limit is in the 70s. It's close enough.

2 Ranibizumab, on the other hand, is 48 kilodaltons, so below

3 that limit.

4 Q. Now, Doctor, as of the priority date, was the

5 efficacy of larger VEGF R1R2 proteins like aflibercept in

6 treating retinal diseases compared by the intravitreal route

7 and the subcutaneous systemic route?

8 A. Yes.

9 Q. Let's take a look at the Saishin article,

10 Exhibit 1785, and at the time at the Ferrara review article,

11 Exhibit 701.

12 Did you review both of these references?

13 A. Yes, I did.

14 Q. Now, Ferrara, is that a review article?

15 A. Yes.

16 Q. And what is a review article?

17 A. Oh, a review article is an article that summarizes

18 what's already in the literature. It typically does not

19 include new results, but it's an analysis of results that are

20 already in the literature.

21 Q. And does it generally reflect the conventional wisdom

22 in the field at the time?

23 A. Yes.

24 Q. Okay.

25 So if we look to -- if we can put up the

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1 demonstrative showing both of those together.

2 On the left-hand side, do we have Figures 1 and 2 of

3 Saishin, PTX 1785?

4 A. Yeah, we do.

5 Q. And on the right-hand side, do we have Ferrara at

6 page 5, also page 862?

7 A. Yes. Yes.

8 Q. And Ferrara is PTX 701.

9 Can you explain first what the left-hand side shows,

10 Saishin, and then what the right-hand side, Ferrara, is saying

11 about it?

12 A. Yes, I can.

13 And, Your Honor, you've seen this perhaps a couple

14 times before.

15 So this is a comparison of the effect of the VEGF

16 Trap. Well, the first one is without the VEGF Trap and the

17 second one is with it. And this is subcutaneous injection; in

18 other words, not intravitreal injection. And I think the

19 analogy was used before this is like golf, not basketball. You

20 want to have as low a score as possible.

21 And that's compared here with the intravitreal

22 administration. And so this is, again, the baseline. You can

23 see a much lower differential here versus subcutaneous.

24 Q. And what was said about this data in the literature?

25 A. Well, so Ferrara, in referencing this -- we can turn

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1 A. Yes, it does.

2 Q. Now, were there risks and drawbacks associated with

3 intravitreal injection?

4 And we'll bring up on the screen PTX 576 again, the

5 Gbate reference, at page 8.

6 A. Yes. And, again, just highlighted this one sentence

7 from Gbate.

8 "It is also the most invasive and the route with the

9 most serious complications," referring again to intravitreal

10 injection right here in the header.

11 Q. And does it further in the next sentence explain one

12 or more of those complications?

13 A. Yes. In the next sentence it talks about the various

14 complications and the rates varying from 0.15 percent to as

15 high as 0.87 percent.

16 Q. And it talks about endophthalmitis. Do you

17 understand that to be infection inside the eye?

18 A. Yes. I wasn't going to go into the details of that

19 term; but yes, my understanding is an infection. But it's a

20 very serious infection.

21 Q. Now, does Saishin teach anything about the

22 appropriate formulation for aflibercept?

23 A. No.

24 Q. Does Saishin indicate anything with respect to

25 whether the VEGF Trap stays in native conformation in a

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1 to the screen here -- says, "The limited efficacy occurred in

2 spite of the high binding affinity of the VEGF Trap for VEGF.

3 And it may be due, at least in part, to the existence of a

4 barrier to the transretinal penetration of large molecules such

5 as the VEGF Trap."

6 Q. Does this reflect what the POSA would have thought at

7 the priority date?

8 A. Yes. Exactly.

9 Q. And does Ferrara analyze the Saishin reference and

10 account for the details of its experimental design?

11 A. Yes. Clearly, Ferrara looked at it closely and

12 analyzed it and led to that conclusion, which would be the

13 conclusion of a POSA.

14 Q. Doctor, on the basis of these data, if the POSA

15 wanted to use a VEGF R1R2 Trap like aflibercept to treat

16 retinal diseases, what kind of administration would the POSA

17 have used?

18 A. Well, if it's going to be the VEGF Trap, the POSA

19 would have used subcutaneous or some kind of systemic

20 injection.

21 Q. Would the POSA who made that choice have practiced

22 the claims of the '865 patent?

23 A. No.

24 Q. Does the '865 patent require intravitreal

25 administration?

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1 formulation?

2 A. No, nothing.

3 Q. Now, if the POSA had decided to treat retinal

4 diseases using an intravitreal injection, on the basis of all

5 of the information you've reviewed, what molecules would the

6 POSA have wanted to use, what kind of molecules?

7 A. Well, the POSA would have wanted to use smaller

8 molecules such as ranibizumab.

9 Q. Was there also a VEGF Trap that fit into that

10 category?

11 A. Yes, there was.

12 Q. If we bring up Demonstrative 6.

13 You've labeled now a third molecule in the

14 demonstrative as Mini-Trap. Can you explain what that is.

15 A. Yes. The Mini-Trap is another molecule that

16 Regeneron was working on.

17 And, Your Honor, you've already seen these two. So

18 this is our favorite molecule here, aflibercept, and this is

19 the ranibizumab.

20 The Mini-Trap is just this top part of aflibercept

21 with a bottom part cut off to make it smaller. So it's about

22 the same size as ranibizumab, maybe even slightly smaller.

23 Q. And did you look at literature relating to the

24 Mini-Trap?

25 A. Yes, I did.

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1 Q. Okay.

2 Let's pull up Exhibit 1757.

3 Do you understand this to be the Daly application?

4 A. Yes. That's correct.

5 Q. And can you explain what Daly is disclosing here on

6 page 11, paragraph 48.

7 A. Yes.

8 At the top it's referring to this Mini-Trap,

9 nonglycosylated and glycosylated. And then it says this

10 Mini-Trap has optimized characteristics for local intravitreal

11 delivery, i.e., shorter serum half-life for faster clearance,

12 and minimizing unwanted systemic exposure.

13 In addition, due to its smaller size, the Mini-Trap

14 has the ability to penetrate through the inner limiting

15 membrane, ILM, in the eye, and diffuse through the vitreous to

16 the retina/retinal pigment epithelial RPE layer, which will

17 help to treat retinal disease.

18 Q. Doctor, on the basis of the prior art as a whole,

19 would the POSA who wanted to use intravitreal injections of a

20 VEGF Trap have wanted to use aflibercept or the Mini-Trap?

21 A. No, the Mini-Trap, the smaller molecule.

22 Q. And was that designed specifically for intravitreal

23 delivery into the eye?

24 A. Yes, it was.

25 Q. Now, we've heard a lot about Avastin during this

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1 And then it continues. It's talking about

2 ranibizumab, among others. And then it says, "It is noteworthy

3 that initial uncontrolled Phase I or II studies with pegaptanib

4 or verteporfin photodynamic therapy suggested a considerably

5 greater benefit in AMD patients than that eventually

6 demonstrated in randomized Phase III studies, further

7 emphasizing the difficulty of interpreting early clinical

8 results."

9 Q. So in view of all the references, including Saishin

10 and Avery, what did Dr. Ferrara ultimately suggest and conclude

11 in his 2006 review article?

12 A. Well, Dr. Ferrara concluded, again, what the person

13 of ordinary skill in the art would understand, which is that

14 that person of ordinary skill in the art would be turned to use

15 the smaller molecules like ranibizumab and others.

16 Q. And so the record's clear, that excerpt that you were

17 discussing on page 8 a moment ago from Ferrara, and it had the

18 Footnote 114, was Ferrara discussing the Avery reference there?

19 A. Oh, yes. And you can see that on the right on the

20 slide, the same Avery reference, correct.

21 Q. And that's the Avery reference that Dr. Rabinow

22 discussed last week at trial?

23 A. Yes.

24 Q. Now, I'd like to shift again, Dr. Trout, and discuss

25 the concentration required by the claims.

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1 trial. Wouldn't that have taught to use a large molecule for

2 intravitreal injection?

3 A. No.

4 Q. Now, Dr. Rabinow addressed the Avery reference.

5 That's DTX 2264. And for now I want you to assume that Avery

6 is prior art.

7 Let's turn to page 368 of Avery. What is the article

8 conveying to the person of ordinary skill?

9 A. Well, it's conveying, as you see in these two

10 excerpts that I've highlighted -- this is in the discussion

11 section -- "We acknowledge the shortcomings of this study:

12 retrospective design, limited number of patients, nonstandard

13 visions, and limited follow-up."

14 And then it further says in the same paragraph a

15 little ways down there, "However, the visual results of this

16 study are difficult to interpret."

17 Q. And did the Ferrara reference you've been discussing,

18 PTX 701, did that address Avery's findings as well?

19 A. Yes, it did.

20 Q. Okay.

21 And if we can pull that up again at page 8.

22 What did Ferrara have to say?

23 A. Well, Ferrara says, "Although intriguing, these early

24 findings are difficult to compare with data from rigorous

25 double-masked controlled Phase III trials."

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1 What is the concentration that all of the asserted

2 claims require?

3 A. Well, of the aflibercept, it's highlighted here,

4 40 mg/mL.

5 Q. And let's go back to the prior art on which

6 Dr. Rabinow relied, Fraser at DTX 729 on the second page.

7 Does Fraser teach 40 mg/mL of VEGF Trap?

8 A. No, not at all. Fraser teaches, as underlined here,

9 24.3 mg/mL.

10 Q. Did you hear Dr. Rabinow's testimony that the POSA

11 would have used the 40 mg/mL concentration from the Lucentis

12 references if we look at Slide 93 of Dr. Rabinow's

13 presentation?

14 A. Yes, I heard him say that.

15 Q. Now, let's look at the Lucentis references. Do you

16 recall that Dr. Rabinow relied on two Lucentis references,

17 Shams and Gaudreault?

18 A. I do recall.

19 Q. Let's take a look at Shams first. That's DTX 726.

20 And we're showing on the screen page 32 of the exhibit.

21 What does Shams teach regarding the concentration of

22 ranibizumab?

23 A. Well, just what's highlighted here regarding that

24 concentration, 6 mg/mL or 10 mg/mL.

25 Q. And just to be clear, is that 40?

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1 A. No.

2 Q. And I think this was discussed last week, but what

3 was the purpose for which Shams was using this ranibizumab?

4 A. Oh, so Shams is disclosing clinical approaches to

5 using ranibizumab, so clinical trials.

6 Q. And let's look at Gaudreault, PTX 1839, and we'll

7 look at page 2.

8 What concentrations does Gaudreault discuss?

9 A. Well, Gaudreault discusses 10 mg/mL and 40 mg/mL.

10 Q. Would Gaudreault have taught the POSA to use 40 mg/mL

11 of aflibercept, Dr. Trout?

12 A. No, sir. On the contrary, Gaudreault teaches away

13 from that. You can see some excerpts here. Actually, if we go

14 back to the previous -- previous one.

15 Thank you.

16 It says that at the 2000 micrograms, that's the

17 40 mg/mL, it causes, at that concentration, moderate to severe

18 inflammation; whereas it is not moderate to severe at the

19 10 mg/mL.

20 Q. And you're reading from pages 2 and 3 of Gaudreault,

21 Exhibit 1839?

22 A. Yes.

23 Q. And how would the person of ordinary skill in the art

24 have interpreted the findings of Gaudreault with respect to the

25 10 mg/mL compared to 40 mg/mL concentrations of ranibizumab?

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1 A. Yes. This is another point from Gaudreault focusing

2 on the 500 micrograms per eye. Again, in the table, you can

3 see that corresponds to 10 mg/mL. And Gaudreault is saying

4 that the retinal exposure was greater than 3,000-fold larger

5 than the retinal exposure to VEGF.

6 So -- and it says suggesting that this ranibizumab

7 dose provides maximum inhibition of VEGF. So the 10 mg/mL

8 dose, according to Gaudreault, provides maximum inhibition. So

9 you don't get more if you go higher anyway.

10 Q. Doctor, are you aware of any use of 40 mg/mL of

11 ranibizumab after Gaudreault?

12 A. No, I'm not.

13 Q. Now, how does the potency of ranibizumab compare to

14 the potency of aflibercept?

15 A. Well, aflibercept has a much higher potency than

16 ranibizumab, 10 to 100 times more. I think I said in my

17 report, 20 times more, so significantly more.

18 Q. Now, if the POSA had relied on ranibizumab as

19 Dr. Rabinow suggests, how would the POSA have applied the

20 teachings of Gaudreault and Shams regarding ranibizumab to the

21 concentration of aflibercept?

22 A. Well, if anything, the POSA would choose a lower

23 concentration. Again, as I said, aflibercept is much more

24 potent than ranibizumab. Even accounting for the difference in

25 the size or the weight, there would be much lower concentration

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1 A. Well, that person again would understand that the 40

2 mg/mL is problematic from an immune response standpoint versus

3 the 10 mg/mL. And this would teach the person away from the

4 40 mg/mL. And I emphasize the bottom two. It basically lasted

5 two to eight days, so seven days.

6 Q. Why do you say that it lasted seven days?

7 A. Well, it says that the inflammation was present at

8 day two. It was a monkey study. The eyes were monitored

9 throughout. So it was present at day two but had completely

10 resolved by day eight.

11 Q. And is that good news or bad news?

12 MR. RAKOCZY: Your Honor?

13 Objection, Your Honor. He obviously has testified

14 about it from the protein formulation perspective. The witness

15 is not an ophthalmologist; so I don't think he's qualified to

16 talk about good or bad from a clinical standpoint here.

17 THE COURT: Understood. Sustained.

18 BY MR. BERL:

19 Q. Doctor, let's take a look -- well, what happened to

20 the 40 mg/mL dose of ranibizumab?

21 A. Well, it wasn't used going forward.

22 Q. Now, I think we had another excerpt that we put on

23 the screen from a moment ago from Gaudreault. Can you explain

24 the relevance of the sentence beginning after administration of

25 500 micrograms per eye?

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1 based on Gaudreault of the aflibercept, much less than the

2 10 mg/mL.

3 Q. Now, let's take a look at Ferrara 2004.

4 Just for the record, this is a different Ferrara

5 article. It's PTX 1838.

6 Did you review this article as well?

7 A. Yes, I did.

8 Q. Okay. And if we look to page 7 of the article, can

9 you explain what Ferrara is disclosing here and how it's

10 relevant to the consideration of an appropriate concentration

11 to use.

12 A. Certainly.

13 So Ferrara -- and, again, different from the Ferrara

14 that we just talked about a little while ago, it's referring to

15 the VEGF Trap again and is basically just relating what I said

16 earlier and what the POSA would know. Because of the fact that

17 this not a natural molecule, it's completely constructed, the

18 junctions between the various structural elements in such

19 multicomponent molecules can generate an immune response,

20 which, again, I think I talked about this last week too, is

21 something that the formulator is very concerned about.

22 Q. What would the relevance of this discussion in

23 Ferrara 2004, Exhibit 1838, have had on the concentration that

24 the POSA would have wanted to use for an intravitreal

25 injection?

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1 A. Well, it would teach the POSA to use a low  
2 concentration. Again, it's going to be much lower than the  
3 10 mg/mL to try to minimize the risk of such an immune  
4 response.  
5 Q. Let's take a look at the Wang reference. That's  
6 PTX 1556.  
7 And we'll blow up part of page 1.  
8 What is Wang teaching here, and how does it relate to  
9 the protein concentration that the person of ordinary skill  
10 would have wanted to use?  
11 A. Well, Wang here -- again, this is a review article.  
12 It says, "Increasing protein concentration generally increases  
13 protein aggregation."  
14 Q. And so how would that be relevant to the POSA who's  
15 trying to choose a concentration to use for intravitreal  
16 injection?  
17 A. Well, it would teach the POSA to use as low a  
18 concentration as possible, again teach away from these higher  
19 concentrations like 40 mg/mL. Again, aggregation can cause  
20 serious problems, as the formulator would understand, not only  
21 in -- you don't want to inject aggregates as such into the eye,  
22 but also the possibility of these immune responses.  
23 Q. Okay.  
24 And for the record, this is page 9 of PTX 1556, the  
25 Wang reference.

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1 the formulation in the first -- or the top excerpt and the  
2 highlighted one -- highlighted sentence for polysorbate, which,  
3 again, I think Your Honor noted correctly that Tween 20 is a  
4 synonym for polysorbate. It teaches 0.05 percent.  
5 THE COURT: I've been right about this for the last  
6 couple weeks, Doctor, if you ask all them out there.  
7 Oh, come on. That was funnier.  
8 MR. BERL: No comment. Too tired to laugh, Your  
9 Honor.  
10 THE COURT: Limping to the finish line, but I thought  
11 that was better than that.  
12 THE WITNESS: That was funny from up here.  
13 THE COURT: Thank you.  
14 BY MR. BERL:  
15 Q. Doctor, did Genentech proceed with this formulation  
16 that has .05 percent polysorbate?  
17 A. No, Genentech did not.  
18 Q. Let's take a look at the Shams reference. And,  
19 actually, we'll look at Dr. Rabinow's discussion of the Shams  
20 reference in regards to this limitation. What does Shams teach  
21 with respect to its formulation and polysorbate 20?  
22 A. Okay. So this is a cutout or excerpt on the bottom  
23 right, again, from Dr. Rabinow from Shams. And you can see  
24 highlighted here 0.01 percent polysorbate 20.  
25 Q. And what is the concentration, Doctor, required by

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1 Doctor, in view of the -- all of the prior art that  
2 you reviewed, what would the POSA have thought in terms of an  
3 appropriate concentration of aflibercept for intravitreal  
4 injection if the POSA had wanted to use aflibercept for  
5 intravitreal injection?  
6 A. Well, the POSA would choose a concentration probably  
7 lower than that of ranibizumab, so lower than 10 mg/mL.  
8 Q. What would the POSA have thought about the idea of  
9 using 40 mg/mL?  
10 A. Well, the POSA would be taught away from using  
11 40 mg/mL. In other words, it wouldn't be a good idea.  
12 Q. Now, I'd like to turn to a new topic, which is  
13 polysorbate 20.  
14 Doctor, if we pull up the claims again, do all of the  
15 asserted claims require polysorbate 20?  
16 A. Yes, they do.  
17 Q. And do you understand Dr. Rabinow in his combination  
18 to have relied on Gaudreault and Shams for this limitation?  
19 A. Yes.  
20 Q. And what do the references -- well, let's first look  
21 at Gaudreault.  
22 And, again, this is page 2 of Gaudreault. What does  
23 Gaudreault teach with respect to its formulation and  
24 polysorbate 20?  
25 A. Well, Gaudreault teaches, as we have here -- this is

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1 Claim 4 of the '865 patent?  
2 A. Claim 4 is about 0.03 percent to about 0.1 percent  
3 polysorbate 20.  
4 Q. And Dr. Rabinow put the .01 percent polysorbate 20  
5 from Shams in green and colored also in green the  
6 about .03 percent to about .1 percent in Claim 4.  
7 Do you agree with his analysis that Shams teaches  
8 that concentration required by Claim 4 of polysorbate 20?  
9 A. No, because Shams teaches 0.01 percent, which doesn't  
10 fall in the range of polysorbate from Claim 4.  
11 Q. What concentration did Genentech ultimately use for  
12 Lucentis?  
13 A. 0.01 percent.  
14 Q. Now, let's discuss Fraser, the last reference in this  
15 combination. Again, that's DTX 729.  
16 Does Fraser say anything about intravitreal  
17 administration?  
18 A. No.  
19 Q. What concentration of Tween 20 or polysorbate 20 does  
20 Fraser disclose, looking at page 2 of the reference?  
21 A. 0.01 percent.  
22 Q. Now, reading --  
23 A. I apologize. Sorry to interrupt.  
24 0.1 percent -- added an extra zero.  
25 0.1 percent, for the record.

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1 THE COURT: Okay. And we anticipate at this point  
2 that Dr. Trout will be the last witness; is that correct?  
3 Anybody being called by Mylan on the back end?  
4 MR. RAKOCZY: Not as far as we know. He'll be the  
5 last one.  
6 THE COURT: Okay. All right. Well, let's do that.  
7 We'll see everyone at 8:30 tomorrow morning. And, again, my  
8 promise to be prompt with notifications about any change in the  
9 lunch run schedule tomorrow. Apologies for any heart  
10 palpitations I gave everybody.  
11 With that, everybody have a pleasant evening, and  
12 we'll see you all tomorrow morning.  
13 Thank you very much.  
14 (Proceedings concluded at 5:07 p.m.)

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## CERTIFICATE

1 I, Cindy L. Knecht, Registered Professional Reporter and  
2 Official Reporter of the United States District Court for the  
3 Northern District of West Virginia, do hereby certify that the  
4 foregoing is a true and correct transcript of the proceedings  
5 had in the above-styled action on June 22, 2023, as reported by  
6 me in stenotypy.

8 I certify that the transcript fees and format comply with  
9 those prescribed by the Court and the Judicial Conference of  
10 the United States.

11 Given under my hand this 22nd day of June 2023.

12 /s/Cindy L. Knecht

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14 Official reporter, United States  
15 District Court for the Northern  
16 District of West Virginia

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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 9  
8 Biocon Biologics,  
9 Defendants.

10 - - -  
11 Proceedings had in the bench trial of the above-styled  
12 action on June 23, 2023, before Honorable Thomas S. Kleeh  
13 District Judge, at Clarksburg, West Virginia.

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BERNHARDT TROUT, PhD - DIRECT 2082

1 A. Yes, I did.

2 Q. And this is an article from 2013, after the priority

3 date.

4 Let's take a look at page 4 of the article. What

5 were the properties that ultimately were shown with Eylea? And

6 were they expected in your view?

7 MR. RAKOCZY: Objection, Your Honor. Two grounds.

8 Number one, they've admitted this is after the priority date;

9 this is not prior art.

10 Number two, they're talking about the aflibercept

11 molecule; they're not actually talking about the claimed

12 formulations here. It's not relevant either.

13 THE COURT: How is it prior art?

14 MR. BERL: It's not prior art at all. That's why I

15 pointed out, in fact, that it's from 2013, after the priority

16 date.

17 The law is that postpriority evidence is relevant to

18 unexpected properties. The Kroll v. Teva [sic] case is sort of

19 the seminal case on this proposition, but other cases

20 afterwards have reiterated that proposition down the line from

21 the Federal Circuit.

22 THE COURT: Mr. Rakoczy.

23 MR. RAKOCZY: Your Honor, we obviously disagree. We

24 will brief this. But beyond that, it still has to establish a

25 nexus to claims. These are claims about formulations, not

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BERNHARDT TROUT, PhD - DIRECT 2084

1 Q. Can you explain how this relates to the formulation

2 rather than just the molecule of aflibercept with respect to

3 the properties you just relied on?

4 MR. RAKOCZY: Objection, Your Honor. He's now trying

5 to tie something up that's actually not in the report anywhere.

6 MR. BERL: I don't agree with that. Let's look at

7 paragraph 347, for example. Your Honor, I think this is in the

8 binder. I believe it's styled as PTX 67, Dr. Trout's report.

9 PTX 67.

10 THE COURT: 67.

11 MR. BERL: Not 367. Sorry.

12 THE COURT: What paragraph is that, Mr. Berl?

13 MR. BERL: 347. You'll see in that paragraph, Your

14 Honor, he's discussing Eylea. He does not say aflibercept. I

15 think -- he says aflibercept too because, of course, Eylea has

16 aflibercept in it, but he says Eylea one, two, three, four

17 times when providing his analysis of this article. This is the

18 Thomas article that we're reviewing and the subject of this

19 paragraph, and he's talking about how Eylea ultimately proved

20 to be unexpectedly safe, how it compares to Lucentis.

21 And so that's what I'm asking him about is how --

22 what is Thomas disclosing about Eylea. That's the subject of

23 the Thomas article and his opinion.

24 THE COURT: Mr. Rakoczy.

25 MR. RAKOCZY: That wasn't the question, Your Honor.

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BERNHARDT TROUT, PhD - DIRECT 2083

1 about the aflibercept molecule itself, which is what this is;

2 so, again, no nexus, after the priority date.

3 THE COURT: Understood. It is after the priority

4 date, obviously, but we need to tie this together, Mr. Berl,

5 how it's related.

6 Objection overruled at this juncture.

7 BY MR. BERL:

8 Q. Were the properties of Eylea expected or unexpected

9 as related by the Thomas article, PTX 1155?

10 A. So they were unexpected, as noted here. I'm going to

11 read on the screen just because of my eyes.

12 On the upper left, "The most captivating aspect of

13 aflibercept is its extended half-life, according to reviews of

14 aflibercept by Stewart and Stewart, et al. The estimated serum

15 half-life of intravitreal aflibercept is approximately 18 days

16 versus ranibizumab and bevacizumab, which have half-lives of

17 approximately 4.75 days and 8.25 days respectively."

18 So it's -- aflibercept -- or really the Eylea, which

19 is an embodiment of the claims of the '865, has over double the

20 half-life.

21 And then just to point to another excerpt from the

22 same article on the right -- I think I can even read this --

23 "In conclusion, aflibercept dosed intravitreally each month or

24 every two months after three initial monthly doses resulted in

25 comparable efficacy and safety to monthly ranibizumab."

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BERNHARDT TROUT, PhD - DIRECT 2085

1 The question was can you explain how this relates to the

2 formulation other than just the molecule?

3 I agree that the report talks about the formulation

4 Eylea. There is nothing in here attempting to give some

5 explanation for why this unexpected result is not just about a

6 molecule.

7 THE COURT: Understood.

8 Sustained. Reword your question.

9 MR. BERL: I'll reword the question.

10 BY MR. BERL:

11 Q. Doctor, can you explain how these properties relate

12 to Eylea?

13 A. Yes. Well, again, these properties are discussion

14 based on the use of Eylea, the whole formulation -- I don't

15 know if I can say that, but Eylea is the formulation we've been

16 talking about.

17 Q. Do you understand Eylea to be an embodiment of the

18 claims of the '865 patent?

19 A. Yes.

20 Q. And can you administer aflibercept by itself without

21 formulation?

22 MR. RAKOCZY: Objection, Your Honor. Again, new

23 opinion. Nowhere in here.

24 MR. BERL: This has nothing to do with Thomas. This

25 is just basic background.

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BERNHARDT TROUT, PhD - DIRECT 2086

1 THE COURT: Overruled.

2 BY MR. BERL:

3 Q. Can you administer aflibercept without a formulation,

4 such as Eylea?

5 A. No.

6 Q. Can you obtain the properties that Thomas is

7 discussing by just administering aflibercept alone?

8 MR. RAKOCZY: Objection, Your Honor. This is well

9 outside the scope.

10 THE COURT: That one's sustained.

11 MR. BERL: I'll withdraw that.

12 BY MR. BERL:

13 Q. Doctor, in your view -- let's look at another part of

14 Thomas on page 4. Can you discuss what Thomas is disclosing

15 here?

16 A. Yes. Again, just to read the excerpt here, "In

17 conclusion, aflibercept dosed" -- and then it talks about the

18 dosing I just read -- "side effects, either ocular or systemic,

19 were similar across treatment groups with no differences

20 between aflibercept administered every two months and monthly

21 ranibizumab," again, referring to the Eylea.

22 Q. And was that expected or unexpected based on what the

23 prior art disclosed about fusion proteins such as aflibercept?

24 A. That was unexpected for all the reasons that I

25 mentioned.

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BERNHARDT TROUT, PhD - DIRECT 2088

1 BY MR. BERL:

2 Q. Did Mylan, in your view, copy the concentration of

3 aflibercept that's in the claims?

4 A. Yes.

5 Q. Did Mylan -- I'll ask this generally. Did Mylan

6 pursue formulations without polysorbate?

7 A. Well, in development, yes.

8 Q. And what was the result of that?

9 A. Mylan decided it had to include polysorbate to have

10 an adequate formulation.

11 Q. In view of -- I just want to ask one final question

12 about obviousness, Doctor.

13 In view of your analysis of motivation, expectation

14 of success, and objective indicia, are the asserted claims of

15 the '865 patent obvious?

16 A. No.

17 MR. BERL: So with that proviso that I might ask one

18 more question at the end, I'm going to move to Section 112.

19 THE COURT: Someone put that last question on a

20 sticky note.

21 MR. BERL: I won't remember; so please.

22 BY MR. BERL:

23 Q. Doctor, did you consider Dr. MacMichael's testimony

24 on enablement?

25 A. Yes, I did.

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BERNHARDT TROUT, PhD - DIRECT 2087

1 Q. Do you understand or consider ranibizumab to be the

2 closest prior art?

3 A. Yes.

4 Q. Now, did you also consider evidence of copying?

5 A. Yes, I did.

6 Q. And in your view, did Mylan copy aspects of Eylea?

7 A. Yes.

8 Q. And what aspects of the claims, for example, did

9 Mylan copy, in your view?

10 A. Well, it copied the aflibercept, of course, with the

11 sequence ID, the polysorbate, the organic cosolvent, the

12 buffer.

13 Q. Well, let's talk about a few of those. Let's talk

14 about the polysorbate.

15 MR. BERL: Actually, if I may pause for a moment. I

16 don't want to do anything that violates Mylan's perceived

17 confidentiality. I think this was disclosed in open court, but

18 I don't want to run afoul of any --

19 THE COURT: If you need to huddle and talk about

20 that, go right ahead, please.

21 MR. BERL: I really don't want to seal the courtroom

22 for one question; so maybe I'll just --

23 THE COURT: Why don't we save that one for last.

24 MR. BERL: Maybe we'll save that one for last.

25 That's a good idea.

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BERNHARDT TROUT, PhD - DIRECT 2089

1 Q. Do you agree with his conclusions?

2 A. No, I do not.

3 Q. Dr. MacMichael talked about the simple Wands factors.

4 Do you remember that?

5 A. Yes, I do.

6 Q. Let's put up the Wands factors on the screen.

7 Did you consider the Wands factors in conducting your

8 enablement analysis?

9 A. Yes, I did.

10 Q. Let's start with the first one, the breadth of the

11 claims. Do you agree with Dr. MacMichael's testimony that the

12 breadth of the claims is very broad?

13 A. No. I think the claims are narrow.

14 Q. Let's take a closer look at that. Let's take a look

15 at 1, 2, and 4 again.

16 Why, in your view, are the asserted claims not very

17 broad?

18 A. Well, let's just start out with the -- where we

19 usually start, with the VEGF antagonist and the specific

20 sequence ID. So it's one specific biologic molecule, no

21 others, with a very specific -- with a specific sequence ID, I

22 should say. It's a vial. It's for intravitreal

23 administration. It's got to have all these other components --

24 the organic cosolvent, the buffer, the stabilizing agent. And

25 then it's got to be at 40 mg/mL. That's very -- I mean, that

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BERNHARDT TROUT, PhD - DIRECT 2090

1 can't get more narrow than that in terms of concentration. And  
2 then it's got to -- this is just Claim 4 -- it's got to have  
3 the polysorbate 20. That's the only possible organic cosolvent  
4 and within this narrow range.

5 Q. Doctor, there's been some discussion for purposes of  
6 enablement about lyophilized or freeze-dried formulations.  
7 We're not going to repeat all of what we did a few moments ago,  
8 but in your view, did the specification also teach how to make  
9 lyophilized formulations?

10 A. Yes, it does.

11 Q. And is lyophilization just another way to make  
12 formulations?

13 A. It is another way of making formulations, yes.

14 Q. And there was also some discussion previously in the  
15 case about suspensions and emulsions.

16 In your view, would the claims be directed to  
17 suspensions and emulsions?

18 A. No. I don't think the claims would be directed, and  
19 I probably should have mentioned this before, but this other  
20 limitation, the 98 percent present in native conformation  
21 following storage at 5 degrees Celsius for two months as  
22 measured by size-exclusion chromatography, that's not an  
23 analytical technique that one would typically use for emulsions  
24 and suspensions.

25 Q. You discussed some of the structures in the claims.

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BERNHARDT TROUT, PhD - DIRECT 2092

1 structural elements recited in the claims that did not meet the  
2 98 percent native conformation limitation?

3 A. No.

4 Q. Are you aware of any such formulations?

5 A. No.

6 Q. Now, let's go to the next Wands factors, the level of  
7 ordinary -- the level of ordinary skill.

8 Was the level of skill high or low?

9 A. High.

10 Q. How so?

11 A. Well, again, it would be a professional with a  
12 master's degree at least in a relevant field, so a technical  
13 field directly relevant to formulations here. I think  
14 Dr. MacMichael said even a PhD, higher, plus several years of  
15 skill. And I think I added in mine it could be a PhD with less  
16 experience than a master's degree but still considerable  
17 experience in formulation.

18 Q. Do you understand yourself to agree with  
19 Dr. MacMichael that the level of skill was high?

20 A. Yes.

21 Q. Now, did you hear Dr. MacMichael's testimony a few  
22 days ago regarding Regeneron's arguments during prosecution of  
23 different patents?

24 A. Yes.

25 Q. Do you agree with Dr. MacMichael's testimony about

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BERNHARDT TROUT, PhD - DIRECT 2091

1 Were the structures that are used in the claims known  
2 or unknown as of the priority date?

3 A. They were known as of the priority date.

4 Q. What about buffers? Were those structures known?

5 A. Yes.

6 Q. And what about polysorbate?

7 A. Yes.

8 Q. And what about aflibercept?

9 A. Yes.

10 Q. And what about stabilizing agents?

11 A. Yes.

12 Q. So, Doctor, what is your opinion regarding the Wands  
13 factor on the breadth of the claims? Does that support  
14 enablement or does it support nonenablement?

15 A. It's pretty narrow; so it supports enablement.

16 Q. Let's take a look at the nature of the invention, the  
17 second Wands factor.

18 What is the nature of the invention claimed here?

19 A. Well, the nature of the invention is a formulation,  
20 an ophthalmic formulation to be specific, suitable for  
21 intravitreal administration, with the various formulation  
22 components, including the aflibercept and with the 98 percent  
23 native after two months storage at 5 degrees Celsius and all  
24 the rest of the specifics.

25 Q. Did Dr. MacMichael identify any formulation with the

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BERNHARDT TROUT, PhD - DIRECT 2093

1 those documents?

2 A. No.

3 Q. Let's first take a look at DTX 5053, and this is on  
4 page 17.

5 Do you recall that this is a sentence that  
6 Dr. MacMichael relied on in his testimony?

7 A. Yes.

8 Q. And can you explain what this sentence means in your  
9 view.

10 A. Yes. It says, "One of ordinary skill in the art upon  
11 reading Remington's would expect to engage in significant  
12 nonroutine experimentation to develop a successful formulation  
13 as claimed herein."

14 Remington's is a general textbook, you could call it.  
15 It's a collection of different chapters, formulation and  
16 others, by experts; so it's a general textbook. And I agree  
17 with this statement, but Remington's doesn't disclose  
18 aflibercept; it doesn't disclose other aspects. Until you have  
19 that information, like the '865 patent discloses, you are in  
20 the situation discussed here.

21 Q. So to be clear, does Remington's disclose any  
22 formulations of aflibercept?

23 A. No.

24 Q. How about intravitreal formulations of aflibercept?

25 A. No.

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BERNHARDT TROUT, PhD - DIRECT 2094

1 Q. How about the concentrations to use for aflibercept  
2 intravitreal formulations?

3 A. Clearly not.

4 Q. Does Remington's disclose what pH to use for  
5 intravitreal formulations of aflibercept?

6 A. No.

7 Q. Now, Doctor, did you consider the Dix declaration  
8 cited by Dr. MacMichael from the prosecution of another patent?

9 A. Yes, I did.

10 Q. Let's take a look at the full context of Dr. Dix's  
11 statement. That's DTX 4430 at pages 3 through 4. It's  
12 paragraph 10. And Dr. MacMichael showed part of this  
13 paragraph.

14 Can you explain this paragraph and how it fits into  
15 your enablement analysis?

16 A. Yes. So, similarly here, Dr. Dix references now  
17 review articles, different from Remington's, but all of these  
18 are review articles that I'm familiar with. This is actually  
19 the same Wang that I talked about before but different review  
20 articles. Wei Wang likes to write review articles.

21 Dr. Dix says, "I am familiar with these literature  
22 articles, all in peer review journals, which all indicate that  
23 arriving at a stable formulation is not a straightforward  
24 matter and is not, for instance, possible to apply a  
25 formulation for one drug to another."

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BERNHARDT TROUT, PhD - DIRECT 2096

1 Q. And what formulations are claimed -- aflibercept or  
2 some other molecule?

3 A. Aflibercept.

4 Q. Now, let's turn next to the next *Wands* factor, the  
5 specification's guidance and then working examples. We can  
6 take those together.

7 How do the specification's guidance, if we could look  
8 at a demonstrative, compare to the prior art's guidance?

9 A. Well, the specification has significant guidance. It  
10 actually has eight examples. I've just put up three here. We  
11 wouldn't be able to see any of them -- you can hardly see it as  
12 it is -- if we put up all eight. Probably couldn't see  
13 anything.

14 And then it has several important disclosures within  
15 the specification, including this one, which is highlighted.  
16 And it talks about what the organic cosolvent might be, and it  
17 talks about different other agents, including the stabilizing  
18 agent and the buffering agent.

19 It also talks in this excerpt in the middle here  
20 about the pH range between about 5.8 and 7. And then it  
21 talks about more specific pH ranges, uses the terms more  
22 specifically, about 6.2 to 6.3.

23 Q. And for the record, the excerpts you're discussing  
24 are in Column 2 of the '865 patent, Exhibit 2; is that right?

25 A. Yes.

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BERNHARDT TROUT, PhD - DIRECT 2095

1 So, again, in the absence of any information once  
2 you're starting out, this is the situation that the skilled  
3 person would be in.

4 Q. And, again, as we discussed with Remington's, do any  
5 of these articles disclose aflibercept formulations,  
6 intravitreal aflibercept formulations, the concentration to use  
7 for aflibercept intravitreal formulations, or the pH to use  
8 for aflibercept intravitreal formulations?

9 A. No, none of them disclose any of those.

10 MR. BERL: I'm sorry about that one. I'll be better.

11 THE COURT: I'll accept on behalf...

12 BY MR. BERL:

13 Q. Doctor, to practice the claims of the '865 patent  
14 with the specification in hand, would the POSA need to apply a  
15 formulation from one drug to another, as Dr. Dix talks about  
16 here?

17 A. Well, Dr. Dix says you don't do that, and I agree  
18 with that. That's not what we do.

19 Q. But if a POSA has the '865 patent in hand and wants  
20 to make formulations claimed in the '865 patent, does that  
21 require applying a formulation from one drug to another drug?

22 A. No. The '865 patent itself teaches how to do it.

23 Q. The '865 patent discloses formulations of  
24 aflibercept?

25 A. Yes, clearly. Yes.

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BERNHARDT TROUT, PhD - DIRECT 2097

1 Q. And you also have Tables 1, 3, and 5 shown on the  
2 screen in this discussion; is that right?

3 A. That's right. Actually, the whole examples including  
4 the tables, but yes.

5 Q. And, Doctor, you talked about some of the ingredients  
6 that are discussed in the '865 patent.

7 Do the claims for some categories narrow those  
8 structural requirements?

9 A. Yes.

10 Q. Now, we'll talk a little bit more about this in a  
11 moment, but the claims you said require a buffer.

12 What is a buffer?

13 A. Well, a buffer is a chemical compound that has a  
14 particular structure that leads to the formulation staying at a  
15 particular pH; so it resists pH changes.

16 Q. Would the POSA have known the structure of buffers  
17 that could be used to practice the claimed invention?

18 A. Yes.

19 Q. You noted that the patent teaches pH ranges, one of  
20 5.8 to 7 and then more specifically 6.2 to 6.3, in Column 2.

21 How does that pertain to the buffer that the person  
22 of ordinary skill would use to practice the claim?

23 A. Well, one would want to select a buffer that its  
24 chemical structure is such that it can maintain the pH within  
25 a given range.

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BERNHARDT TROUT, PhD - DIRECT 2098

1 Q. And is that a limited set of structures that could do  
2 that?

3 A. Yes.

4 Q. Does the patent provide an example of such a buffer  
5 that can be used?

6 A. Yes. The patent specifically -- again, that bottom  
7 left Column 2, it specifically says phosphate buffer.

8 Q. And, Doctor, in view of the specification's  
9 teachings, what buffers would the POSA use to practice the  
10 claims of the '865 patent?

11 A. Well, again, you could use buffers that would buffer  
12 within this range, like phosphate, could be succinate, for  
13 example, histidine.

14 Q. Let's turn to the next limitation, Dr. Trout, organic  
15 cosolvent. We've heard a lot about that. That's in Column 2.

16 And what does Claim 4 require with respect to the  
17 organic cosolvent?

18 A. Well, Claim 4 --

19 Q. What does Claim 4 require with respect to the organic  
20 cosolvent?

21 A. Claim 4 requires a specific one, polysorbate 20, and  
22 a specific range of that organic cosolvent.

23 Q. Do you understand all of the claims to require an  
24 organic cosolvent comprising polysorbate 20?

25 A. Yes. All the asserted claims, yes.

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BERNHARDT TROUT, PhD - DIRECT 2100

1 chromatography limitation?

2 A. Well, it teaches that, given the various formulations  
3 in the examples, if one encompasses the various structures that  
4 are described in the claims, one expects to meet the 98 percent  
5 limitation, or again the 99 under some circumstances with the  
6 different times.

7 Q. Let's take a look at Example 1. What does Example 1  
8 teach, Dr. Trout?

9 A. Well, Example 1 teaches 50 mg/mL VEGF Trap, the exact  
10 one, because it references the sequence ID. It has a phosphate  
11 buffer. It has the polysorbate 20 organic cosolvent. And it  
12 has the sucrose stabilizing agent and pH 6.25 which can be  
13 rounded up to 6.3.

14 Q. Now, Doctor, you said -- well, how much aflibercept  
15 is in this formulation? What's the concentration?

16 A. Yes. I said 50 mg/mL.

17 Q. So is that within the asserted claims?

18 A. No.

19 Q. Does it nevertheless provide relevant guidance or  
20 teaching to the POSA with respect to 40 mg/mL?

21 MR. RAKOCZY: Objection, Your Honor. That's a new  
22 opinion not in the report.

23 MR. BERL: So, Your Honor, if we go to paragraph 387.

24 THE COURT: 387?

25 MR. BERL: Yes. Dr. Trout there addresses the

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BERNHARDT TROUT, PhD - DIRECT 2099

1 Q. Let's go back to the specification and address this  
2 limitation.

3 What does the specification teach with respect to  
4 organic cosolvent?

5 A. Well, it teaches various structures. Again, I'll  
6 look at the monitor here. Maybe polysorbate and, for example,  
7 polysorbate 20 or 80; polyethylene glycol, also abbreviated at  
8 PEG and then gives an example; or propylene glycol or a  
9 combination thereof.

10 Q. Would the POSA understand what those structures are?

11 A. Yes.

12 Q. Now, let's turn to the next limitation, stabilizing  
13 agents. And let's look at Column 2 there as well.

14 What does the patent teach about stabilizing agents?

15 A. Well, it teaches what it also calls sugars, sucrose,  
16 sorbitol, glycerol, trehalose, or mannitol specifically.

17 Q. Are those known structures?

18 A. Yes.

19 Q. Doctor, all of the asserted claims require some  
20 stability limitation as measured by SEC, the 98 percent native  
21 conformation; is that right?

22 A. Correct.

23 Q. And some of them say 99 percent, some of them have  
24 different time periods, but let's -- what does the patent teach  
25 with respect to formulations that meet the size-exclusion

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BERNHARDT TROUT, PhD - DIRECT 2101

1 examples, including Example 1, that I'm taking him through.  
2 And he talks about the specification providing examples that  
3 meet this claimed property. That is the native conformation  
4 limitation. And I'm asking him how that pertains -- how the  
5 Example 1 pertains to the native conformation limitation.

6 THE COURT: Mr. Rakoczy.

7 MR. RAKOCZY: He does lay out the examples. I don't  
8 object to laying out the examples and identifying what they do  
9 and don't contain. But there's no opinion in here about  
10 somehow how 50 informs 40 or 40 informs 50, which I believe was  
11 the question.

12 THE COURT: Where is that specifically, Mr. Berl?

13 MR. BERL: Give me one moment.

14 THE COURT: Sure.

15 MR. BERL: Phone a friend.

16 If we go, Your Honor, to paragraph 395. And here he  
17 addresses more specifically the issue that I'm asking about,  
18 about whether the examples that are not within the scope of the  
19 claim because they have 50 are relevant or irrelevant to how  
20 the POSA would practice the claims. And later in the paragraph  
21 he talks in particular about Example 1, which is what I'm  
22 asking him about.

23 THE COURT: Overruled.

24 BY MR. BERL:

25 Q. Your Honor -- or Dr. Trout -- sorry.

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BERNHARDT TROUT, PhD - DIRECT 2110

1 A. Well, I mean, I guess the VEGF antagonist is one, but  
2 that is one very specific molecule. Categories, then, are the  
3 organic cosolvent, the buffer, and the stabilizing agent.  
4 Q. Were these structures well known in the art?  
5 A. Yes.  
6 Q. Did you understand Mylan's experts to dispute that?  
7 A. No.  
8 Q. Do all of the formulations within the claims share  
9 those common structural features?  
10 A. Yes.  
11 Q. Can the POSA recognize the formulations that were  
12 claimed here?  
13 A. Yes.  
14 Q. And can the POSA visualize the formulations within  
15 the claims?  
16 A. Yes.  
17 Q. Can the POSA recognize from the specification that  
18 the inventors invented the claimed formulations?  
19 A. Yes.  
20 Q. And how and where in the specification would the POSA  
21 recognize that?  
22 A. Well, again, from the examples and -- I mean,  
23 throughout, but specifically the examples, and then the  
24 disclosure on Column 2 that we've been discussing. Those are  
25 the key places.

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BERNHARDT TROUT, PhD - DIRECT 2112

1 Q. Okay.  
2 And let's put up the claims.  
3 Do you understand him to have asserted that the  
4 claim -- the term "suitable for intravitreal administration" is  
5 indefinite?  
6 A. Yes.  
7 Q. Do you agree?  
8 A. No.  
9 Q. Would the POSA be able to interpret the phrase with  
10 reasonable certainty?  
11 A. Yes.  
12 Q. What does suitable for intravitreal administration  
13 refer to?  
14 A. It means does it contain components as described in  
15 the claim that could be used for intravitreal administration,  
16 these structures, as we've been calling them.  
17 Q. Is the term "suitable for intravitreal injection"  
18 subjective?  
19 A. No.  
20 Q. How would the POSA determine whether an ingredient or  
21 an excipient is suitable for intravitreal injection?  
22 A. Well, first of all, the POSA would look to the  
23 teachings in the patent, again, the examples and those places  
24 in Column 2 that we've been looking at. And if a skilled  
25 person wanted to depart from those, a skilled person can go

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BERNHARDT TROUT, PhD - DIRECT 2111

1 Q. Does the '865 patent provide species or examples  
2 representative of the genus?  
3 A. Yes.  
4 Q. Do all of the examples have at least 98 percent  
5 native conformation as measured by SEC after two months?  
6 A. Yes.  
7 Q. And do all the examples meet the turbidity limitation  
8 of Claim 15?  
9 A. Yes.  
10 Q. And are the formulations with 50 mg/mL, those  
11 examples, are those relevant to whether the claims are  
12 described?  
13 A. Yes.  
14 Q. Is that for the reason you discussed a moment ago?  
15 A. Exactly.  
16 Q. Doctor, is the patent here claiming simply by  
17 function or is it claiming structures?  
18 A. These are all structures.  
19 Q. Doctor, in your view, does the '865 patent provide  
20 adequate written description for the asserted claims or not?  
21 A. For all the reasons I mentioned, yes, it does.  
22 Q. Now I'd like to address indefiniteness.  
23 Do you remember Dr. MacMichael's testimony about  
24 indefiniteness?  
25 A. Yes.

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BERNHARDT TROUT, PhD - DIRECT 2113

1 into the literature and find excipients or additives with the  
2 same structure or similar structures that had been used in  
3 intravitreal administration before and, if need be, could  
4 consult an ophthalmologist.  
5 Q. Did your definition of a POSA include someone who  
6 could consult with an ophthalmologist or a clinician as needed?  
7 A. Yes.  
8 Q. Let's take a look at Chang, which is Exhibit 1832.  
9 Did you review this reference?  
10 A. Yes.  
11 Q. And if we go to page 16 --  
12 THE COURT: Yes, Counsel?  
13 MR. RAKOCZY: Objection, Your Honor. This is outside  
14 the scope of the report. The witness's response to this  
15 indefiniteness argument is about ten lines, one paragraph, and  
16 it doesn't cite anything.  
17 THE COURT: What paragraph is that, Mr. Rakoczy?  
18 MR. RAKOCZY: Paragraph 420 of the responsive expert  
19 report if Your Honor has it.  
20 THE COURT: I do. It's PTX 67.  
21 MR. BERL: And, Your Honor, in paragraph 83  
22 Dr. Trout --  
23 THE COURT: One second.  
24 MR. BERL: Sorry to go back and forth.  
25 THE COURT: Paragraph 83. Go ahead.

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BERNHARDT TROUT, PhD - CROSS 2170

1 A. Correct.

2 Q. Now, there's no data in the '865 patent about

3 inflammation, correct?

4 A. There's no data about inflammation, that's correct.

5 Q. There's no data or testing in the '865 patent showing

6 that the claim formulations somehow result in less inflammation

7 than the prior art, correct?

8 A. There's not inflammation data. There's the SEC data

9 that we've been talking about, which is a good indication of --

10 for a formulator again of having a lower risk of inflammation.

11 Q. So your testimony is that SEC data is inflammation

12 data?

13 A. No, Counsel, that's not what I said. I can --

14 Q. So my question is there's no data in this patent

15 showing that these claim formulations somehow result in less

16 inflammation than prior art formulations, correct?

17 A. There's no -- you're correct there's no direct

18 inflammation data. Again, from the standpoint of the skilled

19 person, the SEC data, I should say all the stability data in

20 the patent, would tell me that -- would indicate to the skilled

21 person that there's a relatively lower risk of inflammation.

22 Q. I'm asking about inflammation data. You testified

23 about inflammation data in Gaudreault. There's no such data

24 like that in the patent, correct?

25 A. There's no direct inflammation data in the patent;

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BERNHARDT TROUT, PhD - CROSS 2172

1 correct?

2 A. Yes. It wasn't an intention to leave it out. It

3 lasted two to eight -- from day two to eight, so at least seven

4 days out of a month.

5 Q. Okay.

6 Let's go to page 3, please, Mr. Gibson.

7 This is what you're referring to, right? The

8 inflammation was present at day two, but it completely resolved

9 by day eight, correct?

10 A. Correct.

11 Q. And you haven't heard any clinician in this trial

12 testify that that would dissuade the use of 40 mg/mL, correct?

13 I haven't heard anyone.

14 A. I wasn't here for all of the clinicians' testimony;

15 but from what I heard, I didn't hear that specifically. I'm

16 telling you how a formulator would view this.

17 Q. But you didn't hear any testimony from a clinician,

18 right?

19 A. Again, I wasn't here the whole time. I did hear

20 testimony about having to be careful in injections, about how

21 the injections are done, and general concerns about issues with

22 injections, medical issues.

23 Q. Now, this is a POSA teaching away you testified

24 about. That didn't prevent others in the art like Dr. Dan Dix

25 from filing patents on even higher concentrations of

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BERNHARDT TROUT, PhD - CROSS 2171

1 there's other data.

2 Q. So, again, you're relying on a teaching away of

3 supposed inflammation that the '865 patent itself does not

4 address, correct?

5 A. The '865 doesn't explicitly discuss inflammation, I

6 agree.

7 By the way, it's not just Gaudreault that I'm relying

8 on.

9 Q. I understand. I understand.

10 And in Gaudreault, they actually concluded that

11 ranibizumab was well tolerated, correct?

12 A. Yes. And indicated to use the 10 milligrams per

13 mole.

14 Q. But they said it was well tolerated. That was their

15 first conclusion, correct?

16 A. They do use those terms. And I apologize, Counsel, I

17 gave the wrong units. 10 mg/mL. Sorry about that.

18 Q. We can pull up Gaudreault. Let's just confirm. It's

19 DTX 2265. On page 2 we have the clinical findings.

20 The first finding from Gaudreault is that ranibizumab

21 was well tolerated, correct?

22 A. That's what's listed here. And then it goes and

23 discusses the relative differences in inflammation.

24 Q. And it says transient. That's how it characterizes

25 the inflammation. You left that out. It says transient,

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BERNHARDT TROUT, PhD - CROSS 2173

1 aflibercept, correct?

2 A. Correct. Again, that's how invention works is to go

3 against the prevailing art.

4 Q. Okay.

5 Let's put DTX 13 at page 7 on screen.

6 And this is the Dix '226 we've been talking about,

7 correct?

8 A. I presume so. I didn't see the cover, but this looks

9 like the example.

10 Q. You recognize Example 1, Dr. Dix and his team, they

11 used a 50 mg/mL formulation here, correct?

12 A. 50 mg/mL, correct.

13 Q. So assuming this is prior art -- and I know you and

14 your counsel dispute that. But assuming this is prior art, Dix

15 and colleagues clearly weren't dissuaded or discouraged from

16 high concentrations of aflibercept, correct?

17 A. Well, I think -- I'm sorry. I don't want to get

18 confused here.

19 You're talking about after Dix or before Dix?

20 Q. This is Dix '226.

21 A. Yes. I understand.

22 Q. And Example 1, which is VEGF Trap Sequence ID

23 Number 4, which is aflibercept. And they used 50 mg/mL,

24 correct?

25 A. Yes.

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