

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 - - -

APPEARANCES:

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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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PTX 1170, PTX 0932.

2 THE COURT: I've got two others a little further down
 3 my list.

MS. OBERWETTER: Yes.

THE COURT: DTX 4070.

6 MS. OBERWETTER: That was the Nguyen 2006 reference.
 7 That's correct, Your Honor.

THE COURT: And PTX 0311?

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.

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 --

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 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 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 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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ERIC FURFINE, PhD - CROSS 551

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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ERIC FURFINE, PhD - CROSS 550

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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ERIC FURFINE, PhD - CROSS 552

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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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 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 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 or 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 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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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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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

1 (Video deposition of Karen Chu)

2 Tuesday Morning Session,

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

4 - - -

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

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

7 everybody.

8 Mylan may call its next witness.

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

10 Defendants' next witness will be Karen Chu by video

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

12 30(b)(6) topics identified in DTX 202, including conception and

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

14 relating to aflibercept development and associated clinical

15 trials.

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

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

18 (Video deposition of Karen Chu.)

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

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

21 the record.

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

23 Road, White Plains, New York 10605.

24 Q. And then what was your initial role and

25 responsibilities at Regeneron?

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

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1 (Video deposition of Karen Chu)

2 clinical trial manager. And then as is true, I think, for a

3 lot of small companies in that role, wore several different

4 hats and had a broad range of responsibilities as it related to

5 clinical development. And over the years moved into more of a

6 clinical project management role, and then finally into my

7 current role.

8 Q. Okay. And what -- was your initial title -- I think

9 it was -- what was it? -- director of therapeutic area project

10 management?

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

12 Q. Okay. What was your first title?

13 A. I believe -- my recollection is that my first title

14 was senior clinical trial manager. But the director of

15 therapeutic area project management was promotion into a

16 broader clinical project management role.

17 Q. And then did you ever have any individuals who

18 reported to you in those roles?

19 A. At the time that I was a clinical trial manager I had

20 a group of people that reported to me who -- who were more

21 junior clinical trial managers and involved in the operations

22 of the clinical trials.

23 Q. Okay. How do you differentiate what your role was

24 versus what you call the operation of the clinical trials?

25 A. So within clinical research, there are several people

26 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

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
8 Biocon Biologics, Volume 7
9 Defendants.
10 - - -
11 Proceedings had in the bench trial of the above-styled
12 action on June 21, 2023, before Honorable Thomas S. Kleeh
13 District Judge, at Clarksburg, West Virginia.
14 - - -
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32 Proceedings recorded utilizing realtime translation.
33 Transcript produced by computer-aided transcription.

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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.)

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1 (Courtroom unsealed.)
2 THE COURT: Welcome back, everybody.
3 Counsel, you may proceed.
4 MR. SALMEN: Thank you, Your Honor.
5 BY MR. SALMEN:
6 Q. Dr. MacMichael, do you recall Mr. Berl asking you the
7 question "Polysorbate in Claim 1 is being used as a
8 surface-active agent to prevent aggregation and denaturation?"
9 A. I don't recall the specific question.
10 Q. That appears at trial transcript page 1455. Why
11 don't we put that on the screen to refresh your recollection.
12 I'll give you a moment to read that.
13 A. Yes.
14 Q. Do you recall this question?

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KENNETH S. GRAHAM, PhD - DIRECT 1679

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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KENNETH S. GRAHAM, PhD - DIRECT 1681

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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KENNETH S. GRAHAM, PhD - DIRECT 1680

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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KENNETH S. GRAHAM, PhD - DIRECT 1682

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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KENNETH S. GRAHAM, PhD - DIRECT 1699

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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KENNETH S. GRAHAM, PhD - DIRECT 1701

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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KENNETH S. GRAHAM, PhD - DIRECT 1700

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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KENNETH S. GRAHAM, PhD - DIRECT 1703

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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KENNETH S. GRAHAM, PhD - DIRECT 1705

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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KENNETH S. GRAHAM, PhD - DIRECT 1704

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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KENNETH S. GRAHAM, PhD - DIRECT 1706

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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KENNETH S. GRAHAM, PhD - DIRECT 1707

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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KENNETH S. GRAHAM, PhD - DIRECT 1709

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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KENNETH S. GRAHAM, PhD - DIRECT 1710

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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KENNETH S. GRAHAM, PhD - DIRECT

1 A. Yes. I did.

2 Q. Did you determine in your review of those documents

3 whether or not each of those patents contains the same

4 disclosure as in your '865 patent at Column 2, lines 39 to 57,

5 and Examples 1, 3, and 5?

6 A. All of them contain the same examples, the exact same

7 data. Those paragraphs, although they appear on different

8 pages sometimes in slightly different formatting, are all

9 identical with respect to the words.

10 Q. Thank you, Doctor.

11 Now, were the aflibercept formulations that are

12 reported in your '865 patent the only ones that you tested for

13 stability?

14 A. No.

15 Q. Okay. How many did you make and test, just ballpark?

16 A. 40.

17 Q. I'd like to look at just a couple of those.

18 First, when you varied the ingredients in your

19 formulations, did you ever try stabilizing agents other than

20 sucrose?

21 A. Yes.

22 Q. What did you try?

23 A. We tried -- mannitol was one.

24 Q. Okay. Let's look at your '865 patent, PTX 2, at

25 Column 2, lines 45 or thereabouts. What does this passage of

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KENNETH S. GRAHAM, PhD - DIRECT

1 the patent convey in part?

2 A. It says that you might want to use mannitol as a

3 stabilizing agent.

4 Q. And did you, in fact, do a stability study on a

5 formulation with mannitol as the stabilizing agent?

6 A. We did.

7 Q. Okay. Let's look at PTX 2281 at page 1. What is

8 this document, Doctor?

9 A. This is the 208th stability study protocol.

10 Q. And did you run this study?

11 A. I did.

12 Q. Let's turn to page 2 of this document. This is the

13 mannitol-containing formulation you just referenced?

14 A. Yes, it is.

15 Q. And on page 2, does this indicate whether or not a

16 glass vial was tested as the container?

17 A. Container Number 7 was a glass vial, yes.

18 Q. Let's compare the formulation of Example 3 from your

19 '865 patent, PTX 2, Column 9, with the formulation of SS208,

20 which is PTX 2281, page 1.

21 Do you see these on the screen?

22 A. I do.

23 Q. How do these two formulations compare?

24 A. They're identical.

25 Q. Is the stabilizing agent identical?

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KENNETH S. GRAHAM, PhD - DIRECT

1 A. No. So the formulations are identical with respect

2 to every other component except one has sucrose and the other

3 has mannitol.

4 Q. Did this study involve testing the

5 mannitol-containing formulation by SEC?

6 A. Yes, it did.

7 Q. Let's look at PTX 2282 at page 14. Is this

8 spreadsheet the SEC data for SS208?

9 A. Yes, it is.

10 Q. And this is the glass vial at 5C?

11 A. Yes, it is.

12 Q. What was the percent native conformation as measured

13 by size-exclusion chromatography at 5C, two months' storage in

14 a glass vial?

15 A. 99.05.

16 Q. And is that -- that's greater than 98 percent?

17 A. Yes, it is.

18 Q. Did you do turbidity on this formulation as well?

19 A. Yes, we did.

20 Q. Let's look at PTX 2283, page 12.

21 What is this document?

22 A. So this is the data that was collected for turbidity

23 or optical density at 405.

24 Q. And what does it show for the turbidity of the

25 mannitol-containing formulation following storage at 5C for two

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KENNETH S. GRAHAM, PhD - DIRECT

1 months in a glass vial?

2 A. It shows that it was unchanged from the initial

3 measurement; so it's good stability.

4 Q. Now, in the course of your stability study work on

5 aflibercept formulations, did you also vary the amounts of

6 polysorbate 20?

7 A. We did.

8 Q. Let's look at PTX 2265, page 1.

9 What is this document, Dr. Graham?

10 A. This is the 205th stability study protocol.

11 Q. And what amount of polysorbate did you test here?

12 A. 0.06 percent.

13 Q. And if we look at page 2, Table 1, of PTX 2265, was a

14 glass vial tested in this study as well?

15 A. Yes, it was.

16 Q. Was that Device 7?

17 A. Yes, it is.

18 Q. Let's compare the formulation of the SS205 protocol

19 that we just looked at with the formulation of Example 5 of the

20 '865 patent, PTX 2, page 8, Column 10. How do these two

21 formulations compare, Dr. Graham?

22 A. So they have the same components. The difference is

23 that there is .03 percent polysorbate in Example 5

24 and .06 percent polysorbate in Study 205.

25 Q. Did you look at these -- this .06 percent

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1 polysorbate 20 formulation by size-exclusion chromatography?

2 A. Yes, we did.

3 Q. Let's look at PTX 2266, page 15. Is this the SEC
4 data for the glass vial at 5 degrees C?

5 A. Yes, it is.

6 Q. And what was the percent native conformation as
7 measured by SEC following storage in a glass vial for two
8 months at 5C for this formulation?

9 A. 99.0 percent.

10 Q. Did you run turbidity analysis here as well?

11 A. Yes, we did.

12 Q. Let's look at PTX 2267, page 17.

13 THE COURT: Counsel, once we go through this table,
14 if we're at a spot to take our afternoon break.

15 MR. TRASK: Absolutely, Your Honor.

16 BY MR. TRASK:

17 Q. Is this the turbidity data for the SS205 study?

18 A. Yes, it is.

19 Q. And what was the turbidity at 5 degrees Celsius for
20 two months in a glass vial?

21 A. It was unchanged from the initial measurement.

22 Q. Is that a good result?

23 A. Yes.

24 MR. TRASK: Okay. Happy to break at this point, Your
25 Honor, if you'd like.

1812

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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1814

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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KARL CSAKY, MD, PHD - DIRECT

1 believe everyone should have their advance copies of the binder

2 and slides.

3 THE COURT: I believe I do. Thank you all very much.

4 Good morning again, Doctor. If you wouldn't mind

5 adjusting that mic. Stay close to that for us.

6 Counsel, you may proceed.

7 DIRECT EXAMINATION

8 BY MS. OBERWETTER:

9 Q. Good morning, Dr. Csaky. Can you please reintroduce

10 yourself to the Court.

11 A. Yes. My name is Karl Csaky. I'm a retina specialist

12 from Dallas, Texas.

13 Q. And we're going to cover -- since you were here with

14 us last week, we're going to cover some material today that

15 relates some other of your opinions besides those bearing on

16 infringement. I'd like to start first with your definition of

17 the POSA.

18 If we can please pull that up onto the screen.

19 For the record, that's PDX 8.002.

20 Can you please read for us your definition of the

21 POSA.

22 A. Yes. So this is the definition that I used during my

23 opinions.

24 A person of ordinary skill in the art relevant to the

25 claims is an ophthalmologist with experience in treating

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BERNHARDT TROUT, PHD - DIRECT 2012

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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BERNHARDT TROUT, PHD - DIRECT 2014

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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BERNHARDT TROUT, PHD - DIRECT 2013

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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BERNHARDT TROUT, PHD - DIRECT 2015

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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BERNHARDT TROUT, PHD - DIRECT 2016

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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BERNHARDT TROUT, PHD - DIRECT 2018

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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BERNHARDT TROUT, PHD - DIRECT 2017

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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BERNHARDT TROUT, PHD - DIRECT 2019

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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2020

BERNHARDT TROUT, PHD - DIRECT

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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2022

BERNHARDT TROUT, PHD - DIRECT

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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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 VEGFR1.

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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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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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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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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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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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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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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BERNHARDT TROUT, PHD - DIRECT 2043

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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BERNHARDT TROUT, PHD - DIRECT 2044

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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BERNHARDT TROUT, PHD - DIRECT 2046

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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BERNHARDT TROUT, PHD - DIRECT 2045

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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BERNHARDT TROUT, PHD - DIRECT 2047

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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1 CERTIFICATE
2 I, Cindy L. Knecht, Registered Professional Reporter and
3 Official Reporter of the United States District Court for the
4 Northern District of West Virginia, do hereby certify that the
5 foregoing is a true and correct transcript of the proceedings
6 had in the above-styled action on June 22, 2023, as reported by
7 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
13 Cindy L. Knecht, RMR/CRR
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.
14 - - -
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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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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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THE COURT: Don't ask me.

THE WITNESS: I think by now, Your Honor, you could probably answer all these questions.

MR. BERL: And more interested in the answers.

BY MR. BERL:

Q. Dr. Trout, how is this example of 50 mg/mL, Example 1, relevant to practicing the claim with 40 mg/mL?

A. Well, I think, given the teachings in the '865 patent and general understanding of the literature, the skilled person would understand that if this formulation with 50 mg/mL met that 98 percent or related limitations, then the similar formulation with 40 mg/mL would also meet those limitations, 98 percent, 99, and the different times.

Q. Is that always the case, that if you have a lower concentration of the same formulation, you'll have higher stability, or is it generally the case?

MR. RAKOCZY: That's a new opinion, Your Honor. That's not in this paragraph or the prior one.

MR. BERL: Well, I don't agree, Your Honor. It says "would expect." And so I'm trying to understand what would expect means. That's the language he uses. I'm reading in paragraph 395 of his report. And so I'm trying to understand -- it's a hard-and-fast 100 percent rule or something different than that.

MR. RAKOCZY: And now he's leading and telling the

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witness how to answer the question, Your Honor.

THE COURT: The first one's overruled. Let's rephrase the question and give it a try.

MR. BERL: Sure.

BY MR. BERL:

Q. Dr. Trout, can you explain your opinions with respect to the expectation from the same formulation going from 50 mg/mL of aflibercept to 40 mg/mL of aflibercept?

A. Certainly. So, generally speaking, as you increase the concentration of a protein, you have a higher propensity towards going to nonnative conformation. So that means that, generally, if you decrease the concentration, you're going to have a lower propensity.

In other words, if -- generally, if you meet the -- let's say, the 98 percent limitation and related ones we've been discussing at 50 mg/mL, it's most likely that you will meet that also at 40 mg/mL. It's not guaranteed, but I think in general the skilled person would expect that to be the case.

Q. Let's take a look at Example 3, Dr. Trout.

Can you explain what this example discloses?

A. Yes. So this example discloses 40 mg/mL VEGF Trap -- again, the molecule with that specific sequence ID Number 4 -- phosphate buffer, also the polysorbate 20 organic cosolvent, sucrose as a stabilizing agent, and a pH of 6.3.

Q. Is it your understanding that this is now called

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