

1 UNITED STATES DISTRICT COURT
2 NORTHERN DISTRICT OF WEST VIRGINIA
3 Regeneron Pharmaceuticals, Inc.
4 Plaintiff,
5 VS. CIVIL ACTION NO.
6 1:22-cv-61
7 Mylan Pharmaceuticals, Inc., and Volume 2
8 Biocon Biologics,
9 Defendants.
10 - - -
11 Proceedings had in the bench trial of the above-styled
12 action on June 13, 2023, before Honorable Thomas S. Kleeh
13 District Judge, at Clarksburg, West Virginia.
14 - - -
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1 Tuesday Morning Session,
2 June 13, 2023, 9:30 a.m.
3 - - -
4 THE COURT: Convene for day two of trial. Plaintiff
5 may call its next witness.
6 MS. OBERWETTER: Your Honor, if I may, Ellen
7 Oberwetter for Regeneron. A brief housekeeping matter from
8 yesterday relating to the admission of exhibits used in
9 Dr. Yancopoulos's direct and redirect testimony.
10 I'm happy to handle this however you would prefer. I
11 can either read the list into the record. We've had an
12 opportunity to make sure our list conforms to what Ms. Kinsey
13 had yesterday so that those are moved into the record as
14 evidence.
15 THE COURT: Let's go ahead. If you'll read that
16 slowly for Madam Court Reporter's benefit. Go right ahead.
17 MS. OBERWETTER: I'm happy to do that, Your Honor.
18 PTX 0001, PTX 0003, PTX 3333, DTX 212, PTX 0419.
19 THE COURT: Is that 19 or 91?
20 MS. OBERWETTER: My list says 19.
21 THE COURT: Okay.
22 MS. OBERWETTER: Your list is correct, Your Honor.
23 THE COURT: As is Mr. Ruby's.
24 MS. OBERWETTER: PTX 491, DTX 228, PTX 0311,
25 PTX 0304, PTX 3216, PTX 3187, PTX 3188, PTX 0080, PTX 1028-C,

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1 PTX 1170, PTX 0932.
2 THE COURT: I've got two others a little further down
3 my list.
4 MS. OBERWETTER: Yes.
5 THE COURT: DTX 4070.
6 MS. OBERWETTER: That was the Nguyen 2006 reference.
7 That's correct, Your Honor.
8 THE COURT: And PTX 0311?
9 MS. OBERWETTER: Yes.
10 THE COURT: That's the Heier article on wet
11 age-related macular degeneration.
12 MS. OBERWETTER: Yes, Your Honor. That one was
13 further up in my list. That's correct.
14 THE COURT: Any objection to any of those, Counsel?
15 MS. MAZZOCHI: No. But, again, as long we -- I know
16 you instructed we are going to be doing the issue of whether
17 they are allowed to use their conception surveys --
18 THE COURT: Try it again.
19 MS. MAZZOCHI: Yesterday the Court indicated -- my
20 understanding is that the Court indicated that, to the extent
21 we had an objection as to whether Regeneron can use any of
22 these exhibits in connection with, for example, its conception
23 or reduction practice theories or other theories not disclosed
24 in their interrogatory responses, we will have the opportunity
25 to raise that in posttrial briefing. Thank you.

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1 that we were working on.

2 A second, similar sized part was to really understand
3 what happens in animals, in humans, and to be able to measure
4 those things and prepare drugs to get ready to move into the
5 clinic.

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

8 A. I would say approximately a year after I was there,
9 maybe 2003.

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

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

12 Q. Now, I'm going to place on the screen what's been
13 marked as PTX 2 in this case.

14 Dr. Furfine, is this the patent that describes and
15 claims your inventions working on the project on aflibercept?

16 A. Yes, it is.

17 Q. We've highlighted various people who are listed as
18 inventors. The first one, Eric Furfine, we know.

19 Who is Daniel Dix?

20 A. Daniel Dix was the head of the formulation group that
21 reported to me.

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

23 A. Kenneth was a scientist in the formulation group, and
24 he reported to Dan.

25 Q. And Kelly Frye, who is that?

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1 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 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 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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difficult problem.

Q. Why is that?

A. First of all, aflibercept itself being a fusion protein was a challenge because there just wasn't that much knowledge on how to formulate and what the behaviors of those types of molecules, of fusion proteins general.

And the second reason was there just wasn't a lot of experience in the industry in developing formulations that were going to be injected intravitreally.

Q. Did the fact that aflibercept Trap VEGF mean that it could be used to treat diseases in the retina?

A. No. It had to reach the retina in order to be able to do that, both block VEGF and reach the site of action.

Q. Now, you mentioned ranibizumab, which was one of the two molecules that Genentech was developing.

What was your understanding about for what diseases Genentech was pursuing ranibizumab?

A. My understanding was they were only pursuing retinal diseases with ranibizumab.

Q. Did you consider aflibercept to be like ranibizumab for purposes of treating eye diseases?

A. It was similar in a very high-level sense in that they're both protein therapeutics, but the chemical nature of these two drugs was very, very different, and they were different classes of proteins.

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Q. Did they have any other differences that you considered to be important for purposes of your project?

A. Yes. Aflibercept was considerably larger than ranibizumab was.

Q. What do you mean by larger or smaller in the context of molecules or proteins?

A. So what we mean by larger is molecular weight, kind of the space a molecule takes up. And the ranibizumab molecule was about a third the size of a full antibody. So it's an antibody part. It's in some ways considered an antibody, but it's really a part of an antibody, the FAB domain. And that's about a third of the size of a total antibody.

And the VEGF Trap or aflibercept is much more similar in size to an antibody than it is to ranibizumab.

Q. Was a molecular weight or the weight the only thing you considered in terms of the size?

A. No. So the molecular weight of aflibercept was a little bit smaller than an antibody, but we felt like it behaved more like the size of an antibody. It's kind of like if you -- could make a football analogy where you get somebody who's a fullback might be or a running back might be, this relatively heavy, relatively dense, small, compact person; and then you have a wide receiver who might weigh even maybe a little bit less but be much bigger, might have more trouble fitting in an airplane seat because of their -- they just take

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up more space.

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

A. More like the wide receiver and, therefore, more similar to an antibody in size, despite its actual weight being somewhat less.

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

A. No. As I mentioned, ranibizumab was an antibody or considered an antibody as it was part of an antibody, and aflibercept was a receptor fusion protein. It had receptor domains on it that were previously in a normal setting on the surface of a cell and bore no resemblance to the structures of an antibody.

Q. Based on your understanding at the time, does a formulation that works to stabilize one protein in a class work to stabilize a separate protein in a class?

A. No, not necessarily.

Q. Why not?

A. The chemical nature of even two antibodies can be very different, and it's the chemical nature of those antibodies, how charged they are, hydrophobic they are -- hydrophobic meaning kind of a dislike of water, if you will. Depending on the nature, they could be very different things that are required to maintain their stability in solution.

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Q. Did you understand that a formulation that stabilizes an antibody could be used to stabilize a fusion protein?

A. Definitely not. The differences between a fusion protein's chemical nature is even more different than an antibody to an antibody.

Q. And I should have asked you this before. When you came to Regeneron in 2002, did you start working on protein formulations immediately?

A. Yes.

Q. Was it your understanding, Dr. Furfine, that you could take an existing antibody formulation, take out the antibody, and put in a different molecule such as a fusion protein?

A. No. That's not how we do formulation discovery. We have a path where we do things that are fit for purpose. You decide what's going to be used for, you decide the nature of the molecule you're formulating, and you design the formulation for that.

Q. Would it even be allowed to make that kind of substitution to make your product that way?

A. Absolutely not. It's a cardinal rule of formulation science and drug discovery generally that you only put things in that you need. You have to actually go through the process of showing that you need something and figuring out exactly not 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 discovery almost everything we do is a yin and a yang. There's
2 a benefit to be gotten from having a lot of something, and
3 there's also a downside to be had of those things. And you
4 have to find that balance of safety versus risk, efficacy
5 versus adverse effects. And, you know, the higher you go, the
6 higher the chances you're going to get an adverse effect that
7 may dampen the benefit that you get.

8 Q. What about stability in formulation?

9 A. Higher concentration formulations with proteins in
10 particular are much more challenging to do.

11 Q. What happens when it's challenging? What happens
12 with high concentrations sometimes?

13 A. High-concentration formulations of proteins often
14 aggregate and precipitate out of solution and cause particles.

15 Q. Is that a problem?

16 A. That's a big problem, and it's probably more of a
17 problem for an eye drug than it is for a regular drug.

18 Q. Why is that a problem for an eye drug?

19 A. So there's three big reasons why particles are a
20 problem for an eye drug. These are probably somewhat obvious,
21 but one is, if you put particles in the eye, you can imagine
22 obscuring your vision. And, in fact, that can happen.

23 The other thing is you can induce inflammation,
24 which, in fact, we see inflammation here. We don't know that
25 it was particles, but it very well could have been.

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1 And the third thing is you can stimulate an immune
2 response to the drug that you've injected. And if you get an
3 immune response to the drug, you can end up neutralizing the
4 drug so it doesn't work anymore.

5 Q. And when you said we --

6 THE COURT: I'm sorry. What do you mean when you say
7 "immune response," Doctor?

8 THE WITNESS: So what happens -- immune response can
9 be a number of things; so it's a good question. So a lot of
10 times you get an antibody response, like to COVID. And if you
11 make antibodies to COVID, you clear the COVID. If you make
12 antibodies to your drug, you clear your drug.

13 THE COURT: Understood.

14 Sorry, Mr. Berl.

15 MR. BERL: Thank you. We're all here to help you
16 understand. Doesn't matter if anyone else does.

17 BY MR. BERL:

18 Q. You said in your answer we see inflammation here. I
19 just want the record to be clear. When you said there's
20 inflammation here, were you referring to the Gaudreault
21 reference on the screen, Exhibit 1839?

22 A. Yes.

23 Q. Now, let's go back with that in mind to the rabbit PK
24 study that you had mentioned, which is PTX 3257, and the
25 results at page 100. We looked at this paragraph before. I'd

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1 now like to ask you about the language further down in this
2 paragraph about how long the protein can be present in the
3 tissue.

4 Can you explain what result you obtained in your
5 study?

6 A. Yes. So as you can see here, the drug was present in
7 the tissue for at least through 28 days. And, again, this is a
8 yin and a yang situation. If you have a lot of drug around for
9 a long time, there's a chance it could have an adverse effect.
10 But if you have a drug around for a long time, it could be
11 having efficacy for that time.

12 I was a little bit more on the optimist side of
13 things in this case, but nonetheless one has a concern that you
14 can have a problem with it, and you need to do further testing
15 to sort that out.

16 Q. To be clear, Dr. Furfine, did you expect to obtain
17 this result in the pharmacokinetic study in the rabbits of the
18 protein being present in the tissue for up to 672 hours?

19 A. No, we did not expect this.

20 Q. Is that a high number or a low number?

21 A. It's a high number. This was, roughly speaking,
22 about twice as good as ranibizumab, and that was encouraging to
23 us.

24 Q. And just again so the record's clear, was this public
25 at the time?

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1 A. It was not.

2 Q. Now, given all the concerns that you've mentioned,
3 why did you end up using a higher concentration?

4 A. So when you see one advantage -- in this case, it was
5 how long it was staying in the eye; it was staying in the eye
6 longer than ranibizumab -- you can actually leverage that to
7 your advantage in another way by adding more.

8 So if you add more of something that's longer-lived,
9 you kind of double down on the longer-lived. So every time you
10 double the concentration that you inject, you get an extra
11 half-life. If your half-life is already longer than
12 ranibizumab and now you're getting more of them, this was an
13 exciting possibility to reduce the number of injections a
14 patient would have to get. And so we were excited about that
15 possibility.

16 Q. Did you still have all those concerns you mentioned
17 about toxicity and stability?

18 A. Absolutely.

19 Q. So what did you do in view of those concerns?

20 A. We did a lot of experiments to figure out whether we
21 could make a stable formulation and whether we were going to
22 have toxicology that was associated with higher concentrations.

23 Q. I'd like to discuss some of those experiments with
24 you. Let's turn to Exhibit PTX 81.

25 What is this document, Dr. Furfine?

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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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BERNHARDT TROUT - DIRECT 573

1 The other is of course we talked -- we don't want the needle
2 clogged while doctors or any doctor is giving an injection.
3 And then another aspect is what we call viscosity or
4 the thickness of the formulation. It goes through a very thin
5 needle. And, again, I don't think it's hard to convince
6 everyone that we don't want the needle in there for a long
7 period of time; so it has to be a thin enough fluid so it can
8 go in pretty quickly.
9 BY MR. BERL:
10 Q. Is formulation research as simple as taking a
11 formulation and substituting it into a new molecule?
12 A. No, sir. That's not what we do. That's not how
13 formulation works.
14 Q. Now, I'd like to discuss the concept of solubility
15 with you. What does solubility mean in the context of protein
16 formulations?
17 A. Well, with -- many protein formulations are
18 formulated as liquid in aqueous or water solutions. And
19 solubility is the concept of keeping it in solution under
20 whatever condition it might be subjected to.
21 Q. And is there one solubility for a given protein in a
22 formulation?
23 A. No. Even for a given formulation, that solubility
24 will depend on conditions, for example, temperature and
25 pressure, including shear.

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BERNHARDT TROUT - DIRECT 575

1 can see here is the molecular weight. And that's
2 0.18 kilodaltons. That was brought up yesterday in court. And
3 it's just a measure of the weight but in molecular units like
4 pounds or kilograms. And then the aflibercept is about
5 115 kilodaltons. So it's about 1,000 times bigger in terms of
6 size, which is reflected in the relative scale here.
7 THE COURT: Just so I'm clear, when we say aspirin,
8 we're talking about aspirin?
9 THE WITNESS: Yes, sir. Well, in a certain sense
10 we're talking just about the molecule aspirin, not the
11 formulation aspirin.
12 THE COURT: A singular molecule of aspirin?
13 THE WITNESS: Yes, sir. Correct.
14 THE COURT: Understood. Thank you.
15 BY MR. BERL:
16 Q. So these proteins like aflibercept, do they come in
17 solution, in a liquid state, or are they in a powder state like
18 something like aspirin?
19 A. Not like aspirin. They're in a liquid state from
20 manufacturing. And, again, the idea is to maintain them in a
21 liquid state. Aspirin I think we're familiar with is typically
22 formulated into a tablet, and it comes from manufacturing as a
23 powder and is made into a tablet.
24 Q. So what do solvents do for proteins if it's already a
25 liquid to start with?

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BERNHARDT TROUT - DIRECT 574

1 Q. Is there such a thing as a protein simply being fully
2 in solution without regard to the temperature or pressure
3 conditions?
4 A. No. Those are essential conditions in determining
5 and defining solubility.
6 Q. Dr. Trout, have you prepared demonstratives to help
7 explain the scientific principles relevant to your testimony
8 today?
9 A. Yes, I have.
10 Q. Let's take a look, starting with Demonstrative
11 Slide 3.
12 MR. BERL: And, Your Honor, this has demonstratives
13 as well as portions of documents that we'll be using with
14 Dr. Trout today --
15 THE COURT: Understood.
16 MR. BERL: -- so it's useful to follow along compared
17 to the binder, I hope.
18 BY MR. BERL:
19 Q. We've shown PDX 5-3.0003, Dr. Trout. Can you explain
20 what's shown here?
21 A. Yes. Here I just show a comparison between a typical
22 small-molecule pharmaceutical aspirin and a biologic or
23 large-molecule pharmaceutical like aflibercept. This is more
24 or less to scale. Hopefully, the Court can see there's a
25 little speck there which is represented as aspirin. And you

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BERNHARDT TROUT - DIRECT 576

1 A. Well, solvent does what solvents do to molecules that
2 keep it in solution. For example, water will interact with the
3 protein around the surface of the protein and will orient
4 itself to keep it in solution.
5 Q. Are solvents added to dissolve or remove aggregates
6 in protein formulations?
7 A. No. Typically, aggregates are irreversible. So once
8 they form, they don't go backwards.
9 Q. So is making a protein formulation, is it like what I
10 talked about a moment ago, like taking sugar and dissolving it
11 in your coffee?
12 A. No, on the contrary. Again, aspirin, we could make
13 an analogy with sugar. That can be dissolved and then formed a
14 solid again, a powder. But proteins, typically, we want to
15 keep them in solution. Again, they come in the liquid state
16 from manufacturing. And if they start precipitating or
17 becoming insoluble, it's typically irreversible.
18 Q. I'd like to discuss now with you how that happens and
19 how those aggregates can form.
20 If we could go to Exhibit PTX 1556.
21 Is this an article by Wang in 2005 that you reviewed
22 in connection with your work in this case?
23 A. Yes, it is.
24 Q. If we look at the abstract on the first page, it
25 says, "Protein aggregation is arguably the most common and

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BERNHARDT TROUT - DIRECT 577

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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BERNHARDT TROUT - DIRECT 579

1 solution?

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

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

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

14 What is Wang writing here?

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

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

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

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BERNHARDT TROUT - DIRECT 578

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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BERNHARDT TROUT - DIRECT 580

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

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

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

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

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

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

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

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

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THOMAS A. ALBINI, MD - CROSS 861

1 Q. And even during the Phase III trials for abicipar
2 significant intraocular inflammation issues emerged, correct?

3 A. That's correct.

4 Q. That drug did not make it to the market?

5 A. That's correct.

6 Q. I think you touched on one that passes its Phase III
7 trials and then still runs into problems. Beovu is an example
8 of an anti-VEGF agent in that category, correct?

9 A. That's correct.

10 Q. Beovu came onto the market in early 2020. Do I have
11 that right?

12 A. That sounds right.

13 Q. You only used it twice?

14 A. That's my recollection, yes.

15 Q. All right. And that's because, after launch,
16 everyone learned that there is a 1-in-200 risk of severe vision
17 loss for patients that have Beovu, right?

18 A. That is correct.

19 Q. And those safety issues for Beovu only became known
20 to doctors after Beovu was approved?

21 A. That is correct.

22 Q. And after it passed its Phase III trials?

23 A. That is correct.

24 Q. All right. And, in fact, the experience with Beovu
25 made doctors appreciate how lucky -- and I think you've used

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THOMAS A. ALBINI, MD - CROSS 863

1 the drug might be administered?

2 A. Correct.

3 Q. You need to consider the concentrations of the drug
4 being administered?

5 A. Correct.

6 Q. You need to think about whether and how many loading
7 doses to use?

8 A. That is correct.

9 Q. You need to consider whether to have a fixed loading
10 dose component to the regimen?

11 A. That is correct.

12 Q. And you need to consider whether there's a fixed
13 extended dosing component to the regimen?

14 A. That is correct.

15 Q. You'd have to consider whether to have intervening
16 visits between periods set for fixed dosing intervals, right?

17 A. That is a decision that -- yes, that is a decision
18 that needs to be made when designing protocol for sure.

19 Q. You would agree that in the 2010 time period there
20 was uncertainty as to what the best dosing approaches were for
21 anti-VEGF agents, wouldn't you?

22 A. I think that, as was documented in this -- in my
23 testimony so far, there were a number of protocols that had
24 succeeded with a number of dosing strategies that involved
25 three to six loading doses followed by prn or fixed interval

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THOMAS A. ALBINI, MD - CROSS 862

1 the word "lucky" -- doctors have been on the safety side with
2 the first main anti-VEGF drugs like Eylea and Lucentis and
3 bevacizumab, correct?

4 A. That is correct.

5 Q. And it's certainly possible that more went into that
6 than luck, right?

7 A. Yes.

8 Q. This area of medicine is so difficult that you might
9 not even know if an approved biosimilar will perform the same
10 as the label drug, correct?

11 A. I would say that's not particular to this area of
12 medicine. There are many areas of medicine that are just as
13 difficult or challenging, but I think that, yes, it's -- it is
14 true that the anticipated success doesn't always materialize.

15 Q. When deciding on how to design the arms of a clinical
16 trial using an agent like an anti-VEGF, you would agree there's
17 a lot of moving pieces to that, correct?

18 A. Yes.

19 Q. All right. You need to consider the route of
20 administration?

21 A. Yes.

22 Q. You need to consider how often a drug needs to be
23 administered?

24 A. Yes.

25 Q. You need to consider at which visits to the doctor

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THOMAS A. ALBINI, MD - CROSS 864

1 dosing regimens, either at 4 weeks or with other 8- or even
2 12-week dosing regimens.

3 So I think there were a number of protocols to choose
4 from, but it also wasn't an infinite field of reasonable things
5 to try.

6 Q. You would agree there was uncertainty as to what the
7 best dosing approaches were for anti-VEGF agents?

8 A. Yes.

9 Q. You know that throughout the development period for
10 Eylea, both before 2011 and afterward, Regeneron had access to
11 data about the performance of Eylea that the public didn't,
12 correct?

13 A. I'm aware that such data existed, but I don't know
14 much about it.

15 Q. Okay. They, of course, had access to such data
16 because it was their development program, right?

17 A. That makes sense.

18 Q. I'd like to talk a little bit about some of the
19 terminology that we've been using in this case. Let's talk
20 first about the phrase pro re nata, or prn. Prn means as
21 needed, correct?

22 A. That's correct.

23 Q. All right. And prn means you only treat as needed
24 determined by the findings of an OCT scan and other components
25 like clinical examination and visual acuity measurements,

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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 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 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 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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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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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 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 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 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 2040

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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BERNHARDT TROUT, PHD - DIRECT 2042

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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BERNHARDT TROUT, PHD - DIRECT 2041

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 2066

1 POSA would have combined it with Fraser?

2 A. Yes. And I've highlighted a middle part of this

3 paragraph. Again, this is just a reflection of what the POSA

4 would know. Speaking, though, of antibodies, antibodies tend

5 to form viscous solutions at high concentration because of

6 their macromolecular nature and potential for intramolecular

7 interactions. Moreover, pharmaceutically acceptable sugars are

8 often used in large amounts as stabilizers.

9 Q. So what does that teach in laymen's terms?

10 A. Well, if you have a higher concentration of

11 antibodies, for example -- because Liu is just about

12 antibodies -- that's going to lead to a higher viscosity.

13 Also, if you have a higher amount of sugar, that can lead to a

14 higher viscosity. I think we're familiar with syrup; it's more

15 viscous. And the combination together can lead to an even

16 higher viscosity.

17 And, again, for intravitreal administration, which

18 these references don't teach, we have a very thin-bore needle.

19 High viscosity means potentially very long injection times,

20 which I think we all don't want in the eye. And potentially,

21 if it's too viscous, you won't even be able to use it.

22 Q. And what does Fraser have with respect to

23 concentrations of sugar? Does it use low concentrations or

24 high concentrations?

25 A. No, it uses high concentrations. This is not the

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BERNHARDT TROUT, PhD - DIRECT 2068

1 combination of Fraser plus Liu.

2 Did you hear Dr. Rabinow testify about the Liu

3 reference?

4 A. Yes.

5 Q. Would Liu have informed whether formulations of

6 aflibercept would meet the 98 percent native conformation

7 limitation?

8 A. No.

9 Q. Why not?

10 A. Because Liu talks about different molecules,

11 completely different molecules. It doesn't even tell -- or

12 inform what those molecules are exactly, but they're different

13 from aflibercept.

14 Q. Would the POSA conclude that, because Liu identified

15 antibody formulations that met 98 percent native conformation

16 for those molecules, aflibercept would perform the same way?

17 A. No, not at all.

18 Q. And let's -- again, what's the relevance of

19 aflibercept's structure as a fusion protein to your opinion?

20 A. Well, first of all, as I've been emphasizing, I think

21 it's clear aflibercept is a different molecule than the

22 molecules in the Liu reference. And, furthermore -- I brought

23 this up yesterday also to the Court -- these are -- well, the

24 aflibercept is fusion protein. It's not a natural molecule. I

25 used the term "Frankenstein molecule." And I even quoted some

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BERNHARDT TROUT, PhD - DIRECT 2067

1 Fraser, but it uses high concentration, 20 percent sucrose.

2 Q. So would the person of skill, in view of this

3 teaching of Liu, have wanted to combine Fraser with a high

4 concentration of sugar with Liu?

5 A. No, not at all. I mean -- again, they don't

6 contemplate intravitreal, but certainly you wouldn't want to

7 use these high concentrations for intravitreal.

8 Q. I'd like to move to the 98 percent native

9 conformation limitation with respect to this combination.

10 THE COURT: Mr. Berl, before you ask that question,

11 it just dawns on me I did the same thing today I neglected to

12 do yesterday.

13 We're going to take our lunch break from 11:00 to

14 12:00 today for anyone who needs to -- I saw everybody turn and

15 look at somebody in each corner of the courtroom. You all are

16 the MVPs today. My apologies. I promised you I wouldn't do

17 that to you again, but I just did. We're going to take our

18 lunch break from 11:00 to 12:00 today with apologies.

19 Mr. Berl, if you wouldn't mind starting that question

20 again, sir.

21 MR. BERL: This is the last time we'll do that in

22 this trial.

23 BY MR. BERL:

24 Q. So I'd like to talk about the 98 percent native

25 conformation limitation, Dr. Trout, with respect to this

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BERNHARDT TROUT, PhD - DIRECT 2069

1 of the literature that would reflect the understanding of the

2 skilled person that these molecules would tend to be less

3 stable.

4 Q. Would the POSA have an expectation of success

5 regarding the native conformation of aflibercept in view of

6 Liu?

7 A. No.

8 Q. Let's talk about turbidity briefly. And we can look

9 again -- this is recited in Claim 15 of the '865 patent. Does

10 Dr. Rabinow rely again on Liu for this limitation?

11 A. Yes.

12 Q. Do you agree with Dr. Rabinow that the POSA would

13 expect aflibercept formulations to have the claimed turbidity

14 based on Liu?

15 A. No. Again, completely different molecule.

16 Q. Now, is the analysis you just provided with respect

17 to native conformation the same with respect to the turbidity

18 limitation?

19 A. Yes. That's correct.

20 Q. Now, I'd like to -- well, one final question on this

21 combination.

22 Do you believe that the combination of Fraser and Liu

23 render the asserted claims obvious?

24 A. No.

25 Q. Now, with that, I'd like to turn to Dix.

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BERNHARDT TROUT, PhD - DIRECT 2094

1 Q. How about the concentrations to use for aflibercept
2 intravitreal formulations?

3 A. Clearly not.

4 Q. Does Remington's disclose what pH to use for
5 intravitreal formulations of aflibercept?

6 A. No.

7 Q. Now, Doctor, did you consider the Dix declaration
8 cited by Dr. MacMichael from the prosecution of another patent?

9 A. Yes, I did.

10 Q. Let's take a look at the full context of Dr. Dix's
11 statement. That's DTX 4430 at pages 3 through 4. It's
12 paragraph 10. And Dr. MacMichael showed part of this
13 paragraph.

14 Can you explain this paragraph and how it fits into
15 your enablement analysis?

16 A. Yes. So, similarly here, Dr. Dix references now
17 review articles, different from Remington's, but all of these
18 are review articles that I'm familiar with. This is actually
19 the same Wang that I talked about before but different review
20 articles. Wei Wang likes to write review articles.

21 Dr. Dix says, "I am familiar with these literature
22 articles, all in peer review journals, which all indicate that
23 arriving at a stable formulation is not a straightforward
24 matter and is not, for instance, possible to apply a
25 formulation for one drug to another."

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BERNHARDT TROUT, PhD - DIRECT 2096

1 Q. And what formulations are claimed -- aflibercept or
2 some other molecule?

3 A. Aflibercept.

4 Q. Now, let's turn next to the next *Wands* factor, the
5 specification's guidance and then working examples. We can
6 take those together.

7 How do the specification's guidance, if we could look
8 at a demonstrative, compare to the prior art's guidance?

9 A. Well, the specification has significant guidance. It
10 actually has eight examples. I've just put up three here. We
11 wouldn't be able to see any of them -- you can hardly see it as
12 it is -- if we put up all eight. Probably couldn't see
13 anything.

14 And then it has several important disclosures within
15 the specification, including this one, which is highlighted.

16 And it talks about what the organic cosolvent might be, and it
17 talks about different other agents, including the stabilizing
18 agent and the buffering agent.

19 It also talks in this excerpt in the middle here
20 about the pH range between about 5.8 and 7. And then it
21 talks about more specific pH ranges, uses the terms more
22 specifically, about 6.2 to 6.3.

23 Q. And for the record, the excerpts you're discussing
24 are in Column 2 of the '865 patent, Exhibit 2; is that right?

25 A. Yes.

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BERNHARDT TROUT, PhD - DIRECT 2095

1 So, again, in the absence of any information once
2 you're starting out, this is the situation that the skilled
3 person would be in.

4 Q. And, again, as we discussed with Remington's, do any
5 of these articles disclose aflibercept formulations,
6 intravitreal aflibercept formulations, the concentration to use
7 for aflibercept intravitreal formulations, or the pH to use
8 for aflibercept intravitreal formulations?

9 A. No, none of them disclose any of those.

10 MR. BERL: I'm sorry about that one. I'll be better.

11 THE COURT: I'll accept on behalf...

12 BY MR. BERL:

13 Q. Doctor, to practice the claims of the '865 patent
14 with the specification in hand, would the POSA need to apply a
15 formulation from one drug to another, as Dr. Dix talks about
16 here?

17 A. Well, Dr. Dix says you don't do that, and I agree
18 with that. That's not what we do.

19 Q. But if a POSA has the '865 patent in hand and wants
20 to make formulations claimed in the '865 patent, does that
21 require applying a formulation from one drug to another drug?

22 A. No. The '865 patent itself teaches how to do it.

23 Q. The '865 patent discloses formulations of
24 aflibercept?

25 A. Yes, clearly. Yes.

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BERNHARDT TROUT, PhD - DIRECT 2097

1 Q. And you also have Tables 1, 3, and 5 shown on the
2 screen in this discussion; is that right?

3 A. That's right. Actually, the whole examples including
4 the tables, but yes.

5 Q. And, Doctor, you talked about some of the ingredients
6 that are discussed in the '865 patent.

7 Do the claims for some categories narrow those
8 structural requirements?

9 A. Yes.

10 Q. Now, we'll talk a little bit more about this in a
11 moment, but the claims you said require a buffer.

12 What is a buffer?

13 A. Well, a buffer is a chemical compound that has a
14 particular structure that leads to the formulation staying at a
15 particular pH; so it resists pH changes.

16 Q. Would the POSA have known the structure of buffers
17 that could be used to practice the claimed invention?

18 A. Yes.

19 Q. You noted that the patent teaches pH ranges, one of
20 5.8 to 7 and then more specifically 6.2 to 6.3, in Column 2.

21 How does that pertain to the buffer that the person
22 of ordinary skill would use to practice the claim?

23 A. Well, one would want to select a buffer that its
24 chemical structure is such that it can maintain the pH within
25 a given range.

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BERNHARDT TROUT, PhD - DIRECT 2098

1 Q. And is that a limited set of structures that could do
2 that?

3 A. Yes.

4 Q. Does the patent provide an example of such a buffer
5 that can be used?

6 A. Yes. The patent specifically -- again, that bottom
7 left Column 2, it specifically says phosphate buffer.

8 Q. And, Doctor, in view of the specification's
9 teachings, what buffers would the POSA use to practice the
10 claims of the '865 patent?

11 A. Well, again, you could use buffers that would buffer
12 within this range, like phosphate, could be succinate, for
13 example, histidine.

14 Q. Let's turn to the next limitation, Dr. Trout, organic
15 cosolvent. We've heard a lot about that. That's in Column 2.

16 And what does Claim 4 require with respect to the
17 organic cosolvent?

18 A. Well, Claim 4 --

19 Q. What does Claim 4 require with respect to the organic
20 cosolvent?

21 A. Claim 4 requires a specific one, polysorbate 20, and
22 a specific range of that organic cosolvent.

23 Q. Do you understand all of the claims to require an
24 organic cosolvent comprising polysorbate 20?

25 A. Yes. All the asserted claims, yes.

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BERNHARDT TROUT, PhD - DIRECT 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 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 2101

1 examples, including Example 1, that I'm taking him through.
2 And he talks about the specification providing examples that
3 meet this claimed property. That is the native conformation
4 limitation. And I'm asking him how that pertains -- how the
5 Example 1 pertains to the native conformation limitation.

6 THE COURT: Mr. Rakoczy.

7 MR. RAKOCZY: He does lay out the examples. I don't
8 object to laying out the examples and identifying what they do
9 and don't contain. But there's no opinion in here about
10 somehow how 50 informs 40 or 40 informs 50, which I believe was
11 the question.

12 THE COURT: Where is that specifically, Mr. Berl?

13 MR. BERL: Give me one moment.

14 THE COURT: Sure.

15 MR. BERL: Phone a friend.

16 If we go, Your Honor, to paragraph 395. And here he
17 addresses more specifically the issue that I'm asking about,
18 about whether the examples that are not within the scope of the
19 claim because they have 50 are relevant or irrelevant to how
20 the POSA would practice the claims. And later in the paragraph
21 he talks in particular about Example 1, which is what I'm
22 asking him about.

23 THE COURT: Overruled.

24 BY MR. BERL:

25 Q. Your Honor -- or Dr. Trout -- sorry.

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BERNHARDT TROUT, PhD - DIRECT 2110

1 A. Well, I mean, I guess the VEGF antagonist is one, but
2 that is one very specific molecule. Categories, then, are the
3 organic cosolvent, the buffer, and the stabilizing agent.
4 Q. Were these structures well known in the art?
5 A. Yes.
6 Q. Did you understand Mylan's experts to dispute that?
7 A. No.
8 Q. Do all of the formulations within the claims share
9 those common structural features?
10 A. Yes.
11 Q. Can the POSA recognize the formulations that were
12 claimed here?
13 A. Yes.
14 Q. And can the POSA visualize the formulations within
15 the claims?
16 A. Yes.
17 Q. Can the POSA recognize from the specification that
18 the inventors invented the claimed formulations?
19 A. Yes.
20 Q. And how and where in the specification would the POSA
21 recognize that?
22 A. Well, again, from the examples and -- I mean,
23 throughout, but specifically the examples, and then the
24 disclosure on Column 2 that we've been discussing. Those are
25 the key places.

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BERNHARDT TROUT, PhD - DIRECT 2112

1 Q. Okay.
2 And let's put up the claims.
3 Do you understand him to have asserted that the
4 claim -- the term "suitable for intravitreal administration" is
5 indefinite?
6 A. Yes.
7 Q. Do you agree?
8 A. No.
9 Q. Would the POSA be able to interpret the phrase with
10 reasonable certainty?
11 A. Yes.
12 Q. What does suitable for intravitreal administration
13 refer to?
14 A. It means does it contain components as described in
15 the claim that could be used for intravitreal administration,
16 these structures, as we've been calling them.
17 Q. Is the term "suitable for intravitreal injection"
18 subjective?
19 A. No.
20 Q. How would the POSA determine whether an ingredient or
21 an excipient is suitable for intravitreal injection?
22 A. Well, first of all, the POSA would look to the
23 teachings in the patent, again, the examples and those places
24 in Column 2 that we've been looking at. And if a skilled
25 person wanted to depart from those, a skilled person can go

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BERNHARDT TROUT, PhD - DIRECT 2111

1 Q. Does the '865 patent provide species or examples
2 representative of the genus?
3 A. Yes.
4 Q. Do all of the examples have at least 98 percent
5 native conformation as measured by SEC after two months?
6 A. Yes.
7 Q. And do all the examples meet the turbidity limitation
8 of Claim 15?
9 A. Yes.
10 Q. And are the formulations with 50 mg/mL, those
11 examples, are those relevant to whether the claims are
12 described?
13 A. Yes.
14 Q. Is that for the reason you discussed a moment ago?
15 A. Exactly.
16 Q. Doctor, is the patent here claiming simply by
17 function or is it claiming structures?
18 A. These are all structures.
19 Q. Doctor, in your view, does the '865 patent provide
20 adequate written description for the asserted claims or not?
21 A. For all the reasons I mentioned, yes, it does.
22 Q. Now I'd like to address indefiniteness.
23 Do you remember Dr. MacMichael's testimony about
24 indefiniteness?
25 A. Yes.

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BERNHARDT TROUT, PhD - DIRECT 2113

1 into the literature and find excipients or additives with the
2 same structure or similar structures that had been used in
3 intravitreal administration before and, if need be, could
4 consult an ophthalmologist.
5 Q. Did your definition of a POSA include someone who
6 could consult with an ophthalmologist or a clinician as needed?
7 A. Yes.
8 Q. Let's take a look at Chang, which is Exhibit 1832.
9 Did you review this reference?
10 A. Yes.
11 Q. And if we go to page 16 --
12 THE COURT: Yes, Counsel?
13 MR. RAKOCZY: Objection, Your Honor. This is outside
14 the scope of the report. The witness's response to this
15 indefiniteness argument is about ten lines, one paragraph, and
16 it doesn't cite anything.
17 THE COURT: What paragraph is that, Mr. Rakoczy?
18 MR. RAKOCZY: Paragraph 420 of the responsive expert
19 report if Your Honor has it.
20 THE COURT: I do. It's PTX 67.
21 MR. BERL: And, Your Honor, in paragraph 83
22 Dr. Trout --
23 THE COURT: One second.
24 MR. BERL: Sorry to go back and forth.
25 THE COURT: Paragraph 83. Go ahead.

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BERNHARDT TROUT, PhD - CROSS 2170

1 A. Correct.

2 Q. Now, there's no data in the '865 patent about

3 inflammation, correct?

4 A. There's no data about inflammation, that's correct.

5 Q. There's no data or testing in the '865 patent showing

6 that the claim formulations somehow result in less inflammation

7 than the prior art, correct?

8 A. There's not inflammation data. There's the SEC data

9 that we've been talking about, which is a good indication of --

10 for a formulator again of having a lower risk of inflammation.

11 Q. So your testimony is that SEC data is inflammation

12 data?

13 A. No, Counsel, that's not what I said. I can --

14 Q. So my question is there's no data in this patent

15 showing that these claim formulations somehow result in less

16 inflammation than prior art formulations, correct?

17 A. There's no -- you're correct there's no direct

18 inflammation data. Again, from the standpoint of the skilled

19 person, the SEC data, I should say all the stability data in

20 the patent, would tell me that -- would indicate to the skilled

21 person that there's a relatively lower risk of inflammation.

22 Q. I'm asking about inflammation data. You testified

23 about inflammation data in Gaudreault. There's no such data

24 like that in the patent, correct?

25 A. There's no direct inflammation data in the patent;

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BERNHARDT TROUT, PhD - CROSS 2171

1 there's other data.

2 Q. So, again, you're relying on a teaching away of

3 supposed inflammation that the '865 patent itself does not

4 address, correct?

5 A. The '865 doesn't explicitly discuss inflammation, I

6 agree.

7 By the way, it's not just Gaudreault that I'm relying

8 on.

9 Q. I understand. I understand.

10 And in Gaudreault, they actually concluded that

11 ranibizumab was well tolerated, correct?

12 A. Yes. And indicated to use the 10 milligrams per

13 mole.

14 Q. But they said it was well tolerated. That was their

15 first conclusion, correct?

16 A. They do use those terms. And I apologize, Counsel, I

17 gave the wrong units. 10 mg/mL. Sorry about that.

18 Q. We can pull up Gaudreault. Let's just confirm. It's

19 DTX 2265. On page 2 we have the clinical findings.

20 The first finding from Gaudreault is that ranibizumab

21 was well tolerated, correct?

22 A. That's what's listed here. And then it goes and

23 discusses the relative differences in inflammation.

24 Q. And it says transient. That's how it characterizes

25 the inflammation. You left that out. It says transient,

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BERNHARDT TROUT, PhD - CROSS 2172

1 correct?

2 A. Yes. It wasn't an intention to leave it out. It

3 lasted two to eight -- from day two to eight, so at least seven

4 days out of a month.

5 Q. Okay.

6 Let's go to page 3, please, Mr. Gibson.

7 This is what you're referring to, right? The

8 inflammation was present at day two, but it completely resolved

9 by day eight, correct?

10 A. Correct.

11 Q. And you haven't heard any clinician in this trial

12 testify that that would dissuade the use of 40 mg/mL, correct?

13 I haven't heard anyone.

14 A. I wasn't here for all of the clinicians' testimony;

15 but from what I heard, I didn't hear that specifically. I'm

16 telling you how a formulator would view this.

17 Q. But you didn't hear any testimony from a clinician,

18 right?

19 A. Again, I wasn't here the whole time. I did hear

20 testimony about having to be careful in injections, about how

21 the injections are done, and general concerns about issues with

22 injections, medical issues.

23 Q. Now, this is a POSA teaching away you testified

24 about. That didn't prevent others in the art like Dr. Dan Dix

25 from filing patents on even higher concentrations of

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BERNHARDT TROUT, PhD - CROSS 2173

1 aflibercept, correct?

2 A. Correct. Again, that's how invention works is to go

3 against the prevailing art.

4 Q. Okay.

5 Let's put DTX 13 at page 7 on screen.

6 And this is the Dix '226 we've been talking about,

7 correct?

8 A. I presume so. I didn't see the cover, but this looks

9 like the example.

10 Q. You recognize Example 1, Dr. Dix and his team, they

11 used a 50 mg/mL formulation here, correct?

12 A. 50 mg/mL, correct.

13 Q. So assuming this is prior art -- and I know you and

14 your counsel dispute that. But assuming this is prior art, Dix

15 and colleagues clearly weren't dissuaded or discouraged from

16 high concentrations of aflibercept, correct?

17 A. Well, I think -- I'm sorry. I don't want to get

18 confused here.

19 You're talking about after Dix or before Dix?

20 Q. This is Dix '226.

21 A. Yes. I understand.

22 Q. And Example 1, which is VEGF Trap Sequence ID

23 Number 4, which is aflibercept. And they used 50 mg/mL,

24 correct?

25 A. Yes.

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