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UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF WEST VIRGINIA
Regeneron Pharmaceuticals, Inc.
Plaintiff,
VS. CIVIL ACTION NO.
1:22-cv-61
Mylan Pharmaceuticals, Inc., and
Biocon Biologics, Volume 7
Defendants.

- - -

Proceedings had in the bench trial of the above-styled
action on June 21, 2023, before Honorable Thomas S. Kleeh
District Judge, at Clarksburg, West Virginia.

- - -

APPEARANCES:
On behalf of the Plaintiff:
David I. Berl
Ellen E. Oberwetter
Arthur J. Argall, III
Kathryn S. Kayali
Andrew V. Trask
Williams & Connolly, LLP
680 Maine Avenue, SW
Washington, D.C. 20024
202.434.5000
Andrew E. Goldsmith
Kellogg, Hansen, Todd, Figel & Frederick, PLLC
1615 M. Street NW, Suite 400
Washington, DC 20036
202.326.7945
APPEARANCES CONTINUED ON NEXT PAGE

On behalf of the Plaintiff, continued:

Steven Robert Ruby
Carey, Douglas, Kessler & Ruby, PLLC
797 Virginia Street, East, Suite 901
Charleston, WV 25301
304.345.1234

Petra Scamborova
Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Road
Tarrytown, NY 10591-6717
914.847.7611

On behalf of the Defendant:

Deanne M. Mazzochi
William A. Rakoczy
Heinz J. Salmen
Eric R. Hunt
Lauren M. Lesko
Neil B. McLaughlin
Lawrence Scott Beall
Katie A. Boda
Rakoczy, Molino, Mazzochi & Siwik, LLP
6 W. Hubbard Street, Suite 500
Chicago, IL 60654
312.527.2157

Gordon H. Copland
William J. O'Brien
Steptoe & Johnson
400 White Oaks Blvd.
Bridgeport, WV 26330
304.933.8162

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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.)
23
24
25

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1 over here to your left.

2 **KENNETH S. GRAHAM, PhD, PLAINTIFF'S WITNESS, SWORN**

3 THE COURT: Anticipating a request to approach and
4 distribute, so granted.

5 MR. TRASK: Thank you, Your Honor.

6 MR. RAKOCZY: William Rakoczy from Mylan and Biocon.
7 I'd like to get an objection on the record before this witness
8 begins, if I may.

9 THE COURT: Why don't we distribute materials, and
10 then when it's a little calmer and quieter, Mr. Rakoczy, the
11 floor will be yours again.

12 Mr. Rakoczy, sir.

13 MR. RAKOCZY: Yes, Your Honor. We object to any
14 testimony or proffered exhibits from this witness on invention
15 date. This goes back to our motion in limine.

16 THE COURT: Good thing I waited for calm and still,
17 Mr. Rakoczy.

18 MR. RAKOCZY: We object to any testimony or proffered
19 exhibits from this witness on invention date. This goes back
20 to our Motion in Limine Number 5, which I believe is in the
21 compilation of documents at Docket Number 449. This also goes
22 back to our interrogatories to Regeneron.

23 Interrogatory Number 10 asks for detailed information
24 on the alleged conception and reduction to practice of the
25 invention. We asked for Regeneron to identify with

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1 particularity all documents they would rely on and for
2 knowledgeable witnesses. We received a three-line response to
3 that. They cited no witnesses and cited one page of one
4 document.

5 And for the record, the interrogatory is at DTX 900
6 at page 36, and the response is at DTX 900 and page 37. So
7 this --

8 THE COURT: May I have a copy of that?

9 MR. RAKOCZY: Yes, Judge.

10 THE COURT: I don't believe I have that. If I do, I
11 apologize.

12 Mr. Rakoczy, you said that was Interrogatory
13 Number 10?

14 MR. RAKOCZY: Interrogatory Number 10, which is at
15 the bottom of page 36, and the response on the '865 patent is
16 in the middle of the page on DTX 900 at page 37, where it says
17 "with respect to the '865 patent" and it begins, talks about
18 the inventors conceived, and then it gives a Bates number
19 RGN-EYLEA-MYLAN-00475679. There is no witness identified.
20 There are no documents except, again, one page of one document.

21 Now, two nights ago, Your Honor --

22 THE COURT: What is that document, 475679?

23 MR. RAKOCZY: Your Honor, I believe that is DTX 3580,
24 also PTX 2275. It is a several-page document.

25 The other night I received a list of exhibits that

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1 they intended to go through with this witness which is -- I
2 don't know -- a couple feet high, two large binders, a lot more
3 than is cited in that interrogatory answer, and obviously,
4 Dr. Graham is not named in that interrogatory answer at all.

5 And this is exactly what we had feared and why we
6 filed Motion in Limine Number 5. So at the very least, Your
7 Honor, I want to put that objection on the record and also
8 would like to orally renew Motion in Limine Number 5 as well
9 for the very same reasons.

10 THE COURT: Understood.

11 What is Dr. Graham purportedly going to tell us,
12 Counsel?

13 MR. TRASK: Yes, Your Honor. So Dr. Graham is one of
14 the inventors on the '865 patent, and he's here to describe, in
15 large part, the work that he did leading to the inventions
16 described in the '865 patent.

17 This is, obviously, information about which he has
18 personal knowledge, experience himself.

19 THE COURT: He's been disclosed as a witness
20 presumably, correct?

21 MR. TRASK: Absolutely, Your Honor.

22 The point Mr. Rakoczy made about the Interrog 10
23 conception date, it's important to remember in context there
24 were other interrogatories that were propounded by Mylan
25 which -- to which Regeneron provided responsive information.

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1 Interrogatory 2 asked for documents regarding the
2 development efforts that led to the present formulation of
3 aflibercept. There's a range of documents disclosed in
4 response to that interrogatory.

5 Interrogatory 7 asks for documents underlying the
6 examples in the patent. There's a long list of documents
7 disclosed at page 27 of this interrogatory response.

8 So these are all -- all of the documents about which
9 Dr. Graham will be testifying today are documents that were
10 disclosed to counsel for Mylan and Biocon from essentially day
11 one of this case. They've been aware that Dr. Graham was an
12 inventor of this patent from day one of this case. They took
13 the deposition of Dr. Graham. They asked him about some of
14 these documents. They didn't ask him about other of these
15 documents. And it is routine in patent cases for inventors to
16 testify on the stand about the work they did leading to their
17 inventions.

18 THE COURT: Yes, Mr. Rakoczy.

19 MR. RAKOCZY: Your Honor, it is not routine to
20 testify about an invention date when you didn't respond to the
21 interrogatory on an invention date and you gave a three-line
22 answer citing one document and not identifying that witness as
23 someone who would testify about invention date. That is a
24 problem, and again, it's not routine.

25 We had no reason to believe Dr. Graham would testify

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1 about the invention date or earlier invention date because his
2 interrogatory doesn't identify him, and it certainly doesn't
3 identify all the documents that they've disclosed.

4 MR. TRASK: If I may, Your Honor.

5 THE COURT: Go ahead.

6 MR. TRASK: With respect to the invention date
7 question in particular, so the invention date, of course, is
8 keyed off of defendants' invalidity case. They bear the burden
9 of showing invalidity. And the prior art reference that
10 they've been relying on principally is this Dix reference.
11 That was filed in March -- on March 22, 2006.

12 And so responding to that case, we took the position
13 in this interrogatory response that the invention was conceived
14 no later than March 21, 2006. This is a responsive answer to
15 their asserted prior art.

16 Now, the facts you'll see, if Dr. Graham testifies,
17 are that work was done prior to that date, and he wants to
18 describe the work that he did leading to the invention.

19 But the position we took here was directly responsive
20 to the prior art that they've raised, and so Regeneron had no
21 need to prove up a priority date any earlier than the prior art
22 date on which Mylan and Biocon rely.

23 THE COURT: Understood.

24 Last word, Mr. Rakoczy. Go ahead.

25 MR. RAKOCZY: Your Honor, we could not have asked a

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1 clearer or more unambiguous interrogatory: Identify the date
2 of conception and reduction to practice; identify with
3 particularity the documents you will rely on; identify the
4 witnesses with knowledge you will rely on. And they answered
5 with none of that.

6 THE COURT: I agree. I'm going to hold the objection
7 in abeyance at this point given the totality of the
8 interrogatory responses, the fact that Dr. Graham's disclosed
9 as a witness. Defendants obviously had an opportunity to
10 depose him.

11 I do understand and appreciate the concerns,
12 Mr. Rakoczy, you raised with respect to the response provided
13 in Interrogatory Number 10 and the response thereto, but I'm
14 going to hold it in abeyance at this point finding, at least at
15 this point, there's not sufficient prejudice to preclude the
16 doctor from testifying about it. But I would certainly expect
17 and encourage that to be addressed in posttrial submissions at
18 this point with the distinctive prospect the Court not
19 accepting any of that testimony for the reasons you've
20 articulated.

21 MR. RAKOCZY: Thank you, Judge. And would Your Honor
22 prefer if I objected to each and every document?

23 THE COURT: As a matter of fact, I would not, sir.
24 I'll -- the subject area is noted and, I think, defined by our
25 conversation here, and we are certainly aware of it and mindful

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1 of it, addressing it in posttrial proceedings.

2 MR. RAKOCZY: Thank you, Judge. I just want to make
3 sure the objection is preserved. And I'll just assume I have a
4 continuing objection to all of these exhibits.

5 THE COURT: No, I understood. And I will
6 certainly -- that certainly works for me.

7 MR. RAKOCZY: Thank you, Your Honor.

8 MR. TRASK: Thank you, Your Honor.

9 THE COURT: Thank you, Counsel. You may proceed.

10 MR. TRASK: Thank you.

11 May I proceed, Your Honor?

12 THE COURT: You may.

13 MR. TRASK: Thank you.

14 DIRECT EXAMINATION

15 BY MR. TRASK:

16 Q. Dr. Graham, how are you?

17 A. I'm all right. How are you doing?

18 Q. Fine. Thank you.

19 Would you please introduce yourself to the Court.

20 A. My name is Kenneth Graham. Right now I live in
21 Pleasant Valley, New York. I've been an employee of Regeneron
22 Pharmaceuticals for 22 years and some months at this point in
23 time.

24 Q. What is your role at Regeneron, Dr. Graham?

25 A. So now I am a senior director in charge of one of the

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1 teams in formulation development; so we manage a suite of
2 products.

3 Q. And where are you from originally?

4 A. Well, I was born smack dab in the middle of
5 Pennsylvania in a little town called Bellefonte.

6 Q. Where did you do your undergraduate degree?

7 A. Actually, right down the road at Penn State
8 University, State College, Pennsylvania.

9 Q. What was your major?

10 A. Animal bioscience.

11 Q. And why did you study animal bioscience?

12 A. Well, my family has a farm in Schuylkill County. So
13 I grew up with animals and kind of was looking to be a large
14 animal veterinarian, and I read the James Herriot books and was
15 thinking I want to be a veterinarian and go that route.

16 Q. Did you continue there for a master's degree?

17 A. I did.

18 Q. What was your focus?

19 A. So my focus was actually -- the master's degree was
20 in veterinary science. What I was studying was a number of
21 diseases related to selenium and vitamin D. There's a disease
22 in sheep called white muscle disease, and when lambs are
23 deficient in selenium, they basically lose their ability to
24 walk, become paralyzed.

25 Q. After getting your master's degree at Penn State, did

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1 you go on to do a PhD?

2 A. I did.

3 Q. Where was that?

4 A. That's at the California Institute of Technology,
5 Caltech.

6 Q. What was your PhD thesis in?

7 A. So I was studying the way in which a specific class
8 of proteins bind DNA. So my thesis had a couple of parts. One
9 was what aspects of the protein molecule determine which
10 sequence in the DNA will bind. Another aspect was developing
11 what I refer to as a synthetic enzyme. So I was able to take a
12 part of a human serum albumin binding -- human serum albumin copper
13 binding domain and attach it to this protein that binds the
14 DNA, gamma-delta resolvase. It's the binding agent from that.
15 And then in the presence of nickel and an oxidizing agent, site
16 specifically cut the DNA in much the same way a restriction
17 enzyme does. And I also characterized that reaction doing some
18 kinetic isotope effects studies as well.

19 Q. And did you graduate with your PhD?

20 A. I did.

21 Q. And what did you do after you graduated?

22 A. So immediately after I graduated from my doctoral
23 degree, I went to work at a place called the Beckman Research
24 Institute - City of Hope. It's a private cancer institute that
25 was in Duarte, California, that has a research institute that's

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1 endowed by Beckman Institute. It's an arm of Beckman.

2 Q. How long did you remain at the Beckman Research
3 Institute?

4 A. About ten years.

5 Q. Where did you go after that?

6 A. After that I joined Regeneron.

7 Q. What was your first role at Regeneron, Dr. Graham?

8 A. So I was hired in to manage or supervise the
9 bioanalytical testing lab that was part of our pilot
10 manufacturing facility in Tarrytown, New York.

11 Q. And what was the first product you worked on at
12 Regeneron?

13 A. So the first product I worked on was something we
14 referred to as IL-1 Trap. It's now marketed as a compound
15 called Arcalyst.

16 Q. And what is that product used for?

17 A. So Arcalyst is a IL-1 inhibitor. It is used to treat
18 a disease called FCAS. It is basically an ultra-orphan or
19 orphan indication. There's maybe a thousand people in the
20 world that have this disease. And it works out to be an
21 allergy to the cold.

22 So people that have this disease, if they would walk
23 into an air-conditioned room like this courthouse, mild form,
24 they break out in hives; more severe, they break out in hives,
25 have joint pain; most severe, you know, they start having their

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1 hands and knees get twisted like you do with rheumatoid
2 arthritis. Quite a horrible, actually, disease.

3 I actually met a woman -- I don't know whether I can
4 call it fortunate or not, but my wife and I were waiting to go
5 see a movie, and we were talking and she made some comment
6 about Regeneron. And the woman a couple people behind us said,
7 "Oh, you work for Regeneron." And I said yes. And she
8 proceeded to tell me her story.

9 And she had the disease, both her kids had the
10 disease. And the way she described it, she said, "Prior to
11 your drug, I didn't have a life." Literally, that was her
12 quote. And, basically, she couldn't go out in the summer and
13 go into a theater or anyplace, had problems going outside in
14 the winter just because of the response to the cold.

15 Q. When did you first work on aflibercept, what is now
16 known as the active ingredient in Eylea?

17 A. So at the end of my first year at Regeneron in 2002,
18 the pilot manufacturing facility changed over from IL-1 track,
19 and we set up to work on our new molecule which we were calling
20 VEGF Trap at the time.

21 Q. And what was your contribution at that time to the
22 aflibercept project?

23 A. So in the bioanalytical lab we do in-process testing
24 of the product as it goes through the purification steps. We
25 also monitor some aspects of the product during bioreactor

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1 production.

2 So I set up methods that would be able to follow the
3 product through the purification strain and to ensure the
4 ultimate material that we got out of the bioreactor was of
5 suitable quality.

6 Q. And can you explain, Dr. Graham, how the aflibercept
7 material that you worked on was being purified within your
8 facility was first made?

9 A. Well -- so when you make a protein with CHO cells,
10 Chinese hamster ovary cells, in some ways -- this is going to
11 sound a little weird -- but it's like brewing beer. So you
12 have a big stainless steel vat. You put a bunch of things in
13 that the protein or the yeast -- or the cells or the yeast need
14 to grow.

15 You grow it up for a period of time. And when it's
16 ready, you take the material out of the vat. And in the case
17 of the aflibercept molecules, the cells are expressing the
18 protein into the solution. And you have a solution of
19 aflibercept, just like you have beer with a bunch of cells
20 floating in it like a cloudy IPA.

21 Then you take this through a series of purification
22 steps, and you remove the cell debris. You remove all the
23 unwanted stuff. And you end up with something that's a clear
24 solution and probably looks like more Coors Light.

25 THE COURT: Finally, something I understand. Thank

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1 you, Doctor.

2 MR. TRASK: Happy hour.

3 BY MR. TRASK:

4 Q. So just to be clear, the aflibercept that you were
5 saying is made by these cells, is it in solution from the very
6 beginning?

7 A. Yes.

8 Q. Okay. When you were doing this work on the
9 purification of aflibercept, were you in the formulation
10 development group at the time?

11 A. No. I was in pilot manufacturing.

12 Q. Did you join the formulation development group at
13 some point after that?

14 A. I did. In 2005 Regeneron was having some financial
15 problems. We started off by eliminating redundant functions,
16 one of which was the pilot manufacturing facility. And
17 ultimately they laid off more people beyond that. But I was
18 fortunate enough to be able to transfer into preclinical
19 development and formulation development at that time.

20 Q. And after joining the formulation development group,
21 when did you start working on formulations of aflibercept?

22 A. Probably within the first two, three months, tops.

23 Q. And what was your first project on aflibercept when
24 joining the formulation and development group at Regeneron?

25 A. So we had a formulation that was being tested for

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1 ophthalmic purposes. And that formulation in our formal
2 stability group, which is where our QC group monitors the GNP
3 product that is used for people, they started seeing particles
4 in the formulation.

5 And this is kind of a very serious thing. So I was
6 tasked with what -- why are we seeing these particles? What's
7 going on here? You know, this became an all-hands-on effort,
8 and everybody in the group focused in on this.

9 Q. Who were you reporting to at the time in the
10 formulation development group?

11 A. Dan Dix.

12 Q. And who did Dan report to?

13 A. Eric Furfine.

14 Q. Okay. And did you also work with someone named Kelly
15 Frye?

16 A. Yes. She was one of my colleagues.

17 Q. Are those the four people, including yourself, who
18 are named as inventors on the '865 patent?

19 A. They are.

20 Q. When you joined the formulation development group,
21 did you become aware of work that was previously done as part
22 of that group on formulating aflibercept?

23 A. So when I joined the group, there were several years
24 of research that had been conducted prior to arriving there. I
25 wanted to -- wanted to -- needed to go back, look at what was

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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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1 going to say oh, crap, you know, now what do we do? because
2 everything is falling apart.

3 And it was pretty much, all right, we have to have
4 this trial -- these clinical trials to keep running. We have
5 to be able to dose the patients. What do we do?

6 So we started looking at the cause of what was
7 happening with the first formulation. We figured out -- or I
8 figured out that exposure to the shear stress going through the
9 tiny needle that's used for intravitreal injections was likely
10 causing the particles to form. And we began working on that,
11 really, mid of 2005, May time frame, I would say.

12 Q. Now, when you set out to develop an improved
13 intravitreal formulation of aflibercept, did you have any
14 objectives in mind relating to the stability of the
15 formulation?

16 A. So we wanted to ensure that the product had a minimum
17 two-year shelf life. We were looking to make the most stable
18 product possible; so we were concerned about having very pure
19 aflibercept to start with. That was a focus in the pilot
20 manufacturing, and then we wanted to sustain that.

21 Q. Did you have any objectives in mind regarding the
22 concentration of aflibercept in the intravitreal formulation?

23 A. So the desire was to have a -- I'm going to use the
24 words "high-concentration formulation." And we tested a range
25 of concentrations, but we didn't have a specific one in mind at

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1 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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1 efficacious range as possible.

2 Q. Now, if the goal was to get more drug into the
3 patient's eye, why couldn't we just use a lower concentration
4 formulation and inject more of it?

5 A. Well, the eye is a closed thing. It's kind of
6 like -- I don't know -- a ping-pong ball. You just have that
7 much volume in there. And when you go to inject it, you run
8 the risk of increasing the pressure. So you can't put a lot of
9 volume in it.

10 Based on what I understand to be the limits, you
11 know, you certainly don't want to inject more than 100
12 microliters. You know, 50 microliters is considered to be an
13 optimal injection.

14 MR. RAKOCZY: Objection, Your Honor. This witness
15 has not been qualified as an expert in ophthalmology or
16 intravitreal injections.

17 THE COURT: Understood. Sustained.

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

20 MR. TRASK: Thank you, Your Honor.

21 BY MR. TRASK:

22 Q. So about -- can you just give the Court a sense for
23 how much is the volume that we're talking about here in these
24 formulations that would be injected.

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

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1 old-school glass eyedroppers in, like, elementary school or
2 high school chemistry. It's like one or two drops from one of
3 them.

4 Q. And did the fact that the formulation you were
5 developing would be injected intravitreally pose any challenges
6 to you from a formulation standpoint?

7 A. Okay. Yes. It did.

8 Q. What was that?

9 A. So we knew we had limited volume. We knew that it
10 was going to have to go through a very small needle. You know,
11 the small needle causes what's called shear stress or shear on
12 the drug. And that can be destabilizing to the drug. It can
13 cause the drug to, in the case of aflibercept, precipitate.

14 Q. What was the gauge of the needle that you understood
15 these formulations would be injected through?

16 A. 30-gauge.

17 Q. Did you bring demonstratives with you today to
18 illustrate these needles?

19 A. Yeah. We have a couple examples.

20 MR. TRASK: May I approach with those, Your Honor?

21 THE COURT: You may.

22 MR. TRASK: I'm going to hand up what has been marked
23 for identification as PDX 7.001. This is the 30-gauge needle.
24 And PDX 7.002, this is the 22-gauge needle. I'm going to be
25 very careful with these.

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1 THE COURT: I was going to say marshal services isn't
2 in here. Usually you don't get this close with a sharp object.

3 THE WITNESS: Well, it would take a lot of effort for
4 me to do any appreciable damage.

5 THE COURT: I'm pretty soft. I'd probably crumble
6 pretty quick.

7 THE WITNESS: I don't know. You don't look that soft
8 to me.

9 BY MR. TRASK:

10 Q. Dr. Graham, where did these demonstratives come from?

11 A. Actually, they came out of my lab.

12 Q. And can you explain to the Court what these are.

13 A. All right. So I grabbed the one that was labeled 02
14 out of the baggie. So this is a 22-gauge needle. So this is
15 the typical needle that is used -- or a typical gauge that this
16 is used to do an IV infusion is 22.

17 The other one -- I probably should have pulled both
18 of these out first so I don't stab anybody -- is a 30-gauge.
19 And the 30-gauge is what's typically used to inject somebody in
20 the eye. I don't know if you want to take a look at these.

21 THE COURT: I might as well.

22 MR. TRASK: For the record, there's nothing but water
23 in those needles, Your Honor.

24 THE WITNESS: Please don't stick yourself.

25 THE COURT: I promise I will not.

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1 All right. Thank you so much, Doctor. I'm going to
2 hand those back to you. Thank you, sir.

3 BY MR. TRASK:

4 Q. I'll let you put the caps back on those so we don't
5 have any inadvertent accidents.

6 A. That would be a good thing.

7 Q. And why was the size of the needle through which the
8 formulation would be injected relevant to your work as a
9 formulator, Dr. Graham?

10 A. All right. So I think I said that you encounter
11 something called shear when you go through the needle. What
12 shear is, it's basically like you run down a three-lane highway
13 and you slam into one lane. So everything kind of comes
14 together and bounces up on the walls as well. So the narrower
15 the needle gauge, the greater the amount of shear.

16 Q. Let's take a look at PTX 3327.

17 What is this document, Dr. Graham?

18 A. This is a presentation that I prepared some years
19 ago.

20 Q. Okay. And this document itself isn't dated. But if
21 we can take a quick look at PTX 3326, what is this document?

22 A. It's an email that I sent to Eric Furfine back in
23 April of 2006.

24 Q. And what is the first attachment indicated on this
25 email that you sent?

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1 A. KSG PCD talk, March of 2006.

2 Q. Okay. And which presentation is that?

3 A. The previous document you had up on the screen.

4 Q. Let's then turn back to 3327.

5 You said you yourself prepared this slide deck as
6 part of your work on --

7 A. Yes.

8 Q. -- Eylea -- rather, aflibercept intravitreal
9 injections?

10 A. I did.

11 Q. Let's look at page 44 of this document.

12 Did you prepare this slide, Dr. Graham?

13 A. I did.

14 Q. What does this slide show?

15 A. So what I did is I went back and did some
16 calculations to estimate the shear rate that the formulation
17 would experience when it went through different needle sizes.

18 Q. And if we look at the row labeled "One Second" under
19 "Time to Inject," what did the data show that you calculated
20 for a 22-gauge needle and a 30-gauge needle?

21 A. So for the 22-gauge needle, you've got about 16,000
22 reciprocal centimeters' worth of shear -- or not reciprocal
23 centimeters, reciprocal seconds. So shear is like a frequency.
24 It's seconds to the minus 1.

25 And then when you narrowed that needle gauge -- so

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1 you went down to the 30-gauge -- if you're going at the same
2 rate, that number jumps up to 370,000, about 20, 22 times more.

3 Q. So when comparing the amount of shear experienced by
4 a formulation through a 22-gauge needle versus the amount of
5 shear experienced when passing through a 30-gauge needle, about
6 how much higher is the shear with the 30-gauge needle used for
7 intravitreal injection?

8 A. Massively. I think I said 22 times, but it's a huge
9 difference.

10 Q. And how does that compare to the shear that's
11 experienced by the formulation during normal manufacturing
12 processes?

13 A. So one of the most shear-intensive or stressful parts
14 of the manufacturing process is when you take the formulation
15 through a diafiltration step. At that point you're pushing the
16 formulation up against a membrane with a great deal of force.
17 And that's only about 3,000 reciprocal seconds.

18 Q. So if a formulation is being manufactured and then
19 administered through a 30-gauge needle, what's the point in
20 time at which the formulation experiences the highest shear
21 rate?

22 A. Going through the 30-gauge needle.

23 Q. Now, can changes to the formulation lead to higher
24 shear stress?

25 A. Yes, they can.

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1 Q. How so?

2 A. So as the formulation protein concentration goes up,
3 the solutions become a little bit more viscous and you increase
4 the viscosity. That will increase the shear stress.

5 Q. What is viscosity, Dr. Graham?

6 A. All right. So this is -- the definition is the
7 resistance of a solution to flow. What that means --

8 THE COURT: To what, Doctor? I'm sorry.

9 THE WITNESS: To flow.

10 So what it means is if you take, like, a bottle of
11 water, you go to pour it. Water is 1 centipoise. It starts
12 immediately. You stop; it stops immediately. Take honey, go
13 to pour it, it takes a little while for the honey to start
14 going. Go to stop it, it takes a little while for the honey to
15 stop. Low viscosity/high viscosity.

16 BY MR. TRASK:

17 Q. Why is shear an issue when it comes to the handling
18 of formulations?

19 A. In the case of aflibercept, work that I did
20 identified that shear stress or shear caused the formulation to
21 form particles.

22 Q. And what's the process by which particles are formed?

23 A. So this is one of those things that it's kind of like
24 a spectrum of what you deal with. You have the individual
25 molecules in solution. You know, sometimes a couple slam

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1 together. Sometimes a couple more slam together. When you get
2 to the point you get enough of them stuck together, it falls
3 out of solution and you get a visible particle.

4 Q. Is this related to the concept of aggregation?

5 A. It is.

6 Q. And so what happens when proteins aggregate?

7 A. So if I'm talking about aflibercept, aflibercept
8 exists as what we call a native dimer. It's two of the same
9 protein strands that are hooked together. So if you take two
10 of those native dimers and they come together, that starts to
11 form aggregates or high molecular weight species.

12 Usually what happens first is you'll get to maybe
13 four or eight of these things come together. They stay in
14 solution. And then if it gets bigger, you know, you'll start
15 getting some of these things that show up as turbidity. So if
16 you look at smoke, smoke is particles. Do you see individual
17 smoke particles? No. You see the mass of them, but you can't
18 see one. So turbidity is the whole bunch of these little
19 things that are coming out now that you can't see individually
20 but you see as a group.

21 And then the next step -- or the next step can be
22 these things come together. And then it falls out of solution
23 and becomes something that you can see by your naked eye.

24 Q. From your perspective as a formulator, was the
25 formation of particles in an intravitreal formulation a bad

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1 thing?

2 A. It was an exceptionally bad thing. It's bad in any
3 formulation; but for the eye, it's very bad.

4 Q. Can you explain why that is.

5 A. So I think the eye being a closed system, whatever
6 you put in tends to stay in. You know, one aspect is there's a
7 drain in the back of the eye called the trabecular network.
8 And these particles have a chance to, if they move into that
9 area, plug the drain.

10 What happens when you plug the drain in the back of
11 the eye is you raise the pressure. And this is what happens in
12 glaucoma. So you can cause blindness.

13 MR. RAKOCZY: Objection, Your Honor. Again, the
14 witness has not been qualified as an expert in this area.

15 THE COURT: Understood. Sustained. The Court will
16 disregard that testimony.

17 Next question, Counsel.

18 BY MR. TRASK:

19 Q. I think you touched on this a moment ago, but was the
20 possibility of particle formation in an aflibercept formulation
21 just a theoretical concern to you?

22 A. No.

23 Q. Why not?

24 A. So we had gotten -- I don't know -- a year, year and
25 a half in to a clinical trial. And all of a sudden our

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1 clinical supplies were falling out of solution, forming
2 particles.

3 Q. If particles are forming in a formulation, what does
4 that mean about the formulation's stability?

5 A. That's bad.

6 Q. Now, you mentioned that there was a prior oncology
7 formulation for cancer.

8 A. Yes.

9 Q. What was the concentration in that formulation?

10 A. It was 25 mg/mL.

11 Q. Okay. So if Regeneron had already developed a stable
12 25 mg/mL aflibercept formulation, weren't you sure that you
13 could make a stable 40 mg/mL formulation as well?

14 A. No.

15 Q. Why not?

16 A. So increasing concentration leads to decreasing
17 stability. The challenges with aggregation or particle
18 formation, however you want to describe it, go up as the square
19 of the concentration.

20 Q. And when you set out to develop a 40 mg/mL
21 aflibercept formulation for intravitreal use, were you
22 reasonably sure that you could achieve such a formulation with
23 acceptable chemical and physical stability?

24 A. Certainly not when I'm sitting there staring at vials
25 of IVT1 with particles in it.

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1 Q. I'd like to now switch gears just a bit to some of
2 the analytical techniques that you used in your laboratory to
3 assess the stability of the formulations you were working on.

4 So first if we could take a look at the '865 patent.
5 This is PTX 2.

6 Is this your '865 patent, Dr. Graham?

7 A. Yes, it is.

8 Q. And you're the Kenneth Graham named on the face of
9 it?

10 A. I am.

11 Q. Let's look at Table 3 of this patent. What's shown
12 in Table 3?

13 A. So this is data from a stability study. The study is
14 VGFT-SS207.

15 Q. Okay. And I'd like to ask you about the headings of
16 the different rows here. Are these -- do these reflect
17 different analytical data on the formulation?

18 A. They do.

19 Q. Let's cover each of these just briefly. What is the
20 visual appearance analysis that was done here?

21 A. So visual appearance is simply how does the
22 formulation look in its container. You're looking to see if
23 you've got particles in it. Has it discolored? You know, what
24 does it look like?

25 Q. You mentioned turbidity a moment ago. Can you just

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1 briefly remind us about turbidity analysis.

2 A. All right. So turbidity, we use a machine to measure
3 that. And what we do is we look for a decrease in the amount
4 of light that goes through the sample. As the amount of light
5 drops, the signal goes up. You'll see we're at 00 here. This
6 is a -- not an absolute measure; this is corrected for the
7 first time we make the formulation. So we make it, we test it
8 immediately. And then after time we look at it again and see
9 if it's changing. So we subtract that zero value from the
10 value at the month where we measure it again.

11 Q. What is the pH analysis reported here?

12 A. It tells you the alkalinity or acidity of the
13 formulation. We look for no change.

14 Q. And the last two columns, percent VEGF Trap recovered
15 and percent VEGF Trap native configuration, what analytical
16 technique is used for those measurements?

17 A. Size-exclusion chromatography.

18 Q. Okay. And what does size-exclusion chromatography
19 measure?

20 A. So it's a sieving method, basically. So you have a
21 column. And it separates things -- the material in the column
22 separates things based on their size. Big stuff comes out
23 first, intermediate stuff kind of hangs around for a while, and
24 the small stuff comes out last.

25 Q. Now, over the course of your career at Regeneron,

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1 roughly how many size-exclusion chromatography analyses have
2 you run on aflibercept?

3 A. I don't know. 100,000. Tens of thousands. More
4 than I can count.

5 Q. And what does SEC tell you -- if I use SEC to refer
6 to size-exclusion chromatography, you'll understand that?

7 A. Yes.

8 Q. What does that technique tell you?

9 A. So SEC gives you an indication of the molecule in its
10 native state. So it tells you what percentage of the molecules
11 in that solution are hanging out as they're individuals. It
12 also tells you when the molecules start coming together and
13 have -- and form the soluble aggregates that I described
14 earlier.

15 Q. And now beyond the ones that we've just discussed
16 here from the example in the patent, did Regeneron use other
17 techniques for analyzing the formation of insoluble
18 particulates in formulations?

19 A. Yes, we did.

20 Q. Why did you need so many different analytical
21 techniques to understand aggregation and particle formation in
22 formulations?

23 A. Well, first off, they cover a range of sizes. So you
24 have techniques that are dialed in for each size of particle.

25 Secondly, the formation of particles in a formulation

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1 is very bad. You know, we talk about the stability of the
2 formulation. The problem is with these particles or
3 aggregates, it can cause the drug to become either inactive or
4 worse. In some cases it can lead to, you know, autoimmune
5 responses or immune responses to the drug.

6 MR. RAKOCZY: Objection, Your Honor. Again, he's not
7 qualified as an expert in that area.

8 THE COURT: Understood. Sustained. I'll disregard
9 that last portion of the testimony.

10 BY MR. TRASK:

11 Q. Let me just ask, Doctor, in the course of your duties
12 at Regeneron, do you meet with ophthalmologists to understand
13 their concerns regarding aflibercept formulations?

14 A. Yes, I have.

15 Q. And do you take into account the information you
16 learn from ophthalmologists in designing the formulations that
17 you've done as part of your invention and on other molecules as
18 well?

19 A. Yes, absolutely.

20 Q. Do you analyze particle formation using a technique
21 called HIAC, H-I-A-C?

22 A. We did, yes.

23 Q. Let's return to Exhibit 3327. And I'd like to look
24 at page 34 of this document now.

25 What is this page of the presentation, Doctor?

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1 A. So this is a -- kind of a section divider. So I was
2 talking about one topic and then I switched over to talk about
3 HIAC.

4 Q. Okay. And did you prepare this section of the
5 presentation as well?

6 A. Yes, I did.

7 Q. At the time you prepared these slides, who was the
8 in-house specialist in Regeneron's formulation development
9 group on the HIAC analysis?

10 A. That would be me.

11 Q. And did you actually perform the HIAC analysis in
12 this section of the slide deck?

13 A. Yes.

14 Q. Let's take a look at page 46 of the same exhibit,
15 3327. What's shown on this slide, Doctor?

16 A. So this is a summary table taking account the impact
17 of needle shear on a number of different protein formulations
18 and --

19 Q. And what -- I'm sorry.

20 A. Go ahead.

21 Q. What's shown -- the first row of the table is
22 highlighted in blue. What does that show?

23 A. So the one that's highlighted in blue is the clinical
24 oncology formulation that we had at the time. You'll note
25 there's a note on the backside of it that says 22-gauge needle.

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1 So what we did is we took the oncology formulation,
2 pushed it through the 22-gauge needle four times, and looked to
3 see how many particles we had when we began and after we did
4 it. And we showed that there were really no difference. You
5 know, it only went up a small amount.

6 Q. And what about the fourth line down that's
7 highlighted in red? What does that convey?

8 A. So the IVT1 formulation that we were looking at that
9 was forming particles, this is that formulation four times
10 through a 30-gauge needle. So in that case we got about a
11 tenfold increase in particles.

12 Q. And what about all of the rows below the fourth row
13 labeled "Formulations" numbered 2 through Number 9. What is
14 the information conveyed there?

15 A. So those are a series of different formulations that
16 we made seeking to come up with an improved ITV formulation.
17 What that data shows is our improved versions were all better
18 than the original. Some of them are better than each other.
19 But said that yes, we had demonstrated something that works
20 better.

21 Q. And let's turn to page 60 of this slide deck.

22 Are these some of the conclusions you drew from the
23 data we just looked at?

24 A. Yes.

25 Q. Can you explain what's conveyed in the first bullet

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1 point.

2 A. Well, the first one's pretty straightforward. The
3 small 30-gauge needle caused more shear than the bigger needle
4 and more particles.

5 Q. What about the third bullet point highlighted on the
6 screen?

7 A. So what that is is we had the improved IVT
8 formulations, those 9s that you were talking about. And
9 basically it showed that, compared to our original formulation,
10 we were at least three times better with the worst ones that we
11 were dealing with.

12 Q. And the fourth bullet point?

13 A. So it said that when we added polysorbate, we had
14 more resistance than when we added PEG.

15 Q. Okay.

16 We can take that down, please.

17 I'd now like to look at your '865 patent, again,
18 PTX 2.

19 Can we look at the provisional application date on
20 the face of the patent.

21 Doctor, what was the filing date of the provisional
22 application for your '865 patent?

23 A. June 16th, 2006.

24 Q. And were you involved in the preparation of that
25 provisional application?

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1 A. Yes, I was.

2 Q. What was your involvement?

3 A. So I supplied data and data tables to the attorney
4 who drafted the document.

5 Q. Were those the same data tables that appear in the
6 '865 patent itself?

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

8 Q. And did you also review the provisional application
9 before it was filed on June 16th, 2006?

10 A. Yes, I did.

11 Q. And you're familiar with the contents of that
12 provisional application?

13 A. Yes, I am.

14 Q. All right. I'd like to ask you about some of the
15 internal work you did at Regeneron leading and relating to your
16 invention.

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

18 What is this document, Dr. Graham?

19 A. It's one of Regeneron's laboratory notebooks. It
20 looks like it belonged to Kelly Frye.

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

22 A. So she was one you of my colleagues. She worked in
23 the lab alongside of me.

24 Q. Does she have a PhD as well?

25 A. She does.

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1 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 and check how it is.

2 Q. So if we look at the second paragraph shown on this
3 page of the exhibit, can you make out what's written there
4 highlighted in yellow?

5 A. It's getting to be a stretch; but yes, it says,
6 "There is a problem with the physical stability of VEGF Trap in
7 the current IVT formulation above 10 mg/mL, VEGF Trap.
8 Specifically, particulate is seen after high-concentration
9 formulations are pulled into a syringe and ejected into vials
10 or into a vial. Therefore, a more stable ITV formulation is
11 essential."

12 Q. Does this help explain why your group was researching
13 more stable intravitreal formulations of aflibercept?

14 A. Yes.

15 Q. What are the types of stress conditions that were
16 used in the stability studies your group ran?

17 A. It was dependent on the study. But, typically, we
18 would look at agitation stress. Agitation stress is you take
19 the container of the formulation and you put it on a lab scale
20 vortexer, which is like a paint shaker. And it just shakes it
21 up.

22 We would do thermal stress. So we would look at it
23 at a range of temperatures. Sometimes we would just use
24 accelerate and stress temperatures like 25, 37, and 45 to kind
25 of get an early read on what's going on.

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1 We'd also do freeze/thaw, is another one that we
2 would use.

3 Q. Let's take a look at the formulations that you tested
4 in this SS195 stability study. This is under the heading
5 "Procedure" on page 58 of PTX 2293.

6 Doctor, how many different formulations did you test
7 in this study?

8 A. There were five.

9 Q. And can you make out what is the makeup of the
10 Formulation Number 2 in the study?

11 A. Okay. So what we would do is we had a base
12 formulation which was common to all the formulations that are
13 being tested in the study. That's in the little snippet out
14 above. And that says that we used 10 millimolar
15 phosphate, .03 percent polysorbate 20, 40 mg/mL of VEGF Trap,
16 and the pH was 6.25.

17 In addition, that formulation also contained
18 40-millimolar sodium chloride and 5 percent sucrose.

19 Q. And does that Formulation Number 2 stand out to you
20 today, Dr. Graham?

21 A. It does.

22 Q. Why is that?

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

25 Q. And does this laboratory notebook also indicate when

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1 that formulation was first made?

2 A. Yes, it does.

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

4 What's shown here, Dr. Graham?

5 A. So this is the compounding record; so the mixing of
6 the formulation. And it's for Formulation Number 2 with a
7 specific lot number. And it was conducted on September 30th of
8 2005.

9 Q. To your knowledge, is this the very first time that
10 the formulation was made that is known today as the Eylea
11 formulation?

12 A. I believe it is, yes.

13 Q. And who made this formulation?

14 A. This was done by Kelly.

15 Q. Okay. And what was the date?

16 A. September 30th, 2005.

17 Q. Did your group test the stability of this formulation
18 that was run as part of Stability Study SS195?

19 A. Yes, we did.

20 Q. And what did you find?

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

22 Q. Is there stability data for this same composition in
23 the '865 patent?

24 A. For the same composition in terms of the excipients,
25 yes, there is. It's for a different lot of material.

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

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

5 Q. And so as of September 30th, 2005, had you and your
6 coinventors made and tested the stability of the formulation
7 that eventually became the commercial Eylea formulation?

8 A. Yes, we did.

9 Q. Let's look at Example 1 of the '865 patent. You see
10 that on the screen, Doctor?

11 A. Yes, I do.

12 Q. Do you see that the formulation in Example 1 is
13 highlighted in yellow?

14 A. Yes, I do.

15 Q. What's the term VGFT-SS065 that's shown as part of
16 Example 1?

17 A. So that's our stability study number. The VGFT
18 identified the product. 065 is it's the 65th study we put up.

19 Q. Was there a protocol associated with this stability
20 study?

21 A. Yes, there was.

22 Q. Let's look at PTX 2292.

23 What's this document, Doctor?

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

25 Q. And are you familiar with that document?

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1 A. Yes, I am.

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

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

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

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

7 A. It says that the protocol for stability VEGF
8 Trap 065.

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

10 A. Yes, there is.

11 Q. Can you make out the date?

12 A. It was signed by Kelly on December 4th of 2003. I
13 can't make out the other signature.

14 Q. That's okay.

15 Let's look at the procedures section of this protocol
16 on page 34. What types of things were varied with respect to
17 the formulations studied in this stability study?

18 A. So a couple things. There were different buffers
19 used. We changed the concentration of sodium chloride. We
20 tested 50 and 100 millimolar. We tested polysorbate. We
21 tested PEG. We tested a couple of different concentrations of
22 sucrose.

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

24 A. Formulation Number 2 was a 50 mg/mL VEGF Trap
25 formulation with 10-millimolar phosphate, 50-millimolar sodium

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

2 Q. Let's compare this formulation, Formulation Number 2
3 in Stability Study SS065, with the formulation in Example 1 of
4 the '865 patent.

5 Do you see those both on the screen?

6 A. Yes, I do.

7 Q. Can you confirm whether or not the same formulation
8 is used in both of these documents?

9 A. They're identical.

10 Q. Does this formulation have a buffer?

11 A. Yes, it does.

12 Q. What's that?

13 A. 10-millimolar phosphate.

14 Q. Does it have an organic cosolvent?

15 A. Yes, it does.

16 Q. What's that?

17 A. Polysorbate 20.

18 Q. Can that also be called a stabilizer?

19 A. Yes, it can.

20 Q. Does it also have a stabilizing agent?

21 A. That would be 5 percent sucrose.

22 Q. Is the VEGF Trap referenced here in these
23 formulations aflibercept?

24 A. It is.

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

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1 formulation?

2 A. 50 mg/mL.

3 Q. Did you do size-exclusion chromatography analysis on
4 this study?

5 A. Yes, we did.

6 Q. Let's look at PTX 1921.

7 Is this the SEC data for SS065?

8 A. Yes, it is.

9 Q. For Formulation Number 2 stored at 5 degrees C, what
10 was the starting percent native VEGF Trap percent?

11 A. It was 98.8 percent.

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

13 A. 98.7 percent.

14 Q. And what about at six months?

15 A. 98.3 percent.

16 Q. What does that tell you about the percent native
17 conformation of this sample at two months at 5 degrees Celsius?

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

19 Q. Why is that?

20 A. So when a protein aggregates, it's like rolling a
21 ball downhill. It goes -- the level of purity goes down. It
22 doesn't roll back up.

23 Q. Let's look at the bottom of this spreadsheet,
24 PTX 1921. Does this information tell you when the six-month
25 pull sample in Stability Study 065 was analyzed by SEC?

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

2 Q. Let's look back up at the Formulation Number 2 in
3 this spreadsheet. Now, you've said that this formulation
4 involved aflibercept at 50 mg/mL, right?

5 A. Yes, it does.

6 Q. What did this tell you about the percent native
7 conformation of 40 mg/mL formulation of aflibercept stored at
8 5 degrees Celsius for two months?

9 MR. RAKOCZY: Objection, Your Honor. Again, the
10 witness has not been qualified as an expert.

11 MR. TRASK: Your Honor, if I may, this is data from
12 his group that he would -- he testified he routinely relied
13 upon in performing the studies that led to the claimed
14 invention, and he testified that he's run over 100,000
15 size-exclusion chromatography analyses during his time at
16 Regeneron. He has personal knowledge of this data and relied
17 upon it in the course of developing the inventions.

18 THE COURT: Understood.

19 Counsel.

20 MR. RAKOCZY: Your Honor, that didn't have anything
21 to do with my objection. My objection is -- let me back up.

22 I'm not objecting that this formulation tested a
23 50 mg/mL. That's the whole point. That's what this is. The
24 question was asking for an opinion on how does that bear on a
25 40 mg/mL, a different formulation. That's asking for an expert

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1 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 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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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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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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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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1 Number 7.

2 Q. Okay. Was there a pull schedule for this stability
3 study as well?

4 A. Absolutely.

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

6 Is this the pull schedule for SS207?

7 A. Yes, it is.

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

9 A. March 21st of 2006.

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

12 A. So this is for a 5-degree C condition. That meant on
13 the 21st analysts went in, removed the samples from the
14 5-degree, and began performing the tests that were outlined in
15 the protocol.

16 Q. And was size-exclusion chromatography one of the
17 tests performed on these samples?

18 A. Yes, it was.

19 Q. Let's look at PTX 2277 at page 15. This is a
20 spreadsheet produced in native format.

21 Does the spreadsheet shown in this document report
22 the SEC data for the glass vial Device Number 7?

23 A. It does.

24 Q. What did the SEC data show after two months' storage
25 at 5C?

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1 A. It showed that the percent native VEGF Trap is
2 99.18 percent or -- which rounds to 99.2 percent.

3 Q. What did that tell you about this formulation's
4 stability?

5 A. That it had good stability, yes.

6 Q. Let's look at the bottom of the same document.

7 Does this tell you when the size-exclusion
8 chromatography data was obtained for this sample at two months,
9 5 degrees Celsius in a glass vial?

10 A. Yes, it does.

11 Q. When was that?

12 A. So this is a different date format than what we had
13 been using earlier. We transitioned to going year-month-date;
14 so we had the whole list of things in the computer you could
15 find by year.

16 So 06 is 2006, 03 is March, and 20 is the 20th of
17 March.

18 Q. Was this the first time you'd made an aflibercept
19 formulation achieving at least 98 percent native conformation
20 after two months at 5C?

21 A. No, it wasn't.

22 Q. Had you done that sooner?

23 A. Yes.

24 Q. Did you analyze the stability in SS207 by more than
25 just size-exclusion chromatography?

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1 A. We did.

2 Q. Let's look at PTX 2278, page 9.

3 What type of data do we have here, Doctor?

4 A. This is turbidity or OD at 405.

5 Q. Does the column on the right report when the
6 turbidity analysis was performed for the 5C two-month sample in
7 a glass vial?

8 A. The two-month samples were analyzed on March 21st of
9 2006.

10 Q. And what were the results reported here?

11 A. So for the glass vial, the value was -- is
12 negative .003, which is reported as 0.00.

13 Q. And what did that tell you about this formulation's
14 stability?

15 A. It was stable. It was not changing from the initial
16 state.

17 Q. Did you analyze the pH of the samples in this study
18 as well?

19 A. We did.

20 Q. Let's look at page 10 of this document, again,
21 PTX 2278. Is this pH data?

22 A. Yes, it is.

23 Q. Can you tell when the pH was measured at the
24 two-month time point for the sample stored at 5 degrees Celsius
25 in a glass vial?

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1 A. March 21st of 2006.

2 Q. And is the pH result reported here a good one?

3 A. Yes, it is.

4 Q. What did it indicate to you about the stability of
5 the sample?

6 A. That the sample was stable.

7 Q. Let's turn back to the size-exclusion chromatography
8 data spreadsheet at PTX 2272. Now, you testified that there
9 was a two-month pull and a sample was analyzed at that time?

10 A. Yes.

11 Q. Was that the end of the study?

12 A. Oh, no.

13 Q. What happened?

14 A. So we wanted to understand how the formulation
15 performed at 5 degrees C over a number of years. So we
16 continued to pull samples monthly through six months. So we
17 had a three-, four-, five-, and six-month pull.

18 After that we pulled samples every three months,
19 which was 9, 12, 15, and 18. And then after 18 months, we went
20 every six months, which worked out to 24, about 31 months, and
21 then 36 months.

22 Q. And why were you testing the stability of this sample
23 at so many different time points?

24 A. So we were making decisions pretty much on the fly.
25 We had a lot of pressure to come up with what is going to go

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1 into the clinic, go into the patient. We were getting early
2 reads, and we were trying to confirm that yes, our projections
3 are right. And if by some quirk of fate something went wrong,
4 we would know it immediately and be able to course correct.

5 Q. Thank you, Doctor. And just for the record, I think
6 I may have misspoken. If I said PTX 2272, I meant to say
7 PTX 2277, the exhibit we're looking at with this data.

8 Turning now, Doctor, to Example 5 of your '865
9 patent, do you see that on the screen?

10 A. I do.

11 Q. And do you see the formulation that was tested in
12 this example?

13 A. Yes, I do.

14 Q. And there's a term here "VGFT-SS203." Is that
15 another stability study you ran?

16 A. That was the 203rd stability study.

17 Q. Let's look at that one. This is PTX 1860. Is this
18 the protocol for SS203?

19 A. It looks like it's a pull schedule, actually.

20 Q. I'm sorry. It's a pull schedule. Thank you.

21 If we turn to page 122 of this document, is this the
22 stability study protocol for this study?

23 A. That's the first page of the stability study
24 protocol.

25 Q. And this again was produced as part of a larger

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1 collection of documents relating to Stability Study 203. Is
2 this also how these documents were kept in the ordinary course?

3 A. Yes.

4 Q. Now, I'd like to -- I'd like for you to compare, if
5 you could, Doctor, the formulation investigated here in SS203,
6 page 122, of PTX 1860, with the formulation in Example 5 of the
7 '865 patent, PTX 2, page 8, Column 10.

8 Do you see those both on the screen?

9 A. I do.

10 Q. Are these the same formulations?

11 A. Yes, they are.

12 Q. Let's go back to the protocol, SS203. This is
13 PTX 1860, page 129. Is this the approvals page for the SS203
14 protocol?

15 A. Yes, it is.

16 Q. Is that your signature next to -- above study
17 director?

18 A. It is.

19 Q. Were you the study director for this?

20 A. Yes, I was.

21 Q. And when was this protocol approved?

22 A. The 19th of January 2006.

23 Q. All right. Let's turn back to the first page of the
24 protocol. This is page 122 of PTX 1860. What was the -- let's
25 turn to page 123, actually, with the Table 1 displayed.

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1 Was this a study that involved testing the
2 formulation in different containers?

3 A. It did.

4 Q. And were glass vials tested in this study?

5 A. Yes.

6 Q. Which device is that?

7 A. So it's Number 6.

8 Q. And if we look at page 8 of PTX 1860, what is this
9 document?

10 A. So this is the pull schedule for that study.

11 Q. And what does it tell you about the two-month 5C
12 sample pull date?

13 A. So it was scheduled to be pulled on the 12th of
14 February; and it actually was pulled on the 13th of February.

15 Q. Okay. And did you do size-exclusion chromatography
16 analysis in this study as well?

17 A. Yes, we did.

18 Q. Let's look at a spreadsheet marked as PTX 2238,
19 page 14. Is this the SEC data for the formulation in SS203
20 sorted 5C in a glass vial at different time points?

21 A. Yes, it is.

22 Q. What was the native conformation you found for the
23 vial at two months?

24 A. 99.2 percent.

25 Q. That's greater than 98 percent, of course?

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1 A. Yes, it is.

2 Q. What did that tell you about the formulation's
3 stability?

4 A. That it had good stability.

5 Q. Let's look at the bottom of this page. Does this
6 document also tell you when the size-exclusion chromatography
7 test was run?

8 A. Yes, it does.

9 Q. What does it say?

10 A. So 06, year, so 2006; 02, February; 14, 14th.

11 Q. If we could turn to page 156 of PTX 1860, is this
12 more data from the Stability Study SS203?

13 A. Yes, it is.

14 Q. What's shown here?

15 A. So it's the osmolality of the formulation.

16 Q. And what osmolality is reported here, Doctor?

17 A. 287.

18 Q. And what units are those?

19 A. Milliosmoles.

20 Q. And so is the formulation that was analyzed in SS203
21 an isotonic formulation?

22 A. No, it's not.

23 Q. What's your understanding of what's isotonic?

24 A. 300, 320, that range.

25 Q. And you said earlier that the formulation in SS203 is

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1 the same as the formulation reported in Example 5 of the '865
2 patent. Was that right?

3 A. Yes, it is.

4 Q. So what does that mean about the tonicity of the
5 formulation disclosed in Example 5 of the '865 patent?

6 A. So it's hypertonic, below iso-osmolar.

7 Q. Did you say hypo, H-Y-P-O?

8 A. H-Y-P-O.

9 Q. Now, I next would like to look at the disclosure of
10 your '865 patent, Dr. Graham. And I'd like to see if you can
11 confirm whether the data for the native conformation for the
12 stability studies we just reviewed are the same as the native
13 conformation data disclosed in the examples of your patent.
14 Okay?

15 A. Okay.

16 Q. Let's start by comparing the size-exclusion
17 chromatography data in Table 1 of your '865 patent -- this is
18 PTX 2, page 7, Column 8 -- with the SEC data from study SS065
19 for Formulation Number 2 at 5 degrees Celsius. This is
20 PTX 1921.

21 Do you see both of those on the screen?

22 A. I do.

23 Q. Do the SEC data in these two tables match?

24 A. They do.

25 Q. Next let's compare the SEC data in Table 3 of your

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1 '865 patent -- this is PTX 2, page 8, Column 9 -- with the SEC
2 data from your SS207 study for the glass vial stored at 5C.

3 Do you see those?

4 This is PTX 2277, page 15.

5 A. I see it.

6 Q. Do you see those on the screen?

7 A. Yes, I do.

8 Q. So the SEC data in these two tables match?

9 A. They do when you appropriately round the values in
10 the spreadsheet.

11 Q. And can you explain how the rounding works.

12 A. Yeah. It's very straightforward. If it's .5, it
13 goes up; if it's .4, it goes down. So -- or .5 or greater, .4
14 or less. So if it's 98.49, that becomes 98.5.

15 Q. And next I would like to compare the size-exclusion
16 chromatography data from Table 5 of your '865 patent, PTX 2,
17 page 8, Column 10, with the SEC data from the SS203 study for
18 the glass vial at 5C. This is PTX 2238, page 14.

19 Do you see those on the screen?

20 A. Yes, I do.

21 Q. Do the SEC data in these two tables match?

22 A. Yes, they do.

23 Q. Okay.

24 Let's take that down, please.

25 Now, we've been looking at your issued '865 patent up

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1 till now, right, Doctor?

2 A. Yes, we have.

3 Q. Were there earlier related patent filings that
4 preceded the '865 patent?

5 A. Yes, there were.

6 Q. And when did you first disclose the data in the '865
7 patent to the U.S. Patent Office?

8 A. We filed a provisional patent.

9 Q. And you testified earlier that you were involved in
10 the preparation of that provisional patent?

11 A. Yes.

12 Q. Is the data in the examples of your provisional
13 patent application the same as the data in the examples of the
14 '865 patent?

15 A. Yes, they are.

16 Q. Let's take a brief look at that.

17 Let's look at PTX 3249.

18 Do you recognize this document, Doctor?

19 A. This is the -- it looks like the title page for the
20 provisional filing.

21 Q. Okay. And let's compare a few of the examples and
22 data in your provisional application with the corresponding
23 examples and data in your '865 patent.

24 And before we do that, can we just zoom in on the
25 date on which this is filed on the bottom right.

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1 Does this show when the provisional application was
2 filed, Doctor?

3 A. June 16th of 2006.

4 Q. Okay. Let's first look at Example 1 from your
5 provisional application, PTX 3249 at page 17, with Example 1
6 from your '865 patent. This is PTX 2, page 7, Column 8.

7 Do you see both of those on the screen?

8 A. Yes, I do.

9 Q. How do those examples and data compare?

10 A. They're identical.

11 Q. Next let's compare Example 3 from your provisional
12 application, PTX 3249, pages 18 to 19, with Example 3 of your
13 '865 patent, PTX 2, page 8, Column 9.

14 You've reviewed both of these previously, Doctor?

15 A. I have.

16 Q. How do these examples and data compare?

17 A. They're identical.

18 Q. Next let's look at Example 5 of your provisional
19 application, PTX 3249, pages 19 to 20, with Example 5 of your
20 '865 patent, PTX 2, page 8, Column 9.

21 You've reviewed both of these previously?

22 A. Yes, I have.

23 Q. How do these examples and data compare?

24 A. They're identical.

25 Q. So to sum up on this point, then, are the data in

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1 examples -- in Examples 1, 3, and 5 of your '865 patent and
2 your provisional application the same as one another?

3 A. Yes, they are.

4 Q. And are those data also the same as the data that was
5 originally collected from your laboratory at Regeneron?

6 A. Yes, it is.

7 Q. Let's take a look at -- again at PTX 1825, page 172.
8 This is the pull schedule for Stability Study 207,
9 Doctor.

10 A. Okay.

11 Q. What is the two-month pull date for the 5C storage
12 condition?

13 A. March 21st, 2006.

14 Q. Of the various stability studies that you've
15 addressed during your testimony today, were any of the
16 two-month pull dates after March 21, 2006?

17 A. No.

18 Q. And so, Dr. Graham, in your view, had you conceived
19 of the inventions claimed in your '865 patent no later than
20 March 21, 2006?

21 A. Well, we first made it in September of 2005; but yes,
22 no later than March of 2006.

23 Q. Let's --

24 MR. RAKOCZY: Your Honor, I'd just again renew my
25 objection to make sure it's preserved.

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1 THE COURT: No. Understood. Preserved from my
2 perspective, certainly, Counsel, and will be addressed
3 presumably in posttrial submissions and in the Court's final
4 order.

5 MR. RAKOCZY: Thank you, Your Honor.

6 MR. TRASK: And just to note, Your Honor, that's the
7 same date that was in our interrogatory response, March 2006.

8 THE COURT: Yes. Thank you.

9 BY MR. TRASK:

10 Q. Let's look at the examples in your '865 patent. So
11 here we've tried to show on the screen many of the examples
12 from your '865 patent. I know it's a little too small to read.
13 But we've been discussing Examples 1, 3, and 5 up to this
14 point, right?

15 A. Yes.

16 Q. Are all of those liquid formulations in vials in
17 Examples 1, 3, and 5?

18 A. 1, 3, and 5 are all liquid formulations in vials,
19 yes.

20 Q. Are there also examples in your patent that involve
21 prefilled syringes and lyophilized formulations?

22 A. Yes, there are.

23 Q. So for purposes of your invention involving liquid
24 formulations in vials, what's more relevant, the examples
25 involving prefilled syringes and lyophilization or Examples 1,

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1 3, and 5?

2 A. So the most relevant is the examples in the vial.

3 Q. I'd also like you to compare, Doctor, the passage in
4 your '865 patent, PTX 2, at page 4, Column 2, lines 39 to 57,
5 with the passage in your provisional application at
6 paragraphs 7 and 8. This is PTX 3249 at page 11.

7 Do you see those two passages side by side on the
8 screen?

9 A. I do.

10 Q. Have you reviewed these passages previously?

11 A. Yes, I have.

12 Q. Can you confirm whether or not these two passages
13 convey the same information?

14 A. They do.

15 Q. All right. Let's turn back to your '865 patent once
16 more. Have you reviewed the section of your patent titled
17 "Related U.S. Application Data" on the face of the patent?

18 A. Yes, I did.

19 Q. Let's take a look at that in PTX 2.

20 Now, you are aware, of course, Doctor, that after
21 your provisional application was filed but before your '865
22 patent issued, there were nine intervening related patent
23 applications filed and issued naming you as an inventor?

24 A. Yes, I am.

25 Q. Have you reviewed each of those?

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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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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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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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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.

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1 THE COURT: Why don't we go ahead and do that, then.
2 We're going to take ten minutes. We'll resume at 3:00, a
3 couple minutes after that.

4 Doctor, you haven't been in the courtroom; so this
5 may be a new speech for you. Because you're midstream on your
6 testimony, no one can speak with you in particular about your
7 testimony. So everyone would run the other way as opposed to
8 greeting you.

9 THE WITNESS: Sounds good.

10 THE COURT: You're welcome.

11 I just didn't want you to think that anyone was being
12 rude or discourteous to you. But you can go ahead and step
13 down, sir. But you're a man without a country for the next ten
14 minutes or so.

15 We'll see everyone in a few. Thank you.

16 (A recess was taken from 2:54 p.m. to
17 3:15 p.m.)

18 THE COURT: Apologies. That break ran over. We had
19 a cataclysmic user error with the Keurig coffee machine. That
20 was my user error. Don't worry. We're getting new carpet as
21 part of the great asbestos project. That's what we're telling
22 ourselves.

23 Counsel, you may proceed.

24 MR. TRASK: It doesn't show on the black robe.

25 THE COURT: That's the beauty of the black robe.

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1 Thank you, sir. Go right ahead.

2 MR. TRASK: Thank you.

3 BY MR. TRASK:

4 Q. If we could turn back to Stability Study 207 briefly,
5 Dr. Graham.

6 A. Sure.

7 Q. And if we look at PTX 2275. And, actually, this one
8 is not in your binder; so I'm going to hand up copies of this.

9 MR. TRASK: With the Court's permission?

10 THE COURT: You may.

11 BY MR. TRASK:

12 Q. Doctor, do you have PTX 2275 in front of you?

13 A. Yes.

14 Q. Okay.

15 And for the record, this is Bates-stamped
16 RGN-EYLEA-MYLAN-00475679. And it's a native Excel file printed
17 as a PDF.

18 Doctor, we previously discussed the two-month
19 5C-degree pull date in exhibit -- in Stability Study SS207.
20 Does this exhibit, PTX 2275, show the same pull date at two
21 months, 5 degrees C, that we discussed in connection with
22 PTX 1825 for Stability Study 207?

23 A. Yes, I believe it does.

24 Q. And for the record, what is the pull date at two
25 months, 5C, in Stability Study SS207?

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1 A. 21 March 2006.

2 Q. Okay. I'd also -- we can put that aside for the
3 moment.

4 I'd also like to discuss or revisit briefly in
5 connection with SS207, PTX 2277, page 15. And this --
6 actually, this is -- if we could look at the bottom of this
7 Excel spreadsheet.

8 So, Doctor, I think you testified about the date at
9 the bottom of this Excel spreadsheet, SS207, indicating when
10 the two months' SEC data was run?

11 A. Yes.

12 Q. Can you explain the date it was run and the
13 connection to the date shown at the bottom of this spreadsheet.

14 A. Okay. So this is a sequence number. What we do is
15 we start the sequence and we assign a date code to it. So 06
16 is 2006, 03 is March, 20 is the 20th of March. The F is the
17 system number or system identifier that we used.

18 So this sequence actually was started the day before
19 the samples were pulled. And we did that because we were
20 running standards and systems suitability, and we wanted to
21 ensure that we got all the standard system suitability, all
22 that done, and then allowed -- had a system that's all set,
23 ready to go, you walk in in the morning, you pull out your
24 samples, you put them on, and you run them that day. We didn't
25 want things drifting later and later. We just wanted to be set

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1 and primed and ready to go.

2 Q. Okay. So what was the date that you were getting the
3 size-exclusion chromatography analysis machine ready?

4 A. So the date we were getting it ready was the 20th,
5 which was the date before the pull.

6 Q. And that's March 20th, 2006?

7 A. Yes.

8 Q. And then what's the date on which you actually ran
9 the sample for 5 degrees C, two months?

10 A. They would have gone up on the 21st, the day they
11 were pulled.

12 Q. And that's March 21, 2006?

13 A. Yes.

14 Q. Okay.

15 We can take that down.

16 Thank you, Doctor.

17 Doctor, did you sit for a deposition in this case?

18 A. Yes, I did.

19 Q. Do you recall during your deposition counsel for
20 defendants showed you some internal Regeneron documents where
21 polysorbate was referred to as a stabilizing agent?

22 A. Yes, I did.

23 Q. During your work involving formulations of
24 aflibercept, did you sometimes call polysorbate 20 a stabilizer
25 or a stabilizing agent?

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1 A. Yes, I did.

2 Q. Did you also refer to polysorbate 20 as an organic
3 cosolvent in connection with that work?

4 A. Yes, I did.

5 Q. And did you also call polysorbate 20 at times a
6 surfactant?

7 A. Yes.

8 Q. Can you explain why you were using these different
9 labels?

10 A. So surfactant is kind of self-explanatory. It's the
11 chemical structure of the polysorbate.

12 Cosolvent is, you know, what we were using it for
13 within the formulation. And a cosolvent stabilizes the
14 formulation; so hence stabilizer or stabilizing agent.

15 Q. So would I be mistaken if I called polysorbate 20 a
16 stabilizing agent?

17 A. No, you would not be.

18 MR. RAKOCZY: Your Honor, I'm going to object.
19 Again, expert testimony. Also, he's offering opinions on
20 construction of claims. He didn't offer any of that before.
21 We're hearing this for the first time.

22 THE COURT: Counsel?

23 MR. TRASK: This is not in connection with the claim,
24 Your Honor. I'm referring to the documents that he prepared in
25 the course of his development of the invention.

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1 THE COURT: Well, let's stick to those actual
2 documents as opposed to what's his interpretation thereof.

3 Otherwise, sustained.

4 MR. TRASK: Thank you, Your Honor.

5 BY MR. TRASK:

6 Q. Let's look at PTX 672.

7 What is this document, Doctor?

8 A. So this is the pharmaceutical development section
9 that I wrote for Eylea.

10 Q. Section of what?

11 A. The BLA.

12 Q. Is this the Eylea BLA?

13 A. Yes.

14 Q. Okay. And you're familiar with this document?

15 A. Yes.

16 Q. It's a long document, 483 pages. What was your
17 specific involvement with this document?

18 A. I wrote it.

19 Q. The whole thing?

20 A. Yes.

21 Q. Okay. If we turn to page --

22 A. Sorry.

23 THE COURT: Understood, Doctor.

24 BY MR. TRASK:

25 Q. If we turn to page 26 of this document, Dr. Graham,

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1 did you write this section of the document as well?

2 A. I did.

3 Q. And what is this section of the document?

4 A. It is describing the choice of organic cosolvent and
5 the selection of the concentration for the formulation.

6 Q. If we look at the last paragraph on page 26 of
7 Exhibit PTX 672, do you see where it says polysorbate 20 was
8 selected as the organic cosolvent?

9 A. Yes. It says polysorbate 20 was selected as the
10 organic cosolvent because a lower concentration was required to
11 stabilize the VEGF Trap when subjected to agitation stress.

12 Q. Why did you call polysorbate 20 an organic cosolvent
13 in this document?

14 A. Because that's what I was using it for in the
15 formulation.

16 Q. And you understood, when you wrote this document,
17 that it would be submitted to the FDA?

18 A. Yes.

19 Q. And was it, in fact, submitted to the FDA?

20 A. Yes, it was.

21 Q. And this is an accurate statement?

22 A. Yes, it is.

23 Q. Okay.

24 We can take that down.

25 Now, when you were working to develop more stable

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1 intravitreal formulations of aflibercept, were you aware of
2 public information about other existing protein formulations?

3 A. Some, yes.

4 Q. And in the course of your work, did you ever consider
5 taking the aflibercept and just plugging it into a formulation
6 that had been used to stabilize a different protein?

7 A. No.

8 Q. Why not?

9 A. All right. So proteins are individuals. No two
10 proteins really behave exactly the same. They have different
11 likes and dislikes. So a formulation that works well for one
12 protein may not work well for another one. Things like pH
13 are critical. Choice of stabilizer can be critical.

14 MR. RAKOCZY: Again, objection, Your Honor. Again,
15 that's expert opinion testimony. He can testify about his
16 personal experience with aflibercept, but now he's venturing
17 into other proteins and what would and would not work.

18 THE COURT: That's sustained.

19 BY MR. TRASK:

20 Q. Moving on, when developing your invention, was
21 tonicity a consideration for you, Doctor?

22 A. To a degree.

23 Q. Okay. Can you explain that?

24 A. So we knew that we -- or thought that we did not want
25 to inject something that was 1,000 milliosmoles. We thought

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1 that could potentially be bad. But we weren't necessarily
2 concerned that we had to be exactly isotonic with the
3 environment. We figured we had wiggle room.

4 Q. And you testified earlier that Example 5 of your '865
5 patent was not an isotonic formulation; is that right?

6 A. That is correct.

7 Q. Did you nonetheless consider the formulation of
8 Example 5 to be a candidate formulation for intravitreal
9 injection?

10 A. Yes.

11 Q. Now, does -- the '865 patent on which you're named as
12 an inventor, does that identify which of the formulations it
13 discloses is the one that corresponds to Regeneron's Eylea
14 formulation?

15 A. No, it does not.

16 Q. Does it indicate anything about whether Regeneron
17 preferred one of those formulations over another?

18 A. Not that I've seen in the document, no.

19 Q. Were you permitted as a Regeneron employee to
20 publicly identify the formulation for Eylea before the Eylea
21 product was released onto the market?

22 A. I was not.

23 Q. And to your knowledge, prior to Eylea's launch, was
24 the formulation that you invented that eventually became the
25 commercial Eylea formulation ever publicly identified as

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1 Regeneron's commercial formulation?

2 A. Not to my knowledge, no.

3 Q. Now, you invented formulations of aflibercept that
4 have greater than 98 percent native conformation following
5 storage?

6 A. Yes.

7 Q. To your understanding at the time, did the FDA
8 require some degree of stability in the products that it
9 approves?

10 A. Yes.

11 Q. To your understanding at the time, did the FDA
12 require at least 98 percent native conformation for an approved
13 intravitreal product?

14 MR. RAKOCZY: Your Honor, I'm going to object to the
15 extent he's asking what the FDA did or didn't think, did or
16 didn't require.

17 MR. TRASK: He just testified that he wrote part of
18 the BLA --

19 THE COURT: Understood, but let's focus on his
20 understanding as to why or why not certain things might or
21 might not be included in there.

22 Overruled with that caveat.

23 BY MR. TRASK:

24 Q. Okay. Dr. Graham, when you were developing your
25 aflibercept formulations, did you understand that you needed to

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1 achieve at least 98 percent native conformation in order for
2 the product to be approved?

3 A. That would not have been an obligate requirement. We
4 needed a stable formulation. A stable formulation is supported
5 based on what your clinical experience is. We wanted the 98
6 percent or -- as pure as we could possibly get it because we
7 wanted the best possible product, you know, for the patient.
8 That was our goal.

9 Q. Now, is aflibercept a fusion protein, Doctor?

10 A. Yes, it is.

11 Q. Is aflibercept an antibody?

12 A. No.

13 Q. Are fusion proteins and antibodies the same thing?

14 A. No, they are not.

15 MR. RAKOCZY: Objection, Your Honor. Again, expert
16 testimony.

17 THE COURT: Sustained.

18 BY MR. TRASK:

19 Q. Okay. So one brief point to wrap up, Doctor.

20 You've been working as a scientific researcher for
21 about how long?

22 A. Well, 22 years at Regeneron, ten years at the City of
23 Hope, and then -- god -- since probably -- what? -- '81 at Penn
24 State. So what? 42 years, give or take.

25 Q. And of all the scientific work you've done over the

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1 course of your career, where did the inventions of the '865
2 patent rank?

3 A. Well, that's probably at the top of the heap.

4 Q. Why is that?

5 A. Well, I have a very personal story with respect to
6 Eylea. My mother suffered from wet AMD. I knew that my
7 grandmother, her mom, had gone blind. I didn't know why. Now,
8 my mom was a very, very private person. She never revealed
9 what was going on with her. She had basically gone blind in
10 one eye from the disease, and we didn't know this. And then
11 she started complaining about her eyesight. And then we
12 realized or learned, she finally fessed up, that she had the
13 disease in the other eye.

14 You know, she was getting regular doses of Lucentis
15 every month, but her vision was getting worse. My wife and I
16 were, like, trying to find every opportunity so she could see
17 my daughter, you know, get to see her at swim meets and get to
18 see her and spend time with her while she still could see her.

19 And by the time or before -- shortly before Eylea was
20 approved, her vision had gotten to 21/20, 21/40. She wasn't
21 driving anymore. You know, she was somebody that always liked
22 to do crossword puzzles and word things, couldn't see to do
23 those. So it was kind of very dire.

24 Eylea got approved. I had seen the clinical data and
25 thought, well, this looks better. I started having

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1 conversations with her ophthalmologist, which she didn't like
2 much, but I kind of was I'm not going to sit there and let you
3 go blind; I want to see if there's something we can do. I
4 suggested Eylea. I got back oh, these things are all the same.

5 I finally, in March of 2011, got to the point where I
6 stood and looked at him and said, okay, why are you sentencing
7 my mother to blindness? What we're doing right now is not
8 working. It's just getting worse. Can we just try something
9 better or different? If it doesn't work, we're no worse off.

10 And he agreed at that point to order the drug in.
11 She did her three loading doses. Her vision improved. She got
12 to the point where she was seeing 20/40. With eyeglasses, she
13 was driving again. She got to see Kendra grow up. And it
14 maintained her vision up until the last few months of her life.

15 You know, what can you do better than save your
16 mother's sight?

17 MR. TRASK: Thanks so much, Doctor.

18 Nothing further at this time.

19 THE COURT: Understood.

20 Cross?

21 MR. RAKOCZY: May we approach with some binders, Your
22 Honor.

23 THE COURT: You may.

24 MR. RAKOCZY: Good afternoon, Your Honor. William
25 Rakoczy for Mylan and Biocon.

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1 THE COURT: You may proceed, sir.

2 CROSS-EXAMINATION

3 BY MR. RAKOCZY:

4 Q. Good afternoon, Dr. Graham.

5 A. Good afternoon.

6 Q. Nice to meet you.

7 Dr. Graham, I'd like to start with DTX 722. And
8 we'll pull it up on screen, and it's also in your binder that
9 hopefully you were just handed.

10 A. Yes.

11 Q. I'd like you to look at page 1. You see this is an
12 email dated March 21st, 2006, correct?

13 A. Yes, I do.

14 Q. And it's from Kathleen DeWald to you?

15 A. Yes.

16 Q. Is that right?

17 And I'd like to go to the attachment at page 2. And
18 here you see a product composition, correct?

19 A. I do.

20 Q. It contains phosphate -- strike that.

21 And the formulation, under the "Product Composition"
22 heading, contains phosphate, NaCl, polysorbate 20, sucrose, and
23 40 mg/mL VEGF Trap, correct?

24 A. I do.

25 Q. And I'd like to focus on the first sentence of the

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1 paragraph above it. It states, "This is an unstable
2 formulation for VEGF Trap since there are minimal excipients
3 for intravitreal delivery and the formulation contains a high
4 concentration of VEGF Trap."

5 Is that right?

6 A. That is correct.

7 Q. Now, below that it actually goes on to caution that
8 the drug product should -- being held or stored at 25 degrees C
9 should be kept to a minimum during the manufacturing process,
10 correct?

11 A. Yes. I see those words on the page.

12 Q. And at temperatures above 25 degrees C -- strike
13 that.

14 Temperatures above 25C must be avoided, correct?

15 A. That's correct.

16 Q. And that this drug product should be held or stored
17 at less than minus 20 degrees C, correct?

18 A. I see that, yes.

19 Q. Now, I'd like to look at the table just below that.
20 And in this table we see polysorbate 20 identified as a
21 stabilizer as its function, correct?

22 A. Yes.

23 Q. It's not identified as a solvent, correct?

24 A. The description on the page says stabilizer.

25 Q. And the solvent in this formulation is the water or

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1 the water for injection, correct?

2 A. That is the description for water for injection on
3 the page.

4 Q. Now, let's take a look at one of your signed memos on
5 your ITV formulation.

6 Let's pull up DTX 737.

7 And here we see a signed memo from you dated
8 April 6th, 2006, correct?

9 A. Hang on. I'm trying to follow you.

10 Q. DTX 737. And I have it on the screen as well. We'll
11 go to page 2.

12 A. Yes, I see page 2.

13 Q. And you see your signature dated April 6th, 2006, at
14 the very top, correct?

15 A. Yes, I do.

16 Q. And this is entitled "40 mg/mL VEGF Trap for ITV in a
17 sucrose- and polysorbate-containing formulation," correct?

18 A. That is correct.

19 Q. Now, we see just below that the same cautionary
20 statements on storing the drug product.

21 Do you see that?

22 A. There are cautionary statements. They're not exactly
23 the same, though, no.

24 Q. It says the drug substance, formulated drug
25 substance, or drug product, the time it's held or stored at 25

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1 degrees C should be kept to a minimum during the manufacturing
2 process, correct?

3 A. That's the words on the page, that's correct.

4 Q. And, again, it cautions that temperatures above 25
5 degrees C must be avoided for this formulation, correct?

6 A. That is correct.

7 Q. And it says that this drug product formulation should
8 be held or stored at 2 to 8 degrees C, correct?

9 A. Well, yes, it says 2 to 8 degrees C on this page,
10 correct.

11 Q. Now, let's go down to the table below this as well.
12 And here again, we see that water is identified as the function
13 in the formulation -- or as the solvent in the formulation,
14 correct?

15 A. Well, WFI is identified as the solvent, yes.

16 Q. And that's water for injection; is that right?

17 A. That is correct.

18 Q. And the polysorbate 20, its function is identified as
19 stabilizer, correct?

20 A. Yes, it is.

21 Q. It's not the solvent, correct?

22 A. It's identified as stabilizer.

23 Q. And it's not the solvent in this formulation,
24 correct?

25 A. It's identified as a stabilizer.

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1 Q. My question is it is not the solvent in this
2 formulation? Is that right or is that not right?

3 A. Water is identified as the solvent in the
4 formulation.

5 Q. And water is the only solvent in this formulation; is
6 that right?

7 A. Water is what is identified as the solvent in the
8 formulation.

9 Q. Let's take a look at another one of your memos, DTX--
10 I believe the next one would be -- let me back up. I want to
11 stay on this one.

12 This particular memo does not have any stability data
13 for the formulation in it, correct?

14 A. If -- can you show me the whole screenshot of this.

15 Q. Yes. Can we pull up that whole page, DTX 737,
16 page 2.

17 A. Okay. So this document does not have stability data
18 associated with it. It's a recipe that was provided to the
19 manufacturing group so that they could formulate the material.
20 It's not -- it's not our common practice and has never been our
21 common practice to include stability data with a recipe.

22 Q. My question is simple. In this document there's no
23 stability data, no turbidity data, no native conformation data;
24 is that right?

25 A. That's correct.

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1 Q. Let's go to DTX 736. And we have another one of your
2 memos. Can you confirm for me on page 3 that you, in fact,
3 signed and dated this document April 21st, 2006; is that right?

4 A. Well, I see that on page 1 of 2 I signed it.

5 Q. And that is on page 3 of the exhibit; is that
6 correct?

7 A. Oh. I'm sorry. I didn't understand what you were
8 meaning by page 3.

9 Q. At the bottom you should see DTX 736.0003 of the
10 exhibit.

11 A. Yes, I do.

12 Q. And under the heading "Formulation," you see this
13 formulation contains phosphate, NaCl, polysorbate 20, and
14 40 mg/mL VEGF Trap, correct?

15 A. Yes.

16 Q. And we see similar cautionary statements in this memo
17 as well for the formulation; is that correct?

18 A. That is correct.

19 Q. The time that the drug product is held or stored at
20 25 degrees C should be kept to a minimum, correct?

21 A. During the manufacturing process, yes.

22 Q. And temperatures above 25 degrees C must be avoided,
23 correct?

24 A. Yes.

25 Q. And the drug product should be held or stored at 2 to

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1 8 degrees C, correct?

2 A. That's correct.

3 Q. And like the prior memo, there's no stability,
4 turbidity, or native conformation data in this particular memo;
5 is that right?

6 A. No. It's a recipe.

7 Q. Can we go to the formulation table at the second half
8 of this page. And here again, water for injection, or WFI, is
9 identified as the solvent; is that right?

10 A. That is correct.

11 Q. And polysorbate 20 is identified as the stabilizer,
12 correct?

13 A. Yes.

14 Q. Now, let's look at DTX 725 and look at the lead
15 formulation. And I want to focus in this exhibit first on the
16 email on page 1 which is dated May 8th, 2006, from Dr. Furfine
17 to you.

18 Do you see that?

19 It's in the middle of the page.

20 A. Yes, I do.

21 Q. And you see Dr. Furfine addresses you. He says,
22 "Ken, can you provide to Ellen the two formulations that we are
23 moving into the tox study." Correct?

24 A. Yes.

25 Q. And then you then responded in the email above this

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1 and you provided two formulations; is that right?

2 A. Yes, it is.

3 Q. And the formulation above is entitled the lead
4 formulation; is that right?

5 A. It is.

6 Q. That formulation contains phosphate, NaCl,
7 polysorbate 20, and sucrose, and 5 to 4 mg/mL VEGF Trap; is
8 that right?

9 A. That is what's written on the page, yes.

10 Q. And then there's a backup formulation as well,
11 correct?

12 A. Yes.

13 Q. Now, this email that you forwarded with the lead and
14 the backup formulation, you didn't provide any tox study
15 information in the email, correct?

16 A. No, I did not provide any tox study information.

17 Q. And that's because, as of the date of this email,
18 May 8, 2006, these are the formulations, the lead and the
19 backup, that were going to be moved into the tox study; is that
20 right?

21 A. So as of May 2006, I'm not sure if -- which tox study
22 this is referring to. There were a number of tox studies.
23 Looking at this and knowing Ellen's function, she's
24 pharmacokinetics; so she does PK studies. So she would be
25 looking at a range of these things possibly for an ongoing tox

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1 study. So I'm not sure what you're referring to.

2 Can you be more specific?

3 Q. Well, we can look at Dr. Furfine's email again in the
4 middle of the page. Dr. Furfine asked you to send her the
5 formulations --

6 A. Yeah.

7 Q. -- that you were moving into the tox study, correct?

8 A. Okay.

9 Q. All right. Let's look -- you mentioned the BLA. You
10 worked on and drafted parts of that, right?

11 A. Yes.

12 Q. Excuse me. The Eylea BLA, correct?

13 A. Yes.

14 Q. Let's pull up PTX 1519 and go to page 5. And this is
15 already in evidence. And here we see the description
16 composition of the drug product from the Eylea BLA, correct?

17 A. That is correct.

18 Q. And at Table 1 again we see polysorbate 20 identified
19 as a, quote, stabilizer agent, end quote, correct?

20 A. Yes. It's identified as a stabilizer agent in
21 Table 1 and I think maybe another table or two in the document.
22 But in the pharmaceutical development section, it was described
23 as a cosolvent.

24 Q. We're going to get to the -- I promise you we'll get
25 to the pharmaceutical development section next.

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1 Very quickly, though, the function here on Table 1 in
2 the Eylea BLA is identified as stabilizing agent, correct?

3 A. Yes.

4 Q. And the BLA does not identify polysorbate 20 here in
5 PTX 1519 as a solvent, correct?

6 A. Could you say that again, please.

7 Q. The Table 1 of the Eylea BLA here in PTX 1519 does
8 not identify polysorbate 20 as a solvent, correct?

9 A. That is correct. It's not identified as a solvent.

10 Q. And that's because polysorbate 20 has never been
11 considered to be a solvent, correct?

12 A. For our purposes, we've always used it as a cosolvent
13 or stabilizing agent.

14 Q. Let's pull up your deposition. You recall being
15 deposited in this case, correct?

16 A. Yes, I do.

17 Q. And you understand you were under oath during that
18 deposition, correct?

19 A. Yes, I was.

20 Q. And you swore to tell the truth?

21 A. I did.

22 Q. We're going to pull it up on screen, but it's also in
23 your binder, Dr. Graham, DTX 5103. And the exhibit is page 46
24 of the transcript. We're going to look at transcript page 179,
25 lines 19 to 25.

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1 A. Can you give me the DTX number again, please.

2 Q. Yes. DTX 5103.

3 A. Okay.

4 Q. At page 46. And I also have it on screen for you.

5 Were you asked this question; did you give this
6 answer?

7 "Q So I guess I'm not understanding why
8 Regeneron listed here in its BLA document,
9 Exhibit 738, that the function of polysorbate 20
10 is stabilizing agent and not solvent like water
11 for injection. Can you explain this?

12 "A Well, polysorbate 20 has never been
13 considered to be a solvent."

14 Was that the question you were asked and the answer
15 you gave?

16 A. Yes, they are.

17 Q. And that's a true answer, correct?

18 A. Yes.

19 Q. Now, I think you mentioned -- and I don't need to go
20 through it again, but there are other places in the BLA that
21 identify polysorbate 20 as a stabilizing agent, correct?

22 A. Yes.

23 Q. Well, let's pull up the pharmaceutical development
24 portion that you drafted, which I believe you testified was at
25 PTX 672.

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1 You recall that?

2 A. Yes.

3 Q. Now, you mentioned a portion of this document where
4 you called polysorbate 20 a cosolvent. I'd like to look at a
5 different portion of the same document you drafted. And let's
6 go to page 108 of PTX 672. And I'm going to look at Table 63,
7 I believe. You see Table 63, the document you drafted, is
8 entitled "Role of excipients in the IVT2 VEGF Trap-Eye
9 formulation," correct?

10 A. Yes.

11 Q. And we see polysorbate 20, excipient, the reason for
12 addition is identified as "stabilizing agent," correct?

13 A. That's correct.

14 Q. And it goes on to describe it as "increases stability
15 when agitated or subjected to freeze/thaw stress," correct?

16 A. That is correct, yes.

17 Q. I'd like to switch gears briefly and talk about one
18 of the other excipients you mentioned, which are buffers. Your
19 '865 patent only uses a phosphate buffer; is that right?

20 A. It describes a pH range. And the pH range tells
21 anybody that works in this field that there are a series of
22 compounds that you can use as a buffer.

23 Q. But it doesn't mention any other buffers by name
24 beyond phosphate, correct?

25 A. The phosphate is mentioned as -- by name as an

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1 example of a buffer.

2 Q. And matter of fact, you recall your counsel showed
3 you all those examples on the screen from your patent.

4 You remember that?

5 A. Yes.

6 Q. And they all used a phosphate buffer, correct?

7 A. All the examples used a phosphate buffer, yes.

8 Q. Now, in fact, you don't recall using a histidine
9 buffer to develop an intravitreal formulation of VEGF Trap
10 prior to the filing of your '865 patent application in 2006,
11 correct?

12 A. I don't believe that we did, no.

13 Q. In fact, your boss, who is Dr. Dan Dix; is that
14 correct?

15 A. Yes, my boss was Dan Dix.

16 Q. I think you know where I'm going here. Dr. Dan Dix
17 had Dr. Dan Dix nevers, right?

18 A. Yes, he did.

19 Q. And one his nevers was -- Dan Dix nevers, I believe
20 you said, things that you would never do, according to Dr. Dix,
21 is that you would never have a liquid formulation with a
22 histidine buffer; is that correct?

23 A. So Dan is quite a character. Unfortunately, he's
24 suffering from Parkinson's right now, but he had a list of
25 nevers. And one of the list of nevers he had is you would

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1 never use histidine in a liquid formulation. It was his
2 preference. He had lots of preconceived notions around things.

3 You know, I personally have used histidine buffer in
4 other formulations. And, actually, with one of the products I
5 developed subsequent to Eylea actually completely got rid of
6 all the Dan Dix nevers in one fell swoop with one approved
7 product. So he has those.

8 Q. Let's talk about Dan Dix nevers for aflibercept, not
9 other formulations.

10 A. Well, Dan Dix's nevers were for formulations, period.
11 They were not specifically for aflibercept.

12 Q. And you never used histidine with aflibercept,
13 correct?

14 A. I have used histidine with aflibercept.

15 Q. I believe you just told me that you never used
16 histidine to develop an aflibercept formulation prior to the
17 filing of your patent application.

18 A. Okay. You said prior to the filing of the patent
19 application. You just said I never used.

20 Q. And that's correct?

21 A. So the question is what time frame are you talking
22 about?

23 Q. Prior to your patent, you never used histidine to
24 develop an aflibercept formulation, correct?

25 A. If you're going with prior to the patent validation,

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1 no, I did not. After it, I did.

2 Q. And none of your patent examples, again, use a
3 histidine buffer?

4 A. That's there in black and white. Yes, that's
5 correct.

6 Q. All right. I'd like to talk about some of the
7 stability study documents, or SS documents, that you testified.
8 Do you recall that? We saw quite a few of them.

9 A. Yes.

10 Q. Before we do that, I'd like to pull up DTX 900,
11 pages 36 and 37, and I want to look at and show you a Regeneron
12 discovery response and ask you a couple questions about it if I
13 could, sir.

14 A. All right. Hang on a second. Let me --

15 Q. And we're going to put this on screen to make it
16 easy.

17 A. Well, the challenge is the screen is just a little
18 bit too far for the glasses, and this is a little bit too
19 close; so if I can get to the written document, I think I'll be
20 a little bit better.

21 Q. At the bottom of page 36, you'll see
22 Interrogatory 10. And in the middle of page 37, you'll see a
23 response with respect to your '865 patent.

24 A. And you said bottom of which page?

25 Q. Bottom of page 36 is Interrogatory 10.

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1 A. Okay.

2 Q. You see Interrogatory 10 asks, "For each claim of
3 each of the initial patents, identify (a) the date that the
4 claimed subject matter was first conceived and the date it was
5 reduced to practice, and (b) the diligence leading to such
6 reduction to practice, and for each such date and diligence,
7 identify with particularity the documentary evidence supporting
8 that date or diligence and at least three persons with any
9 knowledge relating to that date or diligence."

10 You see that?

11 A. I see those words on the page, yes, I do.

12 Q. And the response in the middle of page 37 on your
13 '865 patent says, "With respect to U.S. Patent Number
14 11,084,865" -- that's your patent, correct?

15 A. Yes.

16 Q. It goes on to say, "The inventors concede the
17 inventions in the asserted claims of the '865 patent no later
18 than March 21st, 2006, the date on which samples from Stability
19 Study 207 were analyzed after two months' incubation."

20 Do you see that?

21 A. Yes, I do.

22 Q. It cites one page for the record,
23 RGN-EYLEA-MYLAN-00475679. Do you see that?

24 A. Yes, I do.

25 Q. Have you seen this response before?

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1 A. No, I have not.

2 Q. It doesn't identify you as a person to have any
3 knowledge of the date of conception or reduction to practice,
4 correct?

5 A. I don't see my name on the page, but this is getting
6 into the realm of legal things. And if I'm not an expert on
7 intravitreal injections after seeing my mother receive over 90
8 some-odd injections, I can't possibly be an expert on something
9 that's a legal document without a law degree, I don't think.

10 Q. My question is much simpler.

11 You're not identified as a witness with knowledge in
12 this response, correct?

13 A. I don't see my name there.

14 Q. It identifies one page in Stability Study 207,
15 correct?

16 A. I see that it identifies the page. I'm not sure
17 what's on the page, but --

18 Q. And it does not identify all the other stability
19 studies you testified about, like the 065 study, the 203 study,
20 the 205 study. Those aren't mentioned here, correct?

21 A. No, I don't see them.

22 Q. As a matter of fact, you testified about more than
23 one page today, right? I saw dozens of documents you testified
24 about.

25 A. Yeah.

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1 Q. All right. Let's look at one of those. Let's start
2 with PTX 1825. And you recall this document, right?

3 This is the 207 study document.

4 A. Yes.

5 Q. Are you okay for short if I just go by the number,
6 the 207 study?

7 A. I think we can handle that.

8 Q. All right. So I want to start with the first page.
9 For the 207 study, we see Amendment 7.0 dated November 8, 2010;
10 is that right?

11 A. That is correct.

12 Q. Now, you know Michelle Looyenga, correct?

13 A. Michelle? What was the last name?

14 Q. Looyenga, L-O-O-Y-E-N-G-A.

15 A. Okay. It's Looyenga.

16 Q. Looyenga?

17 A. I'm sorry. The Loo threw me.

18 Q. My apologies. Looyenga. Did Michelle Looyenga help
19 make the invention in your '865 patent?

20 A. So Michelle was one of the members of the technical
21 staff that we had. She did help with study analysis. I think
22 she probably helped label some of the samples and things that
23 were put up.

24 Q. So did she help invent the formulation?

25 A. I would say no, she did not.

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1 Q. Let's take a look at one of her lab notebooks. And
2 then we'll jump back to 1825. But for a moment, let's jump to
3 PTX 2304.

4 And you see this is a Michelle Looyenga lab notebook,
5 correct?

6 THE COURT: Counsel, could I ask you to spell
7 Ms. Looyenga's last name for our record, please.

8 MR. RAKOCZY: Michelle, last name L-O-O-Y-E-N-G-A,
9 Looyenga.

10 THE COURT: Thank you. My apologies if I'm
11 mispronouncing that.

12 MR. RAKOCZY: No worries.

13 BY MR. RAKOCZY:

14 Q. And you see this is a lab notebook from Ms. Looyenga
15 dated March 9th, 2006, correct?

16 A. I do.

17 Q. Let's go to page 32 of PTX 2304. And here we see at
18 the top this is the protocol for the 207 study, correct?

19 A. Okay. You're on page what number?

20 Q. 32.

21 A. Okay. I'm trying.

22 Okay. So 32.

23 Q. I just want to confirm this is the 207 stability
24 protocol at the top, correct?

25 A. Okay. By page 32, you don't mean laboratory notebook

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1 page 32.

2 Q. No. I'm sorry, sir. I will always try to refer to
3 the exhibit number.

4 A. I'm sorry. I'm looking at the lab notebook, and I'm
5 going why are we talking about IV mixtures?

6 Q. If you look at the bottom, you see PTX 2304.0032?

7 A. Yes. 0032. All right. I'm getting there.

8 Q. Are you with me?

9 A. I am working on it. If my fingers would work. I'm
10 sorry.

11 Okay. I see 0032, yes.

12 Q. You see the protocol for the 207 study at the top on
13 the left, correct?

14 A. I do.

15 Q. And let's go to the bottom and look at the
16 signatures. And you see this was signed by Ms. Looyenga
17 March 3rd, 2006, correct?

18 A. So the laboratory notebook was signed by Michelle on
19 March 3rd, 2006. The protocol itself is not signed, however.

20 Q. And then it was witnessed August 22nd, 2006, correct?

21 A. Yeah, by Gareth Walsh, it looks like.

22 Q. Now, I want to jump back. And I'm sorry to put you
23 through that. Let's toggle back to PTX 1825. That's the very
24 large 207 document in your binder that you testified about.
25 Let's go to page 85.

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1 And you see here we have the purpose of the 207
2 study, correct?

3 A. And you said this is on page 85?

4 Q. Page 85 of PTX 1825, also on your screen.

5 A. Yes.

6 Q. And you see the purpose at the top is, "Determine the
7 stability of 40 mg/mL VEGF Trap in the polysorbate 20-based
8 intravitreal formulation when packaged in a prefilled syringe
9 with six different component combinations," correct?

10 A. Yep.

11 Q. Now, the test article was the prefilled syringe, and
12 the vial was the control in this study, correct?

13 A. So it goes on to say the stability of VEGF Trap, when
14 filled in grass vials, will serve as a control for the study.
15 So we were performing multiple pieces of work in one study.
16 One, we had the formulations. We wanted to see how they
17 perform in the vial.

18 The other thing is we were tasked with developing a
19 prefilled syringe and had to contract to somebody to fill a
20 prefilled syringe. Studies are a lot of work. So in one study
21 we have six syringes, one vial. Yes, we called the vial as a
22 control for the prefilled syringes because we expected, if
23 anything, the prefilled syringes would perform worse than the
24 vial.

25 Q. You understand the asserted claims in this case are

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1 all to a vial, right?

2 A. Yes.

3 Q. And so in this test, the 207 test, just so the
4 record's clear, the test article was the syringe and the
5 control was the vial, correct?

6 A. Yeah. The control for the syringe was the vial, yes.

7 Q. All right. Let's go to page 92 of the same document.
8 I just want to look at the signature at the bottom. It looks
9 like your boss Dan Dix signed this February 3rd, 2006, correct?

10 A. He signed it for the second time, yes.

11 Q. And this protocol was amended numerous times; is that
12 right?

13 A. Over the course of three years, yes, it was amended a
14 number of times. This, I think, if I look back at it, we
15 identified that there were a number of minor changes that
16 needed to be -- or the lead technician on the study felt needed
17 to be corrected.

18 One of them was we put up 39 vials instead of 42 that
19 we planned. So she initialed and dated the corrections on the
20 17th of January when she realized she was short items, signed
21 it. I signed it very shortly thereafter, and then Dan signed
22 off on the changes as well.

23 Q. Let's go to page 103. I just want to get the dates
24 of some of these amendments.

25 On page 103 we have Amendment 4.0 dated August 21st,

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1 2008, correct?

2 A. Which page number are you on?

3 Q. We're on page 103, on your screen as well.

4 A. Okay.

5 Q. And that amendment is dated August 21st, 2008,
6 correct?

7 A. That's the number in the upper left hand -- or
8 right-hand corner, yes.

9 Q. And the first amendment -- I'm sorry -- the latest
10 amendment, it's on the first page of the exhibit, page 1. And
11 that was Amendment 7.0 all the way up to November 8, 2010,
12 correct?

13 A. Yes.

14 Q. Now, let's go to page 137 and look at some of the
15 data. On 137 at the top you see we have analysis of VEGF Trap
16 by visual inspection, correct?

17 A. Hang on.

18 Yes.

19 Q. And if we look under vial under 5 degrees C, we can
20 see at .5 months the technician wrote filamentous particle and
21 one small particle, correct?

22 A. That is correct.

23 Q. Particles are not good, right?

24 A. Well -- so in this case, these were hand-filled vials
25 in our lab. And we were used to getting extraneous particles

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1 from filaments and fibers. And we had a scoring system that
2 allowed a certain number of particles to be present.

3 This is totally different than GNP product, which is
4 produced in a clean room in an environment that ensures no
5 particles from dust and whatever else is floating around in
6 your lab that's in there.

7 Q. I just asked if particles are bad. And I recall you
8 testifying --

9 A. Particles are bad.

10 Q. Particles are "kind of a serious thing" and "very
11 bad."

12 That's what you said, right?

13 A. That's true.

14 Q. And there are particles in this formulation, correct?

15 A. Yes.

16 Q. Let's look at another one. Let's go to page 142 of
17 the same exhibit at the top. And we see some more visual
18 inspection data. You see that?

19 A. Uh-huh.

20 Q. And for 5 degrees C. And here we see in several
21 places the technician noted small particle, filamentous
22 particle, small particles, particles, correct?

23 A. Yes.

24 Q. Particles all over the place. That's very bad,
25 correct?

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1 A. Well, so -- let's see. This is 2007. You're looking
2 at Syringe Number 1, Syringe Number 2, Syringe Number 3, and
3 Syringe Number 5, if I have the right page, 142. So this is
4 syringes, and this isn't the vial.

5 Q. So this doesn't count? The syringe data doesn't
6 count?

7 A. Well, you know, we're talking about a vial in the
8 patent. One of the things that is a concern, when you move a
9 formulation from a vial into a prefilled syringe, is you
10 encounter a lot of different materials that are not in the
11 vial. So syringes have silicone oil either sprayed or baked on
12 the inside of them. Some syringes -- well, glass syringes have
13 tungsten, and tungsten can cause proteins to precipitate. So
14 it's kind of two different environments.

15 Q. I just want to get it straight.

16 You took us through a dozen studies showing us
17 prefilled syringe data. And so I'm looking at prefilled
18 syringe data that's got particles all over the place. And
19 you're saying that's not relevant to the stability of the vial?

20 A. A vial is a very different environment.

21 Q. So all that syringe data we looked at would not be
22 relevant to the stability of the vial, correct?

23 A. I would assess my stability with things in the vial.
24 If it's unstable in a syringe, doesn't mean it's unstable in a
25 vial. They're different beasts.

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1 Q. All right. Let's go to page 14 of this same exhibit
2 and look at some additional data.

3 And the first thing I want to note on this page, here
4 we have the 207 study data for 5 degrees C. And it's dated --
5 can you tell me, what's that date at the top?

6 A. Which page are you on?

7 Q. We're on page 14 of PTX 1825.

8 A. Okay. So on the screen here, if I'm seeing it right,
9 it looks like the 28th of August 2008.

10 Q. August 28th, 2008, at the top, correct?

11 A. Yes.

12 Q. Now, there are no dates in this table on when exactly
13 the testing was conducted, correct? At least none that I can
14 see.

15 A. So that would be captured at the end with the
16 sequence information.

17 Q. We'll get there. But on this table right here, this
18 doesn't say when this testing was conducted?

19 A. No. I don't see it on the table at all, no.

20 Q. And I see a syringe column but not a vial column,
21 correct?

22 A. Yes. So the reason why you see a syringe column --
23 everything had a syringe column, but that's Device Number 1.

24 Q. I'm just asking do I see a syringe column and not a
25 vial column. That's all I'm asking. Your counsel can ask away

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1 whatever else he wants.

2 A. Okay. Well, you see a syringe column, and it's
3 Device Number 1, which was a syringe.

4 Q. All right. Let's go to page 68 of the same document.
5 And here we see analysis of VEGF Trap by OD at
6 405 nanometers, correct?

7 A. That is correct.

8 Q. So I'll call this OD405 data for short. And at two
9 months, you see the data that's been highlighted?

10 A. Uh-huh.

11 Q. And all this data, it ranges from .047 through about
12 .0 -- 0.053, correct?

13 A. That is correct.

14 Q. And it's all been crossed out and rewritten, correct?

15 A. Yeah. It looks like there were two entries there.

16 Q. Now, let's jump to page 111 of this same document --
17 and let me back up.

18 You said that the way this document is compiled, this
19 is the way that it was kept in the normal course of business?

20 A. So this is a file. It is called a study folder. It
21 collected all the loose paper from the stability study. And
22 things went in. Sometimes things went in in the middle;
23 sometimes things went in the end.

24 Q. Because it kind of looks like a dog's breakfast, like
25 someone threw everything in the air and then just recompiled

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1 it?

2 A. Well, I wouldn't say that they threw it in the air.
3 It was like, I'm stuffing it in, I've got it, I'm stuffing it
4 in, I've got it. You know, that's kind of the way it was done.

5 Q. All right.

6 A. Is it a good way to do it? Well, we have better ways
7 now, but --

8 Q. Let's jump to page 111 of the same exhibit, PTX 1825.
9 And here we see Amendment 5.0 --

10 A. Yeah.

11 Q. -- to the 207 study dated August 19th, 2008, correct?

12 A. That is correct.

13 Q. And I'd like to look at the second paragraph. And
14 you see it states that, "Variability between HPLC systems and
15 HPLC column lots over time may cause variability in purity
16 results between samples run at discrete points in time."

17 Do you see that?

18 A. Yes, I do.

19 Q. And the next sentence continues that "This may impact
20 the ability to confidently identify trends in data which have
21 been processed on different systems and across a wide spectrum
22 of time," correct?

23 A. That is correct.

24 Q. All right. I'd like to switch gears if I could.

25 You testified about your provisional application. Do

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1 you recall that?

2 A. Yes.

3 Q. I want to look at just a couple quick things
4 hopefully. Let's go to PTX 3249. I believe it's already in
5 evidence. And this is your provisional application you were
6 looking at during your direct testimony. And I'd like to go to
7 page 11.

8 THE COURT: I'm sorry, Counsel. What page was that
9 again?

10 MR. RAKOCZY: PTX 3249 at page 11.

11 THE COURT: Thank you.

12 THE WITNESS: Looks like you're having trouble with
13 this too.

14 BY MR. RAKOCZY:

15 Q. I'd like to focus on paragraph 8 starting the third
16 line. You see it describes an ophthalmic formulation.

17 Do you see that?

18 A. You're on which page?

19 Q. I'm on page 11.

20 A. Yeah.

21 Q. Paragraph 8. And the third line down describes an
22 ophthalmic formulation comprises about 40 to 50 mg/mL of the
23 VEGF antagonist Sequence ID Number 4.

24 Do you see that?

25 A. Yes, I do.

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1 Q. So that's disclosing a range of concentrations, 40 to
2 50 mg/mL, correct?

3 A. It lists a range of 40 to 50 mg/mL, yes.

4 Q. It's not describing 40 mg/mL, correct?

5 A. It's listing a range. What that plays out in the
6 patent, I'm not an attorney; so I'm not going to try and
7 interpret that one.

8 Q. Well, my question is simple. This formulation is
9 describing a range, 40 to 50 mg/mL?

10 A. Yes.

11 Q. Not 40 mg/mL, correct?

12 A. That is what I see on the page. There's a range of
13 40 to 50 mg/mL.

14 Q. Now, let's look down on the same page, the next line.
15 You see it describes a range of "0.01 to 3 percent
16 polysorbate."

17 Do you see that?

18 A. Yes, I do.

19 Q. So that is not 0.03 percent polysorbate 20, correct?

20 A. It is a range that encompasses 0.03 percent
21 polysorbate.

22 Q. So that range covers 0.03 percent. Is that what
23 you're saying?

24 A. No. All I'm saying is, mathematically, 0.03 percent
25 falls in between 0.01 and point -- and -- not .3 -- and

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1 3 percent. Interpreting the claim would be something that an
2 attorney would need to do.

3 Q. Under that rationale, 40 mg/mL falls within 40 to
4 50 mg/mL aflibercept, correct?

5 A. Mathematically, yes, it does.

6 Q. Now, this range on screen, 0.01 to 3 percent
7 polysorbate, is different from a range of 0.03 to .1 percent
8 polysorbate 20; is that right?

9 A. Okay. Say that again.

10 Q. The range on screen, 0.01 to 3 percent polysorbate,
11 is different from 0.03 to .1 percent polysorbate 20; is that
12 right?

13 A. The ranges that are described -- in that case, the
14 ranges are different.

15 Q. Now, let's go take a quick look at paragraphs 11 and
16 12. And these, unfortunately, bridge pages 11 and 12 of the
17 same exhibit.

18 And do you see here it discloses 0.03 percent
19 polysorbate; is that right?

20 A. It says 0.03 percent polysorbate, yes.

21 Q. And that is different from a range of 0.03 to
22 0.1 percent polysorbate; is that right?

23 A. If you're asking me within the context of the patent,
24 that's something I would need an attorney to answer.

25 Q. I'm just asking about the number. The number

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1 0.03 percent polysorbate is not 0.03 to 0.1; is that right?

2 A. Well, all right. If I'm not talking about a patent
3 and I'm talking about math --

4 THE COURT: He's just asking about the specific
5 document, Doctor.

6 THE WITNESS: About the specific document?

7 If this is about the document, this is a patent; so I
8 don't feel that I'm the appropriate person to answer that.

9 BY MR. RAKOCZY:

10 Q. So you're not qualified to opine or testify about
11 patents, correct?

12 A. I can tell you about my invention. I can tell you
13 about the work that I've done. If -- and you're looking at
14 what I believe are claims within the patent or a summary of the
15 invention. By the time you're getting down to the very
16 specific meaning, you know, is 0.03 to 1 the same as 0.03, I'm
17 getting to the point where I'm sorry, I'm not an attorney.

18 Q. So when you were -- I'm sorry, sir.

19 When you were comparing with your counsel the text in
20 the provisional application compared to your '865 application,
21 you weren't interpreting any of that; you were just telling us
22 whether the words were the same or not. Is that right?

23 A. So I was looking to see if there was drift or change
24 in the words. I was looking to see if the data was correct.
25 And as near as I could tell, when I laid the documents down

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1 beside one another and looked at them, the words were the same.

2 Q. But you weren't interpreting those words, correct?

3 A. I was looking to see if the words were the same.

4 Q. All right. Let's jump back to some of your stability
5 studies. And I want to start with the 205 study which is at
6 PTX 2265. And it's on screen.

7 Do you see that?

8 A. Okay. Yes.

9 Q. And the 205 study, I want to look at the formulation.
10 And this formulation in the 205 study was phosphate, NaCl,
11 polysorbate 20, and 40 mg/mL of VEGF Trap, correct?

12 A. Phosphate, NaCl, polysorbate 20, and 40 mg/mL VEGF
13 Trap, yes.

14 Q. Now, there's no sucrose in this formulation, correct?

15 A. That is correct.

16 Q. There's no sugar or sugar alcohol stabilizer in this
17 formulation, correct?

18 A. There is not.

19 Q. You're aware all asserted claims require a sugar
20 stabilizer?

21 A. I'm not sure that that is the case. I don't know.

22 Q. You don't know whether the asserted claims require a
23 stabilizer?

24 A. So that would be a question for my lawyer.

25 Q. Okay. Did you look at the asserted claims in

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1 preparation for your testimony today?

2 A. I read through them, yes.

3 Q. Did you ask anybody what the asserted claims were?

4 A. Actually, I don't recall specifically asking to go
5 through the details of the asserted claims.

6 Q. All right. Let's look at another study. I want to
7 very briefly touch on the 065 study.

8 If we could pull up PTX 3266. That may be the wrong
9 exhibit. No, there it is.

10 I just want to confirm. In the 065 study, all the
11 formulations were 50 mg/mL concentration of aflibercept; is
12 that right?

13 A. That is my recollection, yes.

14 Q. And I think you testified earlier you understood that
15 all the asserted claims are to 40 mg/mL aflibercept, correct?

16 A. I believe that I may have made a statement to that
17 effect, yes.

18 Q. So I just want to be clear, then. We can consider
19 the 40 and the 50 mg/mL concentrations equivalent in your view?

20 A. No. They're different.

21 Q. They're different. Okay.

22 All right. I'd like to pull up one of your slide
23 decks, which is PTX 3314. It should be in your binder. We'll
24 pull it up on screen as well. You see this is entitled "ITV
25 Review and Summary," correct?

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1 A. Yes.

2 Q. And this was attached to an email at PTX 3313 from
3 Jennifer Carrier dated March 14th, 2006. So we'll pull that up
4 and confirm it.

5 If we could please see PTX 3313.

6 And you see the email at the top dated March 14th,
7 2006, from Jennifer Carrier. Do you see that?

8 A. Yes, I do.

9 Q. And she's attaching an ITV review and summary, March
10 14th, 2006, laptop presentation, correct?

11 A. Yes.

12 Q. All right. Let's jump back to the presentation. I
13 want to go to page 7. And here we see at the top the title of
14 the slide is "VEGF Trap ITV, the next steps," correct?

15 Do you see that?

16 A. Yes.

17 Q. And the first step or the first bullet is "a more
18 stable ITV formulation was and is desired," correct?

19 A. Yes.

20 Q. And it says "because due to demonstration of
21 instability to vortex in various syringe stresses," correct?

22 A. Yes.

23 Q. And then let's look at the next page, 8. Here you
24 say that you're going to use stability analysis tools to
25 identify superior formulations, correct?

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1 Do you see that?

2 A. Okay. I see two assays. I guess, yes, that is the
3 meaning of what is on the page, yes.

4 Q. Now, I want to very briefly jump to page 22 of your
5 presentation. And here we have some data at 5 degrees C.

6 Do you see that?

7 A. I'm working on it.

8 Okay. 5 degrees C, yes.

9 Q. And you see in the left-hand column you have the
10 formulations, right?

11 A. Yes.

12 Q. And the F2 formulation is the 40 mg/mL VEGF Trap
13 containing 0.03 percent polysorbate 20, correct?

14 A. So yes. It contains -- it's listed as having those
15 components, yes.

16 Q. And then for the length of stress at 5 degrees C, we
17 have one month and five month, correct?

18 A. Yes.

19 Q. And at one month, the native VEGF Trap was less than
20 98 percent, correct?

21 A. So at one month, the native VEGF Trap was 97.9. But
22 I'm not sure what the full composition of this formulation is
23 based on what I'm seeing here. I know it's from Stability
24 Study 191, which I would need that detail to know the actual
25 composition.

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1 Q. I'm just asking if Formulation 2 at the one month was
2 below 98 percent VEGF Trap native. Correct?

3 A. It was. It started out below 98 percent.

4 Q. All right. Let's jump to PTX 3312. And I think you
5 testified about this document, correct, the update on ITV
6 syringe stability studies?

7 A. 3312?

8 Q. Yes.

9 A. No. I think I testified about a different document,
10 but this might have been in my deposition.

11 Q. This is yours as well, correct? It's entitled
12 "Update on ITV Syringe Stability Studies"?

13 A. It's mine and Dan's, yes.

14 Q. By Dr. Dix and yourself, dated March --

15 A. That is correct.

16 Q. I'm sorry. I'll start over.

17 This is one of your presentations along with Dr. Dix
18 dated March 16th, 2006; is that right?

19 A. Yes, it is.

20 Q. Let's go to page 2 of your presentation. And here it
21 says that "studies ongoing, examining the stability of the
22 following formulations," correct?

23 A. That is correct.

24 Q. And at the bottom we see two of the formulations
25 where the studies were ongoing are Formulations 8 and 9?

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1 A. Yes.

2 Q. And both of those are the 40 mg/mL which contains
3 0.03 percent polysorbate; is that right?

4 A. That is correct.

5 Q. Now, let's go to page 27 of this same exhibit. And
6 am I correct? Does it say that the VEGF Trap in the oncology
7 formulation is threefold more stable than the current ITV
8 formulation? Is that right?

9 A. Which page are you on?

10 Q. On page 27.

11 A. Okay. I'm going to lose my mind because I keep
12 looking at the document page and not your page number. I
13 apologize.

14 Q. They're the same on this one. Slide 27 is page 27.

15 A. Yeah, it is. That's pretty good. I'm going wow.

16 So you said the oncology formulation is approximately
17 threefold more stable than the current ITV?

18 Q. Yes. Is that right?

19 A. That's a fair statement, yes.

20 Q. All right. Just a couple more, Dr. Graham.

21 I'd like to go to PTX 3327. And I believe I was
22 mistaken before, but I believe you did testify about this slide
23 deck entitled "Travels through two stability-indicating
24 assays," correct?

25 A. Yes, I did.

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1 Q. And I believe you said this was dated in March or
2 April of 2006, correct?

3 A. I've seen enough dates right now, I'll take the
4 record's word for that. But yes.

5 Q. I'd like to go to page -- sorry. Let's go to page 46
6 and look at formulations listed here.

7 A. Page 46?

8 Q. Yes.

9 A. At least I only have one set of page numbers this
10 time.

11 Q. Are you there?

12 A. I am.

13 Q. And this one you see has total number of particles
14 500 nanometers or larger in 1 mL formulation; is that right?

15 A. That is correct.

16 Q. And if we look near the bottom, Formulations 8 and 9
17 are both 40 mg/mL concentration and they both contain 0.03
18 percent polysorbate.

19 Do you see that?

20 A. Yes.

21 Q. And unstressed, each of these particles -- strike
22 that. Let me back up.

23 I apologize, Your Honor. It's getting late.

24 Unstressed, each of these formulations had over
25 60,000 particles 500 nanometers or larger, correct?

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1 A. Yes, they did.

2 Q. Particles are very serious and very bad, correct?

3 A. They are serious and bad, yes.

4 Q. And when stressed, they each contained over 300,000
5 particles, correct?

6 A. Yes. They increased, yes.

7 Q. I apologize. I forgot to ask about one other study,
8 and then I promise you we're going to leave the studies.

9 Let's jump to PTX 1860, different exhibit.

10 And this is the 203 study. You remember mentioning
11 that, correct? And I want to jump to page 130 and look at the
12 formulation.

13 A. So the exhibit is?

14 THE COURT: You said 1860, Counsel?

15 THE WITNESS: I don't see that.

16 BY MR. RAKOCZY:

17 Q. PTX 1860. Oh, it's in your original binder. I
18 apologize.

19 THE COURT: The other book, Doctor.

20 THE WITNESS: Thank you.

21 BY MR. RAKOCZY:

22 Q. I want to go to PTX 1860, page 130. And I just want
23 to confirm the test article formulation.

24 A. 130.

25 Q. Do you see it?

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1 A. Okay. So --

2 Q. I'm looking at the test article on page 130. It's on
3 screen.

4 A. So you're saying the document is PTX and the page is
5 0130?

6 Q. I believe it's page 130 of PTX 1860. It's on screen
7 as well.

8 A. All right. Now I'm really confused. You said it was
9 the other notebook. Oh, you mean not this other notebook; the
10 other notebook.

11 THE COURT: Yes, Doctor. Yes.

12 THE WITNESS: Don't give me more than two notebooks
13 at a time or I'm in trouble. Okay. And you are on page 130?
14 BY MR. RAKOCZY:

15 Q. Yes. And I want to confirm that the test article in
16 this study did not contain sucrose or another sugar stabilizer;
17 is that right?

18 A. Let me get to 130.

19 So ask your question. I'm there.

20 Q. I just want to confirm the test article -- and we
21 have it on screen -- did not contain sucrose or another sugar
22 stabilizer; is that correct?

23 A. There is no sucrose in the formulation.

24 Q. Now, you testified quite a bit today about the
25 40 mg/mL aflibercept concentration formulations, correct?

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1 A. Yes.

2 MR. RAKOCZY: I have a couple more exhibits, Your
3 Honor. May I approach?

4 THE COURT: You may.

5 BY MR. RAKOCZY:

6 Q. I'm going to give you two more exhibits, Dr. Graham.

7 A. Thank you.

8 Q. All right, Dr. Graham. Let's start with the first
9 one, DTX 4121. We're going to pull it up on screen as well.

10 Do you see this is United States Patent Application
11 Publication Number U.S. 2006/0217311.

12 Do you see that?

13 A. I do.

14 Q. It's entitled "VEGF Antagonist Formulation."

15 Do you see that?

16 A. Yes.

17 Q. And the inventors are two of your colleagues, Dr. Dix
18 and Dr. Frye, correct?

19 A. That is correct.

20 Q. And do you see the file date in the middle of the
21 page, filed March 22nd, 2006, correct?

22 A. Yes, I do.

23 Q. And I want to look below that to the column where the
24 heading "Related U.S. Application Data" -- date -- or data.
25 I'm sorry. It's at the top right hand of the page. My fault.

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1 Do you see in the right "Related U.S. Application
2 Data," correct?

3 A. Yes.

4 Q. And it says, "Provisional Application
5 Number 60/665,125 filed on March 25th, 2005," correct?

6 THE COURT: Yes, Counsel?

7 MR. TRASK: Your Honor, objection. This is outside
8 the scope of the direct examination. This is a document that
9 was never shown to the doctor during his direct examination.
10 And, in fact, it's a document that defendants didn't rely on at
11 this point.

12 MR. RAKOCZY: Your Honor, he testified repeatedly
13 about the 40 mg/mL concentration. This is a U.S. patent
14 publication disclosing 40 mg/mL concentration that I'd like to
15 address with the witness.

16 THE COURT: Overruled.

17 BY MR. RAKOCZY:

18 Q. Let's turn to exhibit page 3, paragraph 17. And I
19 want to go to the ninth line down. And you see in the middle
20 here the document describes "A 40 mg/mL prelyophilized
21 solution."

22 Do you see that?

23 A. So you're on page 3?

24 Q. Paragraph 17.

25 A. And a 40 mg/mL prelyophilized solution. Yes, I see

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1 that.

2 Q. Now let's look at paragraph 36 on page --

3 A. So --

4 Q. -- 5.

5 A. -- you know, a prelyophilized solution is not a
6 formulation.

7 Q. Sir, I was just asking whether it disclose a 40 mg/mL
8 concentration in a prelyophilized --

9 A. It is a prelyophilized solution, but that's never
10 designed to be a -- I'm sorry. I'm looking at the science.
11 And I don't understand how a lyophilized solution or
12 prelyophilized solution matches up with a liquid formulation at
13 the same concentration. It's two different things.

14 Q. Sir, I'm just asking did your boss Dr. Dan Dix
15 disclose a "40 mg/mL prelyophilized solution" in that
16 paragraph?

17 A. That is what's in there, yes.

18 Q. So let's go to paragraph 36, which is on page 5. I
19 want to look at the last sentence. And here you see Dr. Dix
20 describes, "An example of a pharmaceutically acceptable liquid
21 formulation comprises a VEGF-specific fusion protein antagonist
22 in a pharmaceutically effective amount of buffer, a cosolvent,
23 and one or more stabilizers."

24 Do you see that?

25 A. Yes. That's what's written on the page.

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1 Q. Now, I want to compare this to the provisional
2 application which is the second document I handed you, which is
3 DTX 8149.

4 I'm sorry. I misspoke.

5 This document, the provisional, is DTX 8194. It's
6 the second --

7 A. I think we had you. Even with the dyslexia, it was
8 good. That one, I followed.

9 Q. All right. And do you see in the right-hand upper
10 corner we have a stamp? You see that? You see the stamp says
11 "Application 60/665,125."

12 Do you see that in the upper right-hand corner?

13 A. Yes. That's what it looks like.

14 Q. Now, let's go to page 10 of this document, page 34 --
15 paragraph 34. I'm sorry. Here we see that same heading. You
16 see stable liquid formulations, correct?

17 A. So page 10?

18 Q. Paragraph 34. We have a paragraph entitled "Stable
19 Liquid Formulations," right?

20 A. All right. I'm doing it to myself again, following
21 the document pages, not the exhibit pages. Went too far.

22 Okay. Paragraph 34.

23 Q. And you see this -- we see the same sentence, the
24 last sentence, starting, "An example of a pharmaceutically
25 acceptable liquid formulation comprises a VEGF-specific fusion

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1 protein antagonist in a pharmaceutically effective amount, a
2 buffer, a cosolvent, and one or more stabilizers," correct?

3 A. So you're saying the last sentence, correct?

4 Q. Yes.

5 A. Yes, that's what it says.

6 Q. I want to jump to the claims very quickly on page 12.

7 And can you confirm for me Claim 7 is directed to a
8 stable liquid formulation of Claim 1 comprising 1- to
9 10-millimolar phosphate buffer, 1- to 10-millimolar citrate,
10 25- to 150-millimolar NaCl, 5 to 30 percent sucrose, 10 to 50
11 mg/mL of a fusion protein, at a pH of about 6 to 6.5; is that
12 right?

13 A. This is Claim 7?

14 Q. Yes.

15 A. Yes, that's what's written on the page.

16 Q. Just a couple more quick questions, sir.

17 Let's go back to page 8 of the same exhibit,
18 DTX 8194 -- I'm sorry -- page 5. I'm doing it as well.

19 Page 5, paragraph 8, of DTX 8194.

20 A. Doesn't that mean it's time to quit?

21 THE COURT: It's airborne contagious.

22 BY MR. RAKOCZY:

23 Q. Okay. I promise.

24 A. So you're going with paragraph 8?

25 Q. Yes.

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1 A. Okay.

2 Q. And here at paragraph 8 we see a prelyophilization
3 formulation of the invention.

4 Do you see that?

5 A. Yes.

6 Q. And then it also at the end of the paragraph says the
7 polysorbate may also be present, for example, as
8 polysorbate 20, correct?

9 A. Yes.

10 MR. RAKOCZY: Can you give me one moment, Your Honor?

11 THE COURT: Certainly.

12 BY MR. RAKOCZY:

13 Q. A couple more quick items, Dr. Graham.

14 Let's go back to the prior exhibit. So can you
15 switch for me again to the first one I handed you, DTX 4121.
16 Let's go to page 5. And in the right-hand column you see
17 Tables 1 and 2.

18 A. Yes.

19 Q. And Tables 1 and 2 in the titles, you see they
20 reference Stability Study 65?

21 Do you see that?

22 A. Yes, I do.

23 Q. That's one of the stability studies that you worked
24 on that we talked about earlier today and that you talked about
25 on your direct, correct?

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1 A. Yes, it is.

2 Q. So you're not an inventor on this patent, correct?

3 A. That is correct.

4 Q. But that's your stability study?

5 A. Well, I helped it along after I joined the group, but
6 my contributions to the patent were other things. I mean, I
7 ran all the 200 through 207 studies, conducted the shear
8 studies. So yeah, I'm not an inventor on that.

9 Q. All right. Last question, Dr. Graham. And I want to
10 refer to the formulations in your '865 patent.

11 If an ophthalmologist administered the formulation
12 from your '865 patent but without the aflibercept, would that
13 be a safe and effective medicine for treating eye diseases?

14 A. Did you -- would you say that again. I'm sorry.

15 Q. Yes.

16 If a doctor administered the formulation from your
17 '865 patent but without the aflibercept, would that be a safe
18 and effective medication?

19 A. I would not expect so.

20 MR. RAKOCZY: All right. Pass the witness, Your
21 Honor.

22 THE COURT: Thank you.

23 Redirect, Counsel?

24 MR. TRASK: Thank you, Your Honor.

25 THE COURT: Why don't we take five.

KENNETH S. GRAHAM, PHD - REDIRECT

1 You're still off limits for folks to speak with you,
2 but you can step down. We'll take a quick five-minute break
3 and finish the doctor's testimony.

4 THE WITNESS: Thank you.

5 (A recess was taken from 4:44 p.m. to
6 4:51 p.m.)

7 THE COURT: Counsel, you may proceed.

8 MR. TRASK: Thank you, Your Honor.

9 REDIRECT EXAMINATION

10 BY MR. TRASK:

11 Q. Dr. Graham, do you have the binder in front of you
12 that defense counsel handed up?

13 A. Yes.

14 Q. Could we turn to Exhibit DTX 900 in that binder.

15 I'd like to turn to page 37 of that document.

16 And if we could zoom in on the paragraph that starts
17 "with respect" -- actually, "Subject to the foregoing general"
18 and then following paragraph.

19 Doctor, do you see that on the screen?

20 A. Yes, I do.

21 Q. Do you remember defense counsel made a bit of a show
22 about the fact that your name is not identified in this
23 interrogatory response served by Regeneron?

24 A. Yes.

25 Q. Do you see that this document refers to the '865

KENNETH S. GRAHAM, PHD - REDIRECT

1 patent and it says the inventors conceived the inventions?

2 Do you see that?

3 A. Yes, I do.

4 Q. Who are the inventors of the '865 patent?

5 A. Well, that would be Dan Dix, Eric Furfine, Kelly
6 Frye, and myself.

7 Q. Thank you, Doctor.

8 Do you remember you were asked on cross whether
9 polysorbate 20 is a solvent?

10 A. Yes, I was.

11 Q. Is a solvent the same as a cosolvent?

12 A. No.

13 MR. RAKOCZY: Objection, Your Honor. Calls for
14 expert testimony.

15 MR. TRASK: Your Honor, he asked this exact question
16 and tried to impeach the witness about whether polysorbate is a
17 solvent, and I'm just following up on what the doctor
18 understands that to mean.

19 THE COURT: The examination was more what do the
20 papers indicate. Sustained.

21 BY MR. TRASK:

22 Q. Let's turn to the same binder, PTX 2304. That's P as
23 in plaintiff, PTX.

24 A. PTX, not --

25 Q. Correct.

KENNETH S. GRAHAM, PHD - REDIRECT

1 A. Okay. Yes. I see that.

2 Q. And if we could turn to page 32 of that document.

3 Are you there?

4 A. I'm trying to read it on the screen, but I'm going to
5 have to struggle. What was the number again?

6 Q. It's okay. If you can see it on the screen, just a
7 quick question. If you want it, it's PTX 2304.

8 A. 23 -- PTX 23 -- okay. Good with it on the screen.
9 What's your question?

10 Q. So the question, Doctor, is do you remember when
11 counsel for Biocon and Mylan pointed to the signature by your
12 colleague Michelle Looyenga in the bottom left of this page?

13 A. Michelle Looyenga, yes.

14 Q. Can we turn to the next page of this document,
15 PTX 2304, page 33.

16 And do you see that there's a page at the bottom
17 where -- it's not the signature block, but right above that
18 there's a signature line for study director?

19 A. Yes, I do.

20 Q. Now, that's not signed, but this is Stability
21 Study 207, right?

22 A. Correct.

23 Q. Who was the study director for Stability Study 207?

24 A. That would have been me.

25 Q. Let's look at PTX 1825, page 85.

KENNETH S. GRAHAM, PHD - REDIRECT

1 A. Yes, I see that.

2 Q. I'm sorry. Wrong page. Page 137. Sorry about that.

3 And do you remember -- I'll let you get there.

4 A. Okay. I can see this one on the screen.

5 Q. Do you remember when counsel for Biocon and Mylan
6 asked you about the entry under 5C at .5 months that says, I
7 think, clear, one filamentous particle. Do you see that?

8 A. Yes.

9 Q. Does that indicate to you that this formulation is
10 unstable?

11 A. No, not necessarily.

12 Q. Why is that?

13 A. So the filamentous particle, those are typically
14 items that come from the tech's wipes, the things that we use
15 in the lab as part of the routine operations. If it had said
16 one proteinaceous particle, then I might have been concerned.
17 But the subsequent vial also showed clear, no precipitate. And
18 having a particle is not a failure by our definitions.

19 Q. Thank you, Doctor.

20 If we could look in the same exhibit, page 111. And
21 I'm looking at the second paragraph on this page.

22 A. Okay. Variability between HPLC systems and HPLC
23 columns.

24 Q. Yeah. Are you there?

25 A. Yeah.

KENNETH S. GRAHAM, PHD - REDIRECT

1 Q. Do you remember you were asked questions by counsel
2 for Biocon and Mylan about the variability regarding HPLC?

3 A. Yes.

4 Q. Is this referring to SEC or HPLC?

5 A. So this says HPLC in terms of what it's being
6 described.

7 Q. Is that the same as SEC?

8 A. Not necessarily, no.

9 Q. Okay. With respect to SEC, size-exclusion
10 chromatography, do you consider that to be a good assay for
11 analyzing the stability of aflibercept formulations?

12 A. Okay. It is a very good assay. It's what I like to
13 call the sentinel assay.

14 Q. What do you mean when you say SEC is the sentinel
15 assay?

16 A. So it's the one that shows something going wrong,
17 typically, before anything else. You know, unless we have
18 major problems, generally we don't see particles, generally we
19 don't see increases in turbidity; but we always do see some
20 level of change in HPLC.

21 Q. So, Doctor, then, if you had only one assay by which
22 you could analyze the stability of a formulation containing
23 aflibercept, what assay would you choose to use?

24 A. I would use SEC.

25 Q. Let's look at PTX 3314, page 22.

KENNETH S. GRAHAM, PHD - REDIRECT

1 Do you remember being asked for counsel by Biocon and
2 Mylan about the data under percent native VEGF Trap in this
3 exhibit --

4 A. Yes.

5 Q. -- for Formulation 2?

6 A. Yes.

7 Q. And counsel pointed out that the percent native VEGF
8 Trap at that condition was 97.9.

9 Do you remember that?

10 A. Yes.

11 Q. Was the starting percent data of VEGF Trap -- what
12 was the starting percent native VEGF Trap with this material?

13 A. So it was 97.6.

14 Q. And what does that tell you about the stability of
15 this material?

16 A. Well, so generally you have variation in your assay,
17 but you don't go up in purity. So I started off at 97.6 plus
18 or minus .1, .2, ended up at 97.9 plus or minus .2. It shows
19 that there's really no change. It says that the stability is
20 good. The fact that I started out below 98 percent, you know,
21 I would never expect to -- if I start out below, I never would
22 expect to come back up two.

23 Q. And so what does this data tell you as a formulation
24 scientist? If you had started with material that was above 98
25 percent, what would you end up with?

KENNETH S. GRAHAM, PHD - REDIRECT

1 MR. RAKOCZY: Objection, Your Honor. That's asking
2 for opinion testimony and a prediction.

3 MR. TRASK: This is the very slide that counsel asked
4 him about. I'm just asking him to explain the meaning of it,
5 Your Honor.

6 MR. RAKOCZY: He's asking him to predict something
7 that's not on the slide, Your Honor.

8 THE COURT: Understood.

9 Sustained.

10 BY MR. TRASK:

11 Q. Let's turn to Exhibit 3327, please.

12 And we'll look at page 46. Now, do you remember when
13 counsel for Biocon and Mylan asked you about the last two rows
14 of this table, Formulations 8 and 9?

15 A. Yes.

16 Q. And they pointed out that there was an increase in
17 the number of -- I don't remember if it was aggregates or
18 particles shown in this data?

19 A. I think they used the words "particles."

20 Q. How does -- can you explain how the HIAC analysis
21 works that was done to generate this data?

22 A. So this is kind of an internally controlled
23 experiment in that you start off by measuring the formulation
24 and you look at whatever the base level is. Then you subject
25 it to stress and you look for a change.

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1 The bigger the change -- you know, that -- large
2 changes are not good. Small changes are to be expected. You
3 know, there's more to the story that isn't necessarily entirely
4 captured here, but what can happen is you not only get more
5 particles but you get bigger particles.

6 In comparison, if we look at all these formulations
7 and we say, okay, how do their performances compare? 8 and 9
8 are probably two of the top ones. I mean, 8 started out fairly
9 low, went up a little bit. 9 started out at 100,000 and went
10 up.

11 You know, really, the only formulations that are on
12 there that start out significantly lower are ones that are
13 lower protein concentration. There's a couple 10 mg/mL. And,
14 you know, they're down in the 30 thousands. You know, it
15 basically says that these are stable to the stress or more
16 stable to the stress more directly than everything else that's
17 on that page.

18 Q. Thank you. Can we turn to 3312, please, page 27.

19 Do you remember when counsel for Biocon and Mylan
20 asked a question about the fourth bullet down on this slide
21 comparing the oncology formulation stability to the "current
22 ITV formulation"?

23 A. Yes.

24 Q. What is the current ITV formulation here?

25 A. So that was what we had referred to as ITV1. It was

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1 a formulation that contained 40 mg/mL aflibercept,
2 135-millimolar sodium chloride, and 0.1 percent PEG 3350.

3 So it was the formulation that we were seeing the
4 issue with particulate formulation.

5 Q. Okay. Can we look at DTX 4121, please.

6 I believe this is one of the loose-leaf documents
7 that counsel handed you. And I would like to look at page 3,
8 paragraph 17.

9 Do you see that, Doctor?

10 A. I'm doing the wrong page number thing again; but yes,
11 I do.

12 Q. So do you remember when counsel asked you a question
13 about this statement in this document, 40 mg/mL prelyophilized
14 solution?

15 A. Yes.

16 Q. Is a prelyophilized solution an ophthalmic
17 formulation?

18 A. It is not.

19 Q. Why not?

20 A. Well, a prelyophilized solution is designed to have
21 the drug remain stable solely --

22 THE COURT: One second, Doctor.

23 Yes, Counsel?

24 MR. RAKOCZY: Objection, Your Honor. This is calling
25 for expert testimony.

1 THE COURT: It is. It is. Sustained.

2 MR. TRASK: In that event, nothing further, Your
3 Honor. We do have exhibits to move in unless, obviously,
4 there's further from defense counsel.

5 THE COURT: Understood.

6 Recross?

7 MR. RAKOCZY: Depending on the exhibits, I may have
8 none, Your Honor.

9 THE COURT: Let's take the exhibits first, then.
10 Keep our fingers crossed.

11 One second, Doctor, if you'll bear with us. Just
12 housekeeping stuff.

13 THE WITNESS: Okay.

14 THE COURT: Thank you.

15 Slowly counsel, but go ahead.

16 MR. TRASK: Thank you very much, Your Honor.

17 PTX 3327, PTX 3326, PTX 2293, PTX 2292, PTX 1921,
18 PTX 1825, PTX 2277, PTX 2278, PTX 1860, PTX 2238, PTX 3249,
19 PTX 2281, PTX 2282, PTX 2283, PTX 2265, PTX 2266, PTX 2267,
20 PTX 2275, and PTX 672.

21 MR. RAKOCZY: I apologize. That was going too fast
22 for me, Your Honor. Can I compare?

23 THE COURT: Please. Compare notes.

24 MR. RAKOCZY: Your Honor, as you can imagine, I need
25 to preserve an objection for a lot of these. I'll try to do

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 21, 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 21st day of June 2023.

12 /s/Cindy L. Knecht

13 _____
14 Cindy L. Knecht, RMR/CRR
15 Official reporter, United States
16 District Court for the Northern
17 District of West Virginia
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