would find in the specification that says any one of these regimens should be used or called out to be used with DME or diabetic retinopathy?

A. No.

Q. When it came to your testimony that you provided here in court today, did you assume that you had to find an example in order to find enablement or written description?

A. No, I didn't.

Q. Let's go back, then, to the press release, which was DTX 3198. And let's go to the second page of the exhibit.

And let's call up the description of the VEGF Trap-Eye in Phase II development paragraph.

Now, I believe you indicated that what was written on the page for the first indication that involved an eight-week dosing regimen was what? 2 milligrams every eight weeks after three monthly loading doses?

A. The first one was 2 milligram monthly and then 2 milligram every eight weeks after three monthly loading doses was the second option.

Q. Now, even if there's no express recitation of the number five there, does the prn dosing regimen permit dosing that would include five monthly loading doses in the context of this regimen?

A. You could happen upon a scenario where five loading doses are given through the course of using a prn approach.

Q. And would that prn regimen also permit, then, those five loading doses being followed by an eight-week dosing regimen?

A. It could be if that's how circumstances played out for that particular patient.

MS. MAZZOCHI: Nothing further, Your Honor. Thank you.

THE COURT: Recross?

MR. GREGORY: Nothing further, Your Honor.

THE COURT: Any exhibits we need to tidy up with the doctor?

MR. GREGORY: None from us, sir.

THE COURT: Are the stack that was in the binder part of the record, or are you satisfied just --

MR. GREGORY: We are satisfied. We don't need to move them into evidence.

THE COURT: All right. Understood.

Any other exhibits from defense standpoint, then.

MS. MAZZOCHI: Your Honor, because so many of what was in the stack I've never seen before, let me -- can I just have -- to see if I need to put them in the record for this witness just to make sure that the Court has context and completeness. But, otherwise, we don't have anything further. But we'll clean that up tomorrow morning if that's all right.

THE COURT: Understood.

MS. MAZZOCHI: Thank you.

THE COURT: Doctor, thank you. You can step down. You can leave all the documents up there. Someone will tidy those up. Thank you, sir.

If I could ask counsel to grab whatever's up here, whomever it belongs to.

While we're doing that, Mylan may call its next witness.

If everyone has finished rotating and whatnot, Counsel, you may call your next witness.

MR. SALMEN: Thank you, Your Honor. Heinz Salmen on behalf of defendants Mylan and Biocon. We call Dr. Gregory MacMichael as our next witness.

THE COURT: Doctor, if you would come all the way to the front.

You may proceed, Counsel.

MR. SALMEN: Thank you, Your Honor.

GREGORY MACMICHAEL, PhD, DEFENDANTS' WITNESS, SWORN

DIRECT EXAMINATION

BY MR. SALMEN:

Q. Good afternoon, Dr. MacMichael.

A. Good afternoon.

Q. Would you please introduce yourself to the Court.

THE WITNESS: Your Honor, my name is Greg MacMichael.

THE COURT: Good afternoon, sir.

BY MR. SALMEN:

Q. Dr. MacMichael, are you here testifying on behalf of Mylan and Biocon?

A. Yes, I am.

Q. And did you prepare a set of demonstrative slides to assist with your testimony today?

A. Yes, I did.

Q. Okay.

If we could pull up DDX 8 on the screen.

And I believe you've been provided a binder and a printout of these slides. Dr. MacMichael, are these the slides that you prepared?

A. Yes, they are.

Q. Dr. MacMichael, where are you from?

A. I'm from New Jersey.

Q. And turning to your demonstrative slide, DDX 2, on the screen, will you please provide the Court with a summary of your educational background.

A. Yes. I went to Penn State to get a bachelor's degree in microbiology. Subsequent to that, I went to North Carolina State University to get a master's degree in microbiology and biochemistry focusing on the use of -- I went to North Carolina State to get my master's degree in microbiology and biochemistry with a focus on the use of bacteria to break down hazardous wastes and degrade oil spills.

Q. What was your doctoral thesis in?

A. Yes. I got my PhD in microbiology and biochemistry at Mississippi State University, again working on the use of bacteria for the cleanup of hazardous waste and oil spills.

Q. After receiving your doctorate from Mississippi State University in 1984, where did you begin your career?

A. Yeah. My first job after college was working at a company called Techne.

Q. And will you please summarize for the Court your professional experience at Techne.

A. Yes. At Techne I was working with an individual named Norman Burney, who also was a famous innovator. And together we worked on the development of bioreactors for growing up animal cells to produce therapeutic proteins.

Q. How many years were you at Techne?

A. Six years.

Q. After your six years at Techne, where did you continue your career?

A. I moved over to Centocor and was the assistant director of cell culture research and development.

Q. What was the focus of your work at Centocor?

A. It was focused on developing high-cell-density, high-volumetric productivity processes for making monoclonal antibodies.

Q. Will you please explain to the Court what a

monoclonal antibody is.

A. Yes. As you're developing a therapeutic, you will basically genetically modify numerous cells, and then you will look to see which one was the highest level of productivity. You will then pick that specific clone that was obtained from that one cell, and thus the term "monoclonal antibody."

Q. Did you have any notable achievements during your time at Centocor?

A. Yes, I did.

Q. And can you describe for the Court, please.

A. Yes. I developed the high-density upstream processes for Centoxin, the first monoclonal ever approved, Remicade, and ReoPro.

Q. And were those FDA-approved medications?

A. They were all FDA-approved medications.

Q. And what type of drug product is Centoxin?

A. Centoxin is a immunoglobulin M for the treatment of sepsis.

Q. What were your primary contributions to the development of Centoxin?

A. Developing the high cell density processes, doing the tech transfer into manufacturing, and supporting the manufacturing efforts.

Q. What type of drug product is Remicade?

A. Remicade is an IgG monoclonal antibody for the

treatment of autoimmune disorder.

Q. What were your primary contributions to the development of the Remicade product?

A. Again, developing high cell density, high volumetric productivity processes for the manufacturing of Remicade.

Q. And turning to the ReoPro product, what type of drug product is ReoPro?

A. ReoPro is a subclass of a monoclonal. It's a fragment, called Fab -- fragment of an antibody is called a Fab -- and it was actually a fusion protein. It was part human, part mouse.

Q. Can you describe to the Court what your primary contributions were to the development of ReoPro?

A. Again, my focus was on the upstream processes to develop high productivity to be able to meet market demand.

Q. After your time at Centocor, I see you moved on to Chiron. Why did you make the move to Chiron?

A. Yes. My supervisor, the head of development at Centocor, moved over to Chiron to be the senior vice president of development and manufacturing. He asked if I would join him at Chiron, and I became the director of production in vaccines development in St. Louis.

Q. What was the focus of your work at Chiron?

A. It was developing subunit vaccines in a cell line called Chinese hamster ovarian cells.

Q. Will you please explain to the Court what a Chinese hamster ovarian, or CHO, cell is.

A. Yes. In the production of various therapeutic proteins, they use animal cells. A Chinese hamster ovarian cell was proved to be a very robust cell line, reached high levels of cell density and productivity, and also had more favorable what we call glycosylation patterns.

Q. Can you expand on that? What is a glycosylation pattern?

A. Yes. Inside each of our cells, there's a whole set of machinery that synthesizes proteins. And after the primary protein is synthesized, the cells then can further -- what's called posttranslational modification. They can modify those cells by putting sugars on those cells to change the performance in the bloodstream.

Q. Dr. MacMichael, did you invent the glycosylation pattern for the proteins you were working on?

A. No. Every cell in the human body has the ability to glycosylate proteins.

Q. And what notable achievements did you have at Chiron?

A. At Chiron we produced -- we developed multiple vaccines, but one of most interest would be hepatitis B vaccine where I led the global team, which included a clinical, regulatory, and manufacturing and development, and basically developed a new formulation for that vaccine.

Q. Let me follow up on that, Dr. MacMichael. Were you overseeing the formulation activities during that development?

A. Yes, I was.

Q. After Chiron, I see you moved over to Eli Lilly in 1997. Why did you make the move to Lilly?

A. Yes. Eli Lilly was trying to develop a product called Xigris, activated protein C produced in HEK293 cell line, but they lacked the internal experience of how to grow those cells at high cell density. So they recruited me in to help them develop the process.

Q. What was your title at Lilly?

A. Senior director of development.

Q. What type of drug products were you working on at Lilly? What was your focus?

A. The focus was on therapeutic proteins.

Q. Will you please describe to the Court some of your notable achievements at Lilly.

A. Yes. Probably the two more notable achievements was the successful development and registration of Xigris, activated protein C for the treatment of sepsis; and additionally the development of truncated parathyroid hormone, known as Forteo, for the treatment of osteoporosis.

Q. Were those drugs approved by any regulatory authorities?

A. They were approved by the FDA and the EMA.

Q. I see you continued your career at Wyeth. What was your title at Wyeth?

A. At Wyeth I was vice president of vaccines development.

Q. And I see you have a couple drug names listed here on Slide 3 of DDX 8. What are those drugs that you were referring to?

A. They're probably two of my more notable accomplishments while at Wyeth. Prevnar 13 is a pneumococcal vaccine that vaccinates against 13 different types of pneumococcal pneumonia.

Q. Let me ask a follow-up to that, Dr. MacMichael. What was your contribution to the development of the Prevnar 13 formulation?

A. Yes. I had responsibilities from cell line development through upstream process development, purification and final formulation and the development of the analytical -- of the assays required for in process and release testing.

Q. Did you contribute to the stable formulation for the Prevnar 13?

A. Yes.

Q. And how did you achieve a stable formulation in Prevnar 13?

A. Yes. Initially, we found that, heading into Phase I clinical trials, the vials -- just vibration in the

refrigerators was sufficient agitation to cause some undesired aggregation. We addressed that by adding Pluronic -- by adding polysorbate 80 to prevent the aggregation.

Q. The second product on your list at Wyeth is FluMist. What type of drug product is FluMist?

A. FluMist is a more advanced version of the annual flu vaccine that many of us get. The difference with FluMist is it's -- actually, the virus is not inactivated; so it elicits a better immune response. It's sprayed up the nose, and it cannot grow in the lungs. So it gets a very good immune response protecting the recipient against the flu.

Q. Dr. MacMichael, what was the general time frame for your work on the Prevnar 13 and FluMist formulation?

A. 2002 through 2008.

Q. I see you next were the senior vice president of development and manufacturing at Cook Pharmica in 2008.

What was the focus of your work at Cook?

A. Cook was a contract development and manufacturing organization. That is, we didn't have our own products; we developed and manufactured the products for our clients.

Q. And then in 2010 you moved on to Novartis as global head of biologics. What was the focus of your work at Novartis?

A. My focus at Novartis was the development activities required to bring the biologic pipeline in Novartis, which

included cell line development, upstream process development, purification, final formulation development, and the analytics required for all of those activities.

Q. Thank you, Dr. MacMichael.

If we turn to Slide 4 of DDX 8, can you describe to the Court what you have illustrated here on Slide 4.

A. This is a summary of some of the products that we touched on. These are eight products that I successfully developed and supported the registration and the interactions with the FDA and EMA.

Q. Let me ask about that, Dr. MacMichael. In your over 30 years of industry experience, did you gain experience on the regulatory side of product development?

A. Yes, I did.

Q. Can you describe that experience briefly.

A. Yes. To bring these types of molecules successfully forward, you have numerous interactions with the FDA and the EMA. It also requires an understanding of how to construct the various submissions that are required for successful registration.

Q. Dr. MacMichael, are you still active in the pharmaceutical industry?

A. Yes, I am. I founded my own consultancy called CMC Bioservices.

Q. And what types of companies do you generally consult

for?

A. I consult in the pharmaceutical industry everything from a large pharma company down to small startups.

Q. What technical areas do you generally consult in?

A. My focus is on therapeutic proteins, vaccines, and cell and gene therapies, from development of cell lines all the way down through the final drug product.

Q. Last question on your background Dr. MacMichael. Using your own words, how would you describe your areas of expertise?

A. Yeah. My expertise -- CMC stands for chemistry manufacturing control is the term we used for doing process development and manufacturing. My expertise starts with cell line development, and the cell lines that produce therapeutic proteins are put down in vials called cell banks. We do a cell line selection for the highest producer.

Subsequent to that, we develop across the upstream process, grow the cells up, and produce the desired protein. We then need to purify it. And then subsequent to having it purified in what we call bulk. It is then formulated into the final vial.

So in many ways, I have responsibilities from vial to vial, is one way to put it.

Q. Is that vial to vial illustrated on Slide 6 of DDX 8?

A. Yes, it is.

Q. Dr. MacMichael, I see you've cited DTX 7087, pages 1 through 6. There's a copy of it in your binder, but we could also show that on the screen for you.

Is this a copy of your current CV?

A. Yes, it is.

MR. SALMEN: Your Honor, we move to admit DTX 7087 into evidence.

THE COURT: Any objection?

MR. BERL: No objection.

THE COURT: Without objection, so admitted.

(DTX 7087 was admitted.)

MR. SALMEN: And at this time, Your Honor, we proffer Dr. Gregory MacMichael as an expert in the formulation and development of therapeutic proteins.

THE COURT: Any voir dire or objection?

MR. BERL: No, Your Honor.

THE COURT: Without objection then, motion granted. The doctor is deemed so qualified.

You may proceed, Counsel.

MR. SALMEN: Thank you, Your Honor.

BY MR. SALMEN:

Q. Dr. MacMichael, if we turn to Slide 7 of your slide presentation, DDX 8, let's talk about the opinions that you plan to provide to the Court today.

If I could first direct your attention to PTX 2, we

have the first page of PTX 2 here on Slide 8.

What is PTX 2?

A. PTX 2 is the '865 patent.

Q. And did you review and analyze the '865 patent, PTX 2, in forming your opinions?

A. Yes, I did.

Q. And let's also put DTX 0030 on the screen.

Dr. MacMichael, did you review and consider the document known as the prosecution history for the '865 patent in forming your opinions?

A. Yes, I did.

Q. Turning to slide -- back to Slide 8 of DDX 8, Dr. MacMichael, before we go through your opinions, let's just set the stage a little.

Did you conduct your analysis in this case from the perspective of a person of ordinary skill in the art?

A. Yes.

Q. And if we look at Slide 8, top callout, citing DDX 2679, pages 19 to 20, MacMichael opening report, is this the definition for the person of ordinary skill in the art that you applied in forming your opinions?

A. Yes, it is.

Q. And I'll read that definition into the record for you, Dr. MacMichael.

"A POSA during the relevant time period would have a

fairly high level of education and skill. Here, a POSA would have at least a PhD in chemistry, chemical engineering, biochemistry, pharmacology, or a related field, along with one to two years of experience in the development and manufacture of formulations of therapeutic proteins or a lower degree with more practical industrial experience. A POSA would have access to biologists, biochemists, physicians, pharmaceutical formulators, and the like with knowledge and experience in fields such as drug discovery and development and the treatment of ophthalmologic conditions."

Dr. MacMichael, is this the definition of a person of ordinary skill in the art that you applied in forming your opinions?

A. Yes, it is.

Q. Dr. MacMichael, did Dr. Trout also offer for a person of ordinary skill in the art?

A. Yes, he did.

Q. Do you have Dr. Trout's definition illustrated at the bottom right-hand side of Slide 8 of DTX 8, citing DTX 2251, page 11?

A. Yes, I did.

Q. How did Dr. Trout's definition compare to yours?

A. Relatively similar. Dr. Trout just had a master's degree where I had suggested a PhD for the POSA. Other than that, the two definitions were relatively similar.

Q. Dr. MacMichael, would your opinions regarding the '865 patent change at all if the Court were to adopt Dr. Trout's definition?

A. No, they would not.

Q. Now, let's move on to our second foundational point, Dr. MacMichael. Turning to Slide 9 of DDX 8, are you aware that the Court issued a claim construction order regarding certain terms of the '865 patent that are relevant to your opinions?

A. Yes, I am.

Q. And if we look here on Slide 9, we have the Court's claim construction order marked for identification at DTX 6439 here at page 20. I'll read this for you, Dr. MacMichael.

"The Court adopts Mylan's definition of 'cosolvent.' It is an organic substance added to the primary solvent to increase the solubility of the solute, here a VEGF antagonist."

Dr. MacMichael, is this the construction of the claim term "cosolvent" that you applied to your analysis regarding infringement and validity of the '865 patent?

A. Yes, it is.

Q. If we turn to Slide 10, please.

Dr. MacMichael, will you explain to the Court what you have illustrated here in the bubble at the center of Slide 10, DDX 8, citing DTX 6439, page 20.

A. Yes. I took the Court's construction for an organic

cosolvent and edited Claim 1. And as you see in the highlighted yellow -- excuse me -- red is the insertion of the Court's construct.

Q. And, Dr. MacMichael, is that the version of Claim 1 that you applied in your analysis regarding the infringement inquiry?

A. Yes, it is.

Q. If we turn to Slide 11, please, of DDX 11.

Dr. MacMichael, will you please summarize for the Court the opinions you plan to offer today regarding the alleged infringement of the '865 patent against Mylan and Biocon's Yesafili product.

A. Yes. Applying the Court's claim construction order, Yesafili does not infringe on the asserted Claims 4, 7, 9, 11, and 14 through 17 of the '865 patent.

Q. And did you form an opinion regarding whether polysorbate 20 at 0.03 percent in Yesafili is an organic cosolvent?

A. Yes, I did.

Q. And what was your conclusion?

A. My conclusion is that polysorbate 20 at 0.03 percent in Yesafili is not an organic cosolvent.

Q. And did you form an opinion regarding whether polysorbate 20 at 0.03 percent in Yesafili is increasing solubility of the solute aflibercept in the Yesafili product?

A. Yes, I did evaluate.
Q. And what was your conclusion in that regard?
A. My conclusion was that polysorbate 20 at 0.03 percent in Yesafili does not increase solubility of the solute aflibercept.
Q. Dr. MacMichael, I understand that you were unable to attend Dr. Trout's testimony in person. Were you nonetheless able to review Dr. Trout's trial testimony as well as his associated demonstratives?
A. Yes, I was.
Q. Was there any portion of Dr. Trout's testimony that you want to respond to specifically during your testimony today?
A. There's two points where I believe we disagree.
Q. Can you explain to the Court those two points of Dr. Trout's testimony that you would like to respond to.
A. Yes.
Q. First point, please.
A. The first point, Dr. Trout defined inhibiting aggregation as equal to increasing solubility.
Q. Do you agree or disagree with that testimony?
A. I disagree.
Q. And your second point, Dr. MacMichael?
A. The second point where I differ is reducing insolubility is equivalent to increasing solubility. I

disagree.

Q. Dr. MacMichael, I would next like to talk about some of the technology relevant to your opinions in this case. If we could turn to Slide 13. Here on Slide 13 of DDX 8 we have DTX 5172, the Bontempo reference. Dr. MacMichael, did you review and consider the Bontempo reference in forming your opinion?

A. Yes, I did.

Q. Will you please explain to the Court the information you have identified here in Slide 13 from Bontempo that's relevant to your opinions and testimony in this case.

A. Yes. I pulled a list of potential buffers that could be used in a protein formulation.

Q. And that information -- does that information come from page 7 of DTX 5172, Bontempo?

A. Yes, it does.

Q. If we turn to the next slide, Slide 14 -- actually, I'm sorry. I forgot to ask a question.

Could we go back one.

Dr. MacMichael, can you please explain the relevance of the information that you provided in the parentheticals following each of the listed buffers?

A. Yeah. The parentheticals are showing the pH ranges where each of these buffers would -- each one of these moieties would be effective as a buffer.

Q. And, for example, if we look at succinate, what would be the buffering range for that buffer?

A. A pH of 3.2 to 6.6.

Q. And for citrate, what would be the known buffering range for a citrate buffer?

A. 2.1 to 6.2.

Q. For histidine, what would be the known buffering range for a histidine buffer?

A. 5.5 to 6.5.

Q. If we turn to Slide 14, please, of DDX 8.

Here, Dr. MacMichael, we have Exhibit DTX 5196. This is the Strickley reference. Dr. MacMichael, did you review and rely on the Strickley reference?

A. Yes, I did.

Q. And please explain to the Court the teaching in Strickley that you have highlighted here on Slide 14 from page 2 of DTX 5196.

A. Yes. I pulled out Strickley's definition of a cosolvent.

Q. And is that identified in the yellow highlighted language there?

A. Yes, it is.

Q. I'll read that for you, Dr. MacMichael.

"Cosolvents are mixtures of miscible solvents and are often used to solubilize water-insoluble drugs."

Is that part of the information from Strickley that you relied upon?

A. Yes, it is.

Q. And is this disclosure in Strickley consistent with how a person of ordinary skill in the art would understand the use of cosolvents in pharmaceutical formulations?

A. Yes.

Q. Could we turn to Slide 15, please.

Here on Slide 15 we have another passage from the Strickley reference, DTX 5196. This time we're on page 1.

Dr. MacMichael, will you please explain to the Court the information in Strickley that you have identified here to help inform your testimony.

A. Yes. What's pulled out in the paragraph that's being shown is examples of water-soluble organic solvents. Some of the examples would be polyethylene glycol 300, polyethylene glycol 400.

Q. And with regard to the nonionic surfactants that you have highlighted there, does Strickley provide examples of nonionic surfactants?

A. Yes, they do.

Q. What are a couple of the examples of nonionic surfactants that you've highlighted here on Slide 15, DDX 8?

A. For today's discussion I highlighted polysorbate 20 and polysorbate 80.

Q. Dr. MacMichael, are these descriptions from Strickley of polysorbate 20, polysorbate 80, and polyethylene glycol consistent with how a person of ordinary skill in the art would understand and characterize those excipients?

A. Yes.

Q. If we turn to Slide 16, please.

Here, Dr. MacMichael, we have DTX 5011. This is the Akers reference. Did you review and consider the Akers reference, DTX 5011?

A. Yes.

Q. And will you please explain to the Court the information from Akers here on page 3, DTX 5011, that you've identified to help inform your testimony.

A. Yes. Again, it defines a cosolvent and then gives additional information on how a cosolvent works in water.

Q. Let's break that down with the first highlighted language. I'll read that for you, Dr. MacMichael.

"Cosolvents are used to increase the solubility of a poorly soluble drug in water."

Is that part of the disclosure from Akers that you reviewed and considered?

A. Yes, it is.

Q. And can you describe for the Court the importance of the second passage from Strickley that you have here.

A. Yes. The second passage is showing how a cosolvent

changes the overall physical chemistry of the solution. And the way that Akers defines it is a water-miscible cosolvent operates on the principle of lowering the dielectric constant property of water, thereby increasing the aqueous solubility of a poorly water-soluble drug.

Q. If we turn to the next slide, please, Slide 17.

Here, Dr. MacMichael, we have DTX 5012, what's known as the Ansel reference, *Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems*. Dr. MacMichael, did you review and consider DTX 5012 in forming your opinions?

A. Yes, I did.

Q. I see you have two callouts here, Dr. MacMichael, both from page 12 of DTX 5012. Will you please explain to the Court the information from Ansel that you've identified here to help inform your testimony.

A. There's two things I wanted to accomplish. One was the definitions of a solvent and a surfactant. Then secondly to give a list of examples of potential solvents and surfactants.

Q. Let's start with the first definition applied here for solvent. I'll read that for you, Dr. MacMichael.

"Used to dissolve another substance in preparation of a solution."

Dr. MacMichael, is that definition for solvent consistent with how a person of ordinary skill in the art would

understand that excipient?

A. Yes, it is.

Q. And the second definition you've highlighted here is for surfactant. I'll read that for you as well.

"Substances that absorb to surfaces or interfaces to reduce surface or interfacial tension."

Dr. MacMichael, is that definition consistent with how a person of ordinary skill in the art would define and characterize a surfactant?

A. Yes, it is.

Q. We turn now to Slide 18, please.

Here on Slide 18 of DDX 8, we have what's already been admitted as PTX 1817. This is the Randolph and Jones reference, Dr. MacMichael.

Did you review and consider the Randolph and Jones reference to help inform your opinions and testimony?

A. Yes, I did.

Q. And will you please explain to the Court the information from Randolph and Jones that you have identified here to help inform your testimony.

A. Yes. Again, I used the Randolph and Jones to further -- give further support of the definition of a surfactant as being used as a stabilizing agent in a protein formulation, and they're typically nonionic.

Q. And let me ask you, Dr. MacMichael, what subject

matter did Randolph and Jones direct their focus on in this chapter?

A. It focused on the interaction of nonionic surfactants and proteins with respect to developing formulations.

Q. Thank you.

We move to just the next slide, please, Slide 19.

MR. SALMEN: Your Honor, if I may, at this point in time I am going to have to ask to have the courtroom sealed pursuant to Your Honor's previous order. We are going to be getting into the details of Mylan and Biocon's Yesafili product.

THE COURT: Understood.

Any objection to that from Regeneron?

MR. BERL: No objection.

THE COURT: Ladies and gentlemen, consistent with our prior -- I meant to turn that off.

Ladies and gentlemen, consistent with our prior practice, anyone who's not permitted to be in the courtroom consistent with this Court's protective order entered in this case, I would kindly ask you to step out, please. Thank you.

I would continue to ask counsel to assist the Court in policing enforcement of that requirement just with a quick look around.

THE COURT: Seeing no further objections, I'll ask court security to please seal our courtroom, sir. Thank you.

Go right ahead, Counsel.

MR. SALMEN: Thank you, Your Honor.

(The following proceedings (1384/3 to 1416/2) were had under seal, and are filed under separate cover.)

(Record unsealed.)

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

MR. SALMEN: Thank you, Your Honor.

BY MR. SALMEN:

Q. Ready, Dr. MacMichael?

A. Yes, I am.

Q. Dr. MacMichael, have you been asked to offer an opinion regarding the validity of the asserted claims of the '865 patent?

A. Yes, I have.

MR. SALMEN: I just wanted to make sure we unsealed the courtroom, Your Honor.

THE COURT: We have.

MR. SALMEN: Just double-checking.

BY MR. SALMEN:

Q. And, Dr. MacMichael, if we turn to Slide 41 of your presentation here.

Will you please provide the Court with a brief summary of your opinions that you plan to provide today.

A. Yeah. This slide shows three of my opinions.

Q. If we address them one at a time, have you formed an opinion regarding the enablement of the '865 patent?

A. Yes. My first opinion was it lacks enablement. The breadth of the asserted claims is not enabled by the '865

patent specifications.

Q. Will you please summarize for the Court your opinion regarding the written description of the '865 patent.

A. My opinion is the asserted claims do not have sufficient written description. The '865 patent specification fails to inform the skilled person that the named inventors possessed anything but a phosphate-buffered sucrose-stabilized formulation.

Q. And then lastly, Dr. MacMichael, will you please provide a summary of your opinion regarding the indefiniteness inquiry of the '865 patent.

A. Yes. The patent's indefinite because the '865 patent specification fails to inform the skilled person what suitable for intravitreal administration means. That term is subjective and prone to multiple interpretations.

Q. If we turn to Slide 42, please.

Here on Slide 42, Dr. MacMichael, I see you have the enablement legal standard. And I'll read that for you.

"A claimed invention is not enabled and, therefore, is not patentable when the specification does not provide a sufficient description to a person of ordinary skill in the art how to make and use the full scope of the claimed invention without undue experimentation."

Dr. MacMichael, is this the standard you applied in your assessment of whether the '865 patent specification

enables the asserted claims?

A. Yes, it is.

Q. If we turn to the next slide, Slide 43, please. Here on Slide 43, Dr. MacMichael, I see you have a graphic that looks like an upside-down pyramid. Can you please explain to the Court what information you are trying to convey with this graphic.

A. Yes. This graphic is showing that, as you build on the -- the claims build upon one another, there should be a narrowing in scope of the invention.

Q. And I see on the left-hand side of this Slide 43 you have identified claims of the '865 patent, the referenced Claims 2, 5, and 10, followed by the asserted Claims 4, 7, 9, 11, 14, 15, 16, and 17.

Let me ask, Dr. MacMichael, does this graphic on Slide 43 illustrate the breadth of the asserted '865 -- asserted claims of the '865 patent?

A. No, it doesn't.

Q. If we turn to Slide 44, please, please explain to the Court what you have illustrated here in Slide 44.

A. Yes. What we are seeing here, the way these claims are constructed, rather than narrowing -- rather than narrowing the overall claims of the invention, it actually broadens them.

Q. Let's break that down, Dr. MacMichael.

Here from Claim 5 to Claim 7 can you explain how the

claims compare in scope?

A. Yeah. All the claims that are being highlighted with the word "compromises," [sic] as we know just means includes, polysorbate; so it gives various examples of components that could be used and potential concentrations and ranges of -- for example, ranges of pH. So there's an extraordinary -- not extraordinary number, but there's a large number of variables that have to be worked through. And that's not clearly defined within the scope of this claim.

Q. Thank you, Dr. MacMichael. Let's turn to your enablement analysis.

If we turn to Slide 45.

Dr. MacMichael, did you apply each -- here on Slide 45 we have identified the *Wands* factor. Did you apply each of the *Wands* factors in forming your opinion regarding the enablement of the '865 patent claims?

A. Yes, I did.

Q. And let's walk through these. If we turn to Slide 46, I'd like to start at the bottom of this list with *Wands* Factor 8, the breadth of the claims.

Dr. MacMichael, did you form an opinion regarding the breadth of the '865 patent asserted claims?

A. Yes, I did.

Q. And Dr. MacMichael, will you please explain to the Court the conclusions you reached regarding the breadth of the

claims?

A. Yes.

THE COURT: One second, Doctor.

Yes, Counsel?

MR. BERL: Objection, Your Honor. This is leading. I mean, we haven't been sticklers about this, but this is basically having the answers on a screen and asking him to read them. That doesn't seem like an appropriate question.

THE COURT: Overruled at this point.

But it is direct examination, Counsel. Go ahead.

BY MR. SALMEN:

Q. Dr. MacMichael, let me ask the question again.

Will you please explain to the Court the conclusions you've reached regarding the breadth of the claims.

A. Yes. There's different types of formulations that are being cited. There's various types and concentrations of the buffers. Examples are given -- citrate, succinate, phosphate, histidine. However, that claim uses the word "comprise." So those are examples. Multiple other buffers could be, in fact, used.

Secondly, various types and concentrations of stabilizing agents are suggested. And then various types and concentrations of the organic cosolvent are also being suggested. But they use the word "comprises," which leaves it open-ended.

Q. And let me ask, Dr. MacMichael, would a skilled person understand that combinations of different buffers could be used as well?

A. Yes. You could use more than one specific buffer. You can use a combination, which is actually practiced to achieve a desired pH.

Q. And under the claim language here, could combinations of different stabilizing agents be used as well?

A. Yes, they could.

Q. And same question for cosolvents, could combination of organic cosolvents be used here under the claim language?

A. Yes. In fact, we were going to use cosolvents -- various cosolvents could be used and examples were highlighted.

Q. Last question for this part, Dr. MacMichael. Now that you've identified the variables in the claims with respect to each of the required components of Claim 1, do the asserted dependent claims sufficiently narrow this universe of formulations that would lessen the burden on the person of ordinary skill in the art practicing these claims?

A. No, they would not.

Q. If we turn to Slide 47, please.

Did you also consider and apply *Wands* Factors 4, 5, 6, and 7 listed here on Slide 47 on the left-hand side?

A. Yes, I did.

Q. I'll read those for you, Dr. MacMichael. *Wands*

Factor 4, the nature of the invention. Factor 5, the state of the prior art. Factor 6, the relative skill of the art. And Factor 7, the predictability or unpredictability of the art.

Dr. MacMichael, what conclusion did you reach with respect to the amount of experimentation a person of ordinary skill in the art would need to practice the full scope of the claims?

A. There would need to be a significant amount of experimentation.

Q. Dr. MacMichael, did you identify any evidence in the record that supports your opinion that the skilled person would require a significant amount of experimentation?

A. Yes. I cite two examples that are highlighted in yellow.

Q. So let's take those one at a time. DTX 5053, this is at page 17. This is Regeneron's response to an office action.

Dr. MacMichael, did you review and consider this document?

A. Yes, I did.

Q. And I'll read that for you.

"Thus, one of ordinary skill in the art, upon reading Remington's, would expect to engage in significant nonroutine experimentation to develop a successful formulation as claimed herein."

Dr. MacMichael, was that some of the evidence that

you identified --

A. Yes, it is.

Q. -- as support for your opinion that the skilled person would require additional -- undue experimentation?

A. Yes, it is.

Q. If we look at the bottom callout, DTX 4430, at page 3, that's a declaration of named inventor Daniel Dix.

Dr. MacMichael, did you review and consider DTX 4430 with regard to your opinions?

A. Yes, I did.

Q. And I'll read that statement for you.

"Formulation of pharmaceutical preparations and achieving a stable composition is not a simple or routine matter."

Dr. MacMichael, do you agree with that statement from Dr. Daniel Dix?

A. Yes.

Q. And is this part of the evidence that you reviewed and considered to support your opinion that the skilled person would require undue experimentation practicing the asserted claims of the '865 patent?

A. Yes.

Q. And, Dr. MacMichael, if we move to our next slide, Slide 48, did you form an opinion regarding the amount of direct -- I'm sorry.

Did you form an opinion regarding the amount of direction or guidance presented in the '865 patent specification?

A. Yes, I did.

Q. And did you form an opinion regarding the presence of working examples in the '865 patent specification?

A. Yes, I did.

Q. Let's start with *Wands* Factor Number 3. What conclusions did you reach regarding the presence or absence of working examples in the '865 patent specification?

A. Yeah. There were examples given from the phosphate-buffered sucrose-stabilized formulations. However, for the other examples -- the other areas where the term "comprised" was used, there were no examples given.

Q. Were there any examples provided in the '865 patent specification of using any other type of buffer or stabilizer in a stable formulation?

A. I'm trying to recall. I believe it was glycol or glycerol. I'm sorry.

Q. Let me ask a more direct question, Dr. MacMichael.

Does the '865 patent specification provide any example that is not a phosphate-buffered solution?

A. No.

Q. Let's now look at *Wands* Factor 2, the amount of direction or guidance presented.

Dr. MacMichael, what conclusions did you reach regarding the amount of direction or guidance presented in the '865 patent specification?

A. That there was insufficient guidance.

Q. And here on Slide 48 of DDX 8, I see you have a callout from the patent, PTX 2, page 4, Column 2, lines 39 to 48. Will you please explain to the Court the information that you've highlighted here from the patent.

A. Yeah. I wanted to highlight the fact that there was multiple examples that are being given for some of the various constituents for both -- for the stabilizing agents as well as the organic cosolvent.

Q. And what was the purpose of highlighting the language in this passage "for example, for example, or a combination of, maybe," then "maybe, for example."

A. Because it's not specific. It's open-ended, and it allows numerous components to be considered at various concentrations.

Q. Let's turn to Slide 49.

Dr. MacMichael, did you form an opinion regarding the final *Wands* factor listed here, *Wands* Factor Number 1, the quantity of experimentation necessary?

A. Yes, I did.

Q. And what was your conclusion with respect to *Wands* Factor Number 1, the quantity of experimentation necessary?

A. Although there would be a significant amount of experimentation that would be needed, and the screen -- the screening can be significant and the screening can be complex.

Q. Let's move on to Slide 50, please.

Dr. MacMichael, were you asked to provide an opinion regarding the written description requirement as it applies to the '865 patent?

A. Yes, I was.

Q. If we turn to Slide 51, I see here you have the legal standard for a written description. I'll read that for you, Dr. MacMichael.

"The patent must convey with reasonable clarity to persons of ordinary skill in the art that, as of the filing date, the inventor was in possession of the entire claimed genus, not just a species of the genus."

Dr. MacMichael, is this the legal standard that you applied in forming your opinion?

A. Yes, it is.

Q. Let me ask you the first question, Dr. MacMichael.

Does the '865 patent disclose a representative number of species that fall within the scope of the claimed genus of formulations covered by the '865 asserted claims?

A. No, it does not.

Q. How many species of the claimed genus are disclosed in the '865 patent?

A. I'm sorry. Please repeat your question.

Q. Sure.

How many species of the claimed genus are actually disclosed in the '865 patent?

A. I'm trying to recall. The names are given, but not the structural -- structure. So maybe if you could be a little more precise with your question.

Q. Does the patent disclose a phosphate-buffered sucrose-stabilized species?

A. Yes, it does.

Q. And does the patent disclose any other formulation that does not use a phosphate buffer?

A. No, it does not.

Q. And I'll ask you the second question of the written description legal inquiry.

Quote -- excuse me.

Does the '865 patent disclose structural features common to the members of the genus so that a person of ordinary skill in the art can visualize or recognize the members of the genus of formulations?

A. No, it does not.

Q. If we turn to Slide 52 of slide deck DDX 8, Dr. MacMichael, will you please provide the Court with a summary of your opinions with regard to the written description inquiry.

A. My summaries are -- there's three points I'd like to make.

One is every example has phosphate buffer or sucrose stabilizer -- excuse me -- every example has phosphate buffer and a sucrose stabilizer.

Q. And how many embodiments are within the possession of the inventors of the '865 patent according to the '865 specification?

A. There's only one embodiment.

Q. And in your opinion, Dr. MacMichael, would a person of ordinary skill in the art be able to visualize or recognize any other members of the genus of formulations that's claimed by the '865 patent?

A. No.

Q. If we turn to Slide 54, please.

THE COURT: Yes, counsel?

MR. BERL: I just want to note for the record that we did not receive that slide that he just presented.

THE COURT: I'm sorry. Say that again.

MR. BERL: We did not receive the slide that he just presented. The parties have been exchanging demonstratives, objecting. We've all been playing by the rules, and I've never seen that slide before.

MR. SALMEN: Your Honor, I can explain that.

Counsel for Regeneron objected to our original slides

there; so we tried to pare those down in response to their objections. And then we submitted them today.

THE COURT: Is the objection, Mr. Berl, to Slide 54?

MR. BERL: No. 52.

THE COURT: 52.

MR. BERL: They pared it down, I suppose, but they had information there that wasn't on the slide originally, and then they didn't send it to us after they changed it.

THE COURT: Understood.

We've run afoul of any number of agreements in the parties' joint memo. With y'all going forward from here, it is this Court's rule we're going to convene and conduct this trial pursuant to the rules of civil procedure, rules of evidence. Y'all can deal with the fallout of failing to comply and abide by the agreements you reached and the trial had been.

The Court will overrule the objection and the presentation of the slide with that noted.

MR. SALMEN: Thank you, Your Honor.

BY MR. SALMEN:

Q. If we turn to Slide 54, please.

Dr. MacMichael, were you asked to evaluate whether the patent passes the test for indefiniteness?

A. Yes.

Q. And here on Slide 54, I see you have the indefiniteness legal standard. I'll read that for you.

"A patent is invalid for indefiniteness if it claims -- if its claims" -- I'm sorry. Let me start over.

"A patent is invalid for indefiniteness if its claims read in the light of the specification and the prosecution history fail to inform with reasonable certainty those skilled in the art about the scope of the invention."

Dr. MacMichael, is this the legal standard you applied in evaluating the indefiniteness inquiry?

A. Yes.

Q. If we turn to Slide 54, please, Dr. MacMichael, what conclusion did you reach regarding whether the asserted claims of the '865 patent passed the test for indefiniteness?

A. Yes. They weren't -- the claims are indefinite.

Q. And what part of the asserted claims, in your opinion, are indefinite?

A. Well, there's the term "suitable for intravitreal administration." However, what's suitable for intravitreal administration is undefined.

Q. Dr. MacMichael, does the patent specification provide any guidance to a skilled person to understand what is considered suitable for intravitreal administration under the asserted patent claims?

A. No. There's no information on suitability.

Q. And, Dr. MacMichael, because the term is not defined, would persons of ordinary skill in the art be able to identify

a single interpretation of what it means to be suitable -- a suitable formulation under the '865 patent?

A. Different POSAs approaching this could have potentially different interpretations of what suitable means and what's acceptable for the eye.

Q. Let's turn to Slide 57, please.

Dr. MacMichael, were you asked to evaluate the written description requirement of the '572 patent? That's the additional dosing patent that's been asserted against Mylan and Biocon's BLA product.

A. Yes.

Q. And what conclusions did you reach regarding the written description requirement of the dosing patent?

A. Yes. I highlight that it's an aqueous media for injection. There are, for example, physiological saline and isotonic solution.

Q. Dr. MacMichael, does the '572 patent disclose a representative number of species falling within the scope of the genus of isotonic solutions covered by Claim 6 which we have at the top here as PTX 3?

A. No. It only gives one mention of isotonic solution.

Q. What is that one mention of an isotonic solution?

A. Yes. It's given on the physiological saline. And as this paragraph shows, physiological saline is the isotonic solution that's being highlighted.

Q. Dr. MacMichael, does the '572 patent disclose structural features common to the members of the genus of isotonic solutions covered by Claim 6 so that a person of ordinary skill in the art can visualize or recognize all of the members of the genus of isotonic solutions?

A. No, it does not.

Q. If we turn to Slide 58, please.

Dr. MacMichael, were you asked to review and evaluate certain Regeneron aflibercept patents?

A. Yes, I was.

Q. If we turn to Slide 59, please. Dr. MacMichael, I see you have a table here on DDX 8, Slide 59. Will you please identify the information that you're going to provide in these columns.

A. Yes. I'll go across the headers. The first column is the U.S. patent number. The second header is publication date. The third is issue date. The fourth is expiration date, and the fifth is summary of claims/disclosures.

Q. And, Dr. MacMichael, did you review and consider all of the patents and corresponding publications listed in this table?

A. Yes, I did.

Q. Let's go through these one by one, please. First, in Row 1, the '959 patent, did you review that patent?

A. Yes, I did.

Q. And did you form an opinion regarding -- excuse me.

Did you reach a conclusion as to when the information provided in the '959 patent was first published?

A. Yes, I did.

Q. And what was that publication date?

A. December 14th, 2000.

Q. And did you obtain that information from the document here, DTX 3619?

A. Yes.

Q. Did you review and consider that document?

A. Yes.

Q. And what was the summary of your review and analysis of the '959 patent disclosures?

A. Yes. The '959 was -- pertained to the isolation of the nucleic acids that actually coded for aflibercept. The expression vectors used helped to assist with that expression and met this for producing the VEGF Trap-Eye aflibercept.

Q. And based on your review and analysis of the '959 patent and its corresponding publication, would skilled persons have been aware of the isolated nucleic acids expression vectors and methods of producing VEGF Trap-Eye aflibercept as of December 14th, 2000?

A. Yes.

Q. Moving on to the next one, Dr. MacMichael, the '746 patent, did you review and analyze the '746 patent?

A. Yes, I did.

Q. And did you reach a conclusion as to when the information provided in the '746 patent was first published?

A. Yes, I did.

Q. And did you obtain that information from DTX 4229?

A. Yes.

Q. What was the publication date of the information provided in the '746 patent?

A. August 11th, 2005.

Q. Based on your review and analysis of the '746 patent and its corresponding publication, what disclosures would have been available to the skilled person as of August 11, 2005?

A. I'm sorry. Could you please repeat that. I didn't track.

Q. Sure.

Did you provide a summary of the disclosures from the '746 patent and its corresponding publication?

A. Yes.

Q. And what was the summary of the disclosures that you concluded?

A. That the patent was a method of treating retinal neovascularization.

Q. And did that method include the use and administration of aflibercept?

A. Yes, it did.

Q. So based on your review and analysis of the '746 patent and its corresponding publication, would a person of ordinary skill in the art have known as of August 11th, 2005, the method of treating retinal neovascularization with aflibercept?

A. Yes.

Q. And turning to the next row on the table in Slide 59, DDX 8, this is the '747 patent, Dr. MacMichael. Did you review and analyze the '747 patent?

A. Yes, I did.

Q. And did you form a conclusion as to when the information provided in the '747 patent was first published?

A. Yes, I did.

Q. What was that date?

A. February 9th, 2006.

Q. And did you obtain that information from DTX 8209?

A. Yes, I did.

Q. Did you review and analyze that document?

A. Yes, I did.

Q. And what summary did you reach with regard to the disclosures of the '747 patent that would have been available as of that publication?

A. It was a therapeutic method for treating an eye disorder.

Q. And did that therapeutic method for treating an eye

disorder disclosure include the use of aflibercept?

A. Yes, it did.

Q. Turning to the next row, the '799 patent, did you review the '799 patent?

A. Yes, I did.

Q. Did you reach a conclusion as to when the information disclosed in the '799 patent was first published?

A. Yes, I did.

Q. What was that date?

A. November 24th, 2005.

Q. Did you obtain that information from DTX 8208?

A. Yes.

Q. Did you review and analyze that document?

A. Yes, I did.

Q. And what summary did you reach regarding the disclosures of the '799 patent and its corresponding publication?

A. That it was a therapeutic method for treating an eye disorder, including with aflibercept.

Q. If we turn to the next row, the '757 patent, did you review and analyze the '757 patent?

A. Yes, I did.

Q. Did you reach a conclusion as to when the information available in the '757 patent was first published?

A. Yes, I did.

Q. What was that date?
A. July 28th, 2005.
Q. Did you obtain that information from DTX 8206?
A. Yes, I did.
Q. Did you review and analyze that document as well?
A. Yes, I did.
Q. And what conclusion did you reach regarding the disclosure that was available via the '757 patent and its corresponding publication as of July 28th, 2005?
A. Yes. The patent focuses on the VEGF Trap-Eye aflibercept molecule and the nucleotide amino acid sequences that produced the aflibercept product.
Q. Two more, Dr. MacMichael.
Looking at the second-to-last row, the '758 patent, did you review and analyze that patent?
A. Yes, I did.
Q. And did you reach a conclusion as to when the information available -- I'm sorry. Did you reach a conclusion as to when the information provided in the '758 patent was first published?
A. Yes.
Q. And what was that date?
A. November 3rd, 2005.
Q. And did you obtain that information from the documents cited here, DTX 8207?

A. Yes, I did.
Q. Did you review and analyze that document as well?
A. Yes, I did.
Q. And what conclusion did you reach regarding the scope of the disclosure of the '758 patent and its corresponding 2005 publication?
A. That it was a method for inhibiting VEGF activity in a mammal.
Q. Did that method of inhibiting VEGF activity in a mammal include a disclosure of the aflibercept molecule?
A. Yes, it did.
Q. Last one, last row, the '173 patent, Dr. MacMichael, did you review and analyze the '173 patent?
A. Yes, I did.
Q. And did you reach a conclusion as to when the information provided in the '173 patent was first published?
A. Yes, I did.
Q. What was that date?
A. April 10th, 2008.
Q. And what conclusion did you reach regarding the disclosures that were available to a skilled person as of April 10th, 2008, based on the '173 patent?
A. Yes. It was a patent focused on the composition comprising the VEGF Trap-Eye aflibercept molecule.
Q. Dr. MacMichael, one final point I wanted to ask, did

you have an opportunity to review the animations and other demonstratives that Dr. Trout presented to the Court during his direct examination?

A. Yes, I did.

Q. And have you provided your own version of those animations?

A. Yes, I did.

Q. Have you prepared a version of those animations?

A. Yes.

Q. Can you explain to the Court why you wanted to provide your own version of those animations.

A. Yes. Though Dr. Trout's animation was helpful, I thought it could be -- should be a little more realistic and show a little more detail with respect to the overall size of polysorbate with respect to the aflibercept molecule, and the fact that the polysorbate acting as a surface-active agent would have also coated the walls of the vial as well as the exposed portion of the stopper that faces the liquid.

Q. Here on the screen?

A. I'm sorry. I misstated that. It would also coat the stopper, but it would also protect inactivation at the air-water interface. And that was not shown in the diagram either.

Q. And I think we'll cover that in your version of the animation, Dr. MacMichael. Can you please identify for the

Court what we have on the screen here.

A. Yes. What we have on the screen is this is an illustration of a vial containing aflibercept and polysorbate 80.

Q. Is this Dr. Trout's version?

THE COURT: 20, Doctor? Polysorbate 20.

THE WITNESS: I'm sorry. Polysorbate 20. My apologies.

THE COURT: Okay. Just making sure. Thank you.

BY MR. SALMEN:

Q. And if we proceed through this -- turn to the next slide -- what do we have here?

A. Yes. We have illustrated the representations of a polysorbate 20 molecule and an aflibercept molecule.

Q. Is the polysorbate 20 -- again, this is Dr. Trout's characterization of the polysorbate 20 in the aflibercept?

A. Yes. And what Dr. Trout did was he showed where the hydrophobic patches would be shown on the molecule itself are highlighted in red as well as the hydrophobic tail of the polysorbate is highlighted in red.

Q. And how did you want to modify this presentation that Dr. Trout gave to the Court?

A. Just to show a little more realistic representation of the size of the molecules and some of the additional functionality of the surface-active agent of polysorbate 20.

Q. And here on DDX 10, Slide Number 3, is this a replication of one of Dr. Trout's slides, PDX 5004?

A. Yes, it is.

Q. Is this where you obtained the proportionality between the polysorbate 20 and the aflibercept?

A. Yes, it is.

Q. And if we carry on to the next slide here, DDX 10-4, can you please explain to the Court how you modified Dr. Trout's explanation?

A. Yes. We replaced the original illustrations with the previous -- the one from the previous slide which actually show the molecular spinal structure of aflibercept.

Q. And we also have the molecular structure of polysorbate here?

A. As well as polysorbate 20.

Q. And then how did we modify the animation in the box?

A. We basically replaced the illustrations of the aflibercept and the polysorbate with the more representative and more realistic size ratio using the electron cloud structures of the aflibercept and polysorbate 20.

Q. Dr. MacMichael, did you review Dr. Trout's testimony regarding these presentations?

A. Yes, I did.

Q. And what clarification did you want to make with regard to the animated portion of Dr. Trout's presentation?

A. Well, there's two things. One is these -- in chemistry there can be chemical bonds that are called covalent bonds, and it takes energy to break them. What we have here is not a covalent interaction. It's called a hydrophobic interaction. So the light likes to dissolve light. So the hydrophobic portions of the molecule of the polysorbate are being attracted to the hydrophobic portions of the aflibercept.

Q. Okay.

If we run the animation here, Mr. Gibson.

Can you explain to the Court what you've illustrated here, Dr. MacMichael.

A. Yes. What we're showing is, though the aflibercept binds hydrophobically to the hydrophobic patches -- I'm sorry -- the polysorbate 20 binds to the hydrophobic patches of the aflibercept, it can disassociate from those -- and then reassociate to those hydrophobic patches of the aflibercept.

Q. Would you describe this as a static or a dynamic environment?

A. It's dynamic.

Q. If we turn to the next slide here, were there any additional clarifications that you wanted to make?

A. Yeah. I wanted to show that, in fact, the polysorbate 20 puts a layer on the surface of the vial as well as the surface of the stopper and at the surface area interface.

Q. And if we could run the animation here, Dr. MacMichael, would you please explain to the Court.

A. Yes. What we're seeing here is that, by polysorbate adhering to the walls of the vessel and at the air interface, the hydrophobic portions of the polysorbate are interacting with the surface of the vial and the hydrophilic -- or loves water is what hydrophilic means -- is facing out into the aqueous environment.

But the polysorbate is coating the walls of the vessel and the stopper, preventing the aflibercept from adhering to the wall. Though it's not absolute, some aflibercept may -- the polysorbate can disassociate from the wall and reassociate to the wall -- I'm sorry -- the polysorbate can disassociate from the wall and reassociate to the wall.

Q. And this is on Slide 15 and 16 of DDX 10.

Dr. MacMichael, any last clarifications to the animations here?

A. Just that you also can see that it's protecting the aflibercept from denaturation by putting a layer of polysorbate at the air-liquid interface.

MR. SALMEN: Thank you, Dr. MacMichael.

Your Honor, at this time I pass the witness.

THE COURT: Understood.

Cross. Go right ahead, Counsel.

CROSS-EXAMINATION

BY MR. BERL:

Q. Good afternoon, Dr. MacMichael.

A. Good afternoon, Mr. Berl.

Q. First of all, I hope you're having a speedy recovery from your surgery.

A. Yes. Thank you.

Q. Doctor, you're not Mylan-Biocon's only formulation expert on the '865 patent in this case, are you?

A. No.

Q. Dr. Rabinow also testified, correct?

A. Yes.

Q. And you've read Dr. Rabinow's expert report in this case?

A. Yes.

Q. There's a section of your report entitled "State of the Art," right?

A. Yes.

Q. And in that section you undertake an analysis of scores of references, correct?

A. Correct.

Q. Including some of the references you discussed today, right?

A. I'd have to -- yes.

Q. Now, Doctor, if we go to the first slide, there's a

section of Dr. Rabinow's report that's also about the state of the art, right?

A. Yes.

Q. And if we look here on the screen, page 12 of your report is identical, virtually word for word, to page 19 of Dr. Rabinow's report, right?

A. I would have to read through them and do a comparative analysis; but for sake of time, I'll assume you're making an accurate statement.

Q. Let's go to the next page. Page 13 of your report is identical, word for word, with page 20 of Dr. Rabinow's report, right?

A. I would have to read through them; but for today, I'll assume that you're correct.

Q. Looks like it, right?

A. There seem to be similarities as I'm taking a very quick look at it.

Q. And page 21 of Dr. Rabinow's report, if we go to the next, is essentially identical to page 14 of your report, right?

A. Again, I would have to read through it. High level, just taking a quick look, there seems to be similarity.

Q. And, Doctor, the entire section, page after page after page after page of your report, is identical word for word with Dr. Rabinow's report, right?

THE COURT: One second, Doctor.

Yes, Counsel?

MR. SALMEN: Object to that question, Your Honor. He's already stated he would need to do a comparison of this. That's quite a generalization to present to the doctor at this time.

THE COURT: Why don't we go one at a time, Mr. Berl, given that limitation. I mean, I don't have all the reports. I've made that abundantly clear, but I understand the point thus far. But I'm going to sustain the objection.

Ask your next question, sir.

BY MR. BERL:

Q. Doctor, are you aware of any differences of any words of that long substantive section of your report compared to Dr. Rabinow's?

MR. SALMEN: Same objection, Your Honor.

THE COURT: Overruled.

THE WITNESS: I would have to read through both documents and do a comparative analysis.

BY MR. BERL:

Q. You don't deny, Dr. MacMichael, that there are other substantive sections of your report that are identical to the sections of Dr. Rabinow's report, right?

A. I would have to look at both reports and look at the various sections. You just asked me I don't deny that they're

identical. I would have to look at both reports.

Q. You read his report, right, Dr. MacMichael?

A. Yes.

Q. And you have no basis to tell me right now that there are -- or to deny that there are large sections of the report -- multiple sections of your report that are identical to Dr. Rabinow's report, right?

A. I would have to read both reports and do a cross -- a cross comparison of the two reports.

Q. Doctor, the first draft of your expert reports was generated by the lawyers at RMMS, right?

A. No, it wasn't.

Q. The first draft of your expert report was not generated by RMMS?

A. RMMS, using my opinions and my information, helped write the report.

Q. Okay. So my question is really simple.

The first draft of your expert report was generated by RMMS, correct?

A. They took my opinions and put them into the report.

Q. The final report was written by the RMMS attorneys too, right?

A. With my opinions and input.

Q. But they wrote it, right?

A. If you mean wrote it by actually typing it up into

the document, then the answer would be yes.

Q. The actual writing of your reports was performed by an RMMS attorney actually writing the report, right?

A. With strong input from myself.

Q. Well, Doctor, all of the materials considered in preparing your reports were provided for you by the lawyers at RMMS, correct?

A. All the citations that are in these various documents that were cited were also provided in our reading room.

Q. In fact, Doctor, at your deposition you weren't able to point to a single section, paragraph, or even sentence of your expert reports that you yourself wrote. Isn't that true?

A. During my deposition I can't recall that conversation occurring.

Q. Do you deny that at your deposition you were unable to point to a single section, paragraph, or even sentence of your expert reports that you wrote?

A. I'll repeat it. That conversation, I don't recall. So I can't deny it.

Q. Let's take a look at your deposition, Doctor, on page 21. You recall that I deposed you just a few months ago, right?

A. Yes.

Q. In Chicago. It was already spring and warm, right?

A. It was Easter.

Q. Okay.

THE COURT: Doctor, if I could ask you -- I know you're relying on that screen there, but if you wouldn't mind adjusting that mic just to make sure everyone can hear you, in particular Madam Court Reporter.

Thank you so much, sir.

I'm sorry, Mr. Berl. I think we were discussing the weather in Chicago.

MR. BERL: Yes.

BY MR. BERL:

Q. We had a nice day inside while the sun was shining in Chicago; is that right?

A. We had a day inside.

Q. I enjoyed a day inside.

THE COURT: It sounds like a lovely day. Let's get to the substance of the matter.

MR. BERL: The court reporter did not enjoy it.

BY MR. BERL:

Q. Doctor, you were under oath through that day, correct?

A. Yes, I was.

Q. And you were testifying truthfully that day?

A. Yes, I was.

Q. And let's put up page 21 of your deposition starting on line 10 to page -- to line 16.

Doctor, I asked you, "Can you point to any section, paragraph, even sentence of your report and say that's my writing? I wrote those words?"

"A No. But if given time, I'll walk through here and show you the sections that are in here that were my concepts that were then put down by the RMMS attorneys into the document."

Did I ask you that question, and did you give that answer, Doctor?

THE COURT: One second, Doctor.

Yes, Counsel?

Will you repeat that, Mr. Berl.

BY MR. BERL:

Q. Did I ask you that question and did you provide that answer?

A. Well, if this is the written deposition, then I'm going to have to say yes.

MR. SALMEN: I would just object to that as improper impeachment. He stated in response to the first answer that he didn't recall.

THE COURT: Understood. Overruled.

Mr. Berl.

MR. BERL: I'm moving to infringement now. I don't think I'm going to get in for a while into the -- what's been considered by Mylan to be highly confidential material. But I

don't know what the witness is going to say in response to my questions; so I'm not sure what to do. I'm fine proceeding open. But if they want to close it, I have no objection.

THE COURT: Fair enough. But given the interest of a free flow of exchange on cross, it seems that if -- we should seal the courtroom out of abundance of caution unless Mylan has an objection to that.

MR. SALMEN: No objection. That would be our preference, Your Honor.

THE COURT: Understood.

Ladies and gentlemen, those of you who have been kind enough to come and go, if I could ask you to go once again given that we may get into some of the subject matter subject to this Court's protective order. So if you're not permitted to be here pursuant to that order, if I could ask you to step out. Thank you all so very much.

I'll ask court security to seal our courtroom again. Thank you.

(The following proceedings (1451/19 to 1480/8) were had under seal, and are filed under separate cover.)

(Record unsealed.)

THE COURT: Apologies. With my 7-year-old here, there was a line to my private restroom; so it took me longer to get here than I expected.

Mr. Berl, go right ahead.

BY MR. BERL:

Q. Doctor, I would like to discuss the effect of the word "comprising" in the claims which you addressed on direct, right?

A. Yes, I did.

Q. You're not a legal expert on the effect of the word "comprising," correct?

A. No, but I'm getting a lot smarter. You guys are advising me on this stuff.

Q. Someone is.

Doctor, in your view, because of the use of the word "comprising," there are a litany of compounds that could be added to the formulation, right?

A. That's the way I understand it.

Q. For example, you could add hydrochloric acid which would denature the protein?

A. Well, if you look at the claims, there's broad categories that are being proposed and examples given for comprised. There was no example of adding an acid to it.

Q. But your view is, as an example, you could add hydrochloric acid in these claims and denature the protein, right?

A. If you're adjusting the pH, you could, yeah.

Q. Okay. And in your view, the patent doesn't exclude those kinds of inoperative embodiments, right?

A. Well, when you use the word "comprise," which then opens -- very broadly opens up multiple potential compounds that can be used, without experimentation, you could wind up with a formulation that would be detrimental to the protein.

Q. Right. And you think the patent is not enabled because it doesn't exclude those kinds of embodiments that will work, right?

A. What I'm saying is that the claims using the term "comprised" -- and they give examples, four, five, six examples in each of the comprises -- that there's an inordinate number of potential possible formulations. It would require experimentation to determine the ideal formulation.

Q. Okay. Doctor, your enablement analysis is premised on the scope or breadth of the claims as shown in Slide 44 that

you showed, right?

A. I'm sorry.

Yes.

Q. And your Slide 44 suggests that the claims that are asserted like Claim 4 are no narrower than Claim 1, right?

A. That's what we're graphically trying to show.

Q. Okay. But Claim 1 doesn't require 40 mg/mL of aflibercept and Claim 4 does, right?

A. Claim 1 -- I'm sorry. Yeah. Claim 2 is dependent on Claim 1, but -- yeah, you're right.

Q. And, likewise, Claim 1 doesn't require .03 to .1 percent polysorbate but Claim 4 does, right?

A. Yeah, I don't have Claim 1 memorized and it's not on this graphic; so I don't want to answer from memory.

Q. Okay. But you understand that Claim 2 adds the comprises polysorbate limitation, right?

A. Yes. But, again, I'd have to see the entirety, and we're missing Claim 1. I apologize.

Q. Doctor, you know that Dr. Rabinow testified on Friday, right?

A. That's what I was told, yes.

Q. And let's take a look at some of what he said if we go to page 1164 of the transcript.

He was asked, "As of 2006, in your opinion, optimizing the stability of a protein formulation was routine

for the POSA?"

And he answered, "Yes."

Do you see that?

A. It's routine. Yes, I see it.

Q. Do you agree with Dr. Rabinow?

A. Routine in the fact that an organization -- a biotechnology company or a biopharmaceutical company engaged in developing multiple proteins would have a routine for how they screen those products.

Q. So do you agree or do you not with Dr. Rabinow, Doctor?

A. In general.

Q. In general yes?

A. Yes.

Q. And let's take a look at the next thing he said on page 1168.

He was asked, "And it wouldn't require undue experimentation to make formulations falling within the scope of the asserted claims, right?"

And he answered, "Correct."

Do you agree with him?

A. "Undue" is a relative term. It would take a significant amount of experimentation looking at all the possible variables that are proposed in the claims to come up with a formulation that is satisfactory; so I would say

significant experimentation.

Q. Do you agree with Dr. Rabinow or do you disagree?

A. I'm saying it requires significant experimentation. So undue experimentation, meaning that it's impossible? No. But significant experimentation. So I guess with that nuance, I'll agree with Dr. Rabinow.

Q. Okay. Well, I want to make sure I understand your opinion.

You don't have an opinion in this case that making the formulations to practice the claims that are asserted of the '865 patent would be undue experimentation, right?

A. What I've said all along is it would take a significant amount of experimentation.

Q. So you don't have an opinion -- you're not telling the Court as an expert that it would require undue experimentation, right?

A. Well, like I said, "undue" is a relative term. My term "significant" really means a significant amount of work.

Q. I have a single question, Doctor. It's a yes or no.

Are you telling the Court that practicing claim -- the claims that are asserted in the '865 patent would require undue experimentation, or are you not telling the Court that?

A. It would require undue experimentation. It would require a significant amount of experimentation. That's my testimony.

Q. That's as far as you'll go, right?

A. Well, undue means an inordinate number of experiments. But every organization that works in therapeutic proteins has staff and equipment on board with the proper resources to do that significant amount of work to develop the formulations. So undue would mean something that is beyond the realm of being able to be achieved.

Q. In your view, undue experimentation is a very amorphous term, right?

A. It's left open to interpretation.

Q. Undue experimentation, as you've applied the phrase in this case, depends on whether you're a big company or a small company?

A. That's not what I said.

Q. Okay. Let's take a look at your deposition, page 233, line 1. We'll go to line 11.

"Q Right. And why the experimentation to fill in any gaps between the examples would not be undue experimentation, that burden was on Regeneron to show that?

"A Undue experimentation depends -- is a very amorphous term. If I'm a little company, undue; and if I'm a big company, it might not be a big deal to run an inordinate number of experiments. So the word "undue," let's take

that out of it. Additional experiments."

Was that my question and was that your answer, Doctor?

A. Yes. And I believe that you're citing this on this slide. I believe that it agrees with the statement I just made.

Q. Okay. Now, Doctor, you understand that the Court here may have to decide whether the experimentation to practice the claims is routine experimentation or undue experimentation, right?

A. Yes. So what we're saying is that the patent fails to give sufficient information on how to make the formulation; so the patent in itself is indefinite. You have to go out and do experiments to determine which of these various comprises, various stabilizing agents, et cetera, would be acceptable in a final formulation.

So as we've been saying for the last two or three minutes, undue versus significant, these are relative terms. It would take work.

Q. Okay. So it would take work, but you're not taking a position on the question of whether that work would be undue or routine, right?

A. The term "undue" is being -- you know, the term "undue" means if the patent had been properly constructed and gave information to the reader of how to actually develop the

cited product in the patent, then it wouldn't require significant experimentation. But the patent fails to do that. And, therefore, significant experimentation would be required.

Q. Okay. Let me -- I'll give you one more chance to answer the question, and then I'm going to move on.

If the Court has to decide between routine experimentation and undue experimentation, you're not putting your finger on the scale of undue experimentation, right? You're not giving an opinion?

A. I'm saying -- you can use the word "undue," but I'm -- it's undue because the patent wasn't properly constructed. But a significant amount of work would have to be done to do that work.

Q. Now, Doctor, your opinion is that "protein formulations are routinely optimized to improve stability of their active ingredients"?

A. Protein -- can you show me that quote.

Q. Sure. I'll read it again.

"Protein formulations are routinely optimized to improve stability of their active ingredients."

A. Is that from one of my depositions or one article I wrote?

Q. I'm asking whether you agree with that statement, Doctor.

A. Could you repeat it one more time.

Q. Sure.

"Protein formulations are routinely optimized to improve stability of their active ingredients."

A. Yes.

Q. Okay. Now, you and Dr. Rabinow both relied on the Kaisheva reference; isn't that right?

A. Yes. I read the Rabinow testimony, but I can't pull out off the top of my head if he, in fact, looked at that document.

Q. Okay. Let's take a look at what Dr. Rabinow said about it. And that's on page 1020 of the transcript from last week.

And he says, "Kaisheva provides a recipe for how you go about developing protein formulations in terms of a three-step process."

Is that right?

A. That's what it says.

Q. And you said essentially the same thing in your expert report if we pull up paragraph 63 of your first expert report. And you cite Kaisheva at the end of that paragraph.

Do you see that?

A. Yes.

Q. And it says, "The optimization process further involves combining a therapeutic protein with excipients and then varying the concentrations of the excipients. The

formulation development approach is as follows: Selecting the optimum solution pH, selecting buffer type and concentration, evaluating the effect of various excipients of the liquid and lyophilized stability, and optimizing the concentration of the screened excipients."

That's your opinion, correct?

A. Yes. If I had a new protein coming over from discovery that had not been properly formulated and we were needing to get into animal studies and clinical trials, it would require a series of activities to get that into a successful formulation.

Q. But if you know the optimum pH, then you can take that linear approach to select a buffer type and concentration, then various other excipients, then optimize the concentration, right?

A. And what -- these two sentences in this paragraph are talking about is a significant amount of work. Now, that work may be routine, meaning the formulation organization does that work on a repeated basis, thus the term "routine." Let's not take away the fact that it's a significant amount of work.

Q. Okay. In this case, Doctor, the patent already discloses the optimum pH for aflibercept, 6.2 to 6.3, right?

A. So that's one point of the overall formulation. We have the pH.

Q. You agree with me, right?

A. I'd have to go back to the patent, but I do recall that one of the formulations was at pH 6.2. But I don't want to make a sweeping statement.

Q. Now, that information, as far as you know, was not known before the '865 patent, correct?

A. The optimum -- the pI of aflibercept.

Q. The optimum pH formulations for aflibercept for ophthalmologic administration, right?

A. I'd have to look at the sequence, go back and look at the literature, but the pI, where the protein's neutral, meaning it has the same positive and negative charge and there it's neutral, that pI dictate what pH you want to hold it at. And if I was to go back and search the literature, you're asking me was there any previous art that showed aflibercept had a pI that was acceptable at pH 6.2. I just don't have that information in front of me.

Q. Okay. Doctor, in choosing excipients in that process that we've just described from Kaisheva, the POSA would narrow down choices on the basis of their knowledge from the literature, right?

A. If they had a new novel protein coming in, this is how they would approach it. But if they had a protein that had a patent on it, one would expect that there would be more guidance in that patent on how to actually do it without having to go back and de novo do additional experiments to get to that

final point.

Q. Okay. Doctor, you can't imagine a scenario where someone would be working on products for helping with diseases of the eye without referring to the previous literature, right?

A. I've never met a scientist that's developing something that doesn't look at the previous literature.

Q. That would actually be irresponsible not to look at the previous literature, including the prior products that have been approved, right?

A. Well, yeah. I think the hypothetical, if one of my formulation people came to me and said, hey, I didn't look at anything; I'm just going to go ahead and start formulating, I'd be a little uncomfortable with that answer. Well, have you looked at other similar molecules and gotten some guidance on what may be successful?

Q. And included within that literature that the POSA would consult is information about what excipients have been used in intravitreal products, right?

A. Yes.

Q. But in conducting your analysis in this case, you didn't look at all the intravitreal products that FDA had approved and look at all the formulations, right?

A. I looked at a majority of them. I can't recall if I looked at every approved intravitreal eye formulation. I cannot tell you that I have.

Q. Doctor, in fact, other than Lucentis, you couldn't identify any FDA-approved formulation that you looked at in connection with your expert reports in this case, right?

A. I looked at Regeneron's product Eylea. I looked at Lucentis.

Q. That's it, right?

A. Those were two that I looked at, yes.

Q. And neither one of those was approved as of the priority date in the middle of 2006, right?

A. I'd have to go back and look at the approval dates, et cetera.

Q. Doctor, the POSA engaging in experimentation to practice the claim would not make formulations at random, right?

A. Any good formulation scientist would be a POSA, according to either Dr. Trout's or my definition, would have -- you know, in either of our definitions, such a POSA that would be working in your formulation group would at least have some sense of what excipients to use.

I believe that was your question.

Q. And they wouldn't make formulations at random, right?

A. They would do it in a logical manner.

Q. And if you've worked in proteins, you'll have a good understanding of what excipients have been used successfully and what buffers have been used successfully, right?

A. Yes. Yes.

Q. Doctor, in the patent, the '865 patent, there are no new classes of excipients, right?

A. Everything in that patent is -- all the compounds cited in the patent are known molecules. There's no novel new molecule being introduced.

Is that your question? I'm not sure.

Q. Yeah, they're pretty much all household names in excipients and stabilizers, right?

A. Yes, they are.

Q. Now, I'd like to talk about choosing a buffer, which you address.

Another consideration for formulating to avoid aggregation is the choice of a buffer to keep the formulation within the narrow pH range to keep your formulation stable, right?

A. Ideally you want to keep it in a narrow pH range. If you go too basic or too acidic, you can get undesirable changes in the charge of the molecule and undesirable interactions.

Q. And various buffers are available to adjust the pH of protein formulations?

A. There's multiple compounds out there that can be used as a buffering agent.

Q. And, typically, you pick a range for a buffer that's applicable to the pH you're trying to achieve?

A. Yes. What you look at, again, is what they call the pI. That's where the neutral pH of a protein is. Where is it neutral? And from that, you pick a candidate buffer that would then be where the pI of that protein would fall within the range of that buffer.

Q. And the POSA reading the claims and the specification would have considered four buffers as suitable for formulations of the asserted claims: succinate, citrate, phosphate, and histidine. Right?

A. There's other buffers out there that could have been considered.

Q. But those are the ones that the person of skill reading the patent would want to use, correct?

A. You can pull up the claims so I can read it because it comprised those, but I believe it was open-ended.

Q. My question is those are the four buffers that the POSA practicing the claim would want to use, correct?

A. Those were examples that were given by the author. They are buffers that could potentially be used.

Q. Those are the ones that the POSA would want to use, correct?

A. Those are four examples that were used by the authors to give examples of the other potential buffers that could be used. The word "comprised" means that many other buffers could be considered as well.

Q. To choose a buffer, you would look at the prior art for which buffers were used successfully in previous products for injection into the eye, right?

A. That would be a useful guidepost.

Q. And that can narrow down the overall number of candidates you need to screen?

A. It can if you say such and such buffer was used in an approved product by the FDA; therefore, there's precedent for that buffer being previously used in an intravitreal application.

Q. But you never undertook that analysis to look at prior products, correct?

A. I didn't look at all the prior products.

Q. And with respect to a stabilizing agent, Doctor, considerations for formulating a protein to avoid aggregation typically include a choice of a stabilizing agent, right?

A. Yeah, if you're reading off of a document, it would be very helpful if you could share it up on the screen. Is that possible?

Q. Doctor, I'm asking you a question whether you agree or not. Considerations for formulating a protein to avoid aggregation typically include a choice of a stabilizing agent, right?

A. Is that a quote from my deposition?

Q. I just want an answer to my question, Doctor.

A. Say it again, please.

Q. Yes.

Considerations for formulating a protein to avoid aggregation typically include a choice of a stabilizing agent, right?

A. It can require a stabilizing agent. Depending on whether it's a liquid or a lyophilized formulation, you may use certain sugars that you might not use in a liquid formulation.

Q. The patent says the stabilizing agent may be sucrose, sorbitol, glycerol, trehalose, or mannitol, right?

A. That's not what it says. It says "comprises," and it gives examples of those sugars.

Q. Doctor, those are the examples of sugars -- or of stabilizing agents provided in the patent, right?

A. Those were examples that were provided in the patent under the word "comprises," meaning that any other sugar could be considered as well as a stabilizing agent.

Q. Doctor, all five of those options were well-known stabilizing agents?

A. They were known to be stabilizing agents.

Q. If one was developing a formulation, one would screen those stabilizing agents and see which one gave the overall satisfactory performance, right?

A. If those were the five I wanted to look at, I would screen those five.

Q. Now, you also reference in your slides -- so I don't think you actually talked about it today -- something called formulation design systems, right?

A. Are you talking about factorial design?

Q. A formulation design system. You know, something called DOE or --

A. Design of -- yes, there's a book out there that I wrote for cell gene therapy called *Aging* that describes the use and the design of experiments.

Q. Through the design of experiments, or DOE, the whole purpose is to minimize the amount of testing you have to do, right?

A. Yes. Because if we were to run the hypothetical amount of experiments that would have to be ran if you were to make each individual formulation, it would be an inordinate number.

Q. You yourself have either done or supervised design of experiments going all the way back to 1990, right?

A. Yes.

Q. And the bottom line for design of experiments is you look at multiple variables, like what excipients and what buffers, and using various software out there, you can actually achieve a screening of what is successful and not successful, correct?

A. Yes. If I could explain to the Court what a design

of experiment is and how it's used, it might be helpful.

THE COURT: Go ahead, doctor.

THE WITNESS: Yes. A design of experiment you have, Your Honor, have you in a numerous number of variables. And in a traditional manner, you would only -- you would hold everything constant but one variable and then change that variable to see how it influences the outcome.

In a design of experiment, you can change multiple variables, two or three, and then look at the results. And there's software out there. There's one very popular one called JNT, J-N-T, that lets you look at the results. And, therefore, you can then sift through more results quicker and have more variables in play rather than looking at one at a time.

I believe, Mr. Berl, that's what you're referring to.

BY MR. BERL:

Q. Yes, it is. Thank you for the explanation, Dr. MacMichael.

DOE is an intelligent technique to use to minimize the amount of screening that's necessary?

A. Yes. It reduces -- it doesn't reduce the number of candidates; it reduces the amount of work.

Q. It will exclude things that don't work?

A. Yes. The results will show which variables are not getting you to the desired outcome.

Q. And so using design of experiments, you wouldn't have to make every formulation, right?

A. That's correct.

Q. And anybody in the street knows that DOE is what everybody does?

A. Everybody on the street -- I don't know about everybody; but yes, scientists would know that a DOE can be used to effectively reduce the number of variables that have to be looked at in an actual physical wet chemistry lab.

Q. The POSA would conduct the design of experiments, right?

A. The POSA could do a design of experiment.

Q. And, Doctor, you couldn't tell me at your deposition how many formulations the POSA would have to make to practice the claim using design of experiments, correct?

A. Yeah, because you -- and I couldn't answer that today. I'd have to sit down, design the experiments, and look at the number of components -- both the stabilizing agent, the surfactants, et cetera -- and design that and look at which variables I wanted to look at and how I wanted to vary those variables.

Q. All you could say at your deposition was that with design of experiments, the POSA would have to conduct multiple experiments. You couldn't give any more specificity than that, right?

A. And I just gave a little more specificity, yes.

Q. Not much, right? You don't have a number for me, do you, in terms of how many experiments the POSA would have to conduct?

THE COURT: One second, Doctor.

Yes, Counsel?

MR. SALMEN: Objection, Your Honor. He answered the question, and it was consistent with his testimony at his deposition.

THE COURT: Overruled.

Ask your question again, Mr. Berl.

BY MR. BERL:

Q. You don't have a number for me or for the Court today about how many experiments a POSA would have to conduct to practice the claims using a design of experiments, do you?

A. It's a large number. If I took six to seven stabilizers and I took three to five surfactants, et cetera, and I moved that down and multiplied it through, very quickly you get to a very large number.

Q. With design of experiments you don't have a number of how many experiments the POSA would have to conduct to practice the claims, do you?

A. Well, I just explained to you, you're asking me to, off the top of my head, tell you I was going to design a complex experiment with five to six variables with multiple

candidates in each variable and that you would have to sit down and intelligently design that experiment to determine which variables you wanted to change in each experiment.

Q. You haven't undertaken that analysis in this case, right?

A. We've looked at some hypotheticals. I was just going to say, hypothetically, you would come to a very large number.

Q. But with design of experiments, the number is smaller, and you have not provided a number about how many experiments the POSA would have to conduct with design of experiments, correct?

A. As I've explained three times -- I'll explain again -- I would have to sit down and look -- remember, they say comprised; so it isn't just glucose, sucrose, and mannitol; it could be glucose, sucrose, mannitol, galactose, et cetera, because it says "comprises." So the question is how broad am I going on all the various claims that use the term "comprised"? I could -- not just the examples given. Those are just examples. I could wind up with an inordinate number.

Q. Doctor, you didn't consider any studies Regeneron did other than those described in the '865 patent, right?

A. I did not have access to all the experiments that Regeneron did.

Q. You never asked your counsel whether there was SEC data for formulations that met requirements of the claim that

you didn't have already in the patent, right?

A. I don't recall.

Q. Doctor, you did look instead, when you talked today, about various statements and file histories, correct?

A. Various statements and file histories?

Q. Do you remember you presented that earlier today?

A. Yes.

Q. Okay. Let's look at your Slide 47. You relied there on a statement from --

THE COURT: One second, Mr. Berl.

Go ahead.

BY MR. BERL:

Q. You relied here, Doctor, in DTX 5053 on a statement from a different file history, not the file history of the '865 patent, right?

A. These are two documents that were cited on the -- looking at the *Wands* factors and looking on whether or not it would take undue experimentation. And there's two citations here.

Q. My question is, Doctor, that first citation, 5053, is from the prosecution history of a different patent, not the '865 patent, right?

A. I'll take your word for it.

Q. Okay. It's not even in the same family as the '865 patent, right?

A. I don't understand where you're heading with the question. I'd love to answer it, but I'm not quite sure what you're looking for.

Q. Okay. Doctor, you showed a statement on the screen here that one of ordinary skill upon reading Remington's would expect to engage -- would expect to engage in significant nonroutine experimentation to develop a successful formulation as claimed herein.

Is that what you showed?

A. That's what I showed.

Q. Now, Remington's is not the '865 patent, right?

A. No, it's not the '865 patent.

Q. Remington's does not disclose ophthalmologic formulations of aflibercept, right?

A. I can't recall all the content of the Remington article.

Q. As far as you know, Remington's does not disclose the optimal pH range for ophthalmologic formulations of aflibercept, right?

A. Off the top of my head, I can't recall that that document cites that, no.

Q. Now, Doctor, you also cite in the second part of this slide a statement from DTX 4430 that formulations of pharmaceutical preparations and achieving a stable composition is not a simple or routine matter. Is that right?

A. That's what it says.

Q. And you cited that from paragraph 10 of 4430, right?

A. 4430, page 003. I'm not sure -- it's enumerated 10, yes.

Q. Okay.

Can we pull up the entirety of paragraph 10 rather than the expurgated version that was presented by Dr. MacMichael.

Do you see -- you showed the Court the first sentence of paragraph 10; is that right?

A. I showed the first sentence of that paragraph.

Q. And in the last sentence it says, "I am familiar with these literature articles, all in peer-review journals, which indicate that arriving at a stable formulation is not a straightforward matter, and it is not, for instance, possible to apply a formulation for one drug to another."

Do you see that?

A. Yes.

Q. And in practicing the '865 patent, the POSA wouldn't have to go from one drug in the specification to another in the claims. It's aflibercept in the specification and aflibercept in the claims, right?

A. Yes. But I'm not quite sure what the question is.

Q. Okay. You answered it.

Doctor, you understand that Mylan conducted research

in connection with its 40 mg/mL aflibercept formulation, right?

A. Yes.

Q. And you never investigated how much research was required for Mylan with the '865 patent in hand to make formulations within the scope of the claim, right?

A. I read through their formulation development history report. It was a significant amount of work that was required.

Q. Well, you never had any conversation with Mylan personnel about the research, correct?

A. I did not interact with Mylan personnel.

Q. You never had conversations with the RMMS attorneys about Mylan's research, correct?

A. No. We reviewed the development and history report together and went through the content and discussed the meanings of the results.

Q. Well, you never asked the attorneys to show you the experimentation performed by Mylan, did you?

THE COURT: One second.

Yes, Counsel?

MR. SALMEN: I would object that this is getting into attorney work product. I mean, I don't understand the basis for this question.

THE COURT: I think --

MR. SALMEN: What information he's asking of his attorneys.

THE COURT: Understood.

Mr. Berl?

MR. BERL: First of all, it's not privileged. But second of all, if it were, it's waived because this is right from his deposition.

THE COURT: Yeah, I don't believe there is any privilege. He's already testified about it here today, and we've heard from the deposition. I believe it's relevant, as it probes the bases for the doctor's opinions in this case.

Objection overruled.

BY MR. BERL:

Q. Doctor, you never asked the attorneys to show you the experimentation performed by Mylan, correct?

A. I was given the Mylan development history report; I didn't have to ask for it. And I read through it, and we had extensive discussions with the attorneys on the content and how the results could be interpreted.

Q. Doctor, you assumed that the Mylan attorneys would have access to additional information that you didn't have, right?

A. My assumption is yes, they have additional information I'm not privy to.

Q. And you believe that the Mylan -- that the research Mylan conducted to obtain its proposed aflibercept formulation was relevant to the analysis you were conducting in this case,

right?

A. It had some relevancy to it, yes.

Q. And you agree that it would be useful?

A. The data would be useful.

Q. And in retrospect, it would have been beneficial to look at that, right?

A. I'm sorry. I did look at it. I don't understand what you're saying. I did look at it.

Q. Okay.

Let's take a look at the doctor's deposition again. And let's take a look at page 335. Let's start at line 6, go to line 14.

"Q Yeah, the research that Mylan conducted to obtain its proposed aflibercept formulation of 40 mg/mL, did you think that was relevant to the analysis you were conducting in this case or not relevant?

"A It has relevancy. It would be useful.

"Q It would be --

"A In retrospect, would it be beneficial to take a look at that? Sure."

Were those my questions and were those your answers, Doctor?

A. They look familiar, yes, they do, Mr. Berl.

Q. If you could go back in time and ask Mylan's

attorneys whether they had additional information about Mylan's research that led to their proposed aflibercept formulation, maybe you would do that, right?

A. I have done that, and I have read through the development history report multiple times and discussed it at length with the RMMS attorneys.

Q. Doctor, turning to a separate topic, you didn't identify today any particular formulation that would require undue experimentation to make, correct?

A. As opposed to what? With respect to aflibercept or any hypothetical protein or --

Q. Within the claims. You didn't identify a formulation that has the ingredients of the claim that would require undue experimentation to make, did you?

A. All of those examples are examples. So what we have is maybe 12 recipes making a cake, but you're not telling me how to go about making that cake.

Q. Okay. I have a simple question, Doctor.

Did you identify -- because I didn't hear it, but tell me if I missed it.

Did you identify any particular formulation that has the ingredients required by the claims that, in your view, would require undue experimentation to make?

A. If you're asking me just to make that formulation? Is that the question?

Q. Yes, Doctor.
A. Well, how -- making it and how -- ensuring its stability takes experimentation. I'm not following you.
Q. Okay. Doctor, Claim 1 requires a buffer, correct?
A. Claim 1 requires a buffer.
Is it possible to put the claims up on the screen?
Q. Sure. Let me put up the claim that has 1, 2, and 4 together.
There you go, Doctor.
A. Yes. Thank you.
Q. Claim 1 requires a buffer, correct?
A. Yes.
Q. And buffers refer to a known set of structures, right?
A. There's various types of buffers out there, and there's various categories of buffers. There's not one specific category of buffers.
Q. Let me try it again.
Buffers refers to a known set of structures, right, Doctor?
A. No. There's multiple -- there's various types of molecules out there that can function as buffers.
Q. Okay. Let's go to the doctor's deposition again at page 428, line 20. Go into 429, line 3.
Doctor, I asked you:

"Q And I think we've talked about these before, but that was a known set of structures, buffers, right?

"A Uh-huh.

"Q Yes?

"A Yes."

Were those my questions and were those your answers, Doctor?

A. Yes, they were.

Q. Okay. And Claim 1 requires a stabilizing agent, correct?

A. Are we going to put the claims back up on the screen?

Q. We'll try to do that.

You know that Claim 1 requires -- the claims require a stabilizing agent, right, Doctor?

A. It states that Claim 1 requires a stabilizing agent.

Q. And that's a known set of structures too, right?

A. When you say a known set of structures, when you give a specific example, a POSA would know the structure that -- when you start talking about various categories, you have to give examples of what those might be.

So your question was a buffer is a known set of structures. A buffer is a term that can encompass multiple types of molecules; so maybe -- does the word "buffer" give me the structures? The answer is no.

Q. Doctor, I'm asking about the stabilizing agent now. We're past buffers. My question is simple.

Stabilizing agent is a known set of structures, right?

A. There's multiple molecules that can be used as stabilizing agent. Stabilizing agent is very broad. Sugars are stabilizing agents. Surfactants are stabilizing agents.

Q. Is that a known set of structures, Doctor, or not?

A. There's multiple sets of structures.

Q. So no or yes?

A. What I'm saying is this patent fails to define what all the potential structures are.

Q. Okay.

Let's take a look at the doctor's deposition again, right after where we were, page 429, line 4 down to line 11.

"Q Claim 1 requires a stabilizing agent, correct?

"A Yes, it does.

"Q That's a known set of structures too?

"A Well -- I'm going down looking at dependent claims. Yes, it does."

Were those my questions and were those your answers?

A. Those were my answers.

Q. Doctor, Claim 1 recites various structural requirements with respect to both the active ingredient and

with respect to excipients.

A. I'm sorry. Where are we --

Q. Claim 1, Doctor, recites various structural requirements with respect to both the active ingredient and with respect to the excipients, correct?

A. I'm getting lost in your question, Mr. Berl.

Q. Okay. Here it is. I'll try to do it slow.

Claim 1 recites various structural requirements with respect to both the active ingredient and with respect to the excipients, right?

A. Are you reading the claims or is this your statement?

Q. That's my question.

A. Could you repeat it, please.

Q. Yes.

Claim 1 recites various structural requirements with respect to both the active ingredient and with respect to the excipients?

A. Does it require -- yes.

Q. If those structural requirements are met, one is -- well, sorry.

If those structural requirements are not met, one is not within the scope of the claims, right?

A. I'm not aware, but that's my understanding.

Q. Okay. So each formulation, to your understanding, in order to be within the genus of formulations of Claim 1, must

meet every structural requirement of Claim 1, the organic cosolvent, the buffer, the stabilizing agent, and the VEGF antagonist fusion protein with a particular sequence, right?

A. Your question was it has to meet all of the criteria in Claim 1? Was that your question?

Q. Yes.

A. The answer is yes.

Q. So all of the formulations within Claim 1 have those structural features, correct?

A. No.

Q. Okay. Doctor, you talked about the '572 patent for a moment. You have one slide on that, I believe. It's Slide 57.

Can we put that up.

Now, you understand that the '572 patent priority date is several years after the priority date of the '865 patent, right?

A. Yes, I do.

Q. And the POSA practicing the claims of the '572 patent would not make a new formulation, right; they'd use an existing formulation?

A. I cannot read the minds of the inventors, but I'll follow your train of thought.

Q. By 2011 many aflibercept formulations were known, right?

A. Yes. But you're referring to a patent that obviously

had done some variations; so I'm not quite sure where you're heading.

Q. You think the '572 patent had made new formulations?

A. No. I'd have to pull up the '572 patent and look at it to be able to follow your question.

Q. Okay. Doctor, you agree that as of 2011 there were formulations of aflibercept known that the person of skill practicing the '572 patent would use, right?

A. As of?

Q. 2011 or 2013.

A. And if they did have to use what? The '865 patent or the '572?

Q. Sure. They could use the '865 patent.

A. The '865 is patent is not enabled; so they wouldn't know how to make those buffers.

Q. So you don't think that the person of skill could have used the formulations from the '865 patent in practicing the '572 patent?

A. They could with a significant amount of work and effort and studies and screening.

Q. You haven't asserted that the Dix patent is not enabled, have you?

A. Well, let's pull -- I'm not sure -- which Dix patent are you referring to? Doesn't Dix have multiple patents?

Q. The Dix '226 patent that you addressed thoroughly in

your expert report. You don't think that's not enabled, do you?

THE COURT: One second.

Yes, Counsel?

MR. SALMEN: Objection, Your Honor. It's outside the scope of his direct examination.

THE COURT: How is this now -- Mr. Berl, how are we within the scope of his direct?

MR. BERL: Because he opined about how the person of skill would practice this -- the Claim 6 of the '572 patent. And he says it would be really hard. It doesn't disclose anything. And I'm exploring what the person of skill actually would have done.

THE COURT: Overruled.

THE WITNESS: I don't have the '572 patent in front of me; so I'm not going to address the specific detailed content unless we can -- if you have specifics you want to pull up.

Can you rephrase your question again.

BY MR. BERL:

Q. Sure.

A. I'm trying to answer your question, but I just want to get a little more --

Q. I think I asked you whether the person of skill practicing the '572 patent would use the '865 patent

formulations which have been published by that point. And you said no because they're not enabled.

Are we with each other so far?

A. What I said is -- you said, well, they can just use one of the buffers in the '865 patent. And I said no, they're not enabled.

Q. That's not what I said, but let me try it again to make sure we're on the same page.

A. Let's try it again.

Q. In your view, would the person of skill practicing the '572 patent in 2011 or 2013 use as an ophthalmologic formulation the formulations disclosed in the '865 patent which had published by that time?

A. They may have. I don't know that they would have, but they would certainly -- especially because the patents were issued to the same company, one would expect that they were using it at least as a reference document.

Q. And they could use the Dix patent too which was also issued to the same company, Regeneron, correct?

A. Yeah. One would expect, with the normal business practice, to be referring to your own internal prior art.

Q. And it's not your view that the POSA would have had a preference for one of those formulations from the '865 patent or the Dix patent over the others in practicing the '865 patent, right?

A. I would expect that Regeneron personnel might have had some preferences. But you're asking me to ask if a hypothetical POSA would have a preferred buffer? I can't answer what the hypothetical POSA would want.

Q. So you have no -- as someone who opined on the '572 patent as to what formulation in 2011 the POSA would have wanted to use for treating ophthalmic diseases using aflibercept, right?

A. Well, yes. What we're highlighting here is one of -- they're called the quantity attributes of the final product. One of the characteristics. Yes, you'd want an isotonic solution that's physiological with respect to the eye.

Q. Let me try that question again.

Do you have an opinion about whether the POSA would prefer one formulation in the prior art, such as Dix, or a different formulation, such as one of the '865 formulations?

THE COURT: One second.

Yes?

MR. SALMEN: Your Honor, I'd just renew my objection. This goes to the obviousness analysis. And Dr. MacMichael had testified here with regard to a written description of the '572 patent, but we're going way far afield of any opinion that was disclosed in his reports or during direct examination.

MR. BERL: I disagree. He's talking about how the person of skill would practice this. He says basically the

person of skill could practice this. I don't see how they would.

THE COURT: And I disagree.

Sustained.

BY MR. BERL:

Q. Now, Doctor, let me ask you about one final topic, which is indefiniteness.

A. May I correct your inaccurate quote of what I said?

Q. No.

THE COURT: No. I sustained the objection, Doctor.

So moving forward.

BY MR. BERL:

Q. Finally, I want to address indefiniteness.

You're not an expert about the medical aspect of whether something is suitable for intravitreal administration, correct?

A. I am a development and manufacturing expert. I do work very closely with colleagues that are physicians. And so I do have an understanding of what's acceptable from working with physicians and regulatory and quality members. You're never an individual working alone; you're working with a team.

Q. Right. But you on your own don't have that knowledge of what excipients or what formulations would be suitable for intravitreal administration, right?

A. I am not an ophthalmologist.

Q. And you on your own don't have that knowledge of what excipients or what formulations would be suitable for intravitreal administration, right?

A. I have a working knowledge of what excipients and which buffers, et cetera, are acceptable in the human body from all the multiple products I've developed over my career.

Q. I'm asking about intravitreal formulations, Doctor. Let me try it one more time.

You on your own don't have that knowledge of what excipients or what formulations would be suitable for intravitreal administration, right?

A. It's available in the literature.

Q. But you would -- you said at your deposition you would consult other people on a team who have that expertise, like ophthalmologists?

A. Yes. That's what I just said.

Q. Okay. But you didn't consult with an ophthalmologist in preparing your expert reports as to the '865 patent, right?

A. No, I didn't consult with an ophthalmologist.

Q. And you didn't consult with a toxicologist?

A. No, I did not consult with a toxicologist.

Q. You didn't interact or consult with anyone other than the attorneys in connection with your opinions in this case, right?

A. I was asked questions that were related to my

background and expertise in how to manufacture and formulate drug products.

Q. You understand, Doctor, that the issue of indefiniteness is whether the POSA would understand the scope of the claims, right?

A. Yes.

Q. And the POSA would understand the scope of the '865 patent claims, right?

A. They would understand that they're very broad and open, using the term "comprised" in multiple claims.

Q. But they would understand the scope of the claims, right, Doctor?

A. No, they wouldn't, because the scope of the claims is extremely broad and they're open-ended.

Q. Doctor, you're a POSA and you understand the scope of the claims, right?

A. No. I believe the scope of many of the claims is -- because it uses the term "comprises" and gives several examples but it's open-ended. So it's not narrow. It's very broad.

Q. Okay.

Let's take a look at the doctor's deposition hopefully one last time, page 486, line 21, through 487, line 1.

Doctor, I asked:

"Q And the POSA would understand the scope

of the claims?

"A Well, I am a POSA, and I understand this."

Was that my question and was that your answer?

A. Yes. The scope of the claims is open-ended and broad.

Q. Thank you.

MR. BERL: No further questions at this time.

THE COURT: Thank you.

Counsel, I assume redirect would be longer than five minutes?

MR. SALMEN: Unfortunately, yes, Your Honor.

THE COURT: Well, I wasn't going to put an adjective on it.

Doctor, we're going to break for the day. You remain midstream in your testimony; so that means you get through the evening without anyone bothering you.

THE WITNESS: Being a lonely guy.

THE COURT: You do. You are alone. Whether you prefer that or not, I'll leave to you. I won't ask. But just so you understand, no one can talk to you about your testimony because you remain midstream.

We'll resume at 9:00 tomorrow.

You can go ahead and step down, sir.

THE WITNESS: Thank you, Your Honor.

THE COURT: Thank you.

It was my understanding this was Mylan's last witness in this phase of the case; is that correct?

MS. MAZZOCHI: Yes, Your Honor. This is going to be Mylan's last witness as part of its invalidity/infringement response. We do have one live witness for sure, Dr. Hofmann, who is going to be responding to their witness on commercial success.

Whether we need to bring Dr. Albini or Dr. Stewart back after we hear from Dr. Csaky, for example, or any of the other witnesses, particularly on the issue of secondary considerations, we don't know. We're hoping we don't have to. But one of the things that I certainly would say, though, Your Honor, in terms of timing, again, we're very concerned that Regeneron has been really stacking up a lot --

THE COURT: The timekeepers are keeping track of it, Counsel. We are where we are. I've told you guys how much time you have.

MS. MAZZOCHI: We're on track. I just don't want to get stuck.

There are a couple things, though, Your Honor, that have come up, and I did want to preview them for you because I'd like to get some guidance.

THE COURT: I don't need a preview at this point, Counsel. We're going to break for the day. I'm just trying to

get a good feel for where we're headed. We can take those issues up at 9:00 tomorrow morning just before the doctor resumes his testimony.

MS. MAZZOCHI: That's fine. Thank you, Your Honor.

THE COURT: Is Regeneron's plan still the same, Ms. Chu, Dr. Csaky, Dr. Trout. And if Mr. Graham and Mr. Manning are doctors, I apologize to those witnesses.

MR. BERL: Dr. Graham will be after Dr. Chu.

THE COURT: The order was --

MR. BERL: The order was not --

THE COURT: Okay.

MR. BERL: But we're calling those people.

THE COURT: Understood.

All right. We're going to break for the day. I'll see everyone at 9:00 tomorrow.

(Proceedings concluded at 5:22 p.m.)

CERTIFICATE

I, Cindy L. Knecht, Registered Professional Reporter and Official Reporter of the United States District Court for the Northern District of West Virginia, do hereby certify that the foregoing is a true and correct transcript of the proceedings had in the above-styled action on June 20, 2023, as reported by me in stenotypy.

I certify that the transcript fees and format comply with those prescribed by the Court and the Judicial Conference of the United States.

Given under my hand this 20th day of June 2023.

/s/Cindy L. Knecht

_____

Cindy L. Knecht, RMR/CRR
Official reporter, United States
District Court for the Northern
District of West Virginia

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.

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Wednesday Afternoon Session,

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

- - -

THE COURT: Day seven, I think, we convene for trial. Counsel is present. Dr. MacMichael is on the stand. I believe we're ready for redirect.

Is that correct, Counsel?

Madam Court Reporter is ready. You may proceed.

MR. SALMEN: Yes, Your Honor. For the first portion of my redirect, I'm probably going to have to get into some information that has been designated confidential. So pursuant to your previous order, we ask for a sealed courtroom.

THE COURT: Understood.

In an effort to get everyone their steps in early this morning, those of you not permitted to be here under the Court's protective order, if I could ask you to step out. We would certainly appreciate it.

We'll also ask the court security, once those folks have vacated the premises, to seal our courtroom, please. Thank you so much.

(The following proceedings (1527/23 to 1533/12) were had under seal, and are filed under separate cover.)

(Courtroom unsealed.)

THE COURT: Welcome back, everybody.

Counsel, you may proceed.

MR. SALMEN: Thank you, Your Honor.

BY MR. SALMEN:

Q. Dr. MacMichael, do you recall Mr. Berl asking you the question "Polysorbate in Claim 1 is being used as a surface-active agent to prevent aggregation and denaturation?"

A. I don't recall the specific question.

Q. That appears at trial transcript page 1455. Why don't we put that on the screen to refresh your recollection.

I'll give you a moment to read that.

A. Yes.

Q. Do you recall this question?

A. Yes.

Q. Let's take a look at the '865 patent Claim 1, please.

Claim 1 of the '865 patent does not require polysorbate, does it?

A. It does not call out polysorbate.

Q. Dr. MacMichael, you were asked about Dr. Rabinow's testimony. And to refresh your recollection, let's pull up page 1482 to 1483.

Do you recall being shown this testimony from Dr. Rabinow?

A. Yes, I do.

Q. And you see here Dr. Rabinow was being asked about optimizing the stability of a protein formulation, a single formulation, right?

A. Yes.

Q. Were you asked to provide an opinion regarding whether the patent enables just a single formulation or whether the patent enables the full scope of the universe of formulations covered by the asserted claims?

A. Yes, I was asked.

Q. Were you asked whether the patent enables a single formulation or whether the patent enables the full scope of formulations covered by the asserted claims?

A. I apologize. I can't recall the specificity of that question, but I can answer the question. But I believe it does

not give a description on how to make multiple formulations.

Q. Thank you.

Now, Dr. MacMichael, Mr. Berl asked you about undue experimentation and your interpretation of that term. Do you remember those questions?

A. Yes.

Q. Now, you've formed an opinion regarding the amounts of experimentation required to practice the full scope of the asserted claims; is that correct?

A. Correct.

Q. What level of experimentation, in your opinion, is required for the person of ordinary skill in the art to practice the full scope of the asserted claims?

A. It would take a significant amount of experimentation.

Q. When you previously suggested that -- I'm sorry. What was the term you used?

A. I used "significant" as opposed to "undue."

Q. Okay. When you previously suggested that significant experimentation would be necessary, do you consider significant experimentation to be undue in view of the full scope -- the full scope of the '865 patent claims?

A. Yeah. I remember we had quite some discussion on that.

Undue means so much experimentation that you wouldn't

be able to achieve it. What I was testifying yesterday is it would be a significant amount of work, whether it was undue, but it would take a lot of work on the part of the formulation department. So --

Q. Now, Doctor -- I'm sorry.

A. I was just going to say whether you call that undue or significant is a relative term.

Q. Dr. MacMichael, you were also asked by Mr. Berl whether you identified any formulation that you would not be able to make.

Do you recall those questions?

A. Yes.

Q. And is that the evaluation that you were asked to make in determining enablement, whether you could not make a certain formulation, or were you asked to form an opinion regarding whether the skilled person could practice the full scope of the claims?

A. I don't know if I can get to the specifics of the question of how -- what was asked yesterday, but the second part of the question was?

Q. Were you asked whether the skilled person could practice the full scope of the asserted claims?

A. I believe I was.

Q. Dr. MacMichael, you were also asked about the Kaisheva reference. Do you remember that one?

A. Yes.

Q. And in this line of questions Mr. Berl suggested that the '865 patent informed the skilled person of an optimum pH for the formulations in the asserted claims.

Do you recall that?

A. Yes, I do.

Q. And that appears for the record at trial transcript pages 1488 to 1489.

Now, let's take a look at the '865 patent, Claim 1, Dr. MacMichael.

Dr. MacMichael, is Claim 1 limited to a formulation with a pH of 6.2 to 6.3?

A. No.

Q. The full scope of the formulation pH under Claim 1 would be much broader, right?

A. Well, it's not -- I don't see a definition for the value of the pH in Claim 1, so one would assume it's broad.

Q. Now, let's take a look at Claim 4.

Is Claim 4 limited to a specific pH?

A. No.

Q. Let's take a look at Claim 5. Is Claim 5 limited to a specific pH?

A. No.

Q. Let's take a look at the Kaisheva reference, Claim 1 of Kaisheva. This is DTX 3610, page 20 to 21. There is a copy

of it, Dr. MacMichael, in your cross-examination binder, Volume 1, if that helps.

A. That's Volume 2. I'm sorry. Could you give me the --

Q. Yes. DTX 3610. And I think Mr. Gibson has it up on the screen now.

A. Okay. Okay.

Q. And you see there in the third line of Claim 1 it reads "About 5 to 25 millimolar histidine buffer, having a pH from about 5.5 to 6.5."

Do you see that?

A. Yes, I do.

Q. So, Dr. MacMichael, does the claim in the Kaisheva reference identify the specific pH range?

A. Yes, it does -- it uses the term "about." Yes, it does. It gives 5.5 to about 6.5.

Q. Right. And we don't see that specificity in the '865 patent Claims 4 or 5, right?

A. No.

Q. Okay.

We can take that down.

Dr. MacMichael, you recall when Mr. Berl asked you about certain internal documents from Regeneron where they used the term "cosolvent," right?

A. Yes.

MR. SALMEN: And for the record, Your Honor, this is at trial transcript pages 1476.

BY MR. SALMEN:

Q. Dr. MacMichael, you provided your opinion in this case that polysorbate 20 is not -- sorry.

And you provided your opinion in this case that polysorbate 20 is not an organic cosolvent in Mylan's product under the Court's claim construction, right?

A. That's correct.

Q. Okay.

Mr. Gibson, you can take that down.

Were Mr. Berl's questions regarding the internal Regeneron documents specific to the Court's claim construction?

A. I don't believe so.

Q. Do you have any idea whether Regeneron was applying the Court's claim construction when it used the term "cosolvent" in those internal documents?

A. No. I don't know the mind of the Regeneron personnel.

Q. And would the person of ordinary skill in the art have access to the Regeneron internal documents?

A. Well, they're internal documents. They're confidential.

Q. Thank you.

Now, Dr. MacMichael, I'd like to ask you about when

Mr. Berl asked you several questions about preventing aggregation using polysorbate. And I want to first ask you to consider a hypothetical formulation of aflibercept without polysorbate.

A. Okay.

Q. Are you with me?

A. Yes, I am.

Q. That solution would have to be in some kind of a container, right?

A. Yes.

Q. And I believe you testified yesterday that protein interactions with the surface of the container or interactions with the air can result in protein adsorption which can lead to aggregation. Was that right?

A. Yes. And denaturation.

Q. And denaturation. If I had the same solution in three different containers -- one in a smooth glass, a second in a jagged plastic container, and a third in a completely rubber container -- are you still with me?

A. Yes, I am.

Q. The propensity for the protein to aggregate in those various containers is going to be different, right?

A. Yes, it will be.

Q. Now, if I pick the best container, the one where the protein showed the least amount of aggregation -- let's say the

glass. Okay? And I put my solutions in only glass, I would have reduced the propensity for the protein to aggregate by eliminating the rubber or the jagged plastic, right?

A. What you're saying -- you're saying -- through experimentation, we demonstrated that we saw a greater propensity in one container versus another? Is that your question?

Q. Yes.

A. Yes.

Q. And so by putting it in the best container, I would have reduced the propensity for the protein to aggregate now that it's in the glass, right?

MR. BERL: Objection, Your Honor. This is leading.

THE COURT: Sustained.

BY MR. SALMEN:

Q. So, Dr. MacMichael, would you equate removing the rubber interface which reduced the likelihood of protein to aggregate the equivalent of using a cosolvent to increase the protein solubility?

A. No, because if you start getting aggregation, that container, once -- you might change the rate -- depending on the container without polysorbate -- and, again, we're talking hypothetical experimentation here -- once you initiated aggregation, if you're going to see aggregation lesser in the glass and faster in the rubber, ultimately, in the glass you're

still going to get -- hint at the final amount of aggregation. So the rate might be different. So you'd need to add a surfactant whether using glass or rubber to prevent that aggregation.

Q. And would the fact that the surface is glass versus rubber be the equivalent of adding a cosolvent to increase solubility of the protein?

A. Well, first of all, adding a cosolvent -- we're using a generic term -- "cosolvent" here -- to increase solubility?

Q. Yes.

A. The answer would be no.

Q. Thank you.

I think you also testified in response to Mr. Berl's questions that adding hydrochloric acid to protein solutions might cause aggregation by denaturing the protein; is that right?

A. Yes. When you're adjusting the pH of a protein solution, you have to be very careful that there's not -- as you're adding it, that there's not high concentrations of acid before it diffuses. In those areas, you can get denaturation.

Q. But would you then say that not adding hydrochloric acid to my formulation would be the equivalent of using a cosolvent to increase solubility?

A. No. It's two different things. The hydrochloric acid would be a denaturing agent. And not using the

hydrochloric acid doesn't make it equivalent to using a surfactant if that is the question.

Q. Thank you, Dr. MacMichael.

Last questions here, Dr. MacMichael.

You recall the analogy Mr. Berl presented to you about driving your separate cars through a snowstorm, right?

A. Yes.

Q. Let me pose a similar hypothetical. But in mine let's put the person skilled in the art of driving in snowy conditions behind the wheel of the car. Okay?

Now, a person skilled in the art of driving through snow would know that having a good set of snow tires on your car is going to make that car sufficiently stable in the event a snowstorm does occur, right?

A. Correct.

Q. And the skilled person might even have studded snow tires which have been road tested and proven to be sufficiently stable in pretty serious weather conditions, right?

A. Correct.

Q. And the skilled person of driving in the snow would know the snow tires alone would be sufficient to prevent the car from sliding off the road, right?

A. Correct.

Q. So adding chains on top of those snow tires would merely provide the skilled person some added assurance; isn't

that right?

A. Correct.

MR. SALMEN: That's the end of my redirect, Your Honor.

THE COURT: Thank you, Counsel.

Recross?

MR. BERL: Your Honor, I was going to start where Mr. Salmen started; but, unfortunately, that's the confidential document.

THE COURT: No. Understood.

Time for more steps, everyone. I'd like to ask you to step out of the courtroom and ask court security to seal our courtroom once everyone's had a chance to depart.

(The following proceedings (1544/16 to 1550/4) were had under seal, and are filed under separate cover.)

(Courtroom unsealed.)

THE COURT: Thank you, Officer.

Mr. Berl, you may proceed.

BY MR. BERL:

Q. Do you recall a few moments ago you were asked questions about the pH range and whether the claims in the '865 patent were limited to a particular pH range?

A. I recall the questioning around the pH, yes.

Q. You agree that the specification limits the formulation pH to within the range of 5.8 to 7, right?

A. If you could pull up the claims and the specifications, I'd like to see them so I can confirm.

Q. Let's just pull up your expert report, your reply report, PTX 62. This is your reply expert report, sir, correct?

A. I believe so, yes.

Q. And in the second to last bullet point on page 10 it says, "The pH. The specification only limits the formulation of pH to within the wide range of 5.8 and 7.0."

Do you see that?

A. Yes, I do.

Q. And that's a correct statement, right?

A. I made it.

Q. Now, finally, I want to ask you about the testimony you gave about trying to distinguish between a formulation and whether that's routine to make and multiple formulations.

Do you recall that in Mr. Salmen's questioning of you?

A. Yes, I do.

Q. Doctor, just so everyone's clear, your opinion is that protein formulations are routinely optimized to improve the stability of their active ingredients, correct?

A. Yes.

Q. Not a protein formulation; protein formulations. Right?

A. When I said protein formulations, I was talking about the body of biotechnology and multiple companies and multiple products. That's why I used the term in plural. Formulations require significant amount of work. That was what I was referring to.

Q. Okay. So final question. Protein formulations are routinely optimized to improve the stability of their active ingredients.

Do I have that right?

A. That's a fair statement.

MR. BERL: No more questions, Your Honor.

THE COURT: Rereredirect.

MR. SALMEN: No questions, Your Honor.

THE COURT: All right. Do we have any exhibits that we need to -- one second, Doctor. Sorry.

MR. BERL: I just have two, Your Honor. I imagine Mr. Salmen has a lot more than that. So maybe I'll just get my two done, which are PTX 672 and PTX 1948.

THE COURT: Understood.

Any objection to those two documents?

MR. SALMEN: Let me just check, please.

THE COURT: Sure.

MR. SALMEN: Actually, Your Honor, we do object to admitting those documents into evidence with this expert. Those are the two Regeneron internal documents that Dr. MacMichael stated he had not seen before. I don't think this is the witness to properly authenticate those documents.

THE COURT: Mr. Berl.

MR. BERL: Yes, Your Honor. We can admit them through someone else, but the point is we've been admitting throughout the trial cross-examination testimony or -- and the associated documents.

THE COURT: Is there any suggestion that these documents are not actually authentic? That is a low evidentiary hurdle the opponent has to climb over.

MR. SALMEN: We have no objection to their authenticity, Your Honor. It's just -- and that was not the

basis of the objection, but these --

THE COURT: Then what is the basis?

MR. SALMEN: The lack of foundation with this expert.

THE COURT: With respect to authenticity. What other foundation? They were used to cross the bases of the doctor's many opinions, correct, Mr. Berl?

MR. SALMEN: I'll withdraw the objection, Your Honor.

THE COURT: With objection withdrawn, both of those exhibits are hereby deemed admitted.

And, Counsel, if you want to review your list very slowly, please.

(PTX 672 and PTX 1948 were admitted.)

MR. SALMEN: Yes. I'll go through them slowly, Your Honor. DTX 0007, DTX 0030, DTX 2687, DTX 3463, DTX 3465, DTX 3466, DTX 4116, DTX 4229, DTX 4430, DTX 5011, DTX 5012, DTX 5053, DTX 5172, DTX 5196, DTX 5273, DTX 7087, DTX 8206, DTX 8207, DTX 8208, and DTX 8209.

THE COURT: Any objection to any of those items on the list?

MR. BERL: No, Your Honor.

THE COURT: Without objection, each of those shall be deemed admitted.

(DTX 0007, DTX 0030, DTX 2687, DTX 3463, DTX 3465, DTX 3466, DTX 4116, DTX 4229, DTX 4430, DTX 5011, DTX 5012, DTX 5053, DTX 5172, DTX 5196, DTX 5273, DTX 7087, DTX 8206,

DTX 8207, DTX 8208, and DTX 8209 were admitted.)

THE COURT: Anything further we need from the good doctor?

MR. SALMEN: No, Your Honor.

THE COURT: All right. Doctor, thank you so much, sir. You can step down. I throw you back into the waters. They're free to talk to you again.

THE WITNESS: Thank you.

THE COURT: Mylan may call its next witness.

MS. MAZZOCHI: Your Honor, Mylan does not have any further live witnesses for its case in chief. I did, however, before we closed yesterday we had talked about introducing exhibits that were raised by Regeneron at Dr. Stewart's cross.

THE COURT: Correct.

MS. MAZZOCHI: We would like to move into evidence PTX 3348, which is one of his publications that was used on cross.

THE COURT: Any objection to 3348?

MR. GREGORY: No objection.

THE COURT: Without objection, 3348 deemed admitted.

(PTX 3348 was admitted.)

THE COURT: Were there any other loose ends from Dr. Stewart's testimony in terms of exhibits?

MS. MAZZOCHI: I don't believe so. I think we got all the rest of his exhibits into evidence.

THE COURT: Okay. Understood.

Regeneron, any remaining?

MR. GREGORY: Yes, Your Honor. Given that they're moving 448, I'd like to take an opportunity to go back and take a look at the other exhibits moved on cross and see if you wanted to move a couple of those into evidence as well.

THE COURT: Continue to have Dr. Stewart's exhibits at loose end then. That's fine.

So Mylan is resting its case in chief, correct?

MS. MAZZOCHI: Yes. With that, Your Honor, we would rest our case in chief. And then as we had indicated yesterday, however, Mylan does have some objections to the witnesses and some of the deposition designations that Regeneron is proposing to offer today.

I believe one of their next witnesses was going to be Ms. Chu. There were objections that we had to Regeneron calling her in her individual capacity to talk on particular topics. I believe we filed a motion on that this morning.

THE COURT: I believe that you did, 6:49 a.m. It's 21 pages in length with attachments.

MS. MAZZOCHI: Yes. And I can certainly summarize briefly what the issues are. And it's basically this.

THE COURT: Let's pause on that.

Given that Mylan has rested, are there any motions from Regeneron at this juncture?

We'll come back to that.

MR. BERL: Yes, Your Honor. Regeneron moves for judgment under Rule 52(c). I understand, Your Honor, that this is a bench trial; so I'll be brief.

But I would note that beginning with the formulation case, as it relates to invalidity, Mylan's combinations are plainly deficient. Even taking their expert's testimony as true, he failed to show multiple limitations of the claim were met by the asserted combinations, including, but not limited to, the requirement of an ophthalmologic formulation, which is present in neither Fraser nor the Liu reference with which it was combined; and the at least 98 percent native conformation limitation, which is not present with respect to aflibercept in any of their combinations and is not even tested for any product or any molecule or any formulation with respect to the combination of Fraser and Lucentis.

Absent a showing that all limitations of the claim, the claim as a whole, is obvious, an obviousness case simply cannot succeed.

With respect to the Dix reference, Mylan advanced no evidence, zero, that the Dix application and the application at issue here were not commonly owned or were not subject to a common assignment by the same company, Regeneron. It's clear from the face of that; they're all Regeneron's applications. And, accordingly, under 35 U.S.C. 103(c), it cannot be used as

prior art for purposes of obviousness.

With respect to anticipation of Dix, even taking as true everything their expert Dr. Rabinow said, regarding the 40 mg/mL limitation of the claim, it's just not there. He relies only on the disclosure of 10 to 50 mg/mL, a range which is not directed to aflibercept.

But in any event, the law is clear. Disclosure of a range is not the disclosure of any number within that range, and any anticipation argument that Mylan attempts to advance simply is inconsistent with that controlling precedent, and so it cannot succeed either.

Now, with respect to Section 112, Your Honor just heard Dr. MacMichael, and the testimony was clear. He had numerous opportunities, both on cross-examination and again this morning on redirect, to tell Your Honor that the experimentation to practice the claim was undue. He repeatedly declined. And that's the standard from the *Wands* case all the way down to *Alcon v. Barr*. It's routine experimentation or undue experimentation.

They had two experts testify. We haven't gone yet, of course. Their first expert, Dr. Rabinow, said it's routine. Their second expert didn't disagree with that, and he doesn't say it's undue experimentation either. You can't have an enablement case without undue experimentation, and there's no evidence that there is.

With respect to written description, he likewise agreed that this claim recites structure and it's structurally limited. The buffer is a known set of structures. The stabilizing agent is a known set of structures. The organic cosolvent in Claim 4 limited to polysorbate, that's a known structure. The active ingredient, aflibercept, that's a known structure.

These are known structures. A written description case cannot lie where you are reciting structures in your claim because the test for written description is whether a person of skill can envisage or envision what you're claiming. Can they recognize what it is?

And all of the foundational case from the Federal Circuit, beginning with the *Wyeth* case and rapamycin all the way to their en banc *Lilly v. Ariad* case stand for the proposition that you can't just claim function, you can't say I claim anything that will work without regard to what structures it is, because the person of skill can't envision what structures you are claiming.

That's not what we have here, according to Dr. MacMichael himself. We have structures that are being claimed. And Your Honor will search in vain for any claim that is limited to structure which the Federal Circuit has said doesn't meet the written description requirement in a situation like this because, of course, you can envision is. He agreed

it's limited to structures.

The structures are known. And so it's, by definition, something that the skilled artisan can envision. They know this is in or this is out. If it doesn't have a stabilizing agent, it's out. If it has one, it meets that limitation. This is not some amorphous effort to claim only function; and therefore, the written description requirement is met as a matter of law.

Finally, with respect to indefiniteness, Dr. MacMichael agreed that the person of ordinary skill can understand the claims. He agreed that he lacks the expertise to determine what is suitable and what is not suitable. And he didn't consult with anyone, such as an ophthalmologist, who would have that expertise.

So I submit, Your Honor, that we should have judgment with regard to invalidity.

Regarding infringement, I actually think there are not many factual disputes here between Dr. Trout and Dr. MacMichael. Everyone agrees that, if you have polysorbate in the formulation that Mylan has, more of the aflibercept would be in solution under various conditions, conditions that Your Honor has heard from every witness in the case are important, such as going through the needle and creating the shear stress that can make things fall out of solution.

THE COURT: Let me ask you this, Mr. Berl. Does the

label applied to polysorbate 20 matter? Is that a significant issue or dispute?

MR. BERL: No.

THE COURT: Why not?

MR. BERL: The reason is that the question under the Court's claim construction is does it increase the solubility of the aflibercept?

It doesn't matter whether someone labels it a stabilizing agent, a surfactant, or an organic cosolvent. The reason is those are words. Words don't matter. Actions matter. Is it actually increasing the solubility?

And Dr. MacMichael's own Graph 34 showed that it is. Without polysorbate, it was going down like this. And I'm showing for the record the curve where it's crashing out of solution in the black on Slide 34. And he showed with polysorbate, more is in solution. He agreed that that's what happened, and Dr. Trout says that's what happened.

You could call it a stabilizing agent, a surfactant. You can call it a duck. All that matters under Your Honor's construction is is there more polysorbate -- is there more aflibercept in solution with polysorbate than without? The answer to that question I would say undisputedly, according to this record, is yes.

I would also observe that "stabilizing agent" is a general term. And one needs to ask what is it stabilizing

against? And I think both experts agreed what it's stabilizing against is aggregation. And if it stabilizes against aggregation, both experts testified clearly that aggregation then leads to precipitation, which is the opposite of solubility. You're either in solution or you precipitated out of solution.

I don't think there's anything at all inconsistent with calling this a stabilizing agent. That's not a problem because it's stabilizing against it coming out of solution. Put another way, it's stopping it from coming out of solution; it's keeping it in solution. It is increasing the solubility because there will be more with polysorbate in solution than without polysorbate under various relevant conditions such as shear stress.

So I don't think the label matters. As I've said repeatedly, this is not some anthropomorphic exercise where the polysorbate is running around saying, "I wonder what someone calls me." That's not going on here.

We know what it's doing. It's stopping aggregation; it's stopping precipitation; it's keeping the aflibercept in solution. That's what the claim requires, more in solution with than without and under relevant conditions.

I think both experts agreed. You can look at Slide 34. That's exactly what's going on. Y axis there is solubility of the aflibercept. If there's more with

polysorbate than without, I think that ends the infringement inquiry, respectfully.

With respect to the method of treatment, happy to answer any other questions Your Honor has.

THE COURT: Go ahead.

MR. BERL: With respect to the method of treatment, Your Honor, we explained in our infringement case that their label instructs practicing these claims. We heard no response from them in their case, no expert testimony, no other testimony indicating otherwise. The evidence is undisputed that their label instructs use of the claim.

Now, if they have some argument that not everyone practices the claim, that's not a defense to infringement under 35 U.S.C. 271(e), which is the section that we're addressing here in this case. The *AstraZeneca* case clearly stands for that proposition. We cited that in our pretrial papers.

It doesn't matter whether everyone practices the claim. What matters is whether anyone practices the claim. And the testimony was clear that some doctors practice the claim. If that were not right, we would have heard an expert for Mylan come in here and tell you that, but they withdrew their noninfringement expert.

And so they have no contrary interpretation of the evidence because the evidence is undisputed that some doctors will practice this claim. They haven't disputed that their

label sets forth the claim. Under the *Warner-Lambert* case and its progeny, that reflects Mylan's intent.

You can't say I didn't mean it, I don't really care if people do it, I don't want to do it. That's not what happens under Section 271(e). Your label reflects your intent. The evidence is undisputed that their label hits every limitation of the claim and instructs doctors to practice the claim. That's sufficient for intent. That's the beginning and the end of that inquiry.

With respect to invalidity on the method of treatment claim, they have not advanced any argument that there are five loading doses in the prior art for the DME and diabetic retinopathy. It's just not there. They try to massage every single reference they can to make three five or to may pro re nata, prn, dosing somehow turn into five.

You heard yesterday from the witness stand from Dr. Stewart that it's just not there. That's not what it says, and they can't change what the prior art says. And based on the record that they have created, there is no case of obviousness because, again, every limitation in the claim as a whole has to be obvious.

Finally, as to the Claim 6 of the '572 patent, you've heard a lot of testimony about where the prior art was. It was unclear what treatment regimens would go forward. The art was trending away from the dosing regimen that is in the claim

here. Genentech had failed with their efforts to do extended fixed dosing. People were moving toward pro re nata dosing.

Again, I don't think there are all that many factual disputes on this point, and under the facts in the record, there is no obviousness. It was not moving in the direction where the claims went. And we did that, not anyone else.

With respect to their argument on the isotonic limitation, Your Honor, they have not established how far outside of the range of isotonic you would want to go or not want to go. They had one witness testifying about this, Dr. Albini, who said you wouldn't want to use something too isotonic, over 800, because it could create some problems and he provided a reference, but he declined to say how far outside of that range of isotonic -- and we've seen what that is in the record -- you would be willing to go or not willing to go.

And so while they have made some case crediting all their evidence, as one does at the Rule 52 stage, that you wouldn't want to venture too far, all the way over 800, they have not made any case that you can't venture at all outside of the isotonic range to practice the claims. So I think their argument there is deficient as well.

So with that, obviously, open to any questions, but we believe that we should have judgment at this stage on both patents.

THE COURT: Understood. Thank you, Mr. Berl,

Counsel.

Ms. Mazzochi, my apologies. I had some reading materials we discussed early this morning. This is my first cup of coffee; so I somehow combined your name with Mr. Rakoczy, name into one. I assume I'm not the first person to do that, but with my apologies, ma'am, go right ahead.

MS. MAZZOCHI: No worries, Your Honor. I am used to it. I got over that in about third grade, people mispronouncing both my first and last names. So I'm good. As long as you're not shooing me out in the courtroom, I'm happy.

All right. Your Honor, under 52(c), first of all, I'll go in reverse order.

The plaintiffs have suggested -- as we stated in our Rule 52(c) motion, we do not believe the plaintiffs have met their burden, and similarly the evidence that we have set forth in connection with our case in chief actually undermines plaintiff's claims that it would be improper on the infringement side to infer an intent to induce, not only because of the miniscule number of individuals that they, in theory, tried to come up with who might be practicing the claims. They don't dispute that you have to first have a direct infringer before you can have an active indirect infringement. They simply don't have the proof on that.

Furthermore, the Federal Circuit case law is also clear that, even if you want to assume a label indication is an

infringing one, if you have noninfringing label uses -- and that discretion is left up to the clinical judgment of the prescribing physician, which Dr. Csaky admitted it would be -- then there is no inference of an intent to deceive.

Furthermore, with regard to their issues with regard to invalidity, they don't dispute that we really met our burden because, again, they keep focusing on what was expressly stated in a reference as opposed to what was inherently disclosed in a reference. They have -- our experts were firm on that issue that there was inherency through Dixon and other references. Even their attempt to try to get Dr. Stewart to agree with them backfired because he admitted that, as a person who is a prescribing physician, if he was going to apply a prn dosing regimen, he could easily envision how you could get to five loading doses before you go to eight-week dosing. So that pretty much backfired on them.

When it comes to obviousness, again, I'm not quite sure exactly what Mr. Berl is really trying to argue here with regard to the term "isotonic." If someone would have been motivated to make the formulation isotonic, and the undisputed evidence is that they would be, to say, "Well, I can come up with some theory as to why something might not be isotonic" does not negate the motivation of a person of ordinary skill in the art to actually make the formulation obvious.

Likewise, when it comes to these particular dosing

regimens, the motivation in the art was very clear that there was going to be -- that the doctors were already using extension methods, including after a monthly loading dose period. So the fact that Regeneron thinks that maybe they optimized them at five, routine optimization is not something that can be grounds for patentability.

With regard to indefiniteness and some of the other Section 112 issues that Dr. Stewart identified, as Dr. Stewart mentioned, Dr. Csaky has nothing in his expert report suggesting that the particular disease indications he identified will not work. So that nixes Claim 6.

And when it comes to the specification, again, the fact that the number 4 or the number 5 might appear somewhere in a specification does not satisfy the Federal Circuit's blaze marks test.

So we have met our burden to show indefiniteness. We have -- I'm sorry -- nonenablement, written description. We put forth the evidence of indefiniteness. That wasn't even addressed in terms of their inconsistent metrics that Regeneron is trying to propose for the term "approximately." So we have certainly met our burden on each of the elements with regard to the dosing patents and all the defenses that we have raised.

With regard to the formulation, the '865 patent claim, I'm sure Mr. Salmen will kick me off the podium if I say anything wrong, and we'll probably want to add to it, but let

me just try to --

THE COURT: Probably in the form of a sticky note, but go ahead.

MS. MAZZOCHI: We love those sticky notes, especially if they are not going to keep a protein from falling out of solution.

But, you know, on this question of aggregation, again, what I think that Regeneron is really trying to do is they are trying to renegotiate, reopen, and modify the Court's claim construction. The claim construction was clear because the scientific literature is clear that a cosolvent is something that will in fact increase the amount of substance that you have in solution.

And for all of the drama that's been going on back here, nobody's disputing what the phenomenon is. It's just that Dr. Trout is trying to say that, when you're preventing aggregation, that's somehow the flip side of improving solubility. It simply is not.

You know, Mr. Berl keeps saying you put more in there. You are not putting more in there in the context of our formulation. It starts in solution. It stays in solution. And the fact that you've said, well, maybe you've put some bumper guards up to make sure that you don't come out of solution, that is not increasing the overall solubility of the substance.

We're not starting at 30 mg/mL putting a material in there and now it's getting us to 40 mg/mL. That's not -- what's what you actually use a cosolvent for. We're not starting out with a lyophilized formulation that maybe was at half the concentration stored that way for stability purposes. Now we're going to add a cosolvent to it as we reconstitute it so that we can expand the nature of the formulation. That's not what's happening here.

All that's happening is we started at 40 mg/mL. We stay at that concentration. And we don't need to have the polysorbate in there to increase the concentration because we're not increasing the concentration. We're not using it to stuff more aflibercept into the existing formulation.

So, furthermore, when it comes to some of the questions with regard to anticipation, again, I'm going to take issue with Mr. Berl's suggestion that, when the prior art disclosed 10 to 50, that that somehow is not good enough to anticipate a milligram range of 40.

And the arguments that they're trying to make here again, they either have an obvious and anticipation problem or they have a Section 112 enablement problem and they also are not going to be able to claim the benefit back to their earlier applications. Because here again -- when the Federal Circuit has identified situations where you have a range and you are going to now say I've found something within the range I'm

going to call patentable, you also have the burden to come forward and show that it's called a result-effective variable, that there's something unique or special about this particular point in the range that's not shared by other formulations that are within the same scope of the range.

There is no evidence in the record that there's something magical here about 40 mg/mL formulations that's unique, distinct, and different from the 10- to 50-milligram ones. And if it is, then their specification certainly hasn't enabled the person of ordinary skill in the art how to identify it, find it, or get there. And that's part of what our Section 112 arguments are all about.

That's likewise the same argument that condemns their ability to claim backwards in their priority applications. If they're going to start to say that our particular combination -- I call it their particular combination of the jigsaw puzzle that's sitting in the claims.

If they want to say there's really something special about each particular range that we've pinpointed as against the prior art background of this being part of the normal recipe that people were using -- a surfactant, a solubilizer, a buffer -- then their specification doesn't enable it. And that's why, again, they don't have any reason to say that these are unique or distinct. And if they are, then it fails under Section 112.

And that's why, Your Honor, we do keep getting back to -- you know, again, Mr. Berl was saying, oh, well, look, we can find some instances where somebody will routinely optimize a formulation. Yeah, if you actually have an existing formulation, there are routine steps that somebody can go through to try to optimize it.

The problem is that these claims are not limited to just a narrow scope or a narrow range. These claims in the '865 patent are directed to an incredibly broad range. And they have not actually taught the person of ordinary skill in the art how to do that.

That's why -- when you start going through the undue experimentation factors, that's why they exist to determine is -- in the ultimate legal question for you, is it undue? Is the amount of burden that the person of ordinary skill in the art has to go through? Do we have broad claims? We sure do.

Are they saying the art is unpredictable when it comes to the obviousness analysis? They sure are.

Are they saying things like, oh, a person of ordinary skill in the art wouldn't be able to do these things because they were teaching away with motivations against it? Yes.

So even when you have, then, the '865 patent in hand and you ask the person of ordinary skill in the art would you be able to make the full scope of what is claimed? the answer then becomes no, not without a significant massive amount of

experimentation, where you are now back in trial-and-error land.

So yes, could the person of ordinary skill in the art take, for example, the existing census formulations that were designed for intravitreal purposes and actually put them forward -- you know, use them -- put aflibercept into them, for example, or take the Fraser formulation that's existing and optimize that? Of course they could.

But if you want to then say but what about -- but Regeneron didn't limit themselves to just the narrow claim. They went broad. And because they went broad, that's what the *Amgen* case is all about. The minute you decide you're going to go with a very broad claim, you better have the specification disclosure to support it. And here, they simply don't.

So, Your Honor, I know that you're going -- I'm assuming you're going to take all these under advisement and these will be the subject of posttrial briefing; but, again, that's essentially an outline of where things are here.

THE COURT: I'll ask you the same question counsel asked Mr. Berl.

Why should polysorbate care what name we ascribe to it?

MS. MAZZOCHI: I think that what we care about is the Court's claim construction. The Court --

THE COURT: That's a living and breathing

construction, correct?

MS. MAZZOCHI: The Court's claim construction contemplates a behavior profile.

THE COURT: Right. But that can change through completion of trial, correct?

MS. MAZZOCHI: And that's exactly the point, is that there are instances where polysorbate can behave as a cosolvent, when it is driving more aflibercept versus your starting point into solution.

That's not -- that is not what is happening here. So -- and that's where we fundamentally just object to what Dr. Trout is trying to do. He is trying to say that preventing a protein from denaturing or preventing an existing amount of protein from crashing out of solution, that that is somehow equivalent to increasing the amount in solution. They're fundamentally different things.

And I think that what you see, then, at least in Mylan's BLA, is when we're using, for example, the terminology that we do -- and I don't want to get -- I don't remember which part is public or not.

But when we are talking about our -- things within our BLA, we are making representations to the FDA this is the behavioral consequence of what's happening. This is how it is working. This is how it's functioning. This is how it's behaving.

So our terminology that we have presented to the FDA is describing how it's behaving in solution. And what we never said is we are using this to make sure we can fit enough aflibercept in the formulation in order to meet our specification goals. If we did, it would be called a cosolvent; since we're not, that's why it's not there.

So I agree that the Court should be looking at the behavior of what's going on, but what they're trying to do is refine the term "cosolvent" to give it a new scientifically inaccurate reading. They're trying to basically graft the function and behavior of a stabilizer, of a surfactant, into the definition of cosolvent through semantic games. And we just fundamentally disagree that that's appropriate to happen here.

So I don't know if I've -- I don't know If I've answered your question. Maybe I haven't answered your question. But that to me is fundamentally where we're coming from here.

THE COURT: It strikes me at this juncture -- I mean, polysorbate 20, Tween 20, whatever we want to call it in terms of what the substance is, is on the list of ingredients, right?

MS. MAZZOCHI: Sure.

THE COURT: There's no dispute about that. What strikes me is the more operative dispute here is does it matter whether or not the claims of the patent ascribe the right

moniker to it as to what its function is? Is that as dispositive as I intuit at this point?

MS. MAZZOCHI: Yeah. And I think that it is important because when the claim uses the term "cosolvent" -- and remember, Your Honor, they have claims that are specific to polysorbate. That's Claim 51. So they had the ability to say -- and they do have claims that say, "I hereby claim a formulation with polysorbate in it, and we don't care about its function. We don't care about its role."

They have those claims. Those aren't asserted here.

They've tried to use broader claims where they did impart a functional concept, buffer, cosolvent, stabilizing agent. They're trying to take those broad functionally defined terms and say we're now going to cover this ingredient.

By the way, Your Honor, they also clearly thought that the term "cosolvent" was different from a stabilizer. They used both of those terms in Claim 1. So for Regeneron to now turn around and say, oh, well, now I'm going to treat them as if they are synonymous terms violates a whole host of claim construction rules.

So here again, I understand -- and this is where I think, Your Honor, there has been a lot that the parties have agreed on. But what we fundamentally don't -- I mean, when it comes to --

THE COURT: I may not need my second cup of coffee

after this, Counsel, all recently filed pleadings to the contrary. But go ahead. We might just hear what all we've agreed upon.

MS. MAZZOCHI: In the sense of the parties -- the parties are not disputing what's in the formulation. They're not disputing amounts in the formulation. And Regeneron, for example, is not disputing that we have histidine. Histidine is also helping to -- it performs a role within the formulation.

But if you start then getting away from, well, I'm going to let them say that cosolvent can just mean anything that helps or anything that prevents aggregation or anything that helps prevent denaturation, that's fundamentally rewriting the claims.

So they chose to put terms in their claims that had functional aspects to them -- buffer, stabilizer, cosolvent. Our evidence and everything that we've submitted to the FDA, we submit, confirms we are not using that function with that ingredient. We're not using polysorbate to achieve the functional role of a cosolvent.

What is that functional role? It has to be increasing, not keeping it in, not -- if you've got the same number of players on the team or on the roster and you say I want to increase the roster, that means you're putting more on.

But, by contrast, all we're saying is we've got nonplayers on the field and we're just trying to make sure none

of them has to run off. That's not putting more people on the roster; that's just trying to keep everything status quo.

What they're trying to say is that, well, if you're trying to maintain the status quo, then somehow you're increasing and you're changing something. It's just -- it's not.

So that's why, you know, when it comes to what's going on here, it is very important what they actually put in their claim. And we can't start erasing those claim limitations. We just can't.

And frankly, Your Honor, if they had wanted to make a doctrine of equivalence argument, which it seems like they might be trying to now make, they had every opportunity to do that months ago. But then they also would have had to comply with the Federal Circuit standards on equivalent function, equivalent way, equivalent result, showing that they didn't disclose but not claim things, which are legal restrictions. They wouldn't have been able to meet those standards, which is why we don't have a doctrine of equivalence analysis here.

So they offered literal infringement. They have a claim construction. The claim construction requires that a cosolvent has to actually help dissolve, get more things into solution. And they haven't demonstrated that our ingredients are going to do that.

Hopefully, that answers your question.

THE COURT: Understood.

MS. MAZZOCHI: Thank you.

THE COURT: Given the context of a bench trial proceeding and the myriad of questions the Court has to sift through, the Court's going to, under 52(c), decline to render judgment at this point but proceed with hearing evidence on that front.

Who will Regeneron's first rebuttal witness be?

MR. BERL: Your Honor, the first witness will be Karen Chu.

THE COURT: All right. We're going to take ten minutes at this point. I'll give Regeneron an opportunity to respond to the motion concerning Ms. Chu, and we'll go from there. We'll be at ease for ten minutes. Thank you.

(A recess was taken from 10:17 a.m. to 10:36 a.m.)

THE COURT: Regeneron's response to Motion 546.

MR. GREGORY: Good morning again, Your Honor.

THE COURT: Good morning.

MR. GREGORY: Your Honor, obviously, we have not had a chance to fully brief this issue in response to the motion that we received this morning at -- I believe it was around 7:00 a.m.

THE COURT: 6:49.

MR. GREGORY: I was close.

Respectfully, Your Honor, I think that we have a road map for dealing with exactly this situation. We've -- we're having this trial already. It's the same road map that we used with Dr. Yancopoulos and Dr. Furfine. And that is, respectfully, Your Honor, this is a bench trial. And I think Ms. Chu should be able to take the stand, provide her testimony.

If defense counsel feels that, in fact, we verge into issues or material or documents that are inappropriate somehow to use with Ms. Chu or to address through Ms. Chu, they could raise that in the posttrial briefing or in the course of her testimony.

I think that is, frankly, the beginning and end of the issue. I'm happy to discuss with particularity some of the arguments that I can discern from this brief that I've had a little bit of time to digest now.

The overriding argument seems to be that Ms. Chu's testimony -- the subject matter of her testimony is some sort of surprise. I'm not sure how that can be the case. So the facts are as follows:

Ms. Chu has been on our initial disclosures -- our Rule 26 disclosures since --

THE COURT: Yes. I don't think there's any dispute about that. She was deposed.

MR. GREGORY: And she was deposed for over seven

hours, a full day. You heard an hour of her testimony yesterday.

THE COURT: I have not heard what the weather was in the city of her deposition.

Sorry. I couldn't resist. Go ahead.

MR. GREGORY: So -- but to be clear, in those initial disclosures starting back in September, in an interrogatory response filed in January, in her deposition, in all these places, Mylan-Biocon was informed what the subject matter of her testimony would be. That's the conception, reduction to practice of the inventions found in the '601 and the '572 patents as well as the clinical properties of aflibercept. That's been consistent in every one of these written communications.

Ms. Chu has been on both parties' witness lists since the first witness lists were exchanged. I candidly don't know how much more I can explain about what Ms. Chu's going to testify to without actually putting on her testimony and walking through it with Your Honor and with defense counsel here.

THE COURT: Understood.

Counsel, she's been disclosed as a witness. You've had the opportunity to depose her. I'll be candid with you. I'm at a loss.

MS. MAZZOCHI: Sure. Your Honor, we were able to

depose her as a 30(b)(6) witness and a 30(b)(1). But at the outset of her deposition, I put the initial disclosures in front of her and said okay, what are you going to testify to at trial?

THE COURT: Did you ask her what knowledge she had about it?

MS. MAZZOCHI: Yeah. She didn't even --

THE COURT: The words matter. It's a completely different question. I've read the exchange not only in the last volley we had over Ms. Chu's testimony but also the motion that was filed this morning.

The words matter. The objection to what are you going to testify to at trial is, I think, a valid one. But there's different questions that could have been asked, I guess, is my point.

Let me get to this point as well. Ms. Chu testified under oath. If she gets up here and all of a sudden has learned a whole lot of new things that she didn't know at the time, that sounds like a very compelling and rich cross-examination that will weigh heavily in this Court's assessment of her credibility.

But I'm not inclined -- I'll say I'm going to deny the motion at this juncture. I don't think, as a matter of law, it is proper to preclude her testimony consistent with the Court's prior rulings. She was disclosed. She was deposed.

If she's changed her story or augmented her knowledge that she did not have at the time, counsel is certainly welcome and no doubt capable to expose that direct cross. So that motion will be denied.

We'll take up the other motion with respect to Drs. Ryder and Russell when we get to them if Regeneron intends to call them.

Mylan may call its next witness -- I'm sorry.

Regeneron may call its next witness.

MR. GREGORY: Thank you, Your Honor.

Regeneron calls Ms. Karen Chu.

THE COURT: Counsel, before you begin, just a warning, if I get a message that indicates I need to walk out of here in 18 minutes because of traffic to retrieve a kid, I'll let everybody know, but then we may take an early lunch break today. Just FYI.

With apologies to you, Ms. Chu.

MR. GREGORY: Understand, Your Honor. I have a 4-year-old myself and I know how it goes.

THE COURT: Understood. I-79 has been a joy the last few weeks.

With that, Counsel, you may proceed.

MR. GREGORY: Thank you.

KAREN CHU, PLAINTIFF'S WITNESS, SWORN

DIRECT EXAMINATION

BY MR. GREGORY:

Q. Ms. Chu, could you please introduce yourself to the Court.

A. Yes. Good morning. My name is Karen Chu.

Q. Where do you currently work, Ms. Chu?

A. I currently work at Regeneron Pharmaceuticals in Tarrytown, New York.

Q. And I want to come back and talk about how you got there and your role. But just first, what is your job title at Regeneron?

A. My current title is executive director of clinical strategy and execution for ophthalmology.

Q. And what are your current responsibilities generally in that role?

A. My responsibilities are that I oversee all of ophthalmology clinical development alongside our therapeutic area head. And that includes interacting with our research and preclinical groups for molecules coming into the clinic as well as the design, strategy, and execution of clinical trials.

Q. You mentioned just now clinical trials and clinical development. Just so we're clear on what we're talking about, what are clinical trials?

A. So clinical trials are the studies done in humans to support bringing a therapeutic product to potential commercialization.

Q. So I want to back up now and talk a little bit about how you got to where you are today. So can you give us a little bit of background on your education.

A. Sure.

So I have a bachelor's of science in biology from Cal Poly San Luis Obispo. And then I have a master's of science in human nutrition from Columbia University.

Q. How did you come to work at Regeneron?

A. So at the end -- as part of my master's program, I was required to complete thesis research. And I did that research at St. Luke's Roosevelt Hospital in New York City and was exposed to clinical research and clinical trials there. They had an obesity clinical research unit.

And so I knew, coming out of my graduate program, that I was interested in clinical research. I actually moved back to California and was subsequently hired at Sequus Pharmaceuticals as a clinical trial assistant.

Q. And where did you go from Sequus?

A. So from Sequus I subsequently worked for Purdue Pharma as a regulatory compliance or clinical quality assurance associate.

Q. And what was your next stop?

A. After that I went to a CRO, or a contract research organization, called Barton & Polansky. And there I was a clinical project manager helping to oversee the conduct of

Phase IIIB clinical trials in HIV.

Q. So still doing clinical trial work at that point?

A. Absolutely.

Q. And from there what was the next stop in your career path?

A. So after Barton & Polansky I was hired by GenVec. They were a small gene therapy company based in Gaithersburg, Maryland. And they did a lot of work in New York City with their scientific founder at Cornell.

Q. What kind of diseases or disorders was GenVec looking to treat?

A. So we had gene therapy products for both oncology indications as well as a product that we were testing in ophthalmology indications, specifically AMD at the time.

Q. And why did you ultimately leave GenVec?

A. So I was at GenVec for over four years. And towards the end of my time there, there were some changes in the gene therapy field that made it more difficult for the company to stay funded. And we -- the company had to make some hard decisions and laid off a number of people.

At that time I was not laid off, but it certainly didn't portend for a positive future for the company. So I started looking around for other opportunities at that time.

Q. Is that how you ultimately arrived at Regeneron?

A. Exactly. So I knew about Regeneron from mostly the

oncology field, because at that time anti-VEGFs were presenting brand-new data and were very much seen as a revolutionary treatment. And so I knew that Regeneron had an anti-VEGF product that they were developing as well as the fact that they happened to be in New York, which was convenient.

Q. And just so we can put this kind of in time, what year was it when you started with Regeneron?

A. I started with Regeneron in 2003.

Q. And what was your title at that point?

A. I was hired as a clinical trial manager.

Q. And what was your role at that point in 2003 when you first started?

A. So primarily I was brought in to help implement and execute the clinical trials. At that time we had mostly early phase clinical trials. And having had experience in both oncology and ophthalmology, I was a very good fit for the team at the time. But my role quickly pivoted to being very much focused on ophthalmology.

Q. And can you describe for the Court kind of how your responsibilities at Regeneron have changed over the last two decades in your time with the company.

A. Sure. So I've certainly -- my entire career at Regeneron has been in ophthalmology. And, certainly, I have been part of the Eylea development program really from the time that it came from our preclinical group and entered the clinic.

When I started at Regeneron, Regeneron was a small company. We were only about 500 employees total. And in our clinical and regulatory group, I think we were about 30 people total. So everybody wore a lot of different hats. And I had the great opportunity to be involved, really, from the very beginning in discussions around development strategy as well as had input into study designs, et cetera.

Q. Ms. Chu, do you have a medical degree or formal medical training?

A. I do not.

Q. How is it that you're able to contribute to the clinical research and development work at Regeneron without that educational background?

A. Sure. So I have over 25 years of direct experience in clinical development in various therapeutic areas but over 20 years of experience in ophthalmology and specifically in retina clinical development.

Q. So I'd first like to discuss just a little bit Regeneron's clinical development efforts for aflibercept for the treatment of wet age-related macular degeneration. Is that okay?

A. Sure.

Q. Just as some background to begin, can you remind me what stage clinical trials did Regeneron ultimately perform of aflibercept in wet AMD?

A. So we performed Phase I, Phase II, and Phase III clinical trials in wet AMD.

Q. And what do Regeneron's Phase I clinical trials entail in ophthalmology?

A. Yeah. So typically -- so with ophthalmology clinical trials, our Phase I trials are relatively small. These are considered first in human trials; so the primary purpose is to get initial safety information.

So typically these trials would be less than 50 patients total, and we would be looking, as I said, to get initial safety but also to do dose ranging and get additional information around the kinetics of the drug and systemic exposure to the drug.

Q. And what do Regeneron's Phase II ophthalmology trials typically involve?

A. So Phase II trials are what we call proof-of-concept trials. So these are the first trials where we're really looking to get a confirmation of efficacy or biological effect. And we're -- of course, we're always looking for additional safety information. And typically Phase II trials tend to be a bit larger, somewhere between, I would say, 100 to about 300 patients at the most.

Q. And how about Regeneron's Phase III ophthalmology trials? What do those typically look like?

A. So Phase III trials are the pivotal trials that we

plan to, if successful, hopefully submit to health authorities to support a marketing application. And so these are trials that are what we call powered for a statistical difference between treatment groups. And they can typically be very large, so on the order of hundreds to thousands of patients.

Q. Could you give us a sense of how long it typically takes Regeneron to plan and execute its Phase III ophthalmology trials?

A. So the planning for even the late phases of development really begins very, very early in product development. So even before we would bring a product into the clinic, we would be looking at -- we would be laying out what we think the clinical development plan would look like, and that would include kind of a high-level review of Phase I, Phase II, and Phase III clinical trials.

Obviously, as we conduct the clinical trials and receive more information during development, we refine our thoughts and our strategies around how we will move forward. And so from the time that we would have that Phase II or proof-of-concept data to the initiation of a Phase III protocol, it would take somewhere between 18 months to a year.

Q. And how expensive is it for Regeneron to run a Phase III ophthalmology clinical trial?

A. So our -- in my experience, our clinical trials typically cost about 150,000 to $200,000 per patient. So when

you're talking about a trial on the order of, you know, 600 to 1200 patients, that can easily run in the hundreds of millions of dollars.

Q. In your experience, does Regeneron typically disclose publicly the details of its clinical trials or maintain those details confidentially?

A. We're always very careful about ensuring that we have confidentiality agreements in place, even when we're having discussions with external experts about aspects of planning or early, you know, decisions around indications to potentially move into, et cetera.

And during the clinical trials all of the investigators and their stuff operate under the clinical trial agreements, which include a confidentiality clause.

Q. Now, are patients in Regeneron's clinical trials subject to confidentiality agreements?

A. No, they are not.

Q. Have you ever heard of the term "investigator brochure"?

A. Yes, I'm aware of that.

Q. Could you tell us what that is in your experience.

A. Sure. So the investigator brochure is a document that summarizes all of the available data for that investigational product. So it would detail important information for an investigator to know, like the toxicology

results, any safety information we have received from ongoing or if completed clinical trials, as well as any information from the class itself or what we know about the mechanism of the drug.

Q. And do patients or subjects in Regeneron's clinical trials get access to the investigator brochure?

A. No, they do not.

Q. Do patients in Regeneron's clinical trials know what dosing regimen or arm of the trial they're in?

A. No. So, obviously, informed consent is a major focus, and every patient who enters a clinical trial is provided adequate time to ask questions and review the informed consent form before agreeing to enter the trial. And we always strive to put sufficient information into the informed consent form so the patient understands the procedures and the design of the study.

Typically, especially in Phase III trials, the patients as well as the staff are masked to treatment assignment or blinded to treatment assignment. So the patient typically would not know what treatment assignment they were receiving.

Q. Do patients in Regeneron's clinical trials know if they're receiving -- in trials where a sham injection is employed, do patients in those trials know if they're receiving an actual injection as opposed to a sham injection?

A. No, they do not. And the purpose of the sham procedure is really to mimic as closely as possible without actually piercing the globe, the intravitreal injection procedure. So they're prepped in the same way and the needle of the syringe -- or sorry -- the hub of the syringe is pressed against the globe so the sensation is similar.

THE COURT: Counsel, if I could interrupt, and, Ms. Chu, if this is outside your scope. So we're not talking about a placebo. We're talking about a fake injection that doesn't actually puncture the eyeball.

THE WITNESS: That's right.

THE COURT: Okay. All right.

THE WITNESS: If it helps you, I know --

THE COURT: None of this helps me. I'm still having all manner of eyeball and contact fake discomfort. But go ahead, ma'am. Sorry.

THE WITNESS: Well, I hope this will help you.

THE COURT: Thank you.

THE WITNESS: The way that these physicians complete the intravitreal injection, the patient -- they certainly don't come at the patient from right in front of their face with a needle. So you -- typically, a patient is reclined in a chair, and they prepare the injection behind the patient and they come at them from behind so the patient really never has a chance to see the syringe or the needle.

THE COURT: Okay. Don't think that helped, ma'am, but thank you.

Counsel, go ahead.

MR. GREGORY: I have the exact same question, Your Honor.

THE COURT: The sneak attack sham injection. Understood. Go ahead, Counsel.

BY MR. GREGORY:

Q. Ms. Chu, do patients in Regeneron's clinical trials typically know the technical details of the product they're being administered?

A. No. So the investigators brochure, obviously, contains a high-level description of the product, but as we've discussed, that's typically not provided to the patient.

Q. Do patients in Regeneron's clinical trials know the formulation of the drug product they're being administered?

MS. MAZZOCHI: Objection, Your Honor. Calls for speculation as to what the patients know.

THE COURT: Sustained.

BY MR. GREGORY:

Q. Does Regeneron provide information to the patients in its clinical trials about the formulation of the drug product they're being administered?

A. No, we do not.

Q. In the informed consent that is given to the patients

as part of their participation in the clinical trials, it does not contain that information, correct?

A. It does not.

Q. Do you recall a time frame in or around 2007 when Regeneron was engaged in planning for its prospective at that point Phase III wet AMD trials?

A. Yes. We actually began our development in DME back -- all the way back beginning in 2004.

Q. What role did senior management play in those development discussions around the Phase III trials?

A. Yeah. So as I've already mentioned, Regeneron was and in many ways is still a small company, and so our senior management has always been heavily involved in discussions around the clinical development planning and strategy as well as decisions around study design.

Q. Just for clarity, was it the -- what Phase III planning began in 2004? Was it wet AMD? Was it DME? What indications in that planning? What began then?

A. I mean, obviously, in 2004 we were already thinking about development in DME, but in 2004 we were really focused on what we felt was the initial indication or the priority indication, which was neovascular AMD.

Q. What was Dr. Yancopoulos's typical role in those discussions around Phase III wet AMD planning?

A. So Dr. Yancopoulos was heavily involved and certainly

was part of many, many discussions related to the clinical study designs and strategy, and ultimately he was the final decision maker regarding aspects of the study design and clinical development program.

Q. I'd like you to take a look at a document for me, Ms. Chu. And you should have a binder in front of you, and we're also going to put it up on the screen. But I'd like you to take a look at PTX 0188.

Let me know when you have that in front of you.

A. Yes, I see that.

Q. And do you recognize this document?

A. Yes. This is an email from March 28, 2007, regarding decisions that need to be made to facilitate the beginning of the first AMD pivotal study.

Q. And I'd like you to take a look at item number -- just for clarity, you are a recipient of this email, right?

A. Yes, I am on this email as a recipient.

Q. It's dated March 28, 2007?

A. That's correct.

Q. And I'd like you to take a look at Item Number 2 in the body of the email.

Can you please explain to the Court what was under consideration at this time.

A. Yeah. So in this email we were planning on a four-arm study with approximately 1,200 patients with the doses

of .5 milligrams, 2 milligrams, and potentially 4 milligrams with different intervals being considered, q4, q8, and q12.

Q. There hadn't been a decision yet on the exact dosing interval?

A. At this time we had not made a final decision.

Q. Could you please take a look at Item Letter G at the bottom of the email. Do you see that?

A. Yes, I see that.

Q. And so what is being discussed here?

A. So this was an action item for an internal meeting to be set up; so that way we could make decisions -- have discussions and make decisions about these elements that would facilitate the finalization of the -- what we call the clinical study concept document, which was the precursor to the clinical protocol.

Q. And when was that meeting set for?

A. That was set for April 13th, 2007.

Q. Could you take a look back just briefly at that.

A. Oh, sorry.

Q. Just for clarity. The first line reads, "Kathleen to set up a meeting next week, week of April 2nd."

A. Oh, sorry. The week of April 2nd.

Q. Let's look at DTX 227, which should also be in your binder, and we'll also put it up on the screen.

Do you have DTX 227 before you, Ms. Chu?

A. Yes, I see that.
Q. Do you recognize this document?
A. So this is an email from April 2nd, 2007.
Q. And you're a recipient of this email?
A. Yes, I am.
Q. And there's a -- the first line of the body of the email reads, "Below is a summary of the decisions and actions from the AMD Phase III program meeting," right?
A. Right.
Q. Could you please take a look at the decision bullet a little bit further down the page and explain to us what decision had come out of this meeting.
A. So we had made a decision about the study design and the arms that would be included in the Phase III -- one of the Phase III AMD studies, the 0605 study, which was the VIEW 1 study. And we were planning to include a Lucentis group as a control, .5 milligrams aflibercept every four weeks, 2 milligrams every eight weeks after three initial monthly doses, and a 2-milligram-every-four-week group.
Q. Ms. Chu, do you specifically recall how that decision was made in this meeting?
A. I do not specifically recall.
Q. What was the typical practice at Regeneron for making these type of clinical trial design decisions?
A. So typically the study team would be charged with

coming to our senior management with proposals and any supporting data or other aspects of the program that would support our proposals, and then we would have a discussion about it with senior management. And then ultimately a final decision would be made about how to move forward.

Q. What was Dr. Yancopoulos's typical role in those decisions?

A. Dr. Yancopoulos was very involved in the discussions as well as in any analysis of data. He very often would ask for additional data or additional analyses to be presented, and he was ultimately the final decision about the study -- the groups that went into the study.

Q. I want to direct your attention to the final action item, the bottom of the email. It says, "Discussed proposed development plan with Darlene Jody," and then it's Bob, George, Peter.

Who was Darlene Jody?

A. Darlene Jody was with Bayer at the time. She was a senior executive responsible for the collaboration that we had with them for Eylea.

Q. Did Bayer make the Phase III trial design decision that we just saw in the upper part of this email?

A. No, they did not. The nature of our collaboration with Bayer was such that Regeneron held the final scientific decision-making for the program. So while we would certainly

have discussions with them and include members of their team both at the team level as well as the senior management level in our meetings and discussions about aspects of the clinical development program, ultimately Regeneron had the final say.

Q. If Bayer had come up with a decision that we were looking at in the upper part of the email, would the final action item here have been discussed, proposed development plan, with Bayer?

A. Well, they would probably have a set of minutes that said they should discuss it with us.

Q. Okay. Let's take a look -- let's turn our attention, actually, to the question of Regeneron's development of aflibercept for the treatment of diabetic macular edema. Okay?

A. Sure.

Q. And I may slip from time to time and call diabetic macular edema DME, but you'll understand what I'm talking about, right?

A. Yes.

Q. Approximately when did Regeneron begin its clinical development of aflibercept for the treatment of diabetic macular edema?

A. Yeah. So like I already said, we actually began in 2004 with a study utilizing intravenous delivery of aflibercept for the treatment of DME.

Q. And that was a Phase I study?

A. Yes.

Q. Did you eventually also do a Phase I intravitreal study?

A. We did. So we eventually did a small study with five patients with intravitreal delivery.

Q. Did Regeneron perform Phase II studies in DME?

A. Yes. So we conducted the 0706, or DA VINCI study, which was a Phase II study in diabetic macular edema.

Q. Did Regeneron perform or conduct Phase III clinical studies in DME?

A. Yes. Our Phase III studies were called VIVID and VISTA.

Q. I want to put another document before you. I want to direct your attention to, actually, a pair of documents that go together. One is PTX 3150 and the next is PTX 3151, both of which, again, should be in your binder. And we'll put the first of them up on the screen right now.

A. Okay.

Q. Do you recognize this document, 3150?

A. Yes. So this is an email from May 2nd, 2007, with a high-level summary of a DME planning teleconference.

Q. Did you attend that DME planning teleconference?

A. Yes, I did.

Q. So I want to take a look now at the attachment to PTX 3150. This will be PTX 3151.

Do you recognize this document?

A. Yes. So this is a summary of the discussion at that same teleconference.

Q. And I want to direct your attention up to the attendees list at the top of the document here. Could you let me know or tell me who the external doctors were who attended this teleconference.

A. Sure. So Dr. Lloyd Aiello from Harvard University, Neil Bressler from Wilmer Eye Institute, Quan Nguyen also from Wilmer Eye Institute, and Dr. Jeff Heier from Ophthalmologic Consultants of Boston.

Q. Did Regeneron have questions for those assembled doctors about the nature of diabetic macular edema?

A. Yes, we did.

Q. And I want to take a look at the first bullet here, the first item. Coming out of this call with these assembled doctors, what was your understanding about the progression and the nature of DME relative to, for example, wet AMD?

A. Yeah. So I think we understood that, first, this is a very different eye disease because it stems from, obviously, the underlying diabetes that these patients have; and we wanted to know more about exactly how these patients are diagnosed, treated, et cetera.

And out of this teleconference we had a better understanding that DME is -- can be not only a slowly

progressive disease but also one that fluctuates much more than AMD.

So in AMD the typical course for patients was that, within the year after diagnosis with neovascular AMD, patients would precipitously lose vision and that vision could not be regained. But in DME we understood that vision is often more recoverable. And so it was a very different disease from that perspective.

THE COURT: Yes, Counsel.

MS. MAZZOCHI: Your Honor, I think now we're starting get to the point where Ms. Chu is offering the equivalent of expert testimony. She's just expounding on DME generally, not what did she know back at that time period. She's offered as a 30(b)(1).

THE COURT: Understood.

Stay within the lane of Ms. Chu's capacity as a witness here, Counsel.

MR. GREGORY: Yes, Your Honor. My question was specifically about her understanding coming out of this meeting. I'll try to keep it to that narrow lane.

THE COURT: Understood.

BY MR. GREGORY:

Q. Ms. Chu, I want to direct your attention to the third bullet on this page, and I want -- I'm asking some narrow questions here, okay, with the Court's guidance in mind.

Did Regeneron pose to the assembled doctors on this teleconference any questions about the treatment outcomes of patients with DME?

A. Yes. So we were obviously very interested in the current treatment landscape as well as their expectations around what outcomes they could expect or anticipate with the current treatments available, including laser and steroid.

Q. And, again, I want to be narrow here. What was your understanding at the time, including coming out of this call with these doctors, about those treatment outcomes?

MS. MAZZOCHI: Your Honor, I'm just going to object as well to the relevance of this. We're all -- the questions that are before the Court relate to the validity of these patents with regard to the perspective of a person of ordinary skill in the art. And to the extent she's been offered on issues relating to conception or reduction to practice, again, we don't think that it's been established that she has knowledge on that.

But going through all this history is not really relevant to any of the issues here. I'm concerned, again, that Regeneron is trying to just -- actually, I'm not going to predict what's going on in their heads.

I'm just going to object that it's not relevant to the issues before the Court.

THE COURT: How is this line of questioning relevant,

Counsel?

MR. GREGORY: Of course, Your Honor. While the Federal Circuit has been very, very clear that the inventor's path to the invention cannot negate the invention or prove obviousness, the Federal Circuit has also been equally clear that the inventor's efforts, the roads that they went down, the roads that they did not go down, their understanding can be relevant to, for example, the motivation to combine elements of the prior art or whether there was a reasonable expectation of success.

Ms. Chu is here talking about the clinical development. Dr. Yancopoulos's invention occurred within the context of the clinical development program. They didn't occur in a vacuum. It was in the context of this program and Regeneron's understanding of these disease states at the time and of what was going on in the world at this time, and Ms. Chu is providing some of that.

THE COURT: Understood. Overruled.

MR. GREGORY: Your Honor, I'll move on from this document quite quickly.

BY MR. GREGORY:

Q. I want to look at Item Number 1 once more along with an item from the -- I believe it's the third page of the document. We put it up on the screen here.

I want to understand if Regeneron asked the doctors

that it assembled about the available DME treatment options at this point in time.

A. Yes. So we absolutely had a discussion about available treatments. And, you know, certainly, as I already mentioned, laser and steroid were being used as treatments for DME, and we also understood that the patient's underlying diabetic status was something that was a focus for these physicians as well.

Q. I have one more question about this document, Ms. Chu. Can you look at -- I think it's the final page, Item Number 5.

Do you see there's a question there or there's an item about competitive landscape and a reference to Lucentis? Do you see that?

A. I do see that.

Q. What is Lucentis?

A. So Lucentis is another anti-VEGF molecule that was being developed by Genentech.

Q. And was Regeneron monitoring the status of Lucentis's development?

A. Yes. We were very interested in the status as well as their decisions around development with Lucentis.

Q. I want to move to a different document. This is going to be DTX 8190, which again should be in your binder. I will also put it up on the screen.

A. Okay.
Q. Do you have DTX 8190 before you?
A. Yes, I do.
Q. Do you recognize this document?
A. Yes. So this is a summary of the EMEA's scientific advice procedure that was requested by Bayer.
Q. And I want to look -- and Bayer was your codevelopment partner at the time?
A. Correct.
Q. I want to take a look at the third page of the document, and there's a sentence about midway down -- we have it called up right here -- the sentence that begins "based on this experience."
Do you see that sentence?
A. Yes, I do see that.
Q. First, just to be clear, whose position is being set forth here? Is this Bayer's?
A. No. So this would be the joint position between Bayer and Regeneron.
Q. And I just want to be very clear. The sentence reads, "Based on this experience, we believe that the doses and dosing intervals for VEGF Trap-Eye for Phase III in DME can be selected based on the results of the Phase II study in patients with AMD."
Do you see that?

A. I do see that.

Q. To be clear, was it Bayer or Regeneron's position that they could predict the success of a dosing regimen to be employed in the Phase III trial solely on the basis of this Phase II data?

MS. MAZZOCHI: Objection, Your Honor. Again, this is attempting to elicit expert testimony. To the extent Mr. Gregory said that this was going to be relevant to anything on reasonable expectation of success, reasonable expectation of success is assessed from the perspective of a person of ordinary skill in the art. So this is not relevant to that question.

If their expert wanted to rely on it because he thought it was relevant to his opinion, he could have. He didn't. So we don't need this -- so this witness's testimony is simply not germane to that issue.

MR. GREGORY: Again, Your Honor, the inventor's path can be reflective of, in support, a lack of reasonable expectation of success and a lack of motivation to combine the elements in the prior art. This is a Regeneron -- as she just testified, a Regeneron and Bayer joint document that she saw at the time. I'm asking her to clarify the meaning of this sentence.

THE COURT: Understood. And we're going to hear from experts, Counsel, presumably on this very point. Her testimony

is not going to be credited with that respect. This strikes me as background and factual information leading up to what we're going to hear from the experts.

Objection overruled.

BY MR. GREGORY:

Q. I'm not sure if I actually got an answer to that question; so I'm just going to repeat it.

Looking at this first sentence that reads, "Based on this experience, we believe that the doses and dosing intervals for VEGF Trap-Eye for Phase III and DME could be selected based on the results of the Phase II study in patients with wet AMD."

But you had that sentence. My question was, to be clear, was it Bayer or Regeneron's position that they could predict the success of a dosage regimen employed in the Phase III trial solely on the basis of the Phase II data?

A. So, obviously, with any scientific experiment there's the possibility of failure. And although we understood that DME, like neovascular AMD, is a disease driven by overexpression of VEGF which causes the pathological neovascularization, we also understood that DME was a very different disease.

And so typically in our interactions with health authorities, our approach is to ask questions around minimum requirements. And so this was a question intended to frame support for our proposal in the document but not one that was

predictive of what we expected from the Phase III studies certainly.

Q. I want to now shift gears and take a look at a new set of documents. These are going to be PTX 3167 and 3168. Again, it's a paper and an attachment that go together.

Will you please let me know when you have them in front of you, Ms. Chu.

A. Yes, I have them in front of me.

Q. So do you recognize PTX 3167?

A. So 3167 is an email dated January 31st, 2008, highlighting some scenarios for a meeting that would be held the same day.

Q. And the first sentence says, "Enclosed are the DME scenarios that the team has put together for today's meeting"?

A. Right. So there was an attachment with a PowerPoint presentation intended to be presented and discussed at the meeting.

Q. There's an acronym on this page, JSC. Can you tell us what the JSC was.

A. So JSC stands for joint steering committee. And as part of our collaboration agreement with Bayer, we had several joint committees that were formed. The joint development committee was charged with overseeing all development of Eylea and included members from both Regeneron and Bayer. And the joint steering committee was the senior-level committee that

included members from both companies.

Q. I want to now look at the attachment. So this is PTX 3168. And in particular I want to take a look at the second page -- or the second slide.

This is a slide titled "DME Target Product Profile," right?

A. Yes.

Q. What is a target product profile at Regeneron?

A. So a target product profile is a document that we typically put together early in development just highlighting at a high level what we see as the sort of minimal as well as target claims that we would like to strive for for our product to be commercially viable or commercially successful.

Q. So to be clear, these TPPs -- these are a regularly prepared type of Regeneron document?

A. Yes.

Q. And these are commercial documents?

A. Typically they're driven by commercial. Clinical obviously has input in terms of the end points and expectations, but this is typically charged -- the responsibility of our commercial group.

Q. How many monthly loading doses were set forth in the TPP at this point in time?

MS. MAZZOCHI: Again, Your Honor, she's talking about -- she's talking about Regeneron documents, Regeneron's

perspective. She's being offered in her 30(b)(1) capacity. She's testified this is a joint collaborative document between Regeneron and Bayer.

This is not relevant to any of the issues relating to the commercial success or the motivation or any of the things that Mr. Teagan identified. It's not even relevant to his inventor's path because the cover email said that Mr. Yancopoulos was not present at this meeting. So how can this be in any way, shape, or form relevant to either Dr. Yancopoulos's path or --

THE COURT: Commercial success.

MS. MAZZOCHI: -- commercial success.

THE COURT: Counsel?

MR. GREGORY: Your Honor, again, it's the path to the invention. And this invention occurred in the context of this broader clinical development program. There is no, I think, dispute about that. All right? It was part of the clinical development program that these inventions occurred in.

The path to that invention is relevant to both the motivation to combine elements of the prior art as well as reasonable expectation of success. The roads that Regeneron did go down, the roads that it did not go down, the walls they bumped their heads against, that all goes to those issues.

I'm looking at here Regeneron's path to get to five loading doses. And as we see, there's no five loading doses on

this page.

MS. MAZZOCHI: And, Your Honor, again, motivation, reasonable expectation of success is assessed from the perspective of the person of ordinary skill in the art based on the prior art that was available at the time. These are Regeneron's internal documents. That's completely irrelevant to that question.

MR. GREGORY: Your Honor, I would point the Court to *Micro Chemical v. Great Plains Chemical*, 103 F.3d 1538, which I think is clear on this point.

THE COURT: Understood. Overruled.

MR. GREGORY: We can set this document aside.

BY MR. GREGORY:

Q. We've talked a little about Regeneron's planning for its own clinical trials. I think you mentioned previously that Regeneron was also monitoring the clinical trial work being performed by the folks who were developing Lucentis.

Do you recall that?

A. Yes.

Q. And those companies that was Genentech and Novartis, right?

A. Right. So Genentech had rights to Lucentis in the United States and Novartis outside of the United States.

Q. Did Genentech and -- or let's frame it like this: Was Lucentis approved for treatment of diabetic macular edema

in 2010?

A. No. I believe they received their approval for DME in 2012.

Q. And were they approved for -- was Lucentis approved for the treatment of diabetic retinopathy in 2010?

A. No. That came subsequent to their DME approval.

Q. Was Lucentis being explored in clinical trials for the treatment of DME in 2010?

MS. MAZZOCHI: Again, Your Honor --

THE COURT: Stop saying "again." What's the objection?

MS. MAZZOCHI: I object that he hasn't established this is her own personal knowledge. Again, she --

THE COURT: Understood. Sustained.

BY MR. GREGORY:

Q. Ms. Chu --

MR. GREGORY: May I try to lay a foundation, Your Honor?

THE COURT: I would encourage you to do so if you want an answer to that question ultimately, yes, sir.

MR. GREGORY: Thank you.

BY MR. GREGORY:

Q. Ms. Chu, were you monitoring -- you personally monitoring the status of Lucentis's clinical development in mid-2010?

A. Yes. It was part of my role to understand what the competitive landscape was.

Q. Did you have an understanding of -- I'm asking a narrow question right now.

Did you have an understanding of what clinical trials were -- of any clinical trials that were being performed with Lucentis in 2010?

A. So the Phase III RISE and RIDE trials were ongoing as well as, during that period of time, Novartis had a couple of studies called the RESOLVE and RESTORE trials.

Q. And did you personally have knowledge of what the dosing regimens were that were being tested in those trials in 2010?

A. So in RISE and RIDE, it was both .3 and .5 milligram monthly compared to sham. And in the RESOLVE and RESTORE trials -- in RESOLVE it was .3 and .5 milligrams with three initial monthly doses with the ability to double the dose at month one followed by prn dosing. And RESTORE was .5 milligrams with three initial monthly doses followed by prn .5 milligrams, three initial monthly doses followed by prn plus laser photocoagulation. And the control in that group was laser photocoagulation.

Q. Okay. I want to talk about what Regeneron was doing at this same point in time. In mid-2010 what was Regeneron's -- let me reframe the question.

In mid-2010 was there a Regeneron Phase II trial ongoing?

A. Yes. So the 0706, or DA VINCI, trial was ongoing in 2010.

Q. And in mid-2010 had Regeneron received any results from the DA VINCI Phase II DME trial?

MS. MAZZOCHI: Again, Your Honor, can she please not speak on behalf of Regeneron but on her own personal knowledge.

THE COURT: Sustained.

MR. GREGORY: Your Honor, I'm asking if the company received it. I can reframe the question if defense counsel would like.

THE COURT: Please.

BY MR. GREGORY:

Q. Ms. Chu, were you aware of any preliminary results from the Phase II DA VINCI trial as of mid-2010?

A. So the DA VINCI trial was a year-long trial with a week 24 primary end point. So at the beginning of 2010 we had received data from the Week 24 primary end point, but the study was ongoing through 52 weeks, or one year.

Q. Had you, personally, Ms. Chu, seen by mid-2010 mean visual acuity gain data for the DA VINCI trial up through Week 24?

A. Yes. So typically when we execute clinical trials, once the patient has completed the final visit of interest and

the data has been entered into the database, there's a process we go through to clean the data and, quote/unquote, lock the database, which is the initiation of the statistical analysis.

And then the output from the statistical analysis is provided to the clinical group, where we review the detailed data and typically summarize it in PowerPoint presentation format.

Q. I want to skip ahead a little bit, then, from mid-2010 to the fall. Let's look at PTX 3131 and PTX 3133.

Do you recognize this document -- or these documents, Ms. Chu?

A. Yes. So this is an email dated October 6th, 2010, circulating PowerPoint slides related to an upcoming program strategy meeting for VEGF Trap-Eye, or aflibercept.

Q. And I want to take a look, then, at the attachment, the slide deck. So this is PTX 3133. Can you please direct your attention to page 11 of that deck.

A. Okay.

Q. Do you have an understanding at this point in the -- in October of 2010 as to what the planning was as to the design of Regeneron's Phase III DME trial?

A. So at this time we were planning on a three-arm study, 2 milligrams aflibercept every four weeks, 2 milligrams every eight weeks after three initial monthly doses, compared to macular laser photocoagulation.

Q. Okay. And to be clear, your understanding at this point in time was that Regeneron was not planning for a five-loading-dose study?

A. That's correct.

MS. MAZZOCHI: Objection. She can't speak to what Regeneron was thinking; she can only speak to her own personal knowledge.

THE COURT: Sustained.

BY MR. GREGORY:

Q. Ms. Chu, I want to phrase this question very narrowly. I want you to listen to my question. Okay?

Did you have an understanding -- you personally have an understanding of what the planning was as of October 2010 as to the number of loading doses in Regeneron's Phase III clinical trial?

A. Yes. At this time we were still considering three initial monthly doses followed by every eight weeks as one of the dosing arms for the clinical trial.

Q. Ms. Chu, again, to reiterate, at this point in time in October of 2010, how long had you had the Week 24 DA VINCI data? Was that nine months at that point?

A. I believe we had received it in January of that year; so we had had it for nine or ten months.

Q. Let's take a look next at PTX 3188.

Do you recognize this document, Ms. Chu?

A. Yes. So this is a slide presentation from the joint development committee to the joint steering committee.

Q. And I just forget if you provided this elaboration already. So I apologize. I think you've told us what the joint steering committee was.

What is the joint development committee?

A. Yeah. So, again, that's the joint committee between Bayer and Regeneron responsible for the development decisions for aflibercept.

Q. I want to take a look at -- let's just skip ahead here to -- skip ahead here to page 4. There's a reference on this page to the EMA. Do you know what the EMA is?

A. So that's the European Medicines Agency.

Q. And there's a -- the title here is "EMA - Outcome and Consequences." I guess the title of the slide is "Health Authority Feedback."

Do you see that?

A. Yes, I do see that.

Q. Okay. What was your understanding of what was being discussed here?

A. Yeah. So at this time we were seeking health authority feedback about our plans for DME development. And the EMA had pointed out that they did not feel that our AMD safety data could be extrapolated completely to the diabetic macular edema population.

Q. Let's jump to page 19 of this same deck.

And do you see the reference there again in the middle of the page to the safety data?

A. Give me one minute.

Yes, I do.

Q. What was your understanding at this time as to EMA's position on that?

A. So their position was that the diabetic population was distinct from the neovascular AMD population, that this is -- while a younger -- somewhat younger population, that they also had several comorbidities and an increased -- so, for instance, diabetics are more frequently hypertensive as well as they have an increased risk of what we would term thromboembolic events; so things like stroke and heart attack.

And we knew that VEGF inhibitors like aflibercept had certain class effects, especially when delivered systemically, that included increased blood pressure as well as an increased risk for thromboembolic events. So this was a population that we felt could be particularly vulnerable to systemic exposure.

Q. Let's next look at PTX 1028C. Let's put the first page of this up on the screen for you here.

MS. MAZZOCHI: Your Honor, that last part of her answer where she started off from diabetic hypertension through what they thought, that's either getting into what Regeneron thought or it's expert testimony.

THE COURT: Understood. Motion to strike denied, though.

Go ahead, Counsel.

MR. GREGORY: Thank you, Your Honor.

BY MR. GREGORY:

Q. PTX 1028C, which is up on the screen and also should be in the binder, do you recognize this document?

A. Yes. So this a PowerPoint presentation of the one-year data from DA VINCI.

Q. DA VINCI again, that's the Phase II DME trial?

A. That's right.

Q. And how would a document like this -- I think you may have already talked a little bit on this subject, but how would a document like this typically be prepared at Regeneron in your experience?

A. Yeah. So as I mentioned -- so the process is typically that once the last patient completes their -- that last visit of interest, there's a process where the data is entered into the database and any questions about the data are resolved.

Once we lock the database, our statisticians then begin their process of analysis. And from that comes a detailed set of what we call tables, figures, and listings, which really is the -- the raw data from the study as well as any aggregate data or analyses that are performed.

And so the clinical group would be charged with reviewing those tables, figures, and listings and summarizing that in this kind of PowerPoint presentation for disclosure and discussion with management.

Q. And so it gets rolled up, then -- the initial set of data gets rolled up through a series of steps into this type of deck?

A. That's correct.

Q. What becomes of that broader underlying set of data?

A. The tables, figures, and listings become the basis for the clinical study report which is eventually provided to health authorities.

Q. And what, if anything, does senior management do with that broader set of data at Regeneron typically?

A. So I think I already mentioned that our senior management has always been heavily involved in the discussions and decisions. And certainly when we would review this kind of PowerPoint presentation with them, there would often be questions that would require we would pull up raw data. They certainly would have access to the tables, figures, and listings. And frequently they would ask for additional analyses, et cetera. So it was always a very lively discussion.

MR. GREGORY: Your Honor, permission to approach.

THE COURT: Granted.

BY MR. GREGORY:

Q. Ms. Chu, I've just handed you a sizable document marked PTX 1170.

Do you recognize that?

A. So this appears to be tables, figures, and listings from the DA VINCI study, the 0706 study.

Q. Do you recall when a decision was made about the treatment arms to evaluate in Regeneron's eventual Phase III DME trial?

A. I don't recall the specific date that a decision was made.

Q. Do you recall the general time frame?

A. Yes, I do. It would have been the end of 2010 or early -- very early 2011.

Q. And in the meeting that we were just looking at where this deck -- the deck we were just looking at, do you remember exactly when that meeting occurred?

A. I believe it was the beginning of December.

Q. Do you remember who ultimately made the decision about the dosing regimens to be explored in the Phase III DME clinical trial?

A. So it was ultimately George's decision to move forward with the five initial monthly doses followed by q8.

Q. And George, that's George Yancopoulos?

A. Yes. Sorry. That's Dr. Yancopoulos.

Q. Why do you remember that?

A. So part of the landscape in diabetic macular edema is that these are patients that are not only more susceptible to some of what we knew were the potential class effects of anti-VEGF from a safety perspective, but they were also patients that are at working age and have a high burden of healthcare in general.

So the pressure was really to minimize the number of doses. Especially in an investigational arm in a trial, we were really seeking to minimize the treatment burden for these patients. And members of the team disagreed with Dr. Yancopoulos' decision, but it -- ultimately it was his decision based on what he felt would optimize outcomes for patients.

Q. Did the Phase III trials at Regeneron ultimately conducted in DME, did those have names?

A. Yes. So they were called the VIVID and VISTA trials.

Q. And just for clarity, what treatment arms were explored in those trials?

A. So both studies included a 2-milligram monthly treatment group, a 2-milligram every-eight-week treatment group after five initial monthly doses, and the control group was laser photocoagulation.

Q. I want to talk very briefly about Regeneron's development efforts around diabetic retinopathy if that's okay.

A. Sure.

Q. Can we take a look at PTX 3332.

Do you recognize this document?

A. Yes. So this is a section from our supplementary BLA, or biologics licensing application, for diabetic retinopathy in DME.

Q. And there's a reference on -- actually, why don't we go down to page 3 first. That's probably the easiest place to look.

Do you see there's this heading "Summary of the Requests for Breakthrough Therapy Designations"?

A. Yes, I see that.

Q. What's your understanding of what a breakthrough therapy designation is?

A. So a breakthrough therapy designation is a relatively new designation that the FDA allows for products that have shown -- that are indicated for a severe disease and have shown preliminary evidence of significant effect over standard of care or available treatments.

And it allows many aspects of what we call fast-track designation, which essentially facilitates more frequent and more informal interactions with the FDA during your development.

Q. What breakthrough therapy designation -- or what indication did Regeneron seek a breakthrough therapy

designation at this time?

MS. MAZZOCHI: Again, Your Honor, objection. In her personal capacity, not on behalf of Regeneron.

THE COURT: Understood. But given her position and testimony she's offered, I do believe this witness would have personal knowledge about that. Overruled.

MR. GREGORY: Your Honor, I'll just -- we're coming up to the end here. I have three questions left, I think.

THE COURT: Understood.

BY MR. GREGORY:

Q. For what indication did Regeneron seek breakthrough therapy designation for aflibercept?

A. We were seeking a breakthrough therapy designation for diabetic retinopathy broadly.

Q. Can you turn to page 43 of this document.

And embedded within this document we just have this email here from Jennifer Woo.

Do you see that?

A. I do see that.

Q. And could you explain to us what's being discussed here.

MS. MAZZOCHI: Objection, Your Honor. Foundation. She's not on this email.

THE COURT: Sustained.

BY MR. GREGORY:

Q. For clarity, Ms. Chu, let's look back to the first page of the document.

Could you explain what this document is broadly speaking.

A. Yes. So this is a section of the SBLA that would summarize our interactions with the FDA leading up to the filing.

Q. Did you review this document at the time?

A. Yes, I did.

Q. You're familiar with this document?

A. I am.

Q. The email that we were just talking about, that's not a standalone email; it's an email that's included within this section of the supplemental BLA, correct?

A. That's correct. So that was a communication between our regulatory group and the FDA that was included as part of this summary or interactions with the FDA.

MR. GREGORY: Your Honor, with your permission, I'd like to examine her about that.

THE COURT: You may proceed, Counsel.

BY MR. GREGORY:

Q. Ms. Chu, could you look at page 43 again.

A. Sure.

Q. Could you explain to us what's being discussed here.

A. So this is in regards to a teleconference that we had

to the -- with the FDA on August 21st, 2014, to discuss our breakthrough application.

Q. And what did FDA do with your breakthrough therapy designation application for the treatment of DR, diabetic retinopathy?

A. They did not grant our breakthrough designation for DR.

Q. And what was your understanding at the time as to the rationale for that?

A. My understanding was that they did not consider the evidence we had provided of patients achieving a two-or-more-step improvement in diabetic retinopathy severity in the VIVID and VISTA trials, which enrolled patients with DME, as representative of the broader DR population.

Q. Did Regeneron ultimately pursue or forgo approval in DR alone?

A. Yes, we did. We subsequently conducted an additional Phase III trial called the PANORAMA trial in patients with diabetic retinopathy without DME.

Q. And what treatment regimens did Regeneron test in that trial?

A. In the PANORAMA trial we included 2 milligrams dosed every eight weeks after five initial monthly doses, 2 milligrams dosed every 16 weeks after three initial monthly doses and 1q8 interval, and the control group in that study was

sham or observation.

Q. And so those are not exactly the same dosage regimens that you tested in the Phase III DME trials, right?

A. The group that received five initial monthly doses, then every-eight-week dosing, that was the same group as had been used in the VIVID and VISTA studies.

Q. Was there an additional arm, though?

A. Yes. So there was the additional treatment arm with the q16 dosing after the three initial monthly doses and 1q8 interval.

Q. What was your understanding of the basis for including that additional treatment arm?

A. The basis was that again -- so patients with DME have underlying diabetic retinopathy, but patients can have even severe diabetic retinopathy and not have DME, and those patients can have very good vision.

So again, the focus was really on minimizing the treatment burden as well as minimizing the risk, especially for the diabetic retinopathy patients that did not have immediate vision loss.

MR. GREGORY: Thank you, Ms. Chu. I have no further questions at this time, Your Honor. I may have some exhibits to move into evidence before the witness leaves the stand, but I'll wait till the end of cross-examination.

THE COURT: Understood.

Counsel, you may proceed with cross.

MS. MAZZOCHI: Thank you, Your Honor.

May I proceed, Your Honor?

THE COURT: You may.

CROSS-EXAMINATION

BY MS. MAZZOCHI:

Q. Ms. Chu, I'm going to show you DTX 5385, exhibit page 1.

MS. MAZZOCHI: I'm sorry, Your Honor. May we do the ritual distribution of the binders?

THE COURT: Please.

BY MS. MAZZOCHI:

Q. Ms. Chu, I'm going to show you DTX 5385, exhibit page 1, which is titled the "JDC Update to the JSC Clinical Plan" dated January 26, 2011.

And you participated in that discussion, right?

A. I don't remember the specific meeting, but this is the type of meeting that I would participate in.

Q. Let's go to the second page of the exhibit.

You can confirm that the JSC did include Bayer employees, right?

A. Correct.

Q. And the JDC, which included Regeneron and Bayer employees, endorsed running Study B?

A. Yes, I see that here.

Q. Let me take you to the seventh page of DTX 5385. This confirms that the choice of five loading doses for the DME indication was a compromise of the joint development committee, right?

A. Well, this indicates that it was a suggested compromise.

Q. And it says five loading doses was the suggested compromise for DME?

A. It does suggest that, but again, the caveat here is that the -- this included commercial and market access perspective as well.

Q. Okay. But whatever the case may be, five loading doses was the compromise position with the JDC, right?

A. It was suggested, yes.

Q. Okay. And it says in parenthesis after five loading doses, "equals one additional dose," right?

A. I see where it says that, yes.

Q. And your understanding that this five loading dose compromise from the JDC meant just adding in one additional dose at the 12-week mark, right?

A. So, again, the proposal that had been being discussed was the same as what we had utilized in the AMD Phase III trials, which was three initial monthly doses, so -- followed by every eight weeks. So this did represent, at least in the first year, an additional dose.

Q. Right. And that additional dose was going to come at the 12-week mark, right?

A. Correct.

Q. And one of the reasons why this was viewed as an attractive compromise is because it would not have involved changing the primary end point, which would have required a substantial protocol amendment, true?

A. That's actually not true. So the primary end point in these studies was a discussion point from the very beginning because there were -- the EMA accepted a one-year primary end point in Phase III studies with diabetic macular edema while at this time the FDA required a two-year primary end point.

Q. Let's take a look at page 21 in the exhibit where it's talking about Study B and loading doses. If we look at the second dash under the heading "Operational aspects of a potential change of number of loading doses," can you read what it says, please.

A. So sorry. Do you just want me to read this?

Q. Yeah.

A. So the second main bullet is "Operational aspects of a potential change of number of loading doses," subbullet, "Protocol amendment required," subbullet, "Four or six loading doses would result in a shift of the primary end point visit to maintain the paradigm that efficacy should be determined four weeks after the last injection in the 2q8 arm (equals

substantial protocol amendment)."

Q. So we can agree, then, that one of the benefits of the five loading doses as compared to four or six is that it would not require a shift of the primary end point visits to maintain the paradigm that efficacy should be determined four weeks after the last injection in the 2q8 arm, which would have been a substantial protocol amendment?

A. Well, these were design considerations, yes.

Q. Okay. Ms. Chu, let's take a look at PTX 3332, exhibit page 16, the breakthrough therapy application that Regeneron submitted to the FDA, dated July 14th, 2014, which you discussed on your direct examination. And I'd like to direct you to the last paragraph heading "Overall Summary of Study Results."

Do you have that on screen?

A. Sorry. What page is this on?

Q. Exhibit page 16. Well, it will say 12 of 30 on the bottom, but it's PTX exhibit page 16. It's on the screen in front of you as well.

A. Yes, I see that section.

Q. The data that Regeneron relied on as the basis for this application was the Phase III VIVID and VISTA studies, right?

A. Correct.

Q. But neither the clinical trial protocol for the

Phase III VIVID or VISTA studies are set forth in the '572 or '601 patents that are at issue here, right?

A. I would have to look at the patents to be able to answer that sufficiently.

Q. Do you recall being asked at your deposition, "If you can take a look at the '601 patent, is the clinical trial protocol for the Phase III VIVID or VISTA studies set forth in any of the patent examples?"

You gave that same answer. And then after your review you said, "So in my review of Patent '601, I do not see a description of the VIVID or VISTA trials given as an example."

Does that help to refresh your recollection?

A. Okay.

Q. Let me call up DTX 19, exhibit page 2.

You're a named inventor on this patent, true?

A. Sorry. Give me a minute.

Yes, I am a named inventor on this patent.

Q. So this is U.S. Patent Number 10,973,879?

A. Is that a question?

Q. Yes.

A. Yes, 973,879.

Q. Dr. Yancopoulos is not listed as a named inventor on this patent, right?

A. No, he is not.

Q. Let's go to DTX 19 at exhibit page 38, right-hand column 2, lines 48 to 67. We've got that on the screen in front of you.

A. Okay.

Q. Ms. Chu, can you confirm that in your patent, DTX 19, lines 48 to 49, you stated that "The present invention provides a method for treating diabetic retinopathy," right?

A. So our process at Regeneron is that we, as clinicians and scientists, provide information to our intellectual property attorneys for the purpose of patent applications and documents.

Q. Ms. Chu, I'm going to say my question again.

In your patent, DTX 19, lines 48 to 49, you stated, "The present invention provides a method for treating diabetic retinopathy," right?

A. That is what the patent states.

Q. Okay. And if we go down a few more lines to the description of the dosing regimen you consider to be part of the present invention, can you confirm that dosing regimen (ii) is listed as "3 or 4 or 5 monthly doses followed by one or more secondary doses every 8 weeks, wherein the secondary doses initiate 8 weeks after the final of the 3 or 4 or 5 monthly doses and continues with a dose given every 8 weeks thereafter"?

Do you see that?

A. I do see that.

Q. And that's something that your '879 patent, DTX 19, said was your invention, right?

A. That's correct.

Q. Okay. Let's go to the sixth exhibit page of DTX 19. Do you have a Figure 1 there?

A. Sorry. What page?

Q. The 19th -- I'm sorry. It's the sixth page of the exhibit, DTX 19.006, where Figure 1 appears.

A. Yes, I do see that figure.

Q. Does Figure 1 display a dosing regimen with what could be called three monthly doses followed by doses every eight weeks where the eight-week doses initiate after the final of the three monthly loading doses and continue with a dose given every eight weeks thereafter?

A. Sorry. Could you just restate your question.

Q. Sure. Looking at Figure 1, does that figure show a dosing regimen with three monthly doses, or what could be called three monthly doses, followed by doses every eight weeks where the eight-week doses initiate after the final of the three monthly loading doses and continue with a dose given every eight weeks thereafter?

A. Yes. So my understanding of this figure is that there's an initial dose given at baseline, followed by secondary doses at -- it appears to be four and eight weeks,

followed by a tertiary doses, I think, every eight weeks apart.

Q. And if we were to put an arrow at the 12-week mark in your patent's Figure 1, that would be a dosing regimen that would correspond to what we could call five monthly loading doses followed by one or more doses every eight weeks, wherein the eight-week dosing is initiated after the final of the fifth monthly loading dose is given, right?

A. Yes. That would be a graphical representation of that dosing regimen.

Q. You, at your deposition, did not identify George Yancopoulos as the person who first came up with the idea of a five-loading-dose regimen for diabetic retinopathy that we see in Claim 18 of the '601 patent, right?

A. So as I mentioned previously, our process was that the team was charged with bringing proposals for discussion and decision-making by senior management; so I don't know who first came up with that idea.

Q. But Dr. Yancopoulos did not have any input into the particular methodology for the PANORAMA study, for example, right?

A. He definitely did have input into the methodology for the PANORAMA study.

Q. Let me bring -- let me have you take a look at DTX 7212, exhibit page 0024, your deposition testimony. And just to give you context, we'll start at line 17 of page 91 and

we'll go over to page 92, line 6.

Starting at line 25, referring to Dr. Yancopoulos --

A. Sorry. I don't have a page 92.

Q. No. It'll be transcript page 92. So it's exhibit page 24.

THE COURT: Ma'am, if you'll see, there's actually four pages on each page. The upper right-hand corner will be the second page number that counsel's referring to.

BY MS. MAZZOCHI:

Q. And we'll call it up on the screen for you as well.

The question was, referring to George Yancopoulos, "And did he have any input into what this particular methodology in the PANORAMA study was going to look like?"

And did you give the answer, "I don't recall the specific meeting, but we most certainly would have discussed it with him."

A. Yes. I think that's consistent also with our process that I just described.

Q. But the day-to-day involvement was really more with the clinical team, yourself and Dr. Vitti, right?

A. And Dr. Berliner, who is also on the patent.

Yes. I mean, as a clinical team, we're obviously responsible for providing proposals around future development and development strategies.

Q. You mentioned something about filing patent

applications.

Was it your understanding that patent applications would be filed on all of the methods that were going to be tested by Regeneron in human Phase III clinical trials?

A. That was not my understanding. So, typically, we would have discussions with our intellectual property attorneys about the programs and planning and the decisions around what patent applications were to be filed or made by them.

Q. Again, let me pull up your deposition testimony, DTX 7212, page 34. Your testimony at lines 31:12 to 22.

Were you asked the question, "Was it Regeneron's custom and practice to file patent applications on all of the methods that it was going to test in human Phase III clinical trials?"

And did you give the answer, "It's my understanding that Regeneron always seeks to patent any novel inventive aspects of both our -- of any aspect of our development process."

Was that the question you asked and the answer you gave?

A. That's the answer that I gave, but I don't think that's inconsistent with the idea that there's a decision made about what aspects of our development program is inventive and possible to patent.

Q. But we can agree that Regeneron put a five monthly

loading dose regimen followed by every-eight-week dosing for diabetic retinopathy in both your '879 patent, saying it was your invention, as well as in the '601 patent's Claim 18 and 19, right?

A. I understand that regimen appears in both patents.

Q. Okay. Ms. Chu, during your time at Regeneron, did you also become aware of the Protocol T study that was conducted by the Diabetic Retinopathy Clinical Research Network?

A. Yes, I'm aware of that study.

Q. But that Protocol T regimen was not Regeneron's idea, was it?

A. Well, the Protocol T study was conducted by the DRCR, which is a collaborative group funded by the National Eye Institute, and Regeneron did have input into the study design and provided drug for the conduct of the study.

Q. Well, let's take a look at what I will designate as DTX 9002 and exhibit page 1.

Can you confirm this is an email forwarding Protocol T color handouts to Regeneron dated Saturday, March 31st, 2012?

A. So I can see this is an email dated March 31st, 2012, regarding Protocol T color handouts to Regeneron.

Q. Do you know based on -- given your capacity and your involvement in clinical trials, whether Regeneron had ever

given any input into the Protocol T protocol prior to this date?

A. I'm not on this email, and I don't recall specifically what date we had input into the Protocol T protocol.

Q. Well, let's go to the eighth page of the exhibit. And there is a slide that's titled "Visit/Treatment Schedule Year 1, the 4:2:7 Guide."

Do you see that?

A. I see.

Q. Is this Protocol T regimen consistent with your recollection?

A. With the Protocol T study design?

Q. Yes.

A. Yes. So I understand this to be the Protocol T dosing regimens.

Q. And so here for aflibercept, they proposed a mandatory four loading doses every four weeks at the start of the regimen for Protocol T, right?

A. Yes. So this was a comparative study with three different anti-VEGF molecules, and all three dosing groups received four initial monthly injections.

Q. And then on weeks -- those monthly loading doses were to be given on weeks 0, 4, 8, and 12, right?

A. That was the proposed schedule, yes.

Q. Then Protocol T allowed for two required injections if the patient hadn't reached success; but if they had, they could skip a dose at their next four-week visit, right?

A. That was the dosing regimen outlined in the protocol.

Q. And, likewise, in the weeks after that, when the patient showed up at their next four-week office visit, if they had not reached success, they were dosed; if they had reached success, they would skip and come back in four weeks, right?

A. Yes, that's correct. So they were essentially dosed as needed during that period of time, but the visits were still every four weeks.

Q. And that regimen would include an eight-week interval then, right?

A. Well, not necessarily. I mean, obviously, each individual patient was dosed based on the criteria outlined in the protocol.

Q. Right. But this regimen permitted an eight-week dosing regimen dosing interval, right?

A. Potentially. But, again, it wasn't specifically stated that that was the intent.

Q. But -- and, likewise, this Protocol T could permit for five monthly doses before any extended dosing interval, right? Just depended on the characteristics of the patient, to your understanding?

A. It could. But, again, it would be based on the

individual patient status.

Q. And this Protocol T is the only dosing regimen you're aware of where aflibercept was tested head-to-head with ranibizumab and performed better, right?

A. Yes, that's correct.

Q. But this isn't the dosing regimen in the FDA-approved labeling for Eylea, is it?

A. No, it is not. It's not the approved regimen for ranibizumab either.

Q. Ms. Chu, let's put DTX 216 before you.

Can you confirm this is a March 21st, 2006, email from Jesse Cedarbaum to you and others?

A. Yes, I see that this is an email dated March 21st, 2006, from Jesse Cedarbaum and I'm one of the recipients.

Q. And according to the email, the attachment is the final version of the 0502 Part A abstract for the American Society of Retinal Specialists, ASRS, meeting in the fall, yes?

A. Actually, the email states that this is the 0508 Part A abstract for ASRS.

Q. Well, if you take a look at the attachments line, does it say 0502A ASRS attachments -- ASRS abstract?

A. Yes. The attachment was titled "0502A ASRS Abstract."

Q. If you take a look at the second page of DTX 216, does this confirm that you were an author on the abstract to

present the results of the Phase I study of intravitreous VEGF Trap in 2006?

A. Yes. So I was an author on this abstract of the Phase I study in neovascular AMD.

Q. Right. And based on this description here of this being the CLEAR-IT 1 study, this was the 0502 protocol, right?

A. Right.

Q. Not 0508?

A. Correct.

Q. And this CLEAR-IT 1 study is where Regeneron first dosed aflibercept in humans intravitreally, right?

A. Right. So this is summarizing the dose escalation portion of this study, which is where we dosed a small number of patients across a range of doses.

Q. And Dr. Yancopoulos is not listed as a coauthor on this study, is he?

A. He is not on this particular abstract, no.

Q. But you understand this study is found in Example 1 of the '572 and '601 patents?

A. Again, I'd have to review the patent to be sure.

Q. Well, maybe we can shortcut it. I'm happy to call up your deposition testimony, page 169, lines 14 to -- actually we'll do lines 13 to 17.

So this is exhibit page 43.

THE COURT: What page of the deposition again,

Counsel?

MS. MAZZOCHI: It's deposition page 169.

THE COURT: Thank you.

BY MS. MAZZOCHI:

Q. And, Ms. Chu, did you confirm -- "So the study in Example 1 was referred to as the CLEAR-IT 1 study. The study in Example 2 was the CLEAR-IT 2 study."

Was that the testimony you gave?

A. Yes, but I had -- I was provided with the patents as an exhibit at that time. So I'd be happy to look at the patents now. Are they in my binder?

Q. Was that true testimony you gave at your prior deposition?

A. Again, if I had the patents in front of me, I'd be happy to take a look and confirm this.

Q. Well, let's go ahead and put up the '601 patent, PTX 1, exhibit page 14, the '601 patent at Column 8, lines 3 to 27, which corresponds to Example 1.

Do you have that there on the screen?

A. I see it on the screen. Just give me a minute to find it in the document.

Sorry. What page would it be on?

Q. Exhibit page 14.

A. Okay.

Q. So this is the CLEAR-IT 1 study, right?

A. So Example 1 appears to be the CLEAR-IT 1 study, the Phase I study in neovascular AMD, yes.

Q. And looking at the dose listed here in Example 1, what was the volume injected into the eye in your 2005 CLEAR-IT 1 study? Was it 0.05 or 0.1 milliliters?

A. So at this time we were using 100 microliters or .1 milliliters.

Q. At least the 4-milligram dose concentrations that were administered in the study were formed at a 40 mg/mL concentration, correct?

A. In this study, yes.

Q. Regeneron put exactly what amounts it was dosing in its Phase I protocol documents, right?

A. Well, we certainly outlined the doses and dose volume intended.

Q. Okay. Let me take a look at what I've marked as DTX 9005.

Can you confirm that this is an April 5th, 2005, email to -- that you were cc'd on from Sri Vuthoori?

A. Sorry. Did you say DTX 9005?

Q. Yes.

A. I don't have that in my binder.

Q. You should. It should be right before PTX 1.

A. Okay. I see it now. Sorry.

Q. Can you confirm that this is an email to you and

others dated April 5th, 2005, from Ms. Vuthoori?

A. Yes. So this is an email from Sri Vuthoori, dated April 5th, 2005, and I am a recipient of this email.

Q. If we look at the email attachment, can you confirm that this is Regeneron's April 5th, 2005, protocol for the intravitreal Phase I study, protocol VGFT OD 0502?

A. So this is what at the time we called a pass document, which was basically a synopsis intended to be the basis for the final protocol.

Q. But you're familiar with this document?

A. Yes. This is the type of document that we would have written, again, to lead into the writing of the final protocol.

Q. Let's go to the 23rd page of the exhibit that describes the clinical drug supply profile.

Do you have that on screen?

A. Yes, I see that.

Q. All right. And, again, this confirms that the 4-milligram doses were given at a concentration of 40 mg/mL in the CLEAR-IT 1 clinical trial that you published in your abstract in or about 2006?

A. Yes, in the 100 microliter volume.

Q. And Regeneron, according to this document, also proposed having a percent overage in the vials of 30 percent, right?

A. That appears to be in this document, yes.

Q. And the total fill size was 1.2 milliliters with a max withdrawable volume of 1 milliliter, right?

A. That's what's specified in this document, but I'm not the manufacturing expert. So if you're asking me to confirm that that's what was actually in the trial, I would defer that to the expert.

Q. Well, this is what you were using to prepare the protocol, right?

A. These were assumptions that were being used to prepare the protocol, yes.

Q. Now, we've talked about the ASRS meeting in 2006, but Regeneron also presented your CLEAR-IT 1 study at the ARVO meeting in Ft. Lauderdale, right?

A. I don't recall, but that's typically one of the meetings where we would seek to present data.

Q. And were you a named author on the abstract that was presented at the 2006 ARVO meeting?

A. I don't recall specifically.

Q. Well, let's take a look at DTX 9003.

This is titled "Results of a Phase I, dose-escalation, safety, tolerability, and bioactivity study of intravitreous VEGF Trap in patients with neovascular age-related macular degeneration."

Do you have that?

A. Yes, I see that.

Q. All right. And you're a named author on that one?
A. Yes, I am.
Q. And this is referring to the CLEAR-IT 1 study?
A. Yes, this would have been the CLEAR-IT 1 study.
Q. And that ARVO meeting where CLEAR-IT 1 was presented was held between April 30th and May 4, 2006, right?
A. I don't remember the exact dates, but that's the time of year where it's typically held.
Q. Okay. Well, just to tie it up because I don't want you to have to take my word for it, let me give you a document. It should be in your binder. And I apologize. I think it's the very last one that's entered in there. It's got the designation DTX 9006.

I'll go to exhibit page 12, citation Number 56.

And is that referring to your abstract results of the Phase I dose-escalation, safety, tolerability, and bioactivity study of intravitreous VEGF Trap in patients with neovascular age-related macular degeneration as something presented at the annual meeting of the -- of ARVO between April 30th to May 4th, Fort Lauderdale, 2006?
A. Yes. This appears to be a reference to that abstract.
Q. Now, Ms. Chu, you indicated that Regeneron was keeping some things secret, but I'd like you to -- when it came to its clinical trial work, but I'd like you to take a look at

DTX 4957.

Do you see that this is Regeneron's Form 10-K for the prior year 2005?

A. I see that this is a Regeneron Form 10-K, yes.

Q. I'd like to direct your attention to this exhibit page 5 in DTX 4957 and specifically under the heading "VEGF Trap - Eye Diseases."

And we'll pull that up for you on the screen.

Do you see that?

A. Yes, I see that.

Q. All right. And do you see in the second paragraph it says, "In February 2006, Regeneron announced positive preliminary results from an ongoing Phase I dose-escalation study of VEGF Trap-Eye"?

That was your ASRS abstract, right?

A. So I actually don't know exactly which meeting this is referring to. February -- ASRS is typically held later in the summer. But it has moved around over the years; so it could be referring to the ASRS abstract.

Q. All right. Well, can we at least agree that your CLEAR-IT 1 0502 protocol Phase I test results we just looked at in DTX 9002, that Regeneron believed they had announced that -- those results at least as early as February 2006?

A. So in this 10-K it indicates that we announced positive preliminary results from the ongoing Phase I

dose-escalation study, which I understand to be the CLEAR-IT 1 study.

Q. And you also -- it was also reported that VEGF Trap-Eye was delivered by intravitreal injection into the eye, right?

A. Yes.

Q. And Regeneron reported in its 10-K that the patients in your CLEAR-IT 1 study where you coauthored the abstract received a high dose of VEGF Trap-Eye of up to 4 milligrams?

A. Right. So the design of the study was to test across a range of doses, those -- some very low and some higher; but yes.

Q. And that 4-milligram formulation was dosed as a 40 mg/mL formulation?

A. So I don't see that as part of this document.

Q. Right. But you know that it was?

A. The concentration used to dose the 4-milligram dose in these studies was 40 mg/mL.

Q. And Regeneron described that dose as well tolerated in its SEC 10-K filing, right?

A. We did describe it as well tolerated in this small, early phase study.

Q. Right. And that was consistent with what you had seen in that study, right?

A. Yes.

Q. And if we take a look at the 51st page of the exhibit, it indicates that this document had been signed off on by your CEO, Len Schleifer, right?

A. Yes. I see that it indicates that Len Schleifer had signed this document.

Q. Dated February 28th, 2006?

A. That's what it appears to be, yes.

MS. MAZZOCHI: Your Honor, I'm about to go into a different set of topics. Would this be a good time for our lunch break?

THE COURT: It probably is. Why don't we go -- let's take a half hour. Let's pick back up at 12:45.

Ms. Chu, ma'am, because you're midstream on your testimony, no one can talk with you about what you've said or anything else. So you'll see folks flee from you in the hallways. They're not being rude or discourteous; they're just following the rules. But I wanted to make sure you understand that.

They are permitted to feed you, however, and they are required to feed you. But, otherwise, they can't interact with you. But, ma'am, you can go ahead and step down, and we'll resume with your testimony at 12:45.

So we'll see everyone at that point.

(A recess was taken from 12:18 p.m. to 12:58 p.m.)

THE COURT: Ms. Mazzochi, you may resume.

MS. MAZZOCHI: Thank you, Your Honor.

BY MS. MAZZOCHI:

Q. Ms. Chu, Mr. Gregory took you to PTX 188 on your direct examination, which was previously your deposition Exhibit 225, to talk about that meeting referenced -- supposedly referenced in the email from April 2nd.

If you slide down just a little bit on the exhibit, we'll put it in front of you, Item G, but let's keep all of Item 2 up on the screen.

Who decided to put the q8 interval on the table for this meeting?

A. I don't recall who specifically put the q8 interval on the table for the meeting.

Q. Mr. Gregory also asked you about DTX 227, where you indicated that some type of decision was made, but you don't actually recall this specific meeting, right?

A. I don't recall this specific meeting.

Q. And you don't recall who actually assembled that particular regimen with 2 milligrams q8 weeks with PIER lead-in, dosed monthly for first three months, as one of the arms to consider for the VIEW 1 Phase III clinical trial, right?

A. I don't recall who specifically proposed that first, but the final decision about the study design would have been made by George.

Q. Ms. Chu, unequivocally, you don't recall specifically who proposed that dosing regimen, right?

A. I don't recall who first proposed it.

Q. Ms. Chu, are you aware that this document, DTX 227, was not identified as a document that Regeneron thought related to conception or reduction to practice for the '572 and '601 patent and Regeneron's discovery response?

THE COURT: Yes, Counsel?

MR. GREGORY: Objection, Your Honor. That's a misrepresentation of our discovery responses.

THE COURT: Overruled. You can address it on redirect.

Repeat your question, please, Counsel.

BY MS. MAZZOCHI:

Q. Ms. Chu, are you aware that this document, DTX 227, was not identified as a document relating to conception and reduction to practice for the '572 and '601 patent in Regeneron's discovery responses?

A. I'm not an attorney; so I don't think I can adequately answer your question.

Q. Do you know if you ever assisted in the preparation of those responses?

A. Sorry. Which responses are you referring to?

Q. Sure. I'll put it up on the screen for you, DTX 7001. And we've also got some hard copies, I believe, that

we can pass out.

A. Sorry. Is this in your binder or --

Q. No. We're going to hand you a copy if we can.

MS. MAZZOCHI: Your Honor, may we approach?

THE COURT: You may.

MS. MAZZOCHI: Thank you.

THE COURT: They're fresh. They're still nice and warm.

BY MS. MAZZOCHI:

Q. Ms. Chu, do you see this is titled "Regeneron Pharmaceutical Inc.'s Objections and Responses to Defendants' First Set of Interrogatories (1 to 17)" as DTX 7001?

A. I see that this document has that title, yes.

Q. Okay. And if you can turn to page DTX 7001, exhibit pages 37 to 38.

A. Okay.

Q. Do you see there's a long list of documents there that have numbers that say RGN-EYLEA-MYLAN and then followed by a more specific number?

A. Yes, I see that beginning on page 37 and continuing on page 38.

Q. All right. Will you accept my representation that a document ending with the number -- with the Bates Number RGN-EYLEA-MYLAN-00631182 is not found on that list?

A. Unless the Court wants me to take the time to review

this whole list, I'll accept your representation.

THE COURT: And I do not, ma'am. The Court will likewise accept that representation.

MS. MAZZOCHI: Thank you.

BY MS. MAZZOCHI:

Q. You describe this document, DTX 228, as the one where Dr. Yancopoulos conveyed to Bayer the optimal designs for the VIEW 1 and VIEW 2 trials, right?

A. I did not. I actually indicated that Dr. Yancopoulos would have spoken with Darlene Jody about the plans.

Q. Let's go to your deposition transcript. It's transcript page 287. I believe it's going to be DTX 7272. Here, we've got it up on the screen for you.

And were you asked about DTX 228, the April 4th, 2007, email from George Yancopoulos to Darlene Jody -- strike that. Let me start over.

Were you asked, "Sure. In your capacity as Regeneron's 30(b)(6) witness, what's the significance of this April 4th, 2007, email from George Yancopoulos to Darlene Jody?"

And did you give the answer, "So this email from George to Darlene Jody, who is a senior executive responsible for the Bayer collaboration with us, is communicating the Regeneron proposal and decisions around the optimal designs for the VIEW 1 and VIEW 2 trials"?

Is that the testimony you gave?

A. Yes.

Q. Okay. And also at your deposition, this document, DTX 228, the April 4th, 2007, email from George Yancopoulos to Darlene Jody, that document was identified by your legal counsel to prepare you for your deposition, right?

A. I don't recall if this specific document was provided to me in preparation for my deposition.

Q. That's fine. I know some time has passed. So let's go back to your deposition transcript, then, DTX 7212. This is exhibit page 73.

And starting around line 13, were you shown this -- were you asked the question, "This is an email dated Wednesday, April 4th, 2007, from George Yancopoulos to Darlene Jody. Do you have that?"

"A Yes. So I have Exhibit 228 dated Wednesday, April 4th, 2007, with the subject 'Summary of Issues for Call, AMD P3 Planning' from George Yancopoulos to Darlene Jody.

"Q Now, earlier in the deposition today you referred to an email that you recalled seeing that you discussed with George Yancopoulos. Was this one of the emails?

"A Yes. This was the email I reviewed in preparation for this deposition."

Was that the testimony you gave?

A. Yes. It appears to be my testimony.

Q. Ms. Chu, let's go to PTX 3167, exhibit page 1, that your counsel took you to. And according to the second-to-last sentence in the top paragraph, the sentence that starts out, "Unfortunately," do you see that on the screen?

A. Sorry. Can I just -- this is in the original binder, right, not in your binder?

Q. Yes. So PTX 3167, exhibit page 1.

A. Okay.

Q. And while you have DME scenarios the team had put together, you did note that, "Unfortunately, George, Len, and Neil are unavailable today, but we can send them the final recommendations after today's meeting."

Is that what's written in the email?

A. That's what's written in the email. It's also consistent with our process of having team discussions before presentation and discussion with senior management.

Q. But these ideas of using no more than three to six monthly doses, if there was any decision made as to choose one amongst them, that was not generated at that meeting attended by -- it would not have been -- if it was generated at that meeting, it was not one attended by Dr. Yancopoulos, right?

A. Again, it was the role of the team to prepare proposals for discussion and decision by senior management.

But Dr. Yancopoulos was, according to this email, not in attendance at this meeting.

Q. Ms. Chu, I believe you also indicated on your direct examination that you believe George Yancopoulos was responsible for the five-loading-dose regimen. And I believe you pointed to PTX 1028 and PTX 1170, that big, thick exhibit, as support for that.

Do you recall that?

A. Yes.

Q. Do you also recall me asking you at your deposition if your theory that George Yancopoulos made the decision about the five loading doses was documented anywhere?

A. I don't recall that specific question.

Q. That's fine.

Let's pull up DTX 7212, exhibit page 21, which is your deposition transcript pages 80 to 81. And feel free to look at your prior answer just to get the context that we were talking about, five loading doses, but I'd like to focus on the question that starts at line 16.

Were you asked the question, "Right. Who decided that the dosing was going to be for the first five injections as opposed to three or four"?

"A My recollection is that George Yancopoulos made that decision.

"Q Is that documented anywhere?

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

Was that the testimony you gave?

A. Yes.

MS. MAZZOCHI: Your Honor, there's several other places where I believe Ms. Chu testified inconsistently with her prior deposition; but because you heard that yesterday, to move things along, we'll save that for the posttrial findings if that's all right.

THE COURT: Understood.

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

With that, I'll pass the witness.

THE COURT: Redirect, Counsel?

MR. GREGORY: Briefly, Your Honor.

REDIRECT EXAMINATION

BY MR. GREGORY:

Q. Hello again, Ms. Chu.

A. Hi.

Q. Defense counsel showed you DTX 7001. I think it was a somewhat lengthy document. It's kind of collected together with a binder clip. Do you have that in front of you?

A. Yes, I do.

Q. And this is Regeneron Pharmaceutical Inc.'s objections and responses to defendants' first set of interrogatories.

Do you see that?

A. Yes. This document has that title.

Q. Now, defense counsel showed you the response to Interrogatory Number 10 set forth on pages 37 and 38.

Do you recall that?

A. Yes.

Q. And do you recall her asking you whether a particular document was within the list of the approximately 50 documents identified on those pages?

A. I remember her asking me to agree with her assertion, and I agreed.

Q. Defense counsel did not show you the interrogatory itself, did she?

A. No.

Q. I want to direct your attention to page 36. And that Interrogatory Number 10 at the bottom of page says, "For each claim of each of the initial patents, identify (a) the date that the claimed subject matter was first conceived and the date it was reduced to practice, and the diligence leading to such reduction to practice, and for each such date and diligence, identify with particularity the documentary evidence supporting that date or diligence and at least three persons with any knowledge relating to that date and diligence."

Do you see that?

A. I see that.

Q. I read that correctly?
A. Yes.
Q. You can set that aside.
Defense counsel asked you some questions about DTX 228.
Do you recall those questions?
A. Let me just find the exhibit first.
Okay. Yes, I have that.
Q. Was DTX 228 the only email you reviewed to prepare for your deposition in this case?
A. No, it was not. I reviewed several emails in preparation for my deposition.
MR. GREGORY: No further questions, Your Honor.
THE COURT: Recross?
MS. MAZZOCHI: Nope. It's all in the record, Your Honor. Thank you.
THE COURT: Ms. Chu, thank you so much. You can step down.
MR. GREGORY: Your Honor --
THE COURT: Oh, no, no. You may not step down.
MR. GREGORY: We have just a few exhibits I think we would move into evidence at this point.
THE COURT: Thank you, Counsel. I forgot about that. Go right ahead. Slowly, please.
MR. GREGORY: Of course. And I'll ask defense

counsel as well to make sure that I'm not reading any that are already in evidence. I think I've done that filtration process myself.

We would move PTX 3131, PTX 3133, PTX 3332, PTX 0188, DTX 227, PTX 3150, PTX 3151, PTX 3167, and PTX 3168. We would move those into evidence.

I believe additional documents we discussed were DTX 8190, PTX 3188, and PTX 1028C, all of which I believe are already in evidence.

THE COURT: Any objection or disagreement with that?

MS. MAZZOCHI: I would like to object to PTX 3151. And the reason for that, Your Honor, is because this is the lengthy list of -- they're basically hearsay statements from a DME expert teleconference. So, again, I had no problem with Ms. Chu discussing something that was in her personal knowledge, but because, again, these are proffering supposed expert opinions, I don't want to see them later on as being proffered as this is what the experts thought or something along those lines.

THE COURT: What is the purpose of offering 3151?

MR. GREGORY: Yes, Your Honor. It's PTX 3151. It's not for the truth of the matter asserted; it's the Regeneron and Ms. Chu's state of mind.

THE COURT: Understood. Objection overruled.

Any other objections other than 3151?

MS. MAZZOCHI: I believe that's the only one, Your Honor.

THE COURT: All right. Subject to that -- I'm sorry, Counsel.

MS. MAZZOCHI: You did not do --

MR. GREGORY: I don't believe I showed those to Ms. Chu.

MS. MAZZOCHI: Yes. Then we're good, Your Honor.

THE COURT: All right. Subject to that ruling on the objection of 3151, each of those identified by counsel are hereby admitted.

(PTX 3131, PTX 3133, PTX 3332, PTX 0188, DTX 227, PTX 3150, PTX 3151, PTX 3167, and PTX 3168 were admitted.)

THE COURT: Any from the defense?

MS. MAZZOCHI: Yes, Your Honor. We have DTX 19, DTX 216, DTX 4957, DTX 5385, DTX 9002, DTX 9005, DTX 9006, DTX 7001, and PTX 3332.

I'm sorry, Your Honor. Hang on.

I might be -- told I might have gotten one of the 9000 numbers wrong.

9006, which was the drugs of the future article.

THE COURT: Any others, Counsel?

MS. MAZZOCHI: Nope. That's it.

THE COURT: Any objection to any of those from plaintiff?

MR. GREGORY: Your Honor, if you give me just a moment to consult with my cocounsel?

THE COURT: Certainly.

MR. GREGORY: No objection, Your Honor.

THE COURT: Without objection, each of those will be admitted.

(DTX 19, DTX 216, DTX 4957, DTX 5385, DTX 9002, DTX 9005, DTX 9006, DTX 7001, and PTX 3332 were admitted.)

THE COURT: Anything further we require of this witness, then?

MS. MAZZOCHI: Nothing from us, Your Honor.

MR. GREGORY: Nor from us, Your Honor. Thank you.

THE COURT: I now reextend my invitation to step down, ma'am. Thank you very much. You can leave whatever there. We will tidy up. Thank you.

MR. GREGORY: May I approach to remove the binders?

THE COURT: You may, yes. It's Ms. Chu's chance to escape.

Regeneron may call its next witness.

MR. TRASK: Your Honor, Regeneron calls Dr. Kenneth Graham.

THE COURT: Dr. Graham, sir, if you wouldn't mind making your way all the way to the front of the courtroom.

You're going to pause here with Madam Clerk so she can swear you in, then we'll ask you to take the witness stand

over here to your left.

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

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

MR. TRASK: Thank you, Your Honor.

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

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

Mr. Rakoczy, sir.

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

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

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

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

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

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

THE COURT: May I have a copy of that?

MR. RAKOCZY: Yes, Judge.

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

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

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

Now, two nights ago, Your Honor --

THE COURT: What is that document, 475679?

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

The other night I received a list of exhibits that

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

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

THE COURT: Understood.

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

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

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

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

MR. TRASK: Absolutely, Your Honor.

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

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

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

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

THE COURT: Yes, Mr. Rakoczy.

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

We had no reason to believe Dr. Graham would testify

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

MR. TRASK: If I may, Your Honor.

THE COURT: Go ahead.

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

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

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

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

THE COURT: Understood.

Last word, Mr. Rakoczy. Go ahead.

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

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

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

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

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

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

of it, addressing it in posttrial proceedings.

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

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

MR. RAKOCZY: Thank you, Your Honor.

MR. TRASK: Thank you, Your Honor.

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

MR. TRASK: Thank you.

May I proceed, Your Honor?

THE COURT: You may.

MR. TRASK: Thank you.

DIRECT EXAMINATION

BY MR. TRASK:

Q. Dr. Graham, how are you?

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

Q. Fine. Thank you.

Would you please introduce yourself to the Court.

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

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

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

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

Q. And where are you from originally?

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

Q. Where did you do your undergraduate degree?

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

Q. What was your major?

A. Animal bioscience.

Q. And why did you study animal bioscience?

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

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

A. I did.

Q. What was your focus?

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

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

you go on to do a PhD?

A. I did.

Q. Where was that?

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

Q. What was your PhD thesis in?

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

Q. And did you graduate with your PhD?

A. I did.

Q. And what did you do after you graduated?

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

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

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

A. About ten years.

Q. Where did you go after that?

A. After that I joined Regeneron.

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

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

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

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

Q. And what is that product used for?

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

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

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

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

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

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

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

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

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

production.

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

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

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

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

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

THE COURT: Finally, something I understand. Thank

you, Doctor.

MR. TRASK: Happy hour.

BY MR. TRASK:

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

A. Yes.

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

A. No. I was in pilot manufacturing.

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

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

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

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

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

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

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

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

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

A. Dan Dix.

Q. And who did Dan report to?

A. Eric Furfine.

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

A. Yes. She was one of my colleagues.

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

A. They are.

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

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

done so I could understand the types of things that had been tested, what the results were. So I went through and reviewed the previous stability studies and things that we had conducted and in formulation development.

Q. Were all of the prior aflibercept formulations intravitreal formulations?

A. No.

Q. What were some of the others used for?

A. So aflibercept was originally developed to treat cancer. So it was -- the idea was it would stop tumors from growing. So we had looked at IV, maybe some subcu routes, but the predominant work was focused on IV.

Q. And when you were tasked with developing an intravitreal formulation of aflibercept, did you consider using the prior formulation for cancer for that purpose?

A. No. So the cancer formulation was designed to be a concentrate that you would put into an IV bag, dilute out, and give to a patient through an IV. So it had a really high osmolality, like 1100, 1160 milliosmoles. It had a lot of sucrose in it, 20 percent sucrose. And there was concerns that sucrose can be toxic to the eye. Different buffer system.

Q. Now, when was it that you first attempted to develop an improved intravitreal formulation of aflibercept?

A. Well, the improved version came after our first version started to fail. And this was -- I'm sorry. I was

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

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

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

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

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

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

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

that point.

Q. Were the objectives of having a formulation that was -- had high stability and a high concentration, were those compatible or in contention with one another?

A. Well, to put it simply, they're like opposites. So if you have a lower concentration formulation, they tend to be more stable. As you make the concentration higher, the stability goes down. And this is because, at least with aflibercept, the primary degradation pathway is molecules coming together.

So it's just -- the more concentrated, the more molecules, the greater the chance that they'll come together and aggregate. You know, if you want to put it in an equation, it goes up as the square of the concentration. So, you know, you double the concentration, you go from 10 to 20, it's the difference between a rate of 100 and a rate of 400 if I can still do math.

Q. Why was it that you were aiming to develop a formulation with a high concentration of aflibercept?

A. So this is for an injection into the eye. Based on my experience when my mother was treated for AMD, an injection into the eye is really traumatic. You know, even if you go once a month, it takes a couple days out of the person's life. There's a lot of risk associated with it. A lot of bad things can happen. And we wanted to be able to have as long an

efficacious range as possible.

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

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

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

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

THE COURT: Understood. Sustained.

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

MR. TRASK: Thank you, Your Honor.

BY MR. TRASK:

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

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

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

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

A. Okay. Yes. It did.

Q. What was that?

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

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

A. 30-gauge.

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

A. Yeah. We have a couple examples.

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

THE COURT: You may.

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

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

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

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

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

BY MR. TRASK:

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

A. Actually, they came out of my lab.

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

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

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

THE COURT: I might as well.

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

THE WITNESS: Please don't stick yourself.

THE COURT: I promise I will not.

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

BY MR. TRASK:

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

A. That would be a good thing.

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

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

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

What is this document, Dr. Graham?

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

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

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

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

A. KSG PCD talk, March of 2006.
Q. Okay. And which presentation is that?
A. The previous document you had up on the screen.
Q. Let's then turn back to 3327.
You said you yourself prepared this slide deck as part of your work on --
A. Yes.
Q. -- Eylea -- rather, aflibercept intravitreal injections?
A. I did.
Q. Let's look at page 44 of this document.
Did you prepare this slide, Dr. Graham?
A. I did.
Q. What does this slide show?
A. So what I did is I went back and did some calculations to estimate the shear rate that the formulation would experience when it went through different needle sizes.
Q. And if we look at the row labeled "One Second" under "Time to Inject," what did the data show that you calculated for a 22-gauge needle and a 30-gauge needle?
A. So for the 22-gauge needle, you've got about 16,000 reciprocal centimeters' worth of shear -- or not reciprocal centimeters, reciprocal seconds. So shear is like a frequency. It's seconds to the minus 1.
And then when you narrowed that needle gauge -- so

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

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

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

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

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

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

A. Going through the 30-gauge needle.

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

A. Yes, they can.

Q. How so?

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

Q. What is viscosity, Dr. Graham?

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

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

THE WITNESS: To flow.

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

BY MR. TRASK:

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

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

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

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

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

Q. Is this related to the concept of aggregation?

A. It is.

Q. And so what happens when proteins aggregate?

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

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

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

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

thing?

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

Q. Can you explain why that is.

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

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

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

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

Next question, Counsel.

BY MR. TRASK:

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

A. No.

Q. Why not?

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

clinical supplies were falling out of solution, forming particles.

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

A. That's bad.

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

A. Yes.

Q. What was the concentration in that formulation?

A. It was 25 mg/mL.

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

A. No.

Q. Why not?

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

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

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

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

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

Is this your '865 patent, Dr. Graham?

A. Yes, it is.

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

A. I am.

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

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

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

A. They do.

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

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

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

briefly remind us about turbidity analysis.

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

Q. What is the pH analysis reported here?

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

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

A. Size-exclusion chromatography.

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

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

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

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

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

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

A. Yes.

Q. What does that technique tell you?

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

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

A. Yes, we did.

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

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

Secondly, the formation of particles in a formulation

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

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

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

BY MR. TRASK:

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

A. Yes, I have.

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

A. Yes, absolutely.

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

A. We did, yes.

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

What is this page of the presentation, Doctor?

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

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

A. Yes, I did.

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

A. That would be me.

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

A. Yes.

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

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

Q. And what -- I'm sorry.

A. Go ahead.

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

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

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

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

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

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

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

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

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

A. Yes.

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

point.

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

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

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

Q. And the fourth bullet point?

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

Q. Okay.

We can take that down, please.

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

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

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

A. June 16th, 2006.

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

A. Yes, I was.
Q. What was your involvement?
A. So I supplied data and data tables to the attorney who drafted the document.
Q. Were those the same data tables that appear in the '865 patent itself?
A. The data is the same that appears in the patent, yes.
Q. And did you also review the provisional application before it was filed on June 16th, 2006?
A. Yes, I did.
Q. And you're familiar with the contents of that provisional application?
A. Yes, I am.
Q. All right. I'd like to ask you about some of the internal work you did at Regeneron leading and relating to your invention.
So first let's take a look at PTX 2293.
What is this document, Dr. Graham?
A. It's one of Regeneron's laboratory notebooks. It looks like it belonged to Kelly Frye.
Q. And remind us. Who's Kelly Frye?
A. So she was one you of my colleagues. She worked in the lab alongside of me.
Q. Does she have a PhD as well?
A. She does.

Q. And she's your coinventor on the '865 patent?
A. Yes, she is.
Q. Did you review this lab notebook, PTX 2293, as part of your role in Regeneron's formulation development group?
A. Yes, I did.
Q. You're familiar with its contents?
A. Yes.
Q. Let's turn to page 58 of this document. What's shown on this page of the laboratory notebook?
A. So this is a protocol for a stability study. This is Protocol Number 195.
Q. What is a stability study, Dr. Graham?
A. So a stability study is a collection of tests and formulations or formulations containers and tests that we assemble and conduct to look at the stability of a formulation. The protocol's kind of like a contract in that it tells you what you're going to test, what tests you're going to do, and when you're going to do them.
Q. And what other types of documentation would be associated with a stability study?
A. So typically we create what's called a pull schedule. And the pull schedule outlines when we're going to do specific thermal tests. So thermal tests basically put the formulation in a refrigerator or a freezer, an oven. And, you know, you say I'm going to come back three days, one month, six months,

and check how it is.

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

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

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

A. Yes.

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

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

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

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

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

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

A. There were five.

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

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

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

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

A. It does.

Q. Why is that?

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

Q. And does this laboratory notebook also indicate when

that formulation was first made?

A. Yes, it does.

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

What's shown here, Dr. Graham?

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

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

A. I believe it is, yes.

Q. And who made this formulation?

A. This was done by Kelly.

Q. Okay. And what was the date?

A. September 30th, 2005.

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

A. Yes, we did.

Q. And what did you find?

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

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

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

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

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

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

A. Yes, we did.

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

A. Yes, I do.

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

A. Yes, I do.

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

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

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

A. Yes, there was.

Q. Let's look at PTX 2292.

What's this document, Doctor?

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

Q. And are you familiar with that document?

A. Yes, I am.
Q. How is it that you're familiar with this notebook?
A. I reviewed its contents when I joined the VEGF Trap team.
Q. Let's turn to page 34 of the notebook.
What's shown on this page, Dr. Graham?
A. It says that the protocol for stability VEGF Trap 065.
Q. And is there a date on this stability study protocol?
A. Yes, there is.
Q. Can you make out the date?
A. It was signed by Kelly on December 4th of 2003. I can't make out the other signature.
Q. That's okay.
Let's look at the procedures section of this protocol on page 34. What types of things were varied with respect to the formulations studied in this stability study?
A. So a couple things. There were different buffers used. We changed the concentration of sodium chloride. We tested 50 and 100 millimolar. We tested polysorbate. We tested PEG. We tested a couple of different concentrations of sucrose.
Q. And what is Formulation Number 2 in this study?
A. Formulation Number 2 was a 50 mg/mL VEGF Trap formulation with 10-millimolar phosphate, 50-millimolar sodium

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

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

Do you see those both on the screen?

A. Yes, I do.

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

A. They're identical.

Q. Does this formulation have a buffer?

A. Yes, it does.

Q. What's that?

A. 10-millimolar phosphate.

Q. Does it have an organic cosolvent?

A. Yes, it does.

Q. What's that?

A. Polysorbate 20.

Q. Can that also be called a stabilizer?

A. Yes, it can.

Q. Does it also have a stabilizing agent?

A. That would be 5 percent sucrose.

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

A. It is.

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

formulation?

A. 50 mg/mL.

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

A. Yes, we did.

Q. Let's look at PTX 1921.

Is this the SEC data for SS065?

A. Yes, it is.

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

A. It was 98.8 percent.

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

A. 98.7 percent.

Q. And what about at six months?

A. 98.3 percent.

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

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

Q. Why is that?

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

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

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

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

A. Yes, it does.

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

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

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

THE COURT: Understood.

Counsel.

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

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

opinion.

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

BY MR. TRASK:

Q. Okay. Doctor, what did you understand the percent native conformation at 50 mg/mL reported in this table would tell you about the percent native conformation of a 40 mg/mL formulation of aflibercept at 5C for two months?

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

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

But I assume, Counsel, this is part of the work in developing the ultimate formulation that results in the patent at issue, correct?

MR. TRASK: Absolutely, Your Honor.

THE COURT: With that understanding, objection overruled. Would you repeat your question, Counsel.

BY MR. TRASK:

Q. Dr. Graham, for the third time, I suppose, what did you understand the percent native conformation at 50 mg/mL, as reported in this data sheet, tell you about the percent native conformation of a 40 mg/mL formulation of aflibercept stored at 5 degrees Celsius for two months?

A. Okay. So as the concentration of a formulation increases -- at least as the concentration of aflibercept

formulation increases, generally the rate of -- the rate of aggregation goes up. So it's more concentrated, more crowded, faster aggregation.

If you got a rate at 50 mg/mL, you can predict reliably that the rate at 40 mg/mL is going to be less in the same formulation.

MR. RAKOCZY: Objection, Your Honor. Again, that's pure expert opinion predicting what would and would not happen. That's for the experts.

MR. TRASK: I disagree, Your Honor. He's a scientist talking about the work he did leading to the inventions claimed in that patent being asserted in the suit. This is routine testimony at patent trials.

THE COURT: I don't believe the word "routine" shows up in the rules of evidence, but I understand the background involved here. Objection overruled.

BY MR. TRASK:

Q. Did you view the results of this study as promising, Dr. Graham?

A. Yes.

Q. Let's turn to Example 3 of your '865 patent, Doctor. You see Example 3 on the screen?

A. I do.

Q. You see the formulation used in this study is highlighted in yellow?

A. Yes, it is.
Q. What is the term there, VGFT-SS207?
A. That is Stability Study 207, 207th study.
Q. That's another stability study you performed?
A. Yes.
Q. Let's look at PTX 1825, and I want to see page 85 of this document.
Now, is this the protocol for Stability Study VGFT-SS207?
A. Yes.
Q. This stability study is part of a larger document that was produced in this case, all of which appeared to relate to SS207.
Is this how the documentation for stability studies was kept in the ordinary course of Regeneron's business?
A. So yes, it was. We kept what was called a study file, and that collected all the paper. We also kept lab notebooks as well.
Q. Okay. Let's turn to page 92 of this exhibit. Is this the approval page for the stability study we just discussed?
A. Yes, it is.
Q. Is that your signature on the page, Doctor?
A. It is.
Q. What does this page indicate your role was with

respect to SS207?

A. It says that I was the study director.

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

A. Well, that meant I was the responsible party. So I had to ensure pulls were done as scheduled, make sure there was staff assigned to do the analysis, do some of the analysis myself, summarize the data, interpret the data, give readouts to management in terms of what we had, prepare presentations. Pretty much name it.

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

A. On the 16th of January 2006.

Q. And so had you made the formulation that was tested in SS207 prior to January 2006?

A. Yes. It actually was made the previous year, I think in October of 2005.

Q. I'd like you to compare the formulation identified in the study protocol for SS207 -- that's PTX 1825, page 85 -- with the formulation in Example 3 of the '865 patent. That's PTX 2, page 8, Column 9.

Do you see those on the screen?

A. I do.

Q. Is the formulation that you studied in Stability Study 207 the same as the one disclosed in Example 3 of the '865 patent?

A. They're identical, yes.

Q. Does this formulation have a buffer?
A. Yes.
Q. What's that?
A. 10-millimolar phosphate.
Q. Does it have an organic cosolvent?
A. Yes, it does.
Q. What's that?
A. .03 percent polysorbate 20.
Q. Is there a stabilizing agent?
A. Yes, there is.
Q. What's that?
A. 5 percent sucrose.
Q. And the VEGF Trap here is aflibercept?
A. Yes, it is.
Q. And what's the concentration?
A. 40 mg/mL.
Q. Let's turn to Table 1 of the SS207 protocol. This is PTX 1825 at page 86.

You see that table on the screen?

A. I do, yes.
Q. Did this study involve testing the formulation stability in different containers?
A. It did.
Q. Was a glass vial one of those containers?
A. So the glass vial was what's listed as Device

Number 7.

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

A. Absolutely.

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

Is this the pull schedule for SS207?

A. Yes, it is.

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

A. March 21st of 2006.

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

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

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

A. Yes, it was.

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

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

A. It does.

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

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

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

A. That it had good stability, yes.

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

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

A. Yes, it does.

Q. When was that?

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

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

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

A. No, it wasn't.

Q. Had you done that sooner?

A. Yes.

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

A. We did.

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

What type of data do we have here, Doctor?

A. This is turbidity or OD at 405.

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

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

Q. And what were the results reported here?

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

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

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

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

A. We did.

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

A. Yes, it is.

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

A. March 21st of 2006.
Q. And is the pH result reported here a good one?
A. Yes, it is.
Q. What did it indicate to you about the stability of the sample?
A. That the sample was stable.
Q. Let's turn back to the size-exclusion chromatography data spreadsheet at PTX 2272. Now, you testified that there was a two-month pull and a sample was analyzed at that time?
A. Yes.
Q. Was that the end of the study?
A. Oh, no.
Q. What happened?
A. So we wanted to understand how the formulation performed at 5 degrees C over a number of years. So we continued to pull samples monthly through six months. So we had a three-, four-, five-, and six-month pull.

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

Q. And why were you testing the stability of this sample at so many different time points?
A. So we were making decisions pretty much on the fly. We had a lot of pressure to come up with what is going to go

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

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

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

A. I do.

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

A. Yes, I do.

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

A. That was the 203rd stability study.

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

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

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

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

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

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

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

A. Yes.

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

Do you see those both on the screen?

A. I do.

Q. Are these the same formulations?

A. Yes, they are.

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

A. Yes, it is.

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

A. It is.

Q. Were you the study director for this?

A. Yes, I was.

Q. And when was this protocol approved?

A. The 19th of January 2006.

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

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

A. It did.

Q. And were glass vials tested in this study?

A. Yes.

Q. Which device is that?

A. So it's Number 6.

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

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

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

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

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

A. Yes, we did.

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

A. Yes, it is.

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

A. 99.2 percent.

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

A. Yes, it is.
Q. What did that tell you about the formulation's stability?
A. That it had good stability.
Q. Let's look at the bottom of this page. Does this document also tell you when the size-exclusion chromatography test was run?
A. Yes, it does.
Q. What does it say?
A. So 06, year, so 2006; 02, February; 14, 14th.
Q. If we could turn to page 156 of PTX 1860, is this more data from the Stability Study SS203?
A. Yes, it is.
Q. What's shown here?
A. So it's the osmolality of the formulation.
Q. And what osmolality is reported here, Doctor?
A. 287.
Q. And what units are those?
A. Milliosmoles.
Q. And so is the formulation that was analyzed in SS203 an isotonic formulation?
A. No, it's not.
Q. What's your understanding of what's isotonic?
A. 300, 320, that range.
Q. And you said earlier that the formulation in SS203 is

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

A. Yes, it is.

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

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

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

A. H-Y-P-O.

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

A. Okay.

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

Do you see both of those on the screen?

A. I do.

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

A. They do.

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

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

Do you see those?

This is PTX 2277, page 15.

A. I see it.

Q. Do you see those on the screen?

A. Yes, I do.

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

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

Q. And can you explain how the rounding works.

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

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

Do you see those on the screen?

A. Yes, I do.

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

A. Yes, they do.

Q. Okay.

Let's take that down, please.

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

till now, right, Doctor?

A. Yes, we have.

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

A. Yes, there were.

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

A. We filed a provisional patent.

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

A. Yes.

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

A. Yes, they are.

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

Let's look at PTX 3249.

Do you recognize this document, Doctor?

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

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

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

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

A. June 16th of 2006.

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

Do you see both of those on the screen?

A. Yes, I do.

Q. How do those examples and data compare?

A. They're identical.

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

You've reviewed both of these previously, Doctor?

A. I have.

Q. How do these examples and data compare?

A. They're identical.

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

You've reviewed both of these previously?

A. Yes, I have.

Q. How do these examples and data compare?

A. They're identical.

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

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

A. Yes, they are.

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

A. Yes, it is.

Q. Let's take a look at -- again at PTX 1825, page 172.

This is the pull schedule for Stability Study 207, Doctor.

A. Okay.

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

A. March 21st, 2006.

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

A. No.

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

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

Q. Let's --

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

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

MR. RAKOCZY: Thank you, Your Honor.

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

THE COURT: Yes. Thank you.

BY MR. TRASK:

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

A. Yes.

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

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

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

A. Yes, there are.

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

3, and 5?

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

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

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

A. I do.

Q. Have you reviewed these passages previously?

A. Yes, I have.

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

A. They do.

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

A. Yes, I did.

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

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

A. Yes, I am.

Q. Have you reviewed each of those?

A. Yes. I did.

Q. Did you determine in your review of those documents whether or not each of those patents contains the same disclosure as in your '865 patent at Column 2, lines 39 to 57, and Examples 1, 3, and 5?

A. All of them contain the same examples, the exact same data. Those paragraphs, although they appear on different pages sometimes in slightly different formatting, are all identical with respect to the words.

Q. Thank you, Doctor.

Now, were the aflibercept formulations that are reported in your '865 patent the only ones that you tested for stability?

A. No.

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

A. 40.

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

First, when you varied the ingredients in your formulations, did you ever try stabilizing agents other than sucrose?

A. Yes.

Q. What did you try?

A. We tried -- mannitol was one.

Q. Okay. Let's look at your '865 patent, PTX 2, at Column 2, lines 45 or thereabouts. What does this passage of

the patent convey in part?

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

Q. And did you, in fact, do a stability study on a formulation with mannitol as the stabilizing agent?

A. We did.

Q. Okay. Let's look at PTX 2281 at page 1. What is this document, Doctor?

A. This is the 208th stability study protocol.

Q. And did you run this study?

A. I did.

Q. Let's turn to page 2 of this document. This is the mannitol-containing formulation you just referenced?

A. Yes, it is.

Q. And on page 2, does this indicate whether or not a glass vial was tested as the container?

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

Q. Let's compare the formulation of Example 3 from your '865 patent, PTX 2, Column 9, with the formulation of SS208, which is PTX 2281, page 1.

Do you see these on the screen?

A. I do.

Q. How do these two formulations compare?

A. They're identical.

Q. Is the stabilizing agent identical?

A. No. So the formulations are identical with respect to every other component except one has sucrose and the other has mannitol.

Q. Did this study involve testing the mannitol-containing formulation by SEC?

A. Yes, it did.

Q. Let's look at PTX 2282 at page 14. Is this spreadsheet the SEC data for SS208?

A. Yes, it is.

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

A. Yes, it is.

Q. What was the percent native conformation as measured by size-exclusion chromatography at 5C, two months' storage in a glass vial?

A. 99.05.

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

A. Yes, it is.

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

A. Yes, we did.

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

What is this document?

A. So this is the data that was collected for turbidity or optical density at 405.

Q. And what does it show for the turbidity of the mannitol-containing formulation following storage at 5C for two