based on Gaudreault of the aflibercept, much less than the 10 mg/mL.

Q. Now, let's take a look at Ferrara 2004.

Just for the record, this is a different Ferrara article. It's PTX 1838.

Did you review this article as well?

A. Yes, I did.

Q. Okay. And if we look to page 7 of the article, can you explain what Ferrara is disclosing here and how it's relevant to the consideration of an appropriate concentration to use.

A. Certainly.

So Ferrara -- and, again, different from the Ferrara that we just talked about a little while ago, it's referring to the VEGF Trap again and is basically just relating what I said earlier and what the POSA would know. Because of the fact that this not a natural molecule, it's completely constructed, the junctions between the various structural elements in such multicomponent molecules can generate an immune response, which, again, I think I talked about this last week too, is something that the formulator is very concerned about.

Q. What would the relevance of this discussion in Ferrara 2004, Exhibit 1838, have had on the concentration that the POSA would have wanted to use for an intravitreal injection?

A. Well, it would teach the POSA to use a low concentration. Again, it's going to be much lower than the 10 mg/mL to try to minimize the risk of such an immune response.

Q. Let's take a look at the Wang reference. That's PTX 1556.

And we'll blow up part of page 1.

What is Wang teaching here, and how does it relate to the protein concentration that the person of ordinary skill would have wanted to use?

A. Well, Wang here -- again, this is a review article. It says, "Increasing protein concentration generally increases protein aggregation."

Q. And so how would that be relevant to the POSA who's trying to choose a concentration to use for intravitreal injection?

A. Well, it would teach the POSA to use as low a concentration as possible, again teach away from these higher concentrations like 40 mg/mL. Again, aggregation can cause serious problems, as the formulator would understand, not only in -- you don't want to inject aggregates as such into the eye, but also the possibility of these immune responses.

Q. Okay.

And for the record, this is page 9 of PTX 1556, the Wang reference.

Doctor, in view of the -- all of the prior art that you reviewed, what would the POSA have thought in terms of an appropriate concentration of aflibercept for intravitreal injection if the POSA had wanted to use aflibercept for intravitreal injection?

A. Well, the POSA would choose a concentration probably lower than that of ranibizumab, so lower than 10 mg/mL.

Q. What would the POSA have thought about the idea of using 40 mg/mL?

A. Well, the POSA would be taught away from using 40 mg/mL. In other words, it wouldn't be a good idea.

Q. Now, I'd like to turn to a new topic, which is polysorbate 20.

Doctor, if we pull up the claims again, do all of the asserted claims require polysorbate 20?

A. Yes, they do.

Q. And do you understand Dr. Rabinow in his combination to have relied on Gaudreault and Shams for this limitation?

A. Yes.

Q. And what do the references -- well, let's first look at Gaudreault.

And, again, this is page 2 of Gaudreault. What does Gaudreault teach with respect to its formulation and polysorbate 20?

A. Well, Gaudreault teaches, as we have here -- this is

the formulation in the first -- or the top excerpt and the highlighted one -- highlighted sentence for polysorbate, which, again, I think Your Honor noted correctly that Tween 20 is a synonym for polysorbate. It teaches 0.05 percent.

THE COURT: I've been right about this for the last couple weeks, Doctor, if you ask all them out there.

Oh, come on. That was funnier.

MR. BERL: No comment. Too tired to laugh, Your Honor.

THE COURT: Limping to the finish line, but I thought that was better than that.

THE WITNESS: That was funny from up here.

THE COURT: Thank you.

BY MR. BERL:

Q. Doctor, did Genentech proceed with this formulation that has .05 percent polysorbate?

A. No, Genentech did not.

Q. Let's take a look at the Shams reference. And, actually, we'll look at Dr. Rabinow's discussion of the Shams reference in regards to this limitation. What does Shams teach with respect to its formulation and polysorbate 20?

A. Okay. So this is a cutout or excerpt on the bottom right, again, from Dr. Rabinow from Shams. And you can see highlighted here 0.01 percent polysorbate 20.

Q. And what is the concentration, Doctor, required by

Claim 4 of the '865 patent?

A. Claim 4 is about 0.03 percent to about 0.1 percent polysorbate 20.

Q. And Dr. Rabinow put the .01 percent polysorbate 20 from Shams in green and colored also in green the about .03 percent to about .1 percent in Claim 4.

Do you agree with his analysis that Shams teaches that concentration required by Claim 4 of polysorbate 20?

A. No, because Shams teaches 0.01 percent, which doesn't fall in the range of polysorbate from Claim 4.

Q. What concentration did Genentech ultimately use for Lucentis?

A. 0.01 percent.

Q. Now, let's discuss Fraser, the last reference in this combination. Again, that's DTX 729.

Does Fraser say anything about intravitreal administration?

A. No.

Q. What concentration of Tween 20 or polysorbate 20 does Fraser disclose, looking at page 2 of the reference?

A. 0.01 percent.

Q. Now, reading --

A. I apologize. Sorry to interrupt.

0.1 percent -- added an extra zero.

0.1 percent, for the record.

Q. My last case in West Virginia was all about something 0.001 percent, and everyone throughout the trial kept adding and subtracting zeros throughout the entire time. So the record was a mess. Thank you for correcting yourself.

Now, Doctor, reading Dr. Rabinow's combination as a whole, the Lucentis plus Fraser, and assuming the POSA combined those references contrary to your opinion, what concentration of polysorbate would the POSA have preferred to use?

A. Well, if one were going to do that, it would be 0.01 percent.

Q. Why?

A. Well, that's what the Shams teaches, and that's what it recommended for the clinical trials. And, in fact, that's what finally Genentech used.

Q. And the clinical trial that Shams is discussing, is that a systemically administered drug as in 729, Fraser, or is that an intravitreal trial?

A. No. Shams teaches intravitreal clinical trials.

Q. And would that have been more relevant to the POSA than formulations like Fraser?

A. Yes. Of course.

Q. Now, let's turn to the next limitation of the claim, the 98 percent native conformation as measured by size-exclusion chromatography limitation.

Do any of Fraser, Gaudreault, or Shams teach the

98 percent native conformation limitation?

A. No, they do not.

Q. Did Dr. Rabinow present any evidence that any of the formulations in Fraser, Gaudreault, or Shams achieved the 98 percent native conformation limitation?

A. No, he did not.

Q. Now, did either of the Gaudreault formulations go into clinical trials?

A. No, they did not.

Q. You mentioned before that Shams went into clinical trials. Does that mean that it met the 98 percent native conformation requirement?

A. No, it does not.

Q. Why not?

A. Well, there's no indication -- it might be stable enough for clinical trials, but there's no indication that it met the 98 percent limitation here.

Q. Did either Gaudreault or Shams teach that the ranibizumab formulations had 98 percent native conformation?

A. No, they did not.

Q. Now, even if one somehow believed that the Shams formulation or the Gaudreault formulation had 98 percent native conformation of ranibizumab, would the POSA have expected that the same formulation with aflibercept would have 98 percent native conformation?

A. Based on that of ranibizumab, no.

Q. Why not?

A. They're different molecules. They're going to behave differently. And as I mentioned, aflibercept is this fusion protein. It's not a natural molecule. So, if anything, if one were -- had that information and were to do the comparison, one would expect it to be less stable.

Q. Let's take a look at Wang again. That's Exhibit 1556. And we'll look at page 7 of the article.

What -- in this Section 2.3.1 in the sentence beginning "mutation of one amino acid," what is Wang teaching here?

A. Well, maybe just to read the whole sentence, "Mutation of one amino acid in a peptide or protein can dramatically increase the aggregation propensity."

That's just one. If we're talking about completely different molecules, that can make them substantially different in terms of --

Q. Was there one amino acid difference between ranibizumab and aflibercept or a lot more than one difference?

A. A lot more than one.

Q. Now, let's move on to discuss the pH limitation and in particular the pH limitation found in Claim 9 of the '865 patent.

And that says about 6.2 to 6.3; is that right?

A. Yes. Correct.

Q. Does the Fraser plus Lucentis prior art, even if combined, teach using the required pH range of Claim 9?

A. No, they do not.

Q. Now, if we look at Shams and Gaudreault again now side by side -- Gaudreault, 1839, and Shams, 726 -- what are the pHs used in those formulations that Dr. Rabinow relies on?

A. Well, the Gaudreault is in the upper left here. That pH is 5.0. The Shams is kind of the bottom right, and that pH is 5.5.

Q. Does that meet the limitation of about 6.2 to 6.3?

A. No. Neither do.

Q. Now, the third reference here, Fraser, if we -- we looked at that a moment ago. That had a pH of 6.0; is that right?

A. Correct.

Q. Would the POSA have just used that pH?

A. No.

Q. Why not?

A. Well, because, first of all, the POSA, in investigating a formulation for the '865 patent, would investigate that for aflibercept with intravitreal administration in mind, whereas Fraser doesn't teach intravitreal administration.

Q. Did Dr. Rabinow ever identify which precise

formulation in his combination the POSA would have used if combining Fraser, Gaudreault, and Shams?

A. No, he did not.

Q. If you assume Dr. Rabinow's hypothesis that the POSA would have substituted aflibercept into the ranibizumab formulation, what pH would the POSA have used?

A. Well, the ranibizumab is at 5.5. So if one were going to do that, it would be 5.5.

Q. What if you performed experimentation to find a different pH, as Dr. Rabinow suggests?

A. Well, then, that would be a whole formulation study, a whole investigation.

Q. Would you end up with the same formulation, or at that point do you have a different formulation than the one you'd have if you combined the references?

A. Well, then, you have likely a different formulation. You're doing a whole research project at that point.

Q. Now, let's turn to the turbidity limitation. And we can look at that in Claim 15.

Does that require a turbidity of 0.01 or lower at OD405 after two months' storage at 5 degrees?

A. Yes. That's correct.

Q. Did Dr. Rabinow present any evidence that a 40-milligram formulation of aflibercept would achieve the claimed level of turbidity in view of Fraser, Gaudreault, or

Shams?

A. No, he did not.

Q. Have you seen any such disclosure or teaching in those references?

A. No.

Q. Can you conclude that the Shams formulation meets the turbidity limitation of Claim 15 on the basis of a disclosure for use in a clinical trial?

A. No.

Q. Is the turbidity limitation synonymous with stable?

A. No.

Q. Is the 98 percent native conformation limitation synonymous with stable?

A. No.

Q. Why do you say no to those questions? Why not?

A. Well, because stable doesn't mean it has to be 98 percent or meet this particular turbidity requirement. It could be stable and not be at 90 percent and not meet this turbidity requirement.

Q. Based on the prior art on which Dr. Rabinow relied for obviousness, even if combined, would the POSA have had any expectation that the formulations Regeneron claimed of the '865 patent would meet the turbidity limitations of the claims?

A. No.

Q. Same question for the 98 percent native conformation,

would the POSA have had any expectation of success?

A. Same answer. No.

Q. Would the prior art formulations on which Dr. Rabinow relied, even if combined, necessarily and always have the turbidity required by the asserted claims?

A. No. There's no reason to think that.

Q. And how about for 98 percent native conformation?

A. Again, no reason to think that either.

Q. Is the claimed protein concentration relevant to turbidity?

A. Yes.

Q. How so?

A. Well, again, generally, the higher concentration leads to a higher aggregation propensity, hence higher insoluble aggregates and hence higher turbidity.

Q. Did Dr. Rabinow point to any prior art turbidity data on 40 mg/mL of aflibercept?

A. No.

Q. Did Dr. Rabinow point to any turbidity data on 40 mg/mL of ranibizumab?

A. No.

Q. In your view, Dr. Trout, are the asserted claims obvious over the combination of Fraser and Lucentis?

A. No.

Q. Now, we're done with Fraser and Lucentis.

MR. BERL: I can keep going, Your Honor. I'm at your pleasure.

THE COURT: Let's call it a day. Let's do that.

Is that all right with you, Doctor?

THE WITNESS: Yes, as long as you give the order that the attorneys can't talk with me.

THE COURT: Motion granted.

Yes, Doctor, because you remain midstream on your testimony, even though you've come and gone once but you're considered midstream again by our rules, you are prohibited from contact with other humanoids about your testimony here.

So you're welcome. You can go ahead and step down, sir. Have a lovely evening in quiet solitude.

THE WITNESS: Thank you.

Thank you, Your Honor.

THE COURT: You're welcome.

Everybody okay with starting at 8:30 tomorrow?

MR. BERL: Absolutely.

THE COURT: Let's do that. And we'll sprint through the tape at that point, as they say.

Anything we need to take up from Regeneron's standpoint at this juncture?

MR. BERL: Not from Regeneron, Your Honor.

THE COURT: Mr. Rakoczy, anything from Mylan?

MR. RAKOCZY: Nothing from Mylan.

THE COURT: Okay. And we anticipate at this point that Dr. Trout will be the last witness; is that correct? Anybody being called by Mylan on the back end?

MR. RAKOCZY: Not as far as we know. He'll be the last one.

THE COURT: Okay. Al right. Well, let's do that. We'll see everyone at 8:30 tomorrow morning. And, again, my promise to be prompt with notifications about any change in the lunch run schedule tomorrow. Apologies for any heart palpitations I gave everybody.

With that, everybody have a pleasant evening, and we'll see you all tomorrow morning.

Thank you very much.

(Proceedings concluded at 5:07 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 22, 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 22nd 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 Volume 9

Biocon Biologics,

Defendants.

- - -

Proceedings had in the bench trial of the above-styled action on June 23, 2023, before Honorable Thomas S. Kleeh District Judge, at Clarksburg, West Virginia.

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Transcript produced by computer-aided transcription.

Friday Morning Session,
June 23, 2023, 8:30 a.m.

- - -

THE COURT: I've gotten my coffee mishap out of the way back there; so it should be smooth sailing from here.

Good morning, Doctor. You remain under oath.

Mr. Berl, you may proceed.

MR. BERL: Thank you, Your Honor.

DIRECT EXAMINATION (CONTINUED)

BY MR. BERL:

Q. Good morning, Dr. Trout.

A. Good morning, Mr. Berl.

Q. I'd like to shift now to Dr. Rabinow's second combination, Fraser plus Liu.

Do you agree with Dr. Rabinow that Fraser and Liu combined render the asserted claims obvious?

A. No, I do not.

Q. Now, before we get into the various limitations of the claims and details of the references, do you think that there's any reason that the POSA would have chosen those two references, Fraser and Liu, from amongst all of the prior art?

A. No, no reason.

Q. And, Doctor, do you believe that there's any reason that the POSA would have sought to combine Fraser plus Liu?

A. No. And, again -- or I guess I'll say a little more

about this, but Liu doesn't have anything to do with aflibercept or anything related.

Q. Now, I understand that opinion, Dr. Trout, but unless I specifically say otherwise, for this portion of the testimony I'd like you to assume that the POSA would have combined Fraser with Liu as Dr. Rabinow asserts.

Can you do that?

A. Okay.

Q. With that, let's look at the first limitations of Claim 1 --

If we can put that on the screen.

-- relating to ophthalmic formulations and intravitreal injection. Do either Fraser or Liu disclose ophthalmic formulations?

A. No.

Q. Let's look at Fraser. It's DTX 729 again, and this is page 1.

What is Fraser discussing?

A. Well, as highlighted here in this excerpt in the lower right side, the aim of the present study was to evaluate the effects of transient inhibition of VEGF on pituitary ovarian function in the macaque, so nothing to do with ophthalmics.

Q. Is there any disclosure in Fraser of intravitreal administration?

A. No.

Q. What kind of administration is Fraser using -- local intravitreal administration or systemic administration?

A. Systemic intravenous, so not intravitreal.

Q. Would the POSA interested in making an ophthalmic formulation for intravitreal administration have looked to Fraser either alone or in combination with Liu?

A. No.

Q. And why does this distinction matter between an IV formulation and an intravitreal formulation? What, if anything, is different about these ophthalmic intravitreal formulations?

A. Well, the current concerns are quite different. I think I testified last week to some of those differences. One major difference, of course, is having to go through this very narrow-bore needle -- which I think Your Honor saw earlier this week -- a very thin needle, which is going to encompass shear.

The other things, issue with particulates and other aspects of -- can be very different for intravitreal.

Q. Would Liu cause the POSA to want to use Fraser or a modified version thereof intravitreally?

A. No.

Q. Does Liu teach anything about intravitreal injections or formulations?

A. No.

Q. Now, I'd like to move to the next limitations of the claim relating to aflibercept.

You already discussed that with respect to Fraser yesterday. Do those same opinions apply to the combination of Fraser with Liu?

A. Yes. That's correct.

Q. And do the opinions you expressed yesterday regarding glycosylation of aflibercept with Fraser, do those apply to the combination of Fraser and Liu?

A. Yes.

Q. Now, the new reference in this combination is Liu. That's DTX 730. Does Liu teach the aflibercept amino acid sequence?

A. No.

Q. Does Liu teach the glycosylation of aflibercept or the sites of glycosylation?

A. No. Of course, it doesn't teach aflibercept; so it doesn't teach the glycosylation of it.

Q. Okay. Let's go to the next limitation of the claim, 40 mg/mL. Dr. Rabinow again cites to Fraser for the 40 mg/mL limitation.

Do the opinions you discussed yesterday about that apply here?

A. Yes.

Q. Now, do you agree with Dr. Rabinow that the POSA

would select an appropriate intravitreal dose based on the amount of a VEGF Trap used to inhibit ovarian function in monkeys in Fraser?

A. No.

Q. Why not?

A. Because they're different types of approaches, different indications, different organs, different parts of the body.

Q. What about Dr. Rabinow's suggestion that the POSA would use a 60-microliter injection rather than a 50-microliter injection for intravitreal administration, if one were applying the prior art, in order to be generous?

A. I didn't see any basis for that.

Q. If one used a higher dose volume than 50 microliters, would one change the concentration of the drug product?

A. Well, it depends; but, generally, one would increase the dosage.

Q. And so you'd use the same concentration if you had an overage?

A. Yes. Well, I think the overage, frankly, would have been in the vial, not in the syringe, but it was a little unclear. But the point is the concentration would be whatever the concentration is in the vial.

Q. Now, let's take a look at Liu with respect to the concentration. And we'll take a look -- again, this is

DTX 730. And we've put on the screen part of page 35 of Liu.

Does Liu teach concentration ranges for formulations of other proteins other than aflibercept?

A. Yes. And I've highlighted a range here in paragraph 13 of Liu. It says -- a little hard to read maybe on the screen, but it does say antibody 40 to 150 mg/mL.

Q. What does Liu teach about the concentration of aflibercept?

A. Nothing.

Q. What about VEGF antagonists?

A. Nothing.

Q. What about an appropriate concentration for intravitreal administration?

A. Nothing.

Q. Would Liu alone or in combination with Fraser motivate the POSA to use a 40 mg/mL formulation of aflibercept intravitreally?

A. No.

Q. On the basis of the combination of Fraser and Liu, would the POSA have used a formulation of 40 mg/mL of aflibercept intravitreally?

A. No. There's no reason.

Q. Now, if we look to page 9 of Liu, Dr. Trout -- this is paragraph 6 of the reference DTX 730 -- did Liu have additional information relevant to the question of whether the

POSA would have combined it with Fraser?

A. Yes. And I've highlighted a middle part of this paragraph. Again, this is just a reflection of what the POSA would know. Speaking, though, of antibodies, antibodies tend to form viscous solutions at high concentration because of their macromolecular nature and potential for intramolecular interactions. Moreover, pharmaceutically acceptable sugars are often used in large amounts as stabilizers.

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

A. Well, if you have a higher concentration of antibodies, for example -- because Liu is just about antibodies -- that's going to lead to a higher viscosity. Also, if you have a higher amount of sugar, that can lead to a higher viscosity. I think we're familiar with syrup; it's more viscous. And the combination together can lead to an even higher viscosity.

And, again, for intravitreal administration, which these references don't teach, we have a very thin-bore needle. High viscosity means potentially very long injection times, which I think we all don't want in the eye. And potentially, if it's too viscous, you won't even be able to use it.

Q. And what does Fraser have with respect to concentrations of sugar? Does it use low concentrations or high concentrations?

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

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

Q. So would the person of skill, in view of this teaching of Liu, have wanted to combine Fraser with a high concentration of sugar with Liu?

A. No, not at all. I mean -- again, they don't contemplate intravitreal, but certainly you wouldn't want to use these high concentrations for intravitreal.

Q. I'd like to move to the 98 percent native conformation limitation with respect to this combination.

THE COURT: Mr. Berl, before you ask that question, it just dawns on me I did the same thing today I neglected to do yesterday.

We're going to take our lunch break from 11:00 to 12:00 today for anyone who needs to -- I saw everybody turn and look at somebody in each corner of the courtroom. You all are the MVPs today. My apologies. I promised you I wouldn't do that to you again, but I just did. We're going to take our lunch break from 11:00 to 12:00 today with apologies.

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

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

BY MR. BERL:

Q. So I'd like to talk about the 98 percent native conformation limitation, Dr. Trout, with respect to this

combination of Fraser plus Liu.

Did you hear Dr. Rabinow testify about the Liu reference?

A. Yes.

Q. Would Liu have informed whether formulations of aflibercept would meet the 98 percent native conformation limitation?

A. No.

Q. Why not?

A. Because Liu talks about different molecules, completely different molecules. It doesn't even tell -- or inform what those molecules are exactly, but they're different from aflibercept.

Q. Would the POSA conclude that, because Liu identified antibody formulations that met 98 percent native conformation for those molecules, aflibercept would perform the same way?

A. No, not at all.

Q. And let's -- again, what's the relevance of aflibercept's structure as a fusion protein to your opinion?

A. Well, first of all, as I've been emphasizing, I think it's clear aflibercept is a different molecule than the molecules in the Liu reference. And, furthermore -- I brought this up yesterday also to the Court -- these are -- well, the aflibercept is fusion protein. It's not a natural molecule. I used the term "Frankenstein molecule." And I even quoted some

of the literature that would reflect the understanding of the skilled person that these molecules would tend to be less stable.

Q. Would the POSA have an expectation of success regarding the native conformation of aflibercept in view of Liu?

A. No.

Q. Let's talk about turbidity briefly. And we can look again -- this is recited in Claim 15 of the '865 patent. Does Dr. Rabinow rely again on Liu for this limitation?

A. Yes.

Q. Do you agree with Dr. Rabinow that the POSA would expect aflibercept formulations to have the claimed turbidity based on Liu?

A. No. Again, completely different molecule.

Q. Now, is the analysis you just provided with respect to native conformation the same with respect to the turbidity limitation?

A. Yes. That's correct.

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

Do you believe that the combination of Fraser and Liu render the asserted claims obvious?

A. No.

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

Do you agree with Dr. Rabinow's opinion that the Dix '226 patent anticipates the asserted claims?

A. No.

Q. Now, Doctor, what priority date -- what priority dates did you assume in forming your opinions?

A. Well, I did the analysis with two different priority dates. One was June 16th, 2006, and the other was March 21st, 2006.

Q. Okay. Let's start with the first one.

If we could put on the screen parts of PTX 55.

This is part of the opening report of Dr. Rabinow. Is this the report you responded to for purposes of the prior art, invalidity, the obviousness, and anticipation arguments?

A. Yes, it looks like that report.

Q. And we've put up on page 164 of PTX 55 in paragraph 198 part of Dr. Rabinow's report entitled "The priority date for the '865 patent."

What priority date did you understand Dr. Rabinow was applying?

A. Well, as highlighted here, that was June 16th, 2006.

Q. Did you understand there to be any dispute as to whether the '865 patent was, as Dr. Rabinow puts it, entitled to a priority date of June 16th, 2006?

A. No. My understanding was there's no dispute.

Q. Let's take a look at Dr. MacMichael's report. That's

PTX 53.

Did you also respond to that report?

A. Yes.

Q. And what priority date was applied in that report by Dr. MacMichael?

A. Well, again, as highlighted here in this excerpt, June 16th, 2006.

Q. Now, you said a moment ago, Doctor, that you also applied a date of March 21, 2006; is that right?

A. Correct.

Q. Did you reach a different conclusion with respect to validity based on that priority date?

A. No.

Q. Now, Dr. Graham discussed all of that a couple days ago with respect to the priority date; so we won't belabor that here. I want you to assume for the rest of my questioning on this topic that Dix is prior art to the '865 patent.

Can you make that assumption?

A. Okay.

MR. BERL: And, obviously, Regeneron disagrees with that, Your Honor, but we want to respond in the alternative.

BY MR. BERL:

Q. Do you agree with Dr. Rabinow that Dix anticipates or renders obvious the asserted claims?

A. No.

Q. Let's go through the limitations, and let's first look at the 40 mg/mL. And we've seen that before. And let's look at page 4 of Dix. This is page 4 of Dix that we'll pull up, Doctor.

What does Dr. Rabinow rely on from Dix with respect to the 40 mg/mL limitation?

A. Well, he relies on this range that's here from Dix, the range of 10 to 50 mg/mL.

Q. Do you agree that the range of 10 to 50 mg/mL teaches 40 mg/mL?

A. No. There's no reason why that would point the POSA to 40 mg/mL.

Q. Do you understand that the disclosure of 10 to 50, do you believe that that discloses every number within that range?

A. No.

Q. Is 10 to 50 a small range?

A. No. It's a significant range.

Q. Is this range here of 10 to 50 in Dix being taught for intravitreal administration?

A. No.

Q. And is the concentration the POSA would understand should be used different for intravitreal administration compared to other kinds of administrations?

A. Yes.

Q. Now, if the POSA were choosing a concentration within

the Dix range for intravitreal administration, what concentration would the POSA want to use?

A. Within Dix? Well, there's no real indication within Dix. But, again, as I talked about earlier from Gaudreault and other parts of the prior art, it would be on the lower end of the concentration, 10 mg/mL or perhaps even lower.

Q. And what would the POSA, in view of the prior art, have thought about using a 40 mg/mL concentration for intravitreal administration?

A. Well, as I discussed yesterday, the prior art teaches away from using the 40 mg/mL; so the POSA wouldn't want to do that.

Q. Does this disclosure of a concentration range on page 4 of Dix, is it teaching the aflibercept molecule with that range?

A. No. It just -- and I've highlighted the excerpt above. It just talks about a VEGF-specific fusion protein antagonist broadly. This is just a very broad disclosure here.

Q. And is aflibercept the only sequence that's taught in Dix?

A. No.

Q. How many sequences are taught in Dix?

A. Well, there are two sequences.

Q. And is this fusion protein antagonist language from Dix limited to those two fusion proteins or could it encompass

others?

A. It could encompass others. In other words -- or again, I should say, as I discussed, this is just a very general disclosure towards the beginning part of Dix.

MR. BERL: With that, Your Honor, the next set of questions of a couple minutes are not in Dr. Trout's report. And the reason they're not in Dr. Trout's report is that they relate to an argument that was not in Dr. Rabinow's report, either the opening report or the reply report.

He said something about it at his deposition. He had it on one of his slides. We objected. That objection was overruled, and he said something very brief about it in cross-examination. So we'd like to respond to it, but it's obviously -- I just wanted to front that issue and not suggest that this was in Dr. Trout's report, because it's not.

THE COURT: Understood.

Any objection from Mylan?

MR. RAKOCZY: I'm not sure what the question --

THE COURT: Well, dust off your crystal ball, Mr. Rakoczy.

MR. RAKOCZY: I suspect I will be objecting, but I need to hear the question.

THE COURT: Understood. Well, let's see what the questions are. Thank you much, Counsel, for the preview, but go right ahead.

BY MR. BERL:

Q. The first question actually is in your report; so the ones after that are not.

Doctor, I want to talk a little bit about lyophilized formulations. Are you familiar with that concept?

A. Yes, I am.

Q. Okay. What steps do lyophilized formulations require before the drug may be administered?

A. Well, first of all, you have to make the lyophilized formulation. So you go through various mixing processes, for example, make a prelyophilized solution, not a formulation, just a solution. And then you would go through the lyophilization process, so freeze-drying. That dried powder is also not an injectable or usable product as such until you add liquid -- generally, water for injection -- and reconstitute it. And so then you have a liquid finally -- a formulation that you can use, for example, for injection.

Q. And this prelyophilized solution that you describe, is that something that's to be administered to patients?

A. No. Not at all.

MR. RAKOCZY: Objection, Your Honor. Number one, not in the report. Number two, the witness isn't qualified to testify as to what is or is not properly administered to a patient.

THE COURT: Sustained on the second grounds. That's

outside of the scope of his expertise as deemed qualified by this Court.

MR. BERL: Okay. So let me ask the question a little differently.

BY MR. BERL:

Q. From a formulator's perspective, is the prelyophilization solution that a formulator would make, is that intended to be administered to patients or is it intended to be freeze-dried as part of the manufacturing process?

MR. RAKOCZY: Same objection, Your Honor. I'm not aware of this being in the report, number one.

Number two, again, that's just repackaging the same question only putting formulator at the front.

MR. BERL: It wasn't. It was slightly different, if I may, Your Honor. I didn't ask him what's appropriate for injection, which I understood to be the subject of the objection, because that might involve some clinical judgment, but rather what is intended by a formulator? Is the formulator making it so that it can be injected as opposed to as a manufacturing process so it can be freeze-dried or lyophilized? That's what I was asking about.

THE COURT: Understood.

In light of the Court overruling the objection with respect to Dr. Rabinow, I'll overrule this one. But I don't think we need to delve too very deep on it.

THE WITNESS: Yeah, as a formulator, again, someone who does pharmaceutical manufacturing, the prelyophilized solution is an intermediate. That's all. And then it would go through further processing.

BY MR. BERL:

Q. Now, I'd like briefly to bring up another section of Dix that Dr. Rabinow very briefly addressed. And it's on page 5 of Dix.

Doctor, we have on the screen part of page 5. And in part it talks about prelyophilized solutions and a 40 mg/mL prelyophilized solution is lyophilized and reconstituted to an 80 mg/mL solution.

Do you think, Dr. Trout, that this teaches the 40 mg/mL limitation of aflibercept for purposes of the claims of the '865 patent?

A. No. Again, it's just a manufacturing intermediate.

Q. Does Dix teach that this 40 mg/mL prelyophilized solution is for aflibercept?

A. No. This is part of a very general disclosure. It just mentions VEGF here. And this is part of a whole column of all kinds of different numbers and various, you know, discussions of prelyophilization and reconstitution.

Q. Would the POSA understand or expect that the 40 mg/mL prelyophilized solution would have 98 percent native conformation after two months at 5 degrees?

THE COURT: One second, Doctor.

MR. RAKOCZY: Objection, Your Honor. That is not in the report.

MR. BERL: I agree completely that that's not in the report, but I'm addressing Dr. Rabinow -- again, I think he said one sentence about this on cross. What I don't want to happen is for them all the sudden to say that's an anticipation, and we can't respond.

MR. RAKOCZY: Your Honor, they did respond in the report. I think the witness took the position that lyophilized formulations are not even within the scope of the claim. So I'm not sure where this is going, but this is a completely new opinion.

THE COURT: I do recall Dr. Rabinow covering it. Subject to the Court's prior ruling on that, I'm going to overrule it at this point.

MR. BERL: I probably need to ask the question again.

THE COURT: Probably.

BY MR. BERL:

Q. Doctor, would the POSA expect or have any reason to believe that the 40 mg/mL prelyophilized solution that's the subject of this disclosure in Dix would meet the 98 percent native conformation as measured by SEC after two months at 5 degrees limitation?

A. No. And the way you would make this -- a formulator

would make this wouldn't be to store it for nearly that long.

Q. In your view, Doctor, taken together, does Dix anticipate or render obvious the asserted claims?

A. No.

Q. And did Dr. Rabinow rely on the same disclosures of Dix for anticipation as he did for obviousness?

A. Yes.

Q. And do the opinions that you just expressed for anticipation apply for obviousness as well?

A. Yes. That's correct.

MR. BERL: And, again, Your Honor, Regeneron disputes that Dix is a proper obviousness reference, including the safe harbor of Section 103(c).

MR. RAKOCZY: We obviously disagree with the 103(c) arguments, which we briefed in summary judgment and we're happy to address again in the proposed findings, Your Honor.

THE COURT: Understood.

MR. BERL: I'm sure Your Honor will read more about that.

THE COURT: I'm looking forward to it.

BY MR. BERL:

Q. Doctor, did you also consider objective indicia of nonobviousness?

A. Yes, I did.

Q. What did you conclude?

A. Well, I conclude that there's objective indicia, or I guess you call it secondary considerations. There are other evidence of nonobviousness.

Q. Did you consider industry skepticism regarding the use of VEGF Traps?

A. Yes, I did.

Q. Let's take a look at Ferrara 2004. Again, there are two Ferraras; this is the 2004 reference, PTX 1838. Let's take a look at page 7 of this article.

Can you explain what's disclosed here and how it relates to your concept and opinion about skepticism?

A. Yes. And, again, this is a review article; so it reflects the understanding in the literature. And, again, it talks about in this paragraph VEGF Trap and then says, "It is also possible that the junctions between the various structural elements in such multicomponent molecules can generate an immune response."

And, Your Honor, I showed you this yesterday also, but -- for the same excerpt but the same significance, but now for secondary considerations.

Q. And would the POSA have considered this warning important regarding immune responses?

A. Yes. Again, this is something that, as a formulator, is foremost in our mind of concern or one of the things that are of foremost concern.

Q. There's been a lot of discussion about the lead author of this article, Dr. Ferrara.

Did researchers in the field consider the paper biased or misleading because Dr. Ferrara worked for Genentech?

A. No, not according to my understanding. As a matter of fact, I think there are over 3,000 citations of this paper.

Q. Is that lot?

A. That is a lot.

Q. Now, was this paper the only evidence of industry skepticism you considered?

A. No.

Q. Did you also consider the 2006 Ferrara review article that you discussed yesterday?

A. Yes.

Q. And we won't rehash that, but in your view, was the skepticism expressed in the prior art directed to the workability of the claimed invention of injecting VEGF Traps, such as aflibercept?

A. Yes, exactly.

Q. Did you also consider evidence of unexpected results, Dr. Trout?

A. Yes, I did.

Q. And let's take a look at the Thomas article. That's PTX 1155. Did you review this article for purposes of your objective indicia analysis?

A. Yes, I did.

Q. And this is an article from 2013, after the priority date.

Let's take a look at page 4 of the article. What were the properties that ultimately were shown with Eylea? And were they expected in your view?

MR. RAKOCZY: Objection, Your Honor. Two grounds. Number one, they've admitted this is after the priority date; this is not prior art.

Number two, they're talking about the aflibercept molecule; they're not actually talking about the claimed formulations here. It's not relevant either.

THE COURT: How is it prior art?

MR. BERL: It's not prior art at all. That's why I pointed out, in fact, that it's from 2013, after the priority date.

The law is that postpriority evidence is relevant to unexpected properties. The Kroll v. Teva [sic] case is sort of the seminal case on this proposition, but other cases afterwards have reiterated that proposition down the line from the Federal Circuit.

THE COURT: Mr. Rakoczy.

MR. RAKOCZY: Your Honor, we obviously disagree. We will brief this. But beyond that, it still has to establish a nexus to claims. These are claims about formulations, not

about the aflibercept molecule itself, which is what this is; so, again, no nexus, after the priority date.

THE COURT: Understood. It is after the priority date, obviously, but we need to tie this together, Mr. Berl, how it's related.

Objection overruled at this juncture.

BY MR. BERL:

Q. Were the properties of Eylea expected or unexpected as related by the Thomas article, PTX 1155?

A. So they were unexpected, as noted here. I'm going to read on the screen just because of my eyes.

On the upper left, "The most captivating aspect of aflibercept is its extended half-life, according to reviews of aflibercept by Stewart and Stewart, et al. The estimated serum half-life of intravitreal aflibercept is approximately 18 days versus ranibizumab and bevacizumab, which have half-lives of approximately 4.75 days and 8.25 days respectively."

So it's -- aflibercept -- or really the Eylea, which is an embodiment of the claims of the '865, has over double the half-life.

And then just to point to another excerpt from the same article on the right -- I think I can even read this -- "In conclusion, aflibercept dosed intravitreally each month or every two months after three initial monthly doses resulted in comparable efficacy and safety to monthly ranibizumab."

Q. Can you explain how this relates to the formulation rather than just the molecule of aflibercept with respect to the properties you just relied on?

MR. RAKOCZY: Objection, Your Honor. He's now trying to tie something up that's actually not in the report anywhere.

MR. BERL: I don't agree with that. Let's look at paragraph 347, for example. Your Honor, I think this is in the binder. I believe it's styled as PTX 67, Dr. Trout's report. PTX 67.

THE COURT: 67.

MR. BERL: Not 367. Sorry.

THE COURT: What paragraph is that, Mr. Berl?

MR. BERL: 347. You'll see in that paragraph, Your Honor, he's discussing Eylea. He does not say aflibercept. I think -- he says aflibercept too because, of course, Eylea has aflibercept in it, but he says Eylea one, two, three, four times when providing his analysis of this article. This is the Thomas article that we're reviewing and the subject of this paragraph, and he's talking about how Eylea ultimately proved to be unexpectedly safe, how it compares to Lucentis.

And so that's what I'm asking him about is how -- what is Thomas disclosing about Eylea. That's the subject of the Thomas article and his opinion.

THE COURT: Mr. Rakoczy.

MR. RAKOCZY: That wasn't the question, Your Honor.

The question was can you explain how this relates to the formulation other than just the molecule?

I agree that the report talks about the formulation Eylea. There is nothing in here attempting to give some explanation for why this unexpected result is not just about a molecule.

THE COURT: Understood.

Sustained. Reword your question.

MR. BERL: I'll reword the question.

BY MR. BERL:

Q. Doctor, can you explain how these properties relate to Eylea?

A. Yes. Well, again, these properties are discussion based on the use of Eylea, the whole formulation -- I don't know if I can say that, but Eylea is the formulation we've been talking about.

Q. Do you understand Eylea to be an embodiment of the claims of the '865 patent?

A. Yes.

Q. And can you administer aflibercept by itself without formulation?

MR. RAKOCZY: Objection, Your Honor. Again, new opinion. Nowhere in here.

MR. BERL: This has nothing to do with Thomas. This is just basic background.

THE COURT: Overruled.

BY MR. BERL:

Q. Can you administer aflibercept without a formulation, such as Eylea?

A. No.

Q. Can you obtain the properties that Thomas is discussing by just administering aflibercept alone?

MR. RAKOCZY: Objection, Your Honor. This is well outside the scope.

THE COURT: That one's sustained.

MR. BERL: I'll withdraw that.

BY MR. BERL:

Q. Doctor, in your view -- let's look at another part of Thomas on page 4. Can you discuss what Thomas is disclosing here?

A. Yes. Again, just to read the excerpt here, "In conclusion, aflibercept dosed" -- and then it talks about the dosing I just read -- "side effects, either ocular or systemic, were similar across treatment groups with no differences between aflibercept administered every two months and monthly ranibizumab," again, referring to the Eylea.

Q. And was that expected or unexpected based on what the prior art disclosed about fusion proteins such as aflibercept?

A. That was unexpected for all the reasons that I mentioned.

Q. Do you understand or consider ranibizumab to be the closest prior art?

A. Yes.

Q. Now, did you also consider evidence of copying?

A. Yes, I did.

Q. And in your view, did Mylan copy aspects of Eylea?

A. Yes.

Q. And what aspects of the claims, for example, did Mylan copy, in your view?

A. Well, it copied the aflibercept, of course, with the sequence ID, the polysorbate, the organic cosolvent, the buffer.

Q. Well, let's talk about a few of those. Let's talk about the polysorbate.

MR. BERL: Actually, if I may pause for a moment. I don't want to do anything that violates Mylan's perceived confidentiality. I think this was disclosed in open court, but I don't want to run afoul of any --

THE COURT: If you need to huddle and talk about that, go right ahead, please.

MR. BERL: I really don't want to seal the courtroom for one question; so maybe I'll just --

THE COURT: Why don't we save that one for last.

MR. BERL: Maybe we'll save that one for last. That's a good idea.

BY MR. BERL:

Q. Did Mylan, in your view, copy the concentration of aflibercept that's in the claims?

A. Yes.

Q. Did Mylan -- I'll ask this generally. Did Mylan pursue formulations without polysorbate?

A. Well, in development, yes.

Q. And what was the result of that?

A. Mylan decided it had to include polysorbate to have an adequate formulation.

Q. In view of -- I just want to ask one final question about obviousness, Doctor.

In view of your analysis of motivation, expectation of success, and objective indicia, are the asserted claims of the '865 patent obvious?

A. No.

MR. BERL: So with that proviso that I might ask one more question at the end, I'm going to move to Section 112.

THE COURT: Someone put that last question on a sticky note.

MR. BERL: I won't remember; so please.

BY MR. BERL:

Q. Doctor, did you consider Dr. MacMichael's testimony on enablement?

A. Yes, I did.

Q. Do you agree with his conclusions?

A. No, I do not.

Q. Dr. MacMichael talked about the simple *Wands* factors. Do you remember that?

A. Yes, I do.

Q. Let's put up the *Wands* factors on the screen.

Did you consider the *Wands* factors in conducting your enablement analysis?

A. Yes, I did.

Q. Let's start with the first one, the breadth of the claims. Do you agree with Dr. MacMichael's testimony that the breadth of the claims is very broad?

A. No. I think the claims are narrow.

Q. Let's take a closer look at that. Let's take a look at 1, 2, and 4 again.

Why, in your view, are the asserted claims not very broad?

A. Well, let's just start out with the -- where we usually start, with the VEGF antagonist and the specific sequence ID. So it's one specific biologic molecule, no others, with a very specific -- with a specific sequence ID, I should say. It's a vial. It's for intravitreal administration. It's got to have all these other components -- the organic cosolvent, the buffer, the stabilizing agent. And then it's got to be at 40 mg/mL. That's very -- I mean, that

can't get more narrow than that in terms of concentration. And then it's got to -- this is just Claim 4 -- it's got to have the polysorbate 20. That's the only possible organic cosolvent and within this narrow range.

Q. Doctor, there's been some discussion for purposes of enablement about lyophilized or freeze-dried formulations. We're not going to repeat all of what we did a few moments ago, but in your view, did the specification also teach how to make lyophilized formulations?

A. Yes, it does.

Q. And is lyophilization just another way to make formulations?

A. It is another way of making formulations, yes.

Q. And there was also some discussion previously in the case about suspensions and emulsions.

In your view, would the claims be directed to suspensions and emulsions?

A. No. I don't think the claims would be directed, and I probably should have mentioned this before, but this other limitation, the 98 percent present in native conformation following storage at 5 degrees Celsius for two months as measured by size-exclusion chromatography, that's not an analytical technique that one would typically use for emulsions and suspensions.

Q. You discussed some of the structures in the claims.

Were the structures that are used in the claims known or unknown as of the priority date?

A. They were known as of the priority date.

Q. What about buffers? Were those structures known?

A. Yes.

Q. And what about polysorbate?

A. Yes.

Q. And what about aflibercept?

A. Yes.

Q. And what about stabilizing agents?

A. Yes.

Q. So, Doctor, what is your opinion regarding the *Wands* factor on the breadth of the claims? Does that support enablement or does it support nonenablement?

A. It's pretty narrow; so it supports enablement.

Q. Let's take a look at the nature of the invention, the second *Wands* factor.

What is the nature of the invention claimed here?

A. Well, the nature of the invention is a formulation, an ophthalmic formulation to be specific, suitable for intravitreal administration, with the various formulation components, including the aflibercept and with the 98 percent native after two months storage at 5 degrees Celsius and all the rest of the specifics.

Q. Did Dr. MacMichael identify any formulation with the

structural elements recited in the claims that did not meet the 98 percent native conformation limitation?

A. No.

Q. Are you aware of any such formulations?

A. No.

Q. Now, let's go to the next *Wands* factors, the level of ordinary -- the level of ordinary skill.

Was the level of skill high or low?

A. High.

Q. How so?

A. Well, again, it would be a professional with a master's degree at least in a relevant field, so a technical field directly relevant to formulations here. I think Dr. MacMichael said even a PhD, higher, plus several years of skill. And I think I added in mine it could be a PhD with less experience than a master's degree but still considerable experience in formulation.

Q. Do you understand yourself to agree with Dr. MacMichael that the level of skill was high?

A. Yes.

Q. Now, did you hear Dr. MacMichael's testimony a few days ago regarding Regeneron's arguments during prosecution of different patents?

A. Yes.

Q. Do you agree with Dr. MacMichael's testimony about

those documents?

A. No.

Q. Let's first take a look at DTX 5053, and this is on page 17.

Do you recall that this is a sentence that Dr. MacMichael relied on in his testimony?

A. Yes.

Q. And can you explain what this sentence means in your view.

A. Yes. It says, "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."

Remington's is a general textbook, you could call it. It's a collection of different chapters, formulation and others, by experts; so it's a general textbook. And I agree with this statement, but Remington's doesn't disclose aflibercept; it doesn't disclose other aspects. Until you have that information, like the '865 patent discloses, you are in the situation discussed here.

Q. So to be clear, does Remington's disclose any formulations of aflibercept?

A. No.

Q. How about intravitreal formulations of aflibercept?

A. No.

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

A. Clearly not.

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

A. No.

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

A. Yes, I did.

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

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

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

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

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

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

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

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

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

BY MR. BERL:

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

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

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

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

Q. The '865 patent discloses formulations of aflibercept?

A. Yes, clearly. Yes.

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

A. Aflibercept.

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

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

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

And then it has several important disclosures within the specification, including this one, which is highlighted. And it talks about what the organic cosolvent might be, and it talks about different other agents, including the stabilizing agent and the buffering agent.

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

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

A. Yes.

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

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

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

Do the claims for some categories narrow those structural requirements?

A. Yes.

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

What is a buffer?

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

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

A. Yes.

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

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

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

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

A. Yes.

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

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

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

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

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

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

A. Well, Claim 4 --

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

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

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

A. Yes. All the asserted claims, yes.

Q. Let's go back to the specification and address this limitation.

What does the specification teach with respect to organic cosolvent?

A. Well, it teaches various structures. Again, I'll look at the monitor here. Maybe polysorbate and, for example, polysorbate 20 or 80; polyethylene glycol, also abbreviated at PEG and then gives an example; or propylene glycol or a combination thereof.

Q. Would the POSA understand what those structures are?

A. Yes.

Q. Now, let's turn to the next limitation, stabilizing agents. And let's look at Column 2 there as well.

What does the patent teach about stabilizing agents?

A. Well, it teaches what it also calls sugars, sucrose, sorbitol, glycerol, trehalose, or mannitol specifically.

Q. Are those known structures?

A. Yes.

Q. Doctor, all of the asserted claims require some stability limitation as measured by SEC, the 98 percent native conformation; is that right?

A. Correct.

Q. And some of them say 99 percent, some of them have different time periods, but let's -- what does the patent teach with respect to formulations that meet the size-exclusion

chromatography limitation?

A. Well, it teaches that, given the various formulations in the examples, if one encompasses the various structures that are described in the claims, one expects to meet the 98 percent limitation, or again the 99 under some circumstances with the different times.

Q. Let's take a look at Example 1. What does Example 1 teach, Dr. Trout?

A. Well, Example 1 teaches 50 mg/mL VEGF Trap, the exact one, because it references the sequence ID. It has a phosphate buffer. It has the polysorbate 20 organic cosolvent. And it has the sucrose stabilizing agent and pH 6.25 which can be rounded up to 6.3.

Q. Now, Doctor, you said -- well, how much aflibercept is in this formulation? What's the concentration?

A. Yes. I said 50 mg/mL.

Q. So is that within the asserted claims?

A. No.

Q. Does it nevertheless provide relevant guidance or teaching to the POSA with respect to 40 mg/mL?

MR. RAKOCZY: Objection, Your Honor. That's a new opinion not in the report.

MR. BERL: So, Your Honor, if we go to paragraph 387.

THE COURT: 387?

MR. BERL: Yes. Dr. Trout there addresses the

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

THE COURT: Mr. Rakoczy.

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

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

MR. BERL: Give me one moment.

THE COURT: Sure.

MR. BERL: Phone a friend.

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

THE COURT: Overruled.

BY MR. BERL:

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

THE COURT: Don't ask me.

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

MR. BERL: And more interested in the answers.

BY MR. BERL:

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

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

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

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

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

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

witness how to answer the question, Your Honor.

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

MR. BERL: Sure.

BY MR. BERL:

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

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

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

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

Can you explain what this example discloses?

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

Q. Is it your understanding that this is now called

Eylea?

A. Yes, this is the formulation of Eylea. Yes.

Q. And what was the level of native conformation as measured by SEC after two months in this formulation?

A. Well, you can see right down here in the table, two months, again at 5 degrees Celsius. Going over, you can see it's 99.2, so greater than 99 percent.

Q. Let's take a look at Example 5.

What's Example 5?

A. Well, Example 5 is another formulation at 40 mg/mL of aflibercept. Again, phosphate buffer. Here it's got an organic cosolvent again, polysorbate 20, the same one. In this case it's got sodium chloride, but it doesn't have a stabilizing agent like the sugars that we've been talking about.

Q. And what is the level of native conformation for this one, Example 5, after two months?

A. Well, again, the native conformation is similar at 5 degrees, two months, and it's 99.2 percent, so greater than 98, greater than 99.

Q. Does the patent express any preference for Example 3 versus Example 5?

A. Well, yes, in the sense that Example 5 -- sorry -- Example 3 has the stabilizing agent.

Q. But in terms of the data or disclosure of the patent,

does it say 3 is better than 5 or 5 is better than 3?

A. No. Actually, this data is very helpful in understanding what we call the robustness or how the structures in the claims should all meet that 98 or other limitations.

Q. Does the patent contain other examples too, Dr. Trout?

A. Yes, it does.

Q. What are Examples 4 and 6 of the patent?

A. Well, those are actually similar examples to 3 and 5, but they're in prefilled syringes instead of vials.

Q. So they're similar with respect to the formulations themselves?

A. Yes. That's right.

Q. And did they also achieve 98 percent native conformation after two months?

A. Yes. And, again, I think that's important for a general understanding of how these formulations work too.

Q. And what about Example 7 and 8?

A. Well, those are lyophilized formulations.

Q. We've discussed those already. We don't need to belabor any of that.

Doctor, let's -- so in view of your analysis of those factors, those *Wands* factors, in particular the guidance from the specification and working examples, does that weigh in favor or against enablement?

A. In favor of enablement.

Q. Now, let's next turn to the state of the prior art. In your view, does the state -- well, did the prior art teach how to substitute one excipient in a category, such as a stabilizing agent or buffer, for another?

A. Yes.

Q. Did the prior art teach how to perform size-exclusion chromatography?

A. Yes.

Q. What about turbidity testing?

A. Yes.

Q. In your view, does this *Wands* factor, the state of the prior art view, weigh in favor of enablement or against enablement?

A. In favor.

Q. Let's finally turn to the last *Wands* factor, the quantity of experimentation. And let's discuss a couple background principles in that regard.

Let's take a look again at the Kaisheva reference. That's DTX 3610. Do you remember that this has been discussed by various experts in the case?

A. Yes.

Q. And if we go to paragraph 54 on page 16 of the Kaisheva reference, what is it disclosing?

A. Well, it talks about the formulation development

approach, selecting optimal solution pH, selecting buffer type, concentration of the buffer, evaluating the effect of various excipients of the liquid and lyophilized stability, and optimizing the concentration of the screened excipients using a specific one, but an experimental design approach.

Q. Is that like the experimental design approach that Dr. MacMichael testified about, this design of experiments?

A. Yes, it is. And, actually, Dr. Rabinow also included this in his slides.

Q. So would the POSA test every possible combination of buffers and stabilizing agents in practicing this claim?

A. No. The POSA would test the various combinations and variations of those combinations as the '865 patent did and via experimental design as needed.

Q. How would the POSA practice the claims in view of the '865 patent's disclosure?

A. Well, the skilled person would practice the claims given the disclosures that we've been discussing, including the examples and in Column 2.

Q. Now, if the POSA -- well, what excipients or what buffers and stabilizing agents would the POSA want to use if the POSA wanted to vary from those used in the examples of the '865 patent?

A. Well, I'd say the POSA would use excipients that have the same structures, same structural characteristics as those

discussed in the various categories in the patent, and would want to make sure that those are suitable for intravitreal administration by looking at the literature, for example, or, if need be, consulting an ophthalmologist.

Q. Doctor, did you hear Dr. MacMichael point to any examples that meet the claim limitations but would take undue experimentation to make and test, any formulations like that?

A. No.

MR. RAKOCZY: Objection, Your Honor. That's a new opinion. That's not in the report.

THE COURT: Mr. Berl?

MR. BERL: I just asked him something about Dr. MacMichael's testimony. Of course it wasn't in the report because Dr. MacMichael's testimony happened after the report.

THE COURT: It can still be a new opinion, correct. Is there any reference or discussion of this in the volley of reports?

MR. BERL: There's a lot of discussion about enablement and whether there's undue experimentation. He said that it's not undue experimentation to make and test the formulations in the claim, and I'm just asking him whether Dr. MacMichael identified anything to the contrary.

MR. RAKOCZY: That's trying to inject a new issue, Your Honor, this whole idea of did someone find a formulation that doesn't work. That's a new opinion, a new issue. And I

don't believe it's in the report.

MR. BERL: I'll withdraw it, Your Honor. Dr. MacMichael's testimony is what it was. I don't need Dr. Trout to reiterate that.

BY MR. BERL:

Q. Doctor, in your view, does practicing the full scope of the claim require routine experimentation or undue experimentation?

A. Routine experimentation.

Q. And if we go back to all of the *Wands* factors, Dr. Trout, taken together in view of all the *Wands* factors, what is your opinion about whether the asserted claims are enabled?

A. That the asserted claims are enabled.

Q. I'd like to turn to a slightly different topic, written description.

Did you consider as part of your written description analysis whether the specification describes structural features common to the genus?

A. Yes.

Q. And what did you conclude?

A. Well, that each of those limitations that we've been discussing have common structural features.

Q. And what are the structural limitations of the claims?

A. Well, I mean, I guess the VEGF antagonist is one, but that is one very specific molecule. Categories, then, are the organic cosolvent, the buffer, and the stabilizing agent.

Q. Were these structures well known in the art?

A. Yes.

Q. Did you understand Mylan's experts to dispute that?

A. No.

Q. Do all of the formulations within the claims share those common structural features?

A. Yes.

Q. Can the POSA recognize the formulations that were claimed here?

A. Yes.

Q. And can the POSA visualize the formulations within the claims?

A. Yes.

Q. Can the POSA recognize from the specification that the inventors invented the claimed formulations?

A. Yes.

Q. And how and where in the specification would the POSA recognize that?

A. Well, again, from the examples and -- I mean, throughout, but specifically the examples, and then the disclosure on Column 2 that we've been discussing. Those are the key places.

Q. Does the '865 patent provide species or examples representative of the genus?

A. Yes.

Q. Do all of the examples have at least 98 percent native conformation as measured by SEC after two months?

A. Yes.

Q. And do all the examples meet the turbidity limitation of Claim 15?

A. Yes.

Q. And are the formulations with 50 mg/mL, those examples, are those relevant to whether the claims are described?

A. Yes.

Q. Is that for the reason you discussed a moment ago?

A. Exactly.

Q. Doctor, is the patent here claiming simply by function or is it claiming structures?

A. These are all structures.

Q. Doctor, in your view, does the '865 patent provide adequate written description for the asserted claims or not?

A. For all the reasons I mentioned, yes, it does.

Q. Now I'd like to address indefiniteness.

Do you remember Dr. MacMichael's testimony about indefiniteness?

A. Yes.

Q. Okay.

And let's put up the claims.

Do you understand him to have asserted that the claim -- the term "suitable for intravitreal administration" is indefinite?

A. Yes.

Q. Do you agree?

A. No.

Q. Would the POSA be able to interpret the phrase with reasonable certainty?

A. Yes.

Q. What does suitable for intravitreal administration refer to?

A. It means does it contain components as described in the claim that could be used for intravitreal administration, these structures, as we've been calling them.

Q. Is the term "suitable for intravitreal injection" subjective?

A. No.

Q. How would the POSA determine whether an ingredient or an excipient is suitable for intravitreal injection?

A. Well, first of all, the POSA would look to the teachings in the patent, again, the examples and those places in Column 2 that we've been looking at. And if a skilled person wanted to depart from those, a skilled person can go

into the literature and find excipients or additives with the same structure or similar structures that had been used in intravitreal administration before and, if need be, could consult an ophthalmologist.

Q. Did your definition of a POSA include someone who could consult with an ophthalmologist or a clinician as needed?

A. Yes.

Q. Let's take a look at Chang, which is Exhibit 1832. Did you review this reference?

A. Yes.

Q. And if we go to page 16 --

THE COURT: Yes, Counsel?

MR. RAKOCZY: Objection, Your Honor. This is outside the scope of the report. The witness's response to this indefiniteness argument is about ten lines, one paragraph, and it doesn't cite anything.

THE COURT: What paragraph is that, Mr. Rakoczy?

MR. RAKOCZY: Paragraph 420 of the responsive expert report if Your Honor has it.

THE COURT: I do. It's PTX 67.

MR. BERL: And, Your Honor, in paragraph 83 Dr. Trout --

THE COURT: One second.

MR. BERL: Sorry to go back and forth.

THE COURT: Paragraph 83. Go ahead.

MR. BERL: This is where Dr. Trout addresses the Chang reference that I was about to ask him about.

THE COURT: Overruled.

BY MR. BERL:

Q. If we could look at page 16 of Chang. Can you explain what Chang is saying here?

A. Yes. I've just highlighted the sentence.

"Generally, it is preferred to select excipients that have been used in marketed products with a relevant route of delivery."

Q. And is that -- can you explain how that relates to the practice of the '865 patent and whether the POSA would be able to know what is suitable for intravitreal injection?

A. Yes. It's just a reflection of what I've been saying and what the POSA would understand.

Q. And have you considered the Peyman reference? That's PTX 1758.

A. Yes.

Q. Okay.

And if we could put that on the screen.

MR. BERL: This, for the record, is page 4 of the Peyman reference.

THE COURT: Yes, Mr. Rakoczy?

MR. RAKOCZY: Objection, Your Honor. Again, I don't believe this is cited in the report on indefiniteness.

MR. BERL: It's cited, Your Honor, at paragraph 175. And I'm going to ask him about an excerpt that is word for word in the report, paragraph 175.

THE COURT: Is it tied in the report in any way to indefiniteness?

MR. BERL: Well, it says "a formulation suitable for the treatment," and that's what indefiniteness is about now.

THE COURT: Yes, Mr. Rakoczy?

MR. RAKOCZY: It's actually not tied to the indefiniteness section, Your Honor, which, again, is paragraph 420. That is the extent of the response on indefiniteness.

THE COURT: Understood. It's in there, though. Overruled.

BY MR. BERL:

Q. So if we put up page 4 of Exhibit 1758, the Peyman reference, under "Summary of the Invention," what language is it using there?

A. Well, it specifically says "formulation suitable for the treatment of ocular and neovascularization."

Q. Is that a term that persons of ordinary skill or a person of ordinary skill would understand?

A. Yes.

Q. Did you understand Dr. Rabinow to conclude that the prior art taught formulations suitable for intravitreal

injection?

A. Yes.

Q. Would the POSA understand the scope of the asserted claims, Dr. Trout?

A. Yes.

Q. What did you conclude as to whether the claims were indefinite?

A. That they are not indefinite.

Q. Now I'd like to shift to a new topic, the '572 patent.

A. Okay.

THE COURT: Mr. Berl, why don't we take ten before we shift topics. We'll take an actual 10-minute break and try to stay on the course today.

Doctor, you remain off limits for conversation during your testimony, but you can go ahead and step down. And we'll take a 10-minute recess. Thank you all very much.

(A recess was taken from 9:46 a.m. to 9:56 a.m.)

THE COURT: Mr. Berl, you were changing topics. Go right ahead.

MR. BERL: Yes. We're in the home stretch, Your Honor.

BY MR. BERL:

Q. Dr. Trout, I'd like to shift to the '572 patent and

the disclosure there in the claim of isotonic solution. Do you understand that the priority date has now shifted? Before, we were talking about 2006. The priority date for the '572 patent is later, right?

A. Yes.

Q. Doctor, does any prior art disclose that aflibercept was formulated as an isotonic solution?

A. No.

Q. Does Dixon, PTX 204, disclose an isotonic formulation of aflibercept to the POSA?

A. No.

Q. Did the Hecht reference, DTX 3588, teach an isotonic solution of aflibercept?

A. No. It doesn't even teach intravitreal administration.

Q. Doctor, did you review the prior art that Dr. Rabinow asserted with respect to the isotonic limitation?

A. Yes.

Q. And is that the Hecht and Dixon references?

A. Yes.

Q. In your view based on your analysis, what is your opinion about whether it was obvious to use an isotonic solution of aflibercept to treat diseases?

A. It was not obvious.

Q. Now, let's take a look at the written description

analysis of Dr. MacMichael with respect to the isotonic solution of the '572 patent. Do you recall Dr. MacMichael testifying that isotonic solution lacked written description?

A. Yes.

Q. Do you agree?

A. No.

Q. Let's take a look at the '572 patent. And we'll look at Column 6 here. And we've put up lines 18 to 35.

What does the '572 patent disclose with respect to isotonic solution?

A. Well, right here in Column 6 it says "isotonic solution."

Q. And what does it say about isotonic solutions?

A. Well, it says that it may be used in combination with appropriate agents and continues that.

MR. RAKOCZY: Objection, Your Honor. I've no objection to the first two lines, 22 to 25, but that is the extent of the opinion in citation in his report, which, again, is ten lines long. He doesn't say anything else about all this other language, solely those first two highlighted lines.

THE COURT: That's paragraph 420, right, Mr. Rakoczy?

MR. RAKOCZY: This is now paragraph 430.

THE COURT: I'm sorry.

MR. RAKOCZY: 430, entitled "Formulated as an isotonic solution." And the fourth line down, you see it's --

'572 patent at 6, lines 22 to 25, that is the only material cited in this entire report.

MR. BERL: With respect to breadth, I mean, the opinions that he was responding to were very brief too. And he responded in kind. And I'm simply asking him about the description here of isotonic solution. This is what everyone was talking about and addressing is whether this description of isotonic solution here is or is not sufficient. That's the entire issue here.

THE COURT: Yes, Mr. Rakoczy?

MR. RAKOCZY: Your Honor, whether that's the entire issue I guess is open to debate. The fact of the matter is the witness cited lines 22 to 25, and that is it. One line.

THE COURT: Understood. And you're certainly free to cross Dr. Trout extensively on that if you believe his -- the grounds for his opinions have been augmented, but I will find they have been sufficiently disclosed in particular relying upon this section of the '572 patent.

Objection overruled.

BY MR. BERL:

Q. Dr. Trout, I forgot exactly the question I asked; so I'll ask this one.

What is the '572 patent disclosing here with respect to the isotonic solution?

A. Well, again, it's disclosing isotonic solution

containing glucose and other auxiliary agents, et cetera. And then it talks about what those auxiliary agents, et cetera, are -- solubilizing agent, polyalcohols, nonionic surfactants, et cetera.

Q. Would the POSA understand what an isotonic solution is?

A. Yes.

Q. Is that a well-understood concept by formulators?

A. Yes.

Q. Was the patent's disclosure sufficient for the POSA to visualize or recognize what an isotonic solution is?

A. Yes.

Q. Would the POSA need more detail to understand what an isotonic solution is than what is provided in the '572 patent?

A. No.

Q. Doctor, what is your conclusion about whether the '572 patent adequately described isotonic solutions?

A. That it does adequately describe isotonic solutions.

MR. BERL: Your Honor, with that, I'm to the end of my outline. There was one question. Honestly, it's probably ten seconds, but -- I hate to do this, but they --

THE COURT: That's all right. We haven't gotten any steps in yet, Mr. Berl.

I assume Mylan would request the courtroom be sealed, given the subject area Mr. Berl indicates his next question

relates to.

MR. RAKOCZY: Yes, Your Honor.

THE COURT: The Court will enforce its prior protective order.

Ladies and gentlemen in the gallery, if you are not specifically permitted to be in the courtroom as we discuss the materials covered by the Court's protective order, I'm going to kindly ask you to step out. Thank you very much.

I'll also ask Court security to seal our courtroom, please.

(The following proceedings (2121/11 to 2122/8) were had under seal, and are filed under separate cover.)

THE COURT: Thank you, everyone. Mr. Rakoczy, I'll just remind you for flow purposes, we do have to break at 11:00, just as an FYI.

MR. RAKOCZY: Thank you, Your Honor.

THE COURT: Thank you. But if you're ready, you may proceed, sir.

MR. RAKOCZY: I am ready. William Rakoczy for Mylan and Biocon.

CROSS-EXAMINATION

BY MR. RAKOCZY:

Q. Good morning still, Dr. Trout.

A. Yes, sir. Good morning.

Q. Good to see you again.

A. You too.

Q. All right. Yesterday and today you discussed the aflibercept molecule or fusion protein quite a bit; so I just want to make one thing clear. The '865 patent is not about the discovery of the aflibercept molecule, correct?

A. Right. It's about formulations of aflibercept.

Q. So the inventors of the '865 patent did not discover or invent the aflibercept molecule, correct?

A. That's my understanding.

Q. Aflibercept was known and invented before the '865 formulation patent, right?

A. Again, yes, that's my understanding. Yes.

Q. And you understand the aflibercept molecule is subject to other patents that were filed years before the '865 formulation patent, right?

A. Again, yes, that's my understanding.

Q. Now, you discussed some of the properties of the aflibercept. I just want to be clear, and we can go through some of these.

For example, there's no affinity or binding data for the aflibercept molecule in the '865 patent, correct?

A. That's correct.

Q. There's no half-life data in the patent for aflibercept, correct?

A. In the patent. Again, some of these -- this information is in a prior art, but correct, in the patent itself.

Q. I'm just asking in the '865 patent itself, there's no binding data, no affinity data, no pharmacokinetics data, no half-life data, no side effect data. None of that's in the

patent, correct?

A. Explicitly in the patent, that's not there, although the 98 percent can speak to some of that.

Q. But, for example, there's no pharmacokinetics data in humans or animals, correct?

A. In the '865, that's correct.

Q. As a matter of fact, there's no testing or data on using aflibercept in humans or animals at all in the '865 patent, correct?

A. Explicitly, again -- there are references in prior art, but explicitly in the '865, that's correct.

Q. There's no retinal penetration data in the '865 patent, correct?

A. Again, with the same proviso, that's correct.

Q. And the asserted claims themselves don't have any limitations regarding efficacy, pharmacokinetics profiles, retinal penetration, binding, or half-life of aflibercept, correct?

A. That specific data is not there, that's correct.

Q. So the claims of the patent are all directed to ophthalmic formulations, I think you said, correct?

A. Yes.

Q. The asserted claims are taking the aflibercept known molecule and putting that in a formulation suitable for an intravitreal administration using known excipients and then

testing that for native conformation and turbidity. Is that fair?

A. I think that's basically fair. I would say that the native conformation and, depending on the claim, the turbidity is part of the invention. So that's part of it.

Q. Yeah. I'll restate it.

So the asserted claims are about taking the aflibercept molecule, putting it into a formulation suitable for intravitreal administration, using known excipients, I think you called it, and then the formulation must meet certain native conformation and turbidity requirements. Is that fair?

A. Depending on the claims, yes, I think that's fair.

Q. All right. I'd like to start, then, talking about some of those excipients.

So you would agree the excipients used in the claimed ophthalmic formulations were known in the prior art, correct?

A. Yes.

Q. And the inventors did not invent any new excipients or classes of excipients, correct?

A. Correct.

Q. So let's start with buffers. I think you mentioned buffers. Buffers were known excipients and have been used for decades to stabilize the pH of solutions, including in formulations, correct?

A. Yes. With other molecules, yes.

Q. And the skilled person would have understood that the role of a buffer in a formulation is to maintain a stable pH; is that right?

A. Yes. To maintain a pH at a certain desired range, yes.

Q. And the skilled person would have understood that buffers have suitable pH ranges at which they function, correct?

A. Generally, correct.

Q. And phosphate was a known buffer, correct?

A. Yes.

Q. And, in fact, the inventors selected phosphate as a buffer for Eylea precisely because it's a natural substance, it was one of the most common buffers, and would have a reasonable probability of being tolerated in the eye; isn't that right?

A. I'm sorry. You're getting that from a document? I don't think that's in the '865 patent.

Q. I can show you your report.

A. Okay.

Q. Let's pull up DTX 7066. It's your responsive report, paragraph 372. And here you see you're citing to Dr. Furfine. He's one of the inventors, right?

A. Yes.

Q. And you say, "Dr. Furfine explained that the inventors selected phosphate for the ultimate formulation used

in Eylea (and described in the '865 patent) because 'phosphate is a natural substance' and 'one of the most common buffers,' and thus 'seemed like something that would have a reasonable probability of being tolerated in the eye,' correct?

A. Yes. Again, that's from Furfine's deposition, not in the '865. But, yes, that's correct.

Q. And you agree with that, correct?

A. Yes.

Q. And the skilled person would have known all of that, correct?

A. Yes.

Q. Now, other intravitreal-administered products like Macugen have also used a phosphate buffer, correct?

A. I believe so.

Q. And prior to 2006, then, you'd agree that the skilled person would have expected that a phosphate buffer was safe to use in an ophthalmic formulation, correct?

A. I think generally that's correct. Again, there are other limitations.

Q. And they could have tested that, correct?

A. Tested what, Counsel?

Q. They could have tested whether phosphate was an appropriate buffer for an ophthalmic formulation, correct?

A. I think I would say it a little different. The skilled person would understand that the phosphate buffer would

be appropriate for an ophthalmic formulation, and then they could test whether it would be -- certain other parameters, like the 98 percent native conformation.

Q. And that testing would have been within the capabilities of our skilled person, correct?

A. Correct.

Q. Now, histidine, I think you said, was also a well-known buffer at the time.

A. Yes.

Q. For example, you mentioned several formulations, but I believe you said the Shams reference at DTX 726, which is already in evidence, disclosed the use of a histidine buffer in a formulation for intravitreal administration. Isn't that right?

A. I think so, but could we just pull that up to make sure.

Q. Sure. We can pull up DTX 726. Go to page 32, bottom of the page. And you see the ranibizumab injection here using a histidine buffer for intravitreal administration, correct?

A. Yes. Thank you.

Q. And I believe you mentioned that Gaudreault reference. You recall that?

A. Yes.

Q. That was DTX 2256, already in evidence.

And I think you mentioned that uses a succinate

buffer for ranibizumab formulation. Is that right?

A. Correct. I know it does, but do we want to pull it up just to make absolutely sure?

Q. You're not sure if it uses --

A. I am sure. I am sure.

Q. That's my only question, it uses succinate.

A. All right.

Q. So based on at least the Shams reference, we can agree the skilled person would have understood that other buffers could be used in an ophthalmic formulation that were suitable for intravitreal administration, such as histidine, correct?

A. Correct.

Q. Now, let's talk about stabilizing agents.

Stabilizing agents, like sugars and sugar alcohols, have been known for over four decades to provide thermal stability to proteins, correct?

A. That sounds like a correct statement.

Q. And trehalose, if I'm saying that correctly, trehalose is a commonly used thermal stabilizer known in the art, correct?

A. I think that's fair. And, yes, Counsel, I believe you're pronouncing it correctly.

Q. And the ranibizumab formulation from Gaudreault at DTX 2265, that used trehalose, correct?

A. Yes.

Q. Now, the skilled person would have expected that 10 percent trehalose, such as that used in the Gaudreault formulation, would be suitable for intravitreal administration, correct?

A. Yes. And, again, I should be clear. I'm interpreting all of your question as with respect to the priority date of the '865 patent. I assume that was the case.

Q. Yes.

A. Yes. So yes.

Q. Yes. And I'm not aware of any dispute of Gaudreault being prior art. I didn't hear you testify to that effect.

A. Correct.

Q. All right. And if the skilled person would have been capable of testing whether trehalose was an appropriate stabilizer in a protein formulation, correct?

A. Again, that's a very broad question. I assume you mean for intravitreal administration, or are you just asking --

Q. Yeah, for intravitreal administration. They could have tested whether that was an appropriate stabilizer, trehalose, correct?

A. I would just say that they would understand that it would be suitable and could test whether it meets other parameters, like the 98 percent.

Q. And that testing would have been within the

capabilities of our skilled person, correct?

A. Correct.

Q. Now, sucrose was another stabilizer known in the art, correct?

A. Yes.

Q. And prior to 2006, the skilled person would have had an expectation that sucrose was safe to use in an ophthalmic formulation, correct?

A. Yes.

Q. Now, let's talk about surfactants like polysorbate. I believe I heard you say polysorbate 20 was a known excipient in protein formulations, correct?

A. Correct.

Q. And the skilled person would have known that other intravitreal formulations in the art also used polysorbate 20, correct?

A. Correct.

Q. The Lucentis, or ranibizumab formulation, from Shams at DTX 726, that used polysorbate 20, correct?

A. Correct.

Q. And I believe the VEGF antagonist Avastin, or bevacizumab formulation, used polysorbate 20 as well, correct?

A. That's what I recall, yes.

Q. And so prior to 2006, the skilled person would have had an expectation that polysorbate was safe to use in an

ophthalmic formulation, correct?

A. Correct.

Q. Now, to the extent the skilled person did not use excipients from the examples in the '865 patent, she could have turned to other excipients that would have been considered suitable for ophthalmic formulations, correct?

A. Yes. With related structures, yes.

Q. So the skilled person could have turned to excipients that were tested or contemplated in other intravitreal drug products, correct?

A. Yes. I think generally, yes.

Q. And they could have used -- they -- strike that.

For example, a skilled person, again, they would have known about the Lucentis intravitreal products from Shams, correct?

A. Yes. They would have known Shams, yes.

Q. And the skilled person would have known that that Lucentis intravitreal product used histidine, trehalose, and polysorbate 20, correct?

A. Yes.

Q. And the skilled person would have understood that the concentration of excipients could be decreased or increased to maintain a desired osmolarity, correct?

A. If one were to target that desired one, yes, it could have been adjusted.

Q. Now, let's talk briefly -- I think you answered some of these, but let's hit the degradation products for protein formulations and how they're measured.

You would agree that techniques were known long before 2006 for how to detect, measure, and elucidate the various types of degradation products in protein samples, correct?

A. There were multiple techniques, yes.

Q. And size-exclusion chromatography, or SEC -- can I call it SEC?

A. Yes.

Q. And SEC was a known and routine method to measure native conformation of a protein, correct?

A. Yes.

Q. The skilled person could have readily performed an SEC test on a protein formulation, correct?

A. Generally. It depends on the formulation and whether it would be applicable, but the person would know SEC.

Q. It wouldn't take undue experimentation for the skilled person to run an SEC test on a formulation, correct?

A. Correct.

Q. Now, the skilled person could have also used other techniques in addition to SEC for assessing protein stability as well, correct?

A. Yes.

Q. All right. Let's switch gears and talk a little bit about the specification.

I believe you testified that the claims are defined by common structural features. Do you recall that?

A. Yes.

Q. And I think you identified some of those common structural features in the claims and the examples.

Do you recall that?

A. Yes.

Q. And some of those structures were the known aflibercept, correct?

A. Correct.

Q. The known buffer, correct?

A. The buffers, yeah.

Q. I think you said the known polysorbate 20, correct?

A. Right.

Q. And I think you said known stabilizing agents, correct?

A. Correct.

Q. So I'd like to pull up a table you created in your expert report. Let's go to demonstrative DDX 9, Slide 1, and I've reproduced it here.

And you recognize this table, Dr. Trout, from your response report?

A. Yes.

Q. And so in this table you laid out kind of in summary fashion all the examples from the '865 patent, correct?

A. Yes.

Q. And I think in your testimony, your direct testimony, you said that these examples are all species representative of the genus. Is that fair?

A. I'm not -- I'm not sure if I said that.

Q. Let's go back to Slide 1, DDX Slide 1.

And could we blow that up, please, Mr. Gibson.

You actually say that right above the table, right? "The '865 patent also describes species representative of the genus," and then you laid out those formulations in the examples, correct?

A. Yes. Yeah. I mean, I'm not saying that each of the examples are representative of the genus of the claims specifically. I'm saying that the tables incorporate species representative of the genus of the various components that we've been talking about, the structural components.

Q. Right.

Let's go back to DDX 9, Slide 2, where we have a bigger table. And I believe all of these examples, they all contain the aflibercept, correct?

A. Correct.

Q. They all contain polysorbate 20, correct?

A. Correct.

Q. They all contain phosphate, correct?
A. Correct.
Q. And then they all contain sucrose except for two of them. So most of them have sucrose, correct?
A. Correct. And we should say that the different components are different concentrations, yes.
Q. Yes. I wasn't trying to mislead you. They're different concentrations for some of these, correct?
A. Correct.
Q. All right. So -- and I believe you testified that each of these examples with these common structural features all achieve the 98 percent native conformation requirement in the claims, correct?
A. Yes.
Q. All right. Now, many of these common structural features or known components are also found in a lot of the other formulations you've discussed today and yesterday, correct?
A. Yes.
Q. Let's look at some of those. On screen we have DDX 9.

Slide 3, please, Mr. Gibson.

And what I've done is -- let's go to Slide 3. And I have added a column to the right.

We can go to the next one, please.

Here, I've added a column on the right for the Shams reference. Do you see that?

A. Yes.

Q. And so we see the Shams reference also contains a VEGF antagonist, correct?

A. Well, it's a different one.

Q. Yeah, it's a different one. It's ranibizumab, correct?

A. Correct.

Q. And to be fair, we've got 6 mg/mL and 10 mg/mL ranibizumab, correct?

A. Correct.

Q. And then Shams' formulation also has 0.01 percent polysorbate 20, correct?

A. Correct.

Q. And then we see it also has the 10-millimolar histidine, correct?

A. Correct.

Q. And then it's got that trehalose stabilizer, 100 mg/mL, right?

A. Yes.

Q. All right. Let's go to DDX 9, Slide 5, and let's add to our table. You see on the right I've added a column for Gaudreault now.

You recall that reference, right?

A. Yes.

Q. And that's at DTX 2265. And the Gaudreault reference also contains ranibizumab, correct?

A. Yes.

Q. But that formulation had slightly different concentrations of the ranibizumab. It was 10 mg/mL and 40 mg/mL, correct?

A. Correct. And I explained why the skilled person would be turned away from the 40.

Q. We're going to get there. I promise you, we're going to get there.

But we can all agree now in my table, the Gaudreault column, that the Gaudreault formulation had 10 and 40 mg/mL ranibizumab formulations, correct?

A. Correct.

Q. And the Gaudreault formulation also had 0.05 percent polysorbate 20, right?

A. Yes.

Q. And it also had 10-millimolar succinate that we just mentioned, correct?

A. Yes.

Q. Lastly, it had 10 percent -- I don't want to butcher it -- 10 percent trehalose.

A. Yes. You're doing great with that pronunciation, Counsel.

Q. All right. Let's go to DDX 9, Slide 7, and let's add another column. Here we've got Fraser's formulation.

Do you see that on the right?

A. Yes.

Q. Now, Fraser had 24.3 mg/mL of a VEGF antagonist called VEGF Trap R1R2, correct?

A. Yes.

Q. All right. We'll get to that more in a moment, but let's go to the next component.

Fraser also had 0.01 polysorbate 20, correct?

A. Yes.

Q. And Fraser also had 5-millimolar phosphate and 5-millimolar citrate, right?

A. Yes.

Q. And then lastly we see that sucrose stabilizer at 20 percent in Fraser, correct?

A. Yes. And I should have added, Counsel, you didn't mention the pHs, but those are also rightly included in your table.

Q. We're going to get to those.

A. Okay.

Q. All right. Let's see if we have any room to add any more. Let's check out DDX 9, Slide 9. Can we squeeze in one more?

All right. There we have Dix '226 and the last

column on the right. I think we're out of room. You see Dix '226?

A. Yes.

Q. Dix '226 at DTX 13. Now, this formulation had 50 mg/mL of VEGF Trap Sequence ID Number 4, correct?

A. Correct.

Q. That's obviously the sequence for aflibercept, correct?

A. Correct.

Q. And Dix '226, the formulation also had 0.1 percent polysorbate 20, correct?

A. Correct.

Q. At 10-millimolar phosphate, correct?

A. Correct.

Q. And 20 percent sucrose, correct?

A. Correct.

Q. And then just to wind all this up, then, we've got the pHs in the bottom row. So Dix '226 had a pH of 6.25, correct?

A. Correct.

Q. Fraser was 6.0 pH?

A. Yes.

Q. And then Gaudreault was 5.0 pH?

A. Yes.

Q. And Shams was 5.5 pH, correct?

A. Correct.

Q. All right. Now, looking at this table on DDX 9, Slide 9, can we agree that we see the common or known structural features from the examples of the '865 patent running throughout all of the Shams, Gaudreault, Fraser, and Dix formulations, correct?

A. Yes. That's correct.

Q. Shams, Gaudreault, Fraser, and Dix '226, those formulations and the species of the '865 patent all contain polysorbate 20, correct?

A. I'm sorry. Could you repeat the question.

Q. Yes.

The Shams, Gaudreault, Fraser, and Dix '226 formulations and the species of the '865 patent examples that we see here all contain polysorbate 20, correct?

A. Well, that's why I paused. And sorry if I didn't say this before, but Example 2 has the PEG. So it's not polysorbate 20 --

Q. I'm sorry.

A. -- just to be clear.

Q. I'm sorry. I'll rephrase. And thank you for catching that.

A. Okay.

Q. So to make sure our record's clear, Shams, Gaudreault, Fraser, and Dix '226 formulations, and most of the

species in the examples of the '865 patent, use polysorbate 20, correct?

A. Yes. I think you might want to say most of the examples, but I think we understand, yes.

Q. Most. All except one, correct?

A. Yes.

Q. And Shams, Gaudreault, Fraser, and Dix '226 formulations and the species of the '865 patent examples all contain a buffer, either phosphate, histidine, or succinate, correct?

A. Yes.

Q. And Shams, Gaudreault, Fraser, and the Dix '226 formulations, and most of the species of the '865 patent examples all contain a stabilizer, either sugar or trehalose, correct?

A. Yes.

Q. Now, I want to stay on this slide and ask you, the skilled person could have easily made the formulations from Shams, Gaudreault, Fraser, and Dix '226, correct?

A. Counsel, you mean given the teachings of those respective references?

Q. Yes. They could have made these. That's within the skilled person's capabilities, correct?

A. Well, I think there's some issue with the Fraser, because it's unclear what the VEGF Trap is; but I think the

others, they could have made.

Q. Well, let's assume the skilled person knew what was in Fraser, what that VEGF Trap was. The skilled person, it was within their skill set or capabilities to just make those formulations, correct?

A. Yes.

Q. And the order of addition of the excipients, the VEGF antagonist, the mixing time, the concentrations, and the temperatures, those are all basic steps that would have been routine in the art, correct?

A. I agree.

Q. Now, the skilled person also, after they made those formulations from Shams, Gaudreault, Fraser, and Dix '226, they could have tested them for native conformation and turbidity, correct?

A. They could have tested them, yes.

Q. That testing would have been within our skilled person's capabilities, correct?

A. The actual performance of the test, yes.

Q. Now, for my next few questions I'm going to ask you to make an assumption. Okay?

A. Okay.

Q. All right. I want you to assume for my next few questions that the skilled person would have been motivated to make a formulation with 40 mg/mL aflibercept. I know you

disagree with that, but I want you to assume the skilled person would have been motivated to do that.

Are you with me?

A. Yes.

Q. Now, with that assumption, the skilled person could have made the formulation from Shams, except they could have substituted in 40 mg/mL aflibercept as the VEGF antagonist, correct?

A. I'm sorry. Just to be clear, I'm supposed to assume that they're going to substitute 40 mg/mL aflibercept?

Q. Yes.

A. That's part of the assumption?

Q. Yes.

A. Okay. Yes.

Q. So you agree the skilled person could have made that formulation, correct?

A. Yes.

Q. And the skilled person could have tested that formulation for native conformation and turbidity, correct?

A. Yes.

Q. So same questions for the rest of these formulations, Gaudreault, Fraser, and Dix '226. The skilled person could have made those formulations except substituted in 40 mg/mL aflibercept, correct?

A. Yes.

Q. And they could have tested those formulations for native conformation and turbidity, correct?

A. They could have with some, again, proviso on what they might expect the results might be.

Q. But they could have -- they could have made the formulation with 40 mg/mL aflibercept from Shams, Gaudreault, Fraser, Dix, and they could have tested it for turbidity and native conformation, correct?

A. They could have done the test, yes.

Q. That's well within the capabilities of our skilled person, right?

A. Yes.

Q. In fact, I believe you testified about the Kaisheva -- and I may be butchering that as well -- Kaisheva 2013 reference.

Do you remember that?

A. I do. And I cannot speak to the pronunciation. I'm sorry.

Q. And let's say -- I'm going to continue saying Kaisheva.

Kaisheva actually laid out a formulation development approach, correct?

A. In, I mean, very broad terms.

Q. So let's go back to my examples on Slide 9.

If the skilled person substituted in 40 mg/mL

aflibercept into each of those Shams, Gaudreault, Fraser, and Dix '226 formulations, they could have then optimized those formulations for stability, correct?

MR. BERL: Your Honor, I just want the record to be clear. Is the assumption still in play? I assume it is, but I just don't want any confusion about this.

THE COURT: Mr. Rakoczy, that was my impression.

MR. RAKOCZY: The assumption is still in play.

THE COURT: Doctor, you understand that, sir?

THE WITNESS: Yes, Your Honor. And that was my assumption too.

BY MR. RAKOCZY:

Q. Do you want me to rephrase it?

A. Please.

Q. So my question is the skilled person, having made the Shams, Gaudreault, Fraser, and Dix '226 formulations, except substituting in 40 mg/mL aflibercept with my assumption, they then could have optimized those formulations for stability, correct?

A. Well, there, there's somewhat of an issue because the skilled person wouldn't, a priori given your hypothetical, have an understanding of what the optimized target might be. So "optimization" is a very broad term, and the question is what the target might be.

Q. You are clairvoyant on my next question. Let's

assume -- let's add to my assumption. Let's assume the target is 98 percent or better native conformation.

Can you assume that?

A. Okay.

Q. All right. So with that assumption, the skilled person could have made the Shams, Gaudreault, Fraser, and Dix '226 formulations using 40 mg/mL aflibercept and then optimized those formulations to meet that 98 percent native conformation requirement, correct?

A. Well, that's correct given the teachings of the '865 patent. But before the '865 patent, the skilled person wouldn't expect what that optimal might be.

Q. No, I'm asking you to assume that they want to hit 98 percent native conformation. Okay? That's part of my assumption. Can you assume that?

A. Okay. Yes.

Q. So my question is -- I'm sorry.

A. No, I did understand that.

Q. Assuming that that's the target the skilled person wants to hit, the skilled person could have optimized Shams, Gaudreault, Fraser, and Dix with 40 mg/mL aflibercept to reach that 98 percent native conformation, correct?

A. Not -- no, Counsel. Before the teachings of the '865 patent, the person wouldn't have expected they could reach that. Given the teachings, in hindsight, I would say yes, they

would have. But they wouldn't have known that, and they could have failed.

Q. They could have failed. But they don't have blinders on, right? They can do screening studies for these excipients. They can vary the concentrations until they reach 98 percent native conformation, correct?

A. First of all, I know we made those assumptions. But I think we're adding an additional assumption of that formulation works in a certain way in which this doesn't. So I already said that you don't substitute one formulation for another. And I think there's literature for that.

But the other thing is now we're just talking about a formulation development; so the formulator may not reach the 98 percent.

Q. So your testimony is, for example, we can take Dix '226 -- let's look at that formulation. Okay?

Your testimony is that taking 40 mg/mL VEGF Trap Sequence ID Number 4, combining that with 0.1 percent polysorbate 20, 10-millimolar phosphate, 20 percent sucrose, and 50-millimolar NaCl, your testimony is that that's not going to achieve 98 percent or better native conformation?

A. No, Counsel, that's not my testimony.

The Dix actually says that this formulation does achieve the 98 percent. And given that, I think the skilled person would think it most likely that going to 40, for all the

reasons I mentioned in my direct, would also achieve that with all of the things being the same.

Q. Okay. So they would have known about the Dix '226 teachings and that that 50 mg was stable in 98 percent native conformation, correct?

A. They would have -- assuming the Dix is prior art, making those assumptions, they would have known that that reaches the 98 percent, the formulation on your slide, yes.

Q. And our skilled person is assumed to know all of this art, correct?

A. Well, again, there's this technical legal issue with the Dix. So if you want to make that assumption, I will --

Q. Well, I'm asking you. Is it your understanding that the skilled person is supposed to have a handle and a familiarity with all of the prior art or just some of the prior art?

A. Well, again, my understanding is the relevant prior art. But, again, that's the legal question perhaps.

Q. Well, let's assume Dix '226 is relevant prior art. You would agree the skilled person would know about all of these formulations, correct -- Shams, Gaudreault, Fraser, Dix '226, right?

A. With that assumption, yes.

Q. And if the skilled person is looking at Dix, 50 mg/mL aflibercept, and they see that that is stable and meets

98 percent native conformation, that's going to assist the skilled person in making a formulation with 40 mg that meets the 98 percent native conformation, correct?

A. Yes. I think I keep saying I agree the skilled person would think it most likely.

Q. All right. Let's move on to aflibercept. Obviously, you've testified quite a bit about the molecule.

Can we agree aflibercept is glycosylated, correct?

A. Yes.

Q. And you mentioned the Holash publication at DTX 3549, I believe, yesterday.

Do you recall that?

A. Yes.

Q. You're familiar with Holash, correct?

A. Yes.

Q. Now, Holash -- strike that.

Aflibercept is described in Holash as VEGF Trap R1R2, correct?

A. I don't think that's an accurate statement.

Q. All right. Let's see what Regeneron told the Patent Office.

Let's pull up DTX 3501, and I want to look at page 1 first.

You see this is an application for extension of patent term. Do you see that?

A. Let me look on my screen. Yes, I see that it says that.

Q. And it's for U.S. Patent Number 7,070,959. Do you see that?

A. Yes.

Q. You're familiar with the '959 patent, correct?

A. I think so. I've reviewed a lot of documents, Counsel.

Q. Let's go -- we'll come back to that.

Let's go to -- sorry, Dr. Trout. Let me start over.

A. Certainly.

Q. Let's go to page 5 of this same exhibit, DTX 3501.

All right. And you see there in the second paragraph, starting around the fifth line, Regeneron said, "Aflibercept is a dimeric glycoprotein with a protein molecular weight of 97 kilodaltons (kDa) and is glycosylated, with the glycosylation constituting an additional 15 percent of the total molecular mass, resulting in a total molecular weight of 115 kilodaltons."

Do you see that?

A. Yes.

Q. And you agree with it. That's aflibercept, correct?

A. Yes. That sounds right.

Q. Now, let's look at the very next paragraph starting on the fifth line. Here Regeneron told the Patent Office,

"Aflibercept is also described in Holash et al., Proc. Natl. Acad. Sci. USA, August 20th, 2002, Volume 99, number 17, pages 11393 through 11398 ('Holash,' Attachment G) as VEGF Trap R1R2."

You see that?

A. Yes.

Q. So Regeneron told the Patent Office that aflibercept is VEGF Trap R1R2 from Holash, correct?

A. Yeah, again, the VEGF Trap R1R2 in Holash is a skeletal disclosure in a general -- or a category, I should say. But I guess that's what they're telling the Patent Office now.

Q. They're not telling the Patent Office it's a category or a catchall or a genus. They said aflibercept is VEGF Trap R1R2, right?

A. Right. But I believe this is after the priority date.

Q. This is Regeneron's representation of Holash, correct?

A. Yes.

Q. Do you have any reason to dispute Regeneron wasn't being honest with the Patent Office when they said aflibercept is described in Holash as VEGF Trap R1R2?

A. No.

Q. So whenever we have VEGF Trap R1R2 in the prior art,

that's aflibercept, correct?

A. Not when you look at the prior art itself as of the priority date of the '865 patent.

Q. If VEGF Trap R1R2 is aflibercept, it's always going to be aflibercept, in the prior art or otherwise, correct?

A. But we don't -- I mean, yes after the fact, but we don't know that as of the priority date.

Q. Well, after the fact or not, VEGF Trap R1R2 is not going to sometimes be aflibercept and sometimes not be aflibercept, right?

A. It may be, Counsel. Right here, I guess Regeneron is describing Holash.

Q. So Holash describes VEGF Trap R1R2. We can agree on that, correct?

A. Yes.

Q. And Regeneron told the Patent Office that's aflibercept, right?

A. Yes again, but you don't get that from Holash.

Q. We don't get that from Holash. So Regeneron was misrepresenting what Holash says in their own article to the Patent Office?

A. No. I don't think that's correct.

Q. So we can agree, according to Regeneron, that aflibercept is VEGF Trap R1R2 in Holash, correct?

A. As they're telling the Patent Office after the

priority date, yes.

Q. And your testimony is that VEGF Trap R1R2, despite Regeneron's representations, could mean something else in the prior art?

A. I don't think that's quite accurate. My testimony, for the reasons that I went through earlier this morning, is that VEGF Trap R1R2 as disclosed in Holash could be different molecules, could be a category.

Q. Could mean lots of things, right?

A. Well, I think if one traces it back to Papadopoulos, there are two options.

Q. Two options, but not according to Regeneron. Regeneron, one option, it's aflibercept, it's glycosylated, correct?

A. Yes. I think we talked about that earlier, but yes.

Q. Now, you haven't offered any opinions on the '959 patent that's the subject of this patent term extension application, have you?

A. I would have to go back. My report's pretty long, but it wasn't the main patents that I opined upon.

Q. Well, I didn't hear you talk about it yesterday or today, correct?

A. Correct.

Q. So you don't know whether the '959 patent discloses the aflibercept molecule itself and all of its properties. Do

you know that?

A. I'm not sure.

Q. All right. Let's move on to some of the testimony you gave on teaching away. Do you recall that?

A. Yes.

Q. So let's talk about the size of aflibercept. If I understood you correctly, you testified the skilled person might be taught away from using aflibercept because of its large size; is that right?

A. Yes.

Q. Now, to be clear, the '865 patent doesn't contain any data or testing on the size of aflibercept, correct?

A. Again, it doesn't explicitly include that; there are references to the prior art.

Q. The '865 patent, you think there are references to the prior art in the '865 patent that talk about the size of aflibercept?

A. Well, I'd have to check exactly the references in the '865, but there are references, as I discussed, in the prior art.

Q. The '865 patent does not teach that only VEGF antagonists of a certain size can penetrate the retina, correct?

A. It doesn't explicitly speak about those issues, correct.

Q. It doesn't have any retinal penetration data in it, correct?

A. Not explicitly, correct.

Q. It doesn't teach that aflibercept is better than any other VEGF antagonist in terms of getting into the eye, correct?

A. It doesn't talk about those issues explicitly, correct.

Q. The '865 patent doesn't teach the skilled person that somehow big molecules won't get into the eye, correct?

A. Not explicitly.

Q. All right. So there was a bigger molecule in the art that got into the -- penetrated the retina, correct?

A. Well, I'm not sure that that was the understanding as of the priority date.

Q. All right.

Let's pull up DDX 2, Slide 1.

Here we have aflibercept, 115 kilodaltons, right?

A. Yes.

Q. All right. Let's pull up the big molecule, bevacizumab. You remember this one. You testified about that yesterday, correct?

A. Yes.

Q. This one's bigger in terms of molecular weight, right?

A. Yes.

Q. So bevacizumab, or Avastin, is 149 kilodaltons, correct?

A. Yes. And, again, I agree that these weights are guides. It's the volume or the radius that's what's most important. But yes.

Q. It looks big. Looks big, doesn't it?

A. Yeah. It's about the same size as aflibercept. Agreed.

Q. Well, in terms of molecular weight, it's actually over 20 percent larger than aflibercept, correct?

A. Yes. Again, I think I said this yesterday. The glycosylation groups in aflibercept make its volume probably a bit bigger.

Q. Help me with my math. It's -- bevacizumab is actually almost -- is it almost 30 percent larger than aflibercept in terms of molecular weight?

A. Almost. And just so you understand, I'm trying to make the point that this is a good guide. It's the volume that's important. This is -- it's related, but it's not exactly the same.

But yes, I grant that these are both large molecules, about the same size.

Q. And you're well aware that by 2006 multiple publications had discussed the effective administration of

bevacizumab injected intravitreally into human patients, correct?

A. Well, I think I testified about that. There was some debate. And I think the consensus before 2006 was that it's unclear that there would be penetration as such.

Q. Well, let's see what actual workers in the field were saying.

Let's pull up DTX 3058, already in evidence.

And I think you're aware or you've seen this, right, the Rosenfeld and colleagues publication?

A. I think so.

Q. Dated July-August 2005 entitled "Optimal Coherence Tomography Findings After an Intravitreal Injection."

Do you see that?

A. Yes.

Q. All right. Let's go to page 1 and look at the abstract.

And you see there it states that "An intravitreal injection of bevacizumab 1.0 mg was given. Within one week, optical coherence tomography revealed resolution of the subretinal fluid, resulting in a normal-appearing macular contour. The improved macular appearance was maintained for at least four weeks, and visual acuity remained stable."

Do you see that?

A. Yes, Counsel. Which exhibit is this in my binder?

Q. This is DTX 3058, already in evidence, I believe.

Now, you would agree that actual workers in the field, Rosenfeld -- or Dr. Rosenfeld and his colleagues, they clearly weren't dissuaded or taught away from using a big molecule like bevacizumab, correct?

Is that correct, Dr. Trout?

A. Well, I think that's correct that they decided to test it. It doesn't mean that the skilled person would do that. This is a research study. And they say on page 333, "This is the first report of injection of bevacizumab into a human eye." So this is part of a research investigation.

Q. But this is an actual worker in the field, an actual researcher in the prior art, who was not dissuaded from using bevacizumab because of its large size, correct?

A. Researcher was testing it, yes.

Q. And Dr. Rosenfeld and colleagues, they would have been aware of the same prior art that you testified about, correct?

Can we assume Dr. Rosenfeld and colleagues would have been aware of all that art back in the day, but yet they were not discouraged from using a big molecule like bevacizumab, correct?

A. Well, I'm not sure if they'd be familiar with all of the art that I mentioned, just certainly familiar with some art and, again, performed the research study.

Q. So he was not discouraged to use bevacizumab by intravitreal injection, correct?

A. He was not discouraged to test it, to investigate it as a research project.

Q. Let's take a look at another one. Let's pull up DTX 9036 and look at page 1 first. And you see this is *Ophthalmology.*

Do you see that?

A. One second, please.

Q. It's on screen as well.

A. Yes.

Q. You see it's *Ophthalmology*, Volume 113, Number 3, from 2006, correct?

A. Yes.

Q. Now, let's go to page 3 and look at the exact date on this.

And you see at the top we have a received stamp?

A. Yes.

Q. You see it says, "Received March 3rd, 2006, Library of Health Sciences, University of Illinois, College of Medicine, Peoria," correct?

A. Yes.

Q. You don't have any reason to doubt that date, do you?

A. Not sitting here.

Q. I think yesterday you said you weren't sure or maybe

your counsel said wasn't sure when the Avery publication came out.

Do you recall that?

A. Yes. Which exact date it came out, yes.

Q. Well, we've got an exact date now, right? March 3rd, 2006?

A. If that stamp is correct, yes.

Q. And that's before the date that you used as an earlier priority date, correct? That's before March 21st, 2006, correct?

THE COURT: One second, Doctor.

Yes, Mr. Berl.

MR. BERL: Yes, Your Honor. They've never asserted this before. This is a new document with a new date stamp, never asserted it as prior art before. We haven't had an opportunity to assess this or its veracity or anything else. Doesn't seem like the time to be asserting the new prior art.

MR. RAKOCZY: It's the exact same -- oh, I'm sorry.

THE COURT: I understand.

Can we unzoom, if that's a word.

MR. RAKOCZY: This is the same Avery document, Your Honor. We just got one with the date on it because yesterday for the first time I hear counsel saying, "I don't know when this came out in March." So I thought I'd give him a date.

THE COURT: How about a proffer of where this copy

with that stamp came from.

MR. RAKOCZY: This proffer -- could we blow it back up, Judge?

THE COURT: Sure, yes, yes. Now that -- I just lost track of which reference material this was. I'm sorry.

MR. RAKOCZY: This came, I believe, from the University of Illinois, College of Medicine in Peoria.

THE COURT: Anything further on this one, Mr. Berl?

MR. BERL: It's not -- it did not just come up yesterday. They asked us to stipulate, as part of the pretrial order, that this was prior art. We said no. We said no. And all they provided was a different copy of Avery without a date stamp. They have no declaration from the librarian. We've had no opportunity to connect the veracity of this Bates stamp or conduct any discovery to assess when it was received or whether this is, in fact, prior art. It doesn't look that way. Last day of trial, they all of a sudden say here's the date of the publication. We've been doing this for nine months.

MR. RAKOCZY: Your Honor, nobody even disputed Avery's prior art. This is the first time hearing it. They never gave a date of Avery.

THE COURT: I'm going to overrule the objection and receive it for what it's worth, which is a -- with all due respect to the University of Illinois, College of Media in Peoria -- a random stamp of some kind that says March 3rd,

2006. It'll be received for what it's worth and afforded weight accordingly.

Objection overruled.

MR. RAKOCZY: Thank you, Judge.

BY MR. RAKOCZY:

Q. Let's flip to page 5 of DTX 9036, and this is the Avery article.

You recognize this, correct, Dr. Trout? You testified about this yesterday?

A. Yes, it looks to be the article.

Q. This is Dr. Avery and colleagues, their publication entitled "Intravitreal Bevacizumab (Avastin) for Neovascular Age-Related Macular Degeneration," correct?

A. Yes, that's the title.

Q. And let's look at the methods section if we could.

And you see here in the methods that Dr. Avery and colleagues said that patients received intravitreal bevacizumab 1.25 milligrams on a monthly basis, correct?

A. Yes.

Q. Let's jump to their conclusions if we could.

Here we see in "Conclusions" Dr. Avery and colleagues reported that "Short-term results suggest that intravitreal bevacizumab, 1.25 milligrams, is well-tolerated and associated with improvement in VA, decreased retinal thickness by OCT, and reduction in angiographic leakage in most patients," correct?

Is that the correct conclusion, Dr. Trout?

A. I'm trying to -- I see. Yeah, but it continues.

Q. Yes, it continues, but that's the conclusion, correct?

A. That's part of the conclusion, yes.

Q. Now, my question is Dr. Avery and colleagues, they were not dissuaded or discouraged from using bevacizumab intravitreally, correct?

A. Well, again, they are attempting to do -- or they are doing a research study, and what you left out was the last sentence of the conclusion: "Further evaluation of intravitreal bevacizumab for the treatment of choroidal neovascularization is warranted."

So this is just an invitation to do an experiment. And if you remember from other parts of the paper, it talks about potential issues with using bevacizumab. And, really, the conclusions and the discussion throughout is tentative at best.

Q. Now, Dr. Trout, these are actual experts working in the field at the time, correct?

A. Yes. I have no reason to doubt that. Yes.

Q. Now, today you're saying the skilled person would be discouraged or taught away from using a big molecule, but people actually working in the field at the time were not discouraged. They used bevacizumab in the eye, despite its

size, correct?

A. I mean, they -- I think they could have been discouraged. They're doing research studies. That's often what I do in my lab, is I do things that the art teaches away from to see if I can advance the field.

And again, the text, partly what I read but also on page 364, talks about the potential of thromboembolic events, and then the discussion on page 370 talks -- basically indicates the tentative results, the tentative nature of the results here.

Q. But that's your view after the fact. Back in the day, these researchers actually used bevacizumab in the eye despite its large size?

A. It's not my view after the fact. I agree they did this research study, but it's also Dr. Ferrara's conclusion, as I quoted this morning and yesterday, I guess.

Q. And these researchers went on to recommend full-blown clinical trials, correct?

A. Well, it says further evaluation is warranted and could be a hope, maybe, for a clinical trial.

Q. And because of the groundbreaking work of Dr. Avery and colleagues and Dr. Rosenfeld and colleagues, bevacizumab, even to this day, is one of the most prescribed VEGF antagonists, correct?

A. I don't have that data in terms of prescription

percentages.

Q. You don't know that? You didn't hear that from the clinicians at trial?

A. I heard that it's used, but I'm not sure what's the most prescribed.

MR. RAKOCZY: All right. Your Honor, I'm about ready to switch topics. Would you like to break, or should we --

THE COURT: Yeah, let's go ahead and do that. It's the last day of volleyball camp. Sometimes that breaks a little early. I'm under strict orders to not be late. I'll leave it at that. Those orders came.

Doctor, one last quiet lunch for you. You're welcome. Counsel is under orders to feed you, but they also can't talk to you, as you well know by this point, sir, but you can go ahead and step down.

THE WITNESS: Thank you, Your Honor.

THE COURT: Thank you.

We'll take our lunch break at this point. We'll pick up at 12:00 with the doctor's cross-examination.

Thank you all very much.

(A recess was taken from 11:00 a.m. to 12:05 p.m.)

THE COURT: Thank you, Doctor.

Mr. Rakoczy, if you're ready to proceed, you may.

MR. RAKOCZY: Good afternoon, Your Honor.

BY MR. RAKOCZY:

Q. Good afternoon, Dr. Trout.

A. Good afternoon, Mr. Rakoczy.

Q. Ready to go?

A. Yes, sir.

Q. I want to return real quick to the big-molecule issue. A couple questions I forgot to ask.

The '865 patent does not teach that the claim formulations were the first to ever get a VEGF antagonist to penetrate the retina, correct?

A. I'm sorry. The first what?

Q. Let me back up.

The patent does not teach that the claim formulations were the first formulations to get a VEGF antagonist to penetrate the retina, right?

A. I think those words as such are not explicitly in the patent.

Q. And, again, there's nothing in the patent about penetrating the retina, correct?

A. I believe that term's not explicitly in the patent, correct.

Q. And the patent doesn't say that it somehow resolved skepticism in the art about getting a big molecule into the retina, correct?

A. Again, those words are not there. I agree.

Q. So I want to make sure we're clear here, then, for the record.

So you're relying on a teaching away that somehow the skilled person would have been taught away from using a big molecule to get into the retina and that teaching or that skepticism is not addressed or resolved in the '865 patent, correct?

A. The skepticism is resolved because of the formulations of the '865 patent. The skepticism, though, I agree is based on reviewing the relevant prior art.

Q. But you just told me that the formulations in the '865 patent were not the first formulations to get a VEGF antagonist into the retina, right?

A. I don't think that's what I said. I think what I said was, in response to your question, the '865 patent doesn't explicitly use those words. And I certainly discussed throughout today and yesterday the relevant art related to that.

Q. But the patent itself does not address this penetration into the retina at all, correct?

A. It doesn't use those specific words.

Q. All right. Now, another teaching away you mentioned was inflammation caused by 40 mg/mL.

Do you remember that?

A. That was part of it. There was other parts too.

Q. You cited the Gaudreault reference for that, I believe?

A. Correct. There was that and the issue of maximum inhibition.

Q. Now, the Gaudreault study, that was the monkey study that showed inflammation with the 40 mg/mL concentration, right?

A. Moderate to severe, yes.

Q. Now, you are not an ophthalmologist, I think we established, correct?

A. That is correct.

Q. You're not an expert in ophthalmology or in treating diseases of the eye, correct?

A. Correct.

Q. Now -- so to be fair, you have no basis to say whether moderate to severe inflammation in a monkey that resolved itself by day eight would have discouraged a clinician from using 40 mg/mL of aflibercept, correct?

A. Correct. I can't speak to what a clinician would say per se; but as a formulator, I look at that. And that would bring serious doubts as to the applicability of the 40 mg/mL formulation. And, remember, as you pointed, this is for seven days at least out of a month.

Q. But you're not the one that's going to be using this to treat an eye disease, correct?

A. Correct.

Q. Now, there's no data in the '865 patent about inflammation, correct?

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

Q. There's no data or testing in the '865 patent showing that the claim formulations somehow result in less inflammation than the prior art, correct?

A. There's not inflammation data. There's the SEC data that we've been talking about, which is a good indication of -- for a formulator again of having a lower risk of inflammation.

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

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

Q. So my question is there's no data in this patent showing that these claim formulations somehow result in less inflammation than prior art formulations, correct?

A. There's no -- you're correct there's no direct inflammation data. Again, from the standpoint of the skilled person, the SEC data, I should say all the stability data in the patent, would tell me that -- would indicate to the skilled person that there's a relatively lower risk of inflammation.

Q. I'm asking about inflammation data. You testified about inflammation data in Gaudreault. There's no such data like that in the patent, correct?

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

there's other data.

Q. So, again, you're relying on a teaching away of supposed inflammation that the '865 patent itself does not address, correct?

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

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

Q. I understand. I understand.

And in Gaudreault, they actually concluded that ranibizumab was well tolerated, correct?

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

Q. But they said it was well tolerated. That was their first conclusion, correct?

A. They do use those terms. And I apologize, Counsel, I gave the wrong units. 10 mg/mL. Sorry about that.

Q. We can pull up Gaudreault. Let's just confirm. It's DTX 2265. On page 2 we have the clinical findings.

The first finding from Gaudreault is that ranibizumab was well tolerated, correct?

A. That's what's listed here. And then it goes and discusses the relative differences in inflammation.

Q. And it says transient. That's how it characterizes the inflammation. You left that out. It says transient,

correct?

A. Yes. It wasn't an intention to leave it out. It lasted two to eight -- from day two to eight, so at least seven days out of a month.

Q. Okay.

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

This is what you're referring to, right? The inflammation was present at day two, but it completely resolved by day eight, correct?

A. Correct.

Q. And you haven't heard any clinician in this trial testify that that would dissuade the use of 40 mg/mL, correct?

I haven't heard anyone.

A. I wasn't here for all of the clinicians' testimony; but from what I heard, I didn't hear that specifically. I'm telling you how a formulator would view this.

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

A. Again, I wasn't here the whole time. I did hear testimony about having to be careful in injections, about how the injections are done, and general concerns about issues with injections, medical issues.

Q. Now, this is a POSA teaching away you testified about. That didn't prevent others in the art like Dr. Dan Dix from filing patents on even higher concentrations of

aflibercept, correct?

A. Correct. Again, that's how invention works is to go against the prevailing art.

Q. Okay.

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

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

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

Q. You recognize Example 1, Dr. Dix and his team, they used a 50 mg/mL formulation here, correct?

A. 50 mg/mL, correct.

Q. So assuming this is prior art -- and I know you and your counsel dispute that. But assuming this is prior art, Dix and colleagues clearly weren't dissuaded or discouraged from high concentrations of aflibercept, correct?

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

You're talking about after Dix or before Dix?

Q. This is Dix '226.

A. Yes. I understand.

Q. And Example 1, which is VEGF Trap Sequence ID Number 4, which is aflibercept. And they used 50 mg/mL, correct?

A. Yes.

Q. Higher than 40?

A. That's right.

Q. So they weren't dissuaded from or taught away from using high concentrations of aflibercept, correct?

A. I don't know about the inventive process. Again, that's how inventions work is going against the prevailing views.

Q. Just like Rosenfeld and Avery and colleagues used a big molecule to get into the retina, Dix and his colleagues used high concentration, contrary to what you said the teaching away was, correct?

A. I think that the use of the 50 mg/mL of VEGF Trap is contrary to teaching away in the prior art, again, depending on the date we're talking about.

Q. But if this is prior art, then it's teaching 50 mg, higher than 40, correct?

A. Well, if it's prior art, it's teaching 50. And we talked about what the significance of that for 40 is, and we talked about the fact that this is not intravitreal. And you can look at the sucrose concentration, which is very high.

Q. My question is high concentration, Dix used 50 mg aflibercept, correct?

A. Correct.

Q. All right. Let's talk about the skepticism you mentioned. And I believe you cited a Ferrara paper.

Do you recall that?

A. Yes.

Q. Okay.

Let's pull up PTX 1838 at page 7. And I believe this is the Ferrara 2004 paper. I saw it cited several times during your direct testimony, this exact same paragraph.

Do you recall that?

A. Yes.

Q. And there's something I wanted to ask you about. So in the highlighted part, that's what you cited during your direct, at least three times to my recollection.

You recall testifying about that, right, this immune response sentence?

A. Yes.

Q. So Ferrara doesn't actually cite any data or support for that sentence, does he?

A. No. This is what would have generally been understood in the art.

Q. So he cites no data; he just says it.

A. Well, I agree there's no citation after the last sentence, because this is what would be generally understood in the art.

Q. And he says it's just possible, right?

A. Correct.

Q. So he must not have had any data that it had actually

happened, right?

A. It's unlikely that he had data. I agree with that.

Q. Now, if we look at the preceding sentence right above that, you see Ferrara says that these fusion proteins "represent an advantage over antibodies because they can result in higher binding affinity."

Do you see that?

A. Yes.

Q. So he's actually promoting the use of the fusion protein here, saying it could be better, right?

A. Right. But, therefore, at lower concentrations, correct.

Q. He's saying this makes the fusion protein a better route, correct?

A. Yes, because it could be formulated at lower concentrations than, for example, ranibizumab.

Q. Now, regardless of this teaching away that you mentioned in Ferrara, we can agree again there's no binding or affinity or immunogenicity data in the '865 patent, correct?

A. Not explicitly, correct.

Q. There's nothing in the '865 patent teaching that somehow those formulations are safer or result in less immunogenicity than other formulations, correct?

A. No, Counsel, that's not correct. As I said, the formulator -- I'm speaking from the standpoint of a formulator,

which I am. The high stability, particularly with respect to SEC and the other data, would give the formulator the idea that there was relatively lower risk.

Q. I'm asking immunogenicity data, this immune response issue. Where is that data in the '865 patent?

A. I think I agreed several times, Counsel, there's no direct immune data explicitly in the '865, correct.

Q. All right. Let's move back to your table. I love that table, DDX 9, Slide 2.

Remember this table?

A. Yes.

Q. All right. Hopefully I can make quick work of this.

I'd like to just go back and talk a little bit about what these examples use and don't use. Is that all right?

A. Of course.

Q. Now, just so the record's clear, all of the examples in the patent use a phosphate buffer, correct?

A. Yes.

Q. No other buffers are even mentioned in the specification, correct?

A. Explicitly, correct. There's the structural category.

Q. But histidine, for example, is not mentioned in the patent, correct?

A. Not explicitly, correct.

Q. Succinate is not mentioned in the patent?

A. Not explicitly, correct.

Q. And there's no stability data in the patent for a histidine or succinate-buffered composition, correct?

A. Not explicitly, correct.

Q. The only stabilizer -- sugar stabilizer used in the patent examples is sucrose, correct?

A. That's the only sugar in the examples. But in Column 2, there are other sugars explicitly mentioned.

Q. Yeah. They mention sorbitol, glycerol, trehalose, and mannitol, correct? Does that sound right?

A. Yes. And sucrose, I guess.

Q. But there's no data or examples on any of those stabilizers except sucrose, correct?

A. Correct. Again, the skilled person would understand, because of the common structure, that they should work in a similar way.

Q. So the skilled person would know that they would all work and expect them to work?

A. I think the skilled person would expect them to work.

Q. Okay. And they would expect them all to be suitable for intravitreal administration, correct?

A. I think that's correct, but I would want to be sure. I would want to go back to the literature for intravitreal injection just to make sure.

Q. And all those stabilizers you told me, they were all known in the art, correct? Those aren't new?

A. Correct.

Q. All right. Let's stay on screen here. And real quick, Examples 1 and 2 are 50 mg/mL, correct?

A. Yes.

Q. So those are not covered by the asserted claims; is that right40?

A. Correct.

Q. And Example 7 and 8 are 20 mg/mL; is that right?

A. Yes.

Q. So those would not be covered by the asserted claims either?

A. Well, again, the 20 mg/mL is the pre-lyo solution. That isn't the formulation. The formulation is the 40 mg/mL. But I agree, because they're reconstituted lyo solution, they would not be covered by the asserted claims.

Q. And Examples 4 and 6 are prefilled syringes, correct?

A. Yes, that's correct.

Q. So those wouldn't be covered by the asserted claims either?

A. That's correct.

Q. And Examples 5 and 6 don't contain a sugar stabilizer, correct?

A. Correct.

Q. So those would not be covered by the asserted claims; is that right?

A. Correct.

Q. Now, Examples 7 and 8, those actually don't contain any data showing percent native conformation following storage of a liquid formulation at 5 degrees C for two months, correct?

A. Yes, that's correct. It was the lyo formulation. That's correct.

Q. Now, let's talk quickly about the breadth of the claims. You testified -- I believe the word you used was that the asserted claims are narrow.

Do you remember that?

A. Yes, sir.

Q. So -- but you didn't attempt to estimate or calculate how many formulations are actually covered by the asserted claims, correct?

A. That's correct.

Q. I apologize. I meant to ask you before. Going a little out of order here.

A. That's okay.

Q. I asked you before, you're not an expert in ophthalmology or treating eye diseases. You told me you weren't, correct?

A. I am not an ophthalmologist, that's correct.

Q. And you're not an expert in the retina or the anatomy

of the eye, correct?

A. That's correct.

Q. And you are not an expert in ocular pharmacokinetics; is that correct?

A. I think that's correct except from the standpoint of formulation, we often deal with pharmacokinetics. I can read the literature on that.

Q. You wouldn't consider yourself an actual expert in it, correct?

A. I would consider myself an expert in ocular pharmacokinetics related to formulation.

Q. Okay. Let's move to a different topic.

MR. RAKOCZY: May I have one moment, Your Honor?

THE COURT: You may.

BY MR. RAKOCZY:

Q. I want to ask you about the Rudge reference.

Do you recall that?

A. Yes.

Q. And I want to pull up your expert report, DTX 7066, at page 184. This is your materials considered where you cite the Rudge paper.

Do you see that?

A. Yes.

Q. And you --

If we could blow that up, Mr. Gibson.

And you have a 2005 publication on Rudge here on your report, correct?

A. Well, that's what's written, but again -- I think we talked about this earlier in the trial -- that doesn't seem to be the date in which it was published.

Q. That's the date you wrote, though, correct?

A. Well, that's the date I reproduced from the cover; but again, there are references which postdate that; so...

Q. So you didn't go and check that? I guess I'm asking. I didn't see you dispute the publication date of Rudge in your report anywhere.

A. Well, I think I did. I can -- remind me which --

Q. I can represent to you there's no dispute about Rudge in your report. And I'm just asking, did you list a 2005 date on Rudge?

A. Well, I listed a date from the cover, again, noting that there are publications from 2006 that are referenced so the Rudge has to be -- has to postdate 2005.

Q. Let's confirm that. Let's pull up PTX 3209 at page 1.

A. I'm sorry, Counsel. Could you give me the --

Q. I'm sorry. PTX 3209.

A. Oh, so is that in your notebook or --

Q. That's in the big binder in front of you. Volume 2. Small binder.

A. The small binder. The other --

Q. Yeah. This is the CV of one of the Rudge coauthors. Do you see that? George Yancopoulos.

A. Yes.

Q. Let's go to page 22 of the Yancopoulos CV, one of the coauthors of Rudge, and you see he also lists a publication date of 2005 for Rudge, correct? It's on screen. Publication 285.

A. Again, first of all, I should say I have not seen Dr. Yancopoulos's CV before; so I haven't seen this document before. But again, I think as we discussed earlier in the week, the 2005 is what's listed on the cover, but there were references from 2006.

Q. Well, he authored it, right?

A. He was one of the authors, I believe.

Q. And he listed 2005 on his CV, correct?

A. As the date that is on the first page of the -- of the article, I should say, publication.

Q. All right. Let's switch gears again, and I want to talk about this Dix '226 issue of whether it's prior art or not.

A. Okay.

Q. I believe you were told by Regeneron's counsel that Dix '226 can't be used as prior art because it's assigned to Regeneron.

Do you recall that?

A. I do recall that. I don't know if those are the exact words, but that sounds like the general point.

Q. Let's pull up DTX 4956, please, page 1.

This is a Regeneron 10-K for the fiscal year ended December 31st, 2004.

A. I'm sorry, Counsel. I think this is in the other binder.

Q. That may be in the big binder in front of you.

MR. BERL: While we're finding that, Your Honor, if I may interpose an objection. This is not disclosed as prior art. I'm not sure what purpose counsel is using it for, but Mylan was required by statute to give us notice of what prior art they would be relying on a month before the trial. They violated that. It's under 35 U.S.C. 282. They sent us, for the '865 patent alone, 35 pages listing prior art, 15 or 20 per page, hundreds. This is not on it. And so --

MR. RAKOCZY: I'm not citing it as prior art, Your Honor. I merely want to explore with the witness whether he looked at some of the agreements referenced in here relative to the 103(c)(1) issue that Regeneron has briefed and argued repeatedly.

THE COURT: Understood. Overruled. I understand in the context of -- what's the date on this 10-K again, Mr. Rakoczy? I'm sorry.

MR. RAKOCZY: This is a Regeneron 10-K dated December 31, 2004.

THE COURT: The information highlighted on the big screen. Yes. Thank you. Thank you, sir. Sorry.

MR. RAKOCZY: Thank you, Your Honor.

BY MR. RAKOCZY:

Q. I'd like to go to page 4, fourth full paragraph. And here, you see -- I want to lay a little foundation, Dr. Trout, and then just ask if you looked at a few things.

It says here, "In September 2003 we entered into a collaboration agreement with Aventis Pharmaceuticals (now part of the Sanofi-Aventis group) to joint development and commercialize the VEGF Trap throughout the world."

Do you see that?

A. Yes.

Q. Did you look at that collaboration agreement?

A. No, not that I recall.

Q. So you didn't review that collaboration agreement in any way, shape, or form to see what the intellectual property rights and licenses were that were part of that collaboration?

A. As far as I recall, I didn't, and from the standpoint of the POSA, I don't even think -- I've never even seen a document like this before, except I think you may have shown something earlier this week. But I've never seen anything like this in my years as a scientist.

Q. That's okay. My only question is you haven't reviewed that, correct?

A. I do not think I've reviewed that, no.

Q. Let's look at page 4, same page, third sentence. You see here it says, "In January 2005 we at Sanofi-Aventis amended our collaboration agreement to exclude rights to develop and commercialize the VEGF Trap for eye diseases through locally -- local delivery systems. We now have the exclusive right to develop and commercialize the VEGF Trap for eye diseases through local administration to the eye."

Do you see that?

A. I'm sorry, Counsel. I didn't want to interrupt you, but I think you went too fast. I didn't see -- could you point me again to where you're reading.

Q. Yes. So it's page 4, halfway down.

A. DTX page 4.

Q. VEGF Trap-Eye diseases, third line down.

A. The bold VEGF Trap-Eye disease.

Q. Yes. And third line down, it references in January 2005 that Regeneron and Sanofi-Aventis amended their collaboration agreement.

Do you see that?

A. Yes. Thank you. Now I see it.

Q. And it says that Regeneron now has the exclusive right to develop and commercialize the VEGF Trap for eye

diseases. Do you see that?

A. Yes.

Q. Did you review the amendment to the collaboration agreement?

A. Not as far as I recall.

Q. Did you review any licenses or any other documents regarding intellectual property or patent rights in connection with the collaboration agreement or the amendment to the collaboration agreement with Sanofi?

A. Again, not as far as I recall, no.

Q. All right. I'd like to pull up -- sorry. I apologize, Dr. Trout. One more question on this.

A. Of course.

Q. Could we please pull up DTX 4986 at page 1. And I think I know the answer to this. I just want to confirm.

This is the second amendment to the collaboration agreement I just referenced. My question is, again, you have not reviewed this second amendment to the collaboration agreement, correct?

A. Okay. Just to be clear, this is another document.

Q. Yes. This is DTX 4986.

A. Have not reviewed this, no.

Q. I'd like to go back to the patent now.

If we could, Mr. Gibson, please go back to the '865 patent, at the top of Column 2, which is PTX 4 -- sorry --

PTX 2 at page 4.

And it's on screen as well, Dr. Trout.

A. Okay.

Q. And you see here at the top of Column 2 it says, "Ophthalmic formulations are known." Do you see that?

A. Yes.

Q. You agree with that, correct?

A. Yes. As a general statement, yes.

Q. And it goes on to say, "An ophthalmic formulation of a VEGF antibody is described in U.S. Patent Number 6,676,941."

Do you see that?

A. Yes.

Q. I'd like to show you the '941 patent here referenced in the '865 patent.

MR. RAKOCZY: Your Honor, may I approach? It's a loose exhibit.

THE COURT: You may.

MR. RAKOCZY: It's DTX 8171 for the record, a very large --

BY MR. RAKOCZY:

Q. So for the record, I have just handed you, Dr. Trout, DTX 8171, and you see it is U.S. Patent 6,676,941, which is the same patent referenced in the specification of the '865 patent that I just referenced, correct?

A. Yes.

MR. BERL: For the record, Your Honor, this likewise was not disclosed in the 35 pages of prior art references. I don't know if he's using this as prior art or not, but he shouldn't be able to.

MR. RAKOCZY: Your Honor, it's admitted prior art in the actual patent specification, which is why I laid the foundation for it.

THE COURT: Overruled.

BY MR. RAKOCZY:

Q. I only want to ask you about a quick part of this. Let's go to page 58 of the patent, please, Dr. Trout, and I'll put it on screen as well.

And in the left-hand column, starting at line 9, should be Column 100.

THE COURT: Column 100, line 9, Counsel?

MR. RAKOCZY: Yes.

Mr. Gibson, could you please pull up Column 100. There it is. Starting at line 8.

BY MR. RAKOCZY:

Q. You see, Dr. Trout, this '941 patent, which is identified in the '865 patent, discloses that "The ophthalmic preparation will preferably be in the form of a sterile aqueous exclusion containing, if desired, additional ingredients, for example, preservatives, buffers, tonicity agents, antioxidants and stabilizers, nonionic wetting or clarifying agents,

viscosity increasing agents, and the like."

Do you see that?

A. Yes, I see that.

Q. And these would have all been known excipients or structures, in your words, correct?

A. Counsel?

Q. Yes.

A. I think broadly speaking, but I have not, that I recall, reviewed this entire document. This is a general disclosure and however many hundreds of columns. So I would want to go and make sure that my general understanding of these terms is also the way it's being used in this document.

Q. My question is simple. You don't see any new classes of excipients here, correct?

A. Again, just in high level, these don't seem new. Again, I don't know what the authors are disclosing throughout this document, but this seems to be just a very general, high-level discussion.

Q. All right. Just a couple more questions, Dr. Trout.

Did I hear you correctly during your direct examination that you said ranibizumab is the closest prior art? Is that your view?

A. Well, ranibizumab and the formulations. So ranibizumab would be the closest prior art to aflibercept in the formulations that we discussed, for example, Gaudreault and

Shams.

Q. So you didn't pick an aflibercept reference as your closest prior art, correct?

A. Correct.

Q. Last question. You mentioned copying. And I just want the record to be clear.

MR. RAKOCZY: And I don't think we need to close the courtroom for this, Your Honor.

BY MR. RAKOCZY:

Q. But you agree -- and I think we established this earlier -- that the Mylan and Biocon formulation, Yesafili, it doesn't copy Eylea, correct? It uses a different buffer, different stabilizer. As a matter of fact, it's patterned after the Lucentis formulation, correct?

A. No. I think it's -- I mean, again, I don't want to get into any specifics, but it copies for the reasons I mentioned.

Q. But Eylea uses a phosphate buffer, correct?

A. Yes.

Q. Yesafili does not use a phosphate buffer, correct?

A. Correct. It has common structure.

Q. Eylea uses a sucrose stabilizer, correct?

A. Correct.

Q. The Mylan/Biocon Yesafili product does not use a sucrose stabilizer, correct?

A. No. One with a common structure, though.

MR. RAKOCZY: Subject to the redirect, Your Honor pass the witness.

THE COURT: Thank you, Counsel.

Mr. Berl.

MR. BERL: Thank you, Your Honor.

REDIRECT EXAMINATION

BY MR. BERL:

Q. Good afternoon, Dr. Trout.

A. Good afternoon, Mr. Berl.

Q. I just want to go through a few items about which Mr. Rakoczy examined you.

Do you recall that he asked you various questions about intravitreal administration of bevacizumab?

A. I do, yes.

Q. And he first showed you the Rosenfeld article; is that right?

A. Yes, I think so.

Q. And is that a -- was that article about administration in one patient?

A. Yes. It specifically said one patient, yes.

Q. Okay. And then he showed you the Avery reference.

Do you recall that?

A. I do.

Q. And he asked you various questions about whether it

was disputed that it was prior art.

Do you remember that?

A. Yes.

Q. Let's take a look at your expert report, if we could, Dr. Trout. That's PTX 67. And we'll try to put that on the screen on the first page.

What --

A. Counsel, just one minute here.

Q. Sure. It's PTX 67. It should be in the binder that we used for your direct examination. We'll also try our best to put the excerpts I'm going to ask you about on the screen.

A. Okay. Thank you.

Q. And my first question is what was the date of the expert report?

A. Oh, March 2nd, 2023.

Q. More than three months ago, right?

A. Yes.

Q. And did you hear counsel for Mylan say that yesterday was the first he heard about the idea that the Avery reference may not be prior art?

A. I think he said that, yes.

Q. Let's take a look at paragraph 170 of your report.

And, Dr. Trout, can you read the second sentence that was in your report on March 2nd, 2023.

A. Yes.

"Dr. Rabinow fails to establish that Avery was published before the invention of the '865 patent" -- which was in parenthesis -- "no later than March 21st, 2006" -- in parenthesis -- "or the filing of the provisional patent on June 16th, 2006." And then it refers to a Section Roman numeral X.

MR. RAKOCZY: Your Honor, I'm going to lodge an objection. That's precisely why I showed the witness the document with an exact date on it prior to that.

THE COURT: Understood. The Court denied the motions for summary judgment in this case because of the factual issues. I'll add this one to that list as well.

Understood. Objection overruled. And I'll sort it out later, obviously, with the benefit of significant briefing from counsel, of course.

MR. BERL: Of course. No question.

BY MR. BERL:

Q. Doctor, he then asked you about Avery.

Do you recall that? That's DTX 2264.

A. I do.

Q. And let's pull that up, if we could.

A. Let me just also get it, Counsel. 2264, right?

Q. Yes. And let's first put up on the screen a slide of Avery. That's 2264 6.1.

Is this a part of the discussion in Avery from

page 6?

A. Yes.

Q. And what is it communicating, Dr. Trout?

A. Well, it's an acknowledgement by the authors themselves of the shortcomings of this study. I was trying to answer some of this when Mr. Rakoczy was asking me. The retrospective design, limited number of patients, nonstandard visions, limited follow-up. And then a couple lines down it says, "However, the visual results of this study are difficult to interpret."

Q. Is that consistent with how the person of skill would have viewed Avery, difficult to interpret?

A. Yes.

Q. And Mr. Rakoczy was asking now about what people back in the day who were actually practicing in this field were saying and thinking.

Do you recall that?

A. Yes.

Q. And did you look at what Dr. Ferrara said about Avery?

A. I did, yes.

Q. Was Dr. Ferrara practicing in the field at the time?

A. Yes.

Q. So let's take a look at Dr. Ferrara's article. We'll do the other Ferrara article. That's 701.

Is this Dr. Ferrara's 2006 article, Doctor?

A. I'm sorry.

MR. BERL: Why don't we go back, Mr. Schliesske, to the cover. And we're showing, for the record, PTX 706.

BY MR. BERL:

Q. And my question is is this Dr. Ferrara's article from 2006?

A. Yes. Thank you.

Q. Yes. And so now let's go to page 8 of Dr. Ferrara's article.

Does Dr. Ferrara cite and discuss Avery?

A. Yes, explicitly. 114.

Q. And is Dr. Ferrara saying that Avery has somehow changed the conventional wisdom you testified about with respect to larger molecules penetrating into the retina upon intravitreal injection?

A. No. The opposite. Dr. Ferrara says, "Although intriguing, these early findings are difficult to compare with data from rigorous double-masked Control 3 trials." And it talks about various of those. I mentioned this before.

"In addition, it is noteworthy that initial uncontrolled Phase I or II studies with pegaptanib or verteporfin photodynamic therapy suggested a considerably greater benefit in AMD patients than that eventually demonstrated in randomized Phase III studies, further

emphasizing the difficulty of interpreting early clinical results."

And then -- in other words, the results are tentative at best.

Q. If we go back to page 4 of Dr. Ferrara's article. That is PTX 701. What does Dr. Ferrara say and ultimately conclude with respect to VEGF Trap-Eye?

A. Well, highlighted here, "Interestingly, these studies show that systemic administration of the VEGF Trap inhibits neovascularization by 75 percent; however, intravitreal administration of the same agent resulted in approximately 25 percent inhibition." It says, "The limited efficacy...may be due, at least in part, to the existence of a barrier to the transretinal penetration of large molecules, such as VEGF Trap."

Q. And is this consistent with what the POSA would have thought at the priority date in view of all the prior art?

A. Yes.

Q. Now, the bevacizumab injections that you were asked about, do those address any of the formulation concerns you raised with respect to formulating 40 mg/mL of aflibercept?

A. No, they do not.

Q. Do they address any of the concerns you raised relating to toxicity or immune reactions to 40 mg/mL of aflibercept injected intravitreally?

A. Not at all.

Q. Now, let's take a look at the Dix patent, which is DTX 13. And if we could try to pull up Column 7 and 8, which Mr. Rakoczy asked you about, Example 1.

Do you recall questions about Example 1 in Dix?

A. Yes.

Q. Let's take a moment to pull that up.

If we could do the bottom of Column 7.

Do you see now shown on the screen is the bottom of Column 7 and the top of Column 8 of DTX 13, Dix?

A. Yes.

Q. And it was pointed out to you that this has 50 mg/mL of aflibercept?

A. That's correct.

Q. Is Dix teaching 50 mg/mL of aflibercept for intravitreal injection?

A. No.

Q. Does Dix thereby somehow address the concerns about high concentrations of intravitreal injections that you discussed from Gaudreault?

A. No, it doesn't.

Q. Did you hear Dr. Graham's testimony earlier this week about the dilution of the Dix formulation before administration?

A. Yes.

MR. RAKOCZY: Objection, Your Honor. I didn't ask about Dr. Graham. Dr. Graham's been on and off the stand. I didn't ask a single question about his testimony.

MR. BERL: I was just asking if he heard it, if he was in the courtroom for it.

THE COURT: Sustained. It's redirect. I heard it.

MR. BERL: That's all that matters.

THE COURT: Thank you, Mr. Berl.

BY MR. BERL:

Q. Doctor, does Dix Example 1 or otherwise inform the person of ordinary skill regarding the moderate to severe inflammation that Gaudreault teaches upon administration of 40 mg/mL of ranibizumab?

A. Not at all.

Q. Now, finally, I want to go back to one of Mr. Rakoczy's slide. It was his Demonstrative 9.9. Do you recall him asking you various questions about this table?

A. I do.

Q. Do you recall that he asked you to make various assumptions regarding what the person of ordinary skill would have been motivated to do and what the person of ordinary skill would have known before the '865 patent?

A. Yes, I definitely do.

Q. Do you believe any of those assumptions are correct?

A. No.

Q. Now, this chart, which combines Shams and Gaudreault and Fraser and Dix, have you seen any assertion in this case that those references would be combined?

A. No.

Q. Do you see that, in any of the reports from Dr. Rabinow, that he would combine all of these references as Mr. Rakoczy did in his slide?

A. No.

Q. Have you even heard, throughout the trial that you've observed, that the person of ordinary skill would have combined all of these references shown in Mr. Rakoczy's slide?

A. No.

Q. Do you believe that the person of ordinary skill -- well, I'll leave that one.

Have you heard, Doctor, with respect to Dix, any evidence or testimony that the Dix patent and the '865 patent are not commonly assigned to Regeneron?

A. No.

Q. Now, even combining all of these references -- and, again, we dispute that the last one is prior art at all or can be used for obviousness. But even if combining these references somehow, Dr. Trout, do they provide any basis to use 40 mg/mL of aflibercept?

A. No, not at all. And as I've said several times, the Shams and Gaudreault specifically teach away from that.

Q. Do they provide any basis even to use 40 mg/mL of ranibizumab?

A. No. They teach away from that. And the Shams, in fact, goes forward with 6 and 10 mg/mL.

Q. Do they provide any basis to use 40 mg/mL of aflibercept intravitreally?

A. No, not at all.

Q. Do these references, even if combined as Mr. Rakoczy did, provide any data or information about 98 percent native conformation by size-exclusion chromatography even for ranibizumab?

A. No.

Q. Are there any data in these references for 98 percent native conformation of ranibizumab from Shams or Gaudreault, for example?

A. There's none in those articles.

Q. And what about turbidity? Any basis in Shams or Gaudreault for 98 percent -- sorry -- for meeting the turbidity limitation of Claim 15 of the '865 patent even for ranibizumab?

A. Nothing.

Q. Do you have any basis to believe that Lucentis -- sorry -- that Genentech continued to pursue 40 mg/mL even for ranibizumab after the data from Gaudreault?

A. I see no evidence.

Q. Even if all of these references were combined as

Mr. Rakoczy did in his Demonstrative 9.9, do you see any disclosure of a pH range of 6.2 to 6.3 for Shams, Gaudreault, or Fraser as Claim 9 requires?

A. No.

MR. BERL: No more questions. Thank you very much, Dr. Trout.

THE WITNESS: Thank you.

THE COURT: Recross?

MR. RAKOCZY: May I have a quick moment, Your Honor?

THE COURT: You may.

MR. RAKOCZY: Your Honor, before we let the good doctor go, I'd like to move in a few exhibits if I could.

THE COURT: Understood.

Assuming that doesn't pose a problem for Madam Clerk, we can start with the defendants' exhibits. Go right ahead slowly, then, Mr. Rakoczy.

MR. RAKOCZY: Defendants move into evidence DTX 3501, DTX 4956, DTX 4986, DTX 9036, DTX 8171, and PTX 1838.

THE COURT: Any objection to any of those?

MR. BERL: Yes, Your Honor, I believe two of them. The first of them was DTX 4986.

THE COURT: Okay. And just -- what is 4986?

MR. BERL: That was, I think, the amendment to an agreement between Sanofi or Aventis and Regeneron. Dr. Trout said he never saw that before. There was no basis laid or

foundation for any of that with any witness, including Dr. Trout.

THE COURT: Understood.

MR. RAKOCZY: Your Honor, that goes right to the 103(c)(1) theory. In fact, the witness who's disputing that it's prior art has not looked at the various intellectual property collaboration agreements is, in our view, admissible evidence because it goes directly to the fact that they can't show that Dix is a prior art. So we believe it's relevant and should be admissible. As a matter of fact, it was their burden to bring that out, not ours.

THE COURT: Mr. Berl?

MR. BERL: If they wanted to dispute that with agreements or otherwise, that's what their experts are for. They should have brought that up and addressed it then. Instead, they're trying to put it in through a witness who's never seen it before, and they didn't lay a foundation for it.

THE COURT: I'm going to overrule the objection and receive it to the limited extent it's information that Dr. Trout could have reviewed but did not. But I'll overrule the objection.

MR. RAKOCZY: I didn't hear the second one.

THE COURT: I think we're about to get there.

MR. BERL: I believe it's 9036, which was the Avery -- the new version of purportedly Avery with the date

stamp.

THE COURT: The Court's already ruled on that. For the same reasons, I'll overrule that objection, understanding it's worth what it's worth.

MR. BERL: And, Your Honor, with your permission, we'd like to move in -- offer various exhibits used with Dr. Trout.

THE COURT: Let me just make sure we've closed the loop.

That was the entire list of exhibits for Mylan; is that correct, Mr. Rakoczy?

MR. RAKOCZY: That's correct, Your Honor, with this witness.

THE COURT: Understood.

MR. BERL: I'll now read ours slowly into the record.

THE COURT: One second.

Sir, if you need to confer, go ahead. The list Mr. Rakoczy identified are deemed admitted subject to the Court's rulings on the objection to two of them.

(DTX 3501, DTX 4956, DTX 4986, DTX 9036, DTX 8171, and PTX 1838 were admitted.)

THE COURT: With that, Mr. Berl, you may proceed slowly.

MR. BERL: PTX 1826, PTX 1835, PTX 1773, PTX 576, PTX 1842, PTX 701, PTX 1757, PTX 1838, PTX 1556, PTX 1155,

PTX 1832, PTX 1758, PTX 753, PTX 53, and PTX 55.

MR. RAKOCZY: Your Honor, we may need a moment to go through that list.

While we're checking that list, Your Honor, I do have -- I promised you to follow up on the Dr. Graham exhibits. Would you like me to wait until the witness is out of the box?

THE COURT: Yeah. Let's do that.

Are there some for Dr. Stewart as well?

MR. BERL: I don't know if that has been tidied up yet.

MR. GREGORY: I think that was me, Your Honor. We had no more exhibits to move in through Dr. Stewart.

THE COURT: All right. Understood.

Don't try to save trees now, Mr. Rakoczy.

MR. RAKOCZY: I'm not. I want the whole thing in, Your Honor.

All right, then. Actually, I take back what I just said. We will not object to any of those.

THE COURT: All right. Without objection, then, the list Mr. Berl identified are hereby deemed admitted.

(PTX 1826, PTX 1835, PTX 1773, PTX 576, PTX 1842, PTX 701, PTX 1757, PTX 1838, PTX 1556, PTX 1155, PTX 1832, PTX 1758, PTX 753, PTX 53, and PTX 55 were admitted.)

THE COURT: Anything further we need the good Dr. Trout up here for?

MR. BERL: Not from Regeneron.

MR. RAKOCZY: Nothing from Mylan and Biocon.

THE COURT: Sir, you may step down. Thank you so very much. Have a safe trip home.

THE WITNESS: Thank you.

MR. RAKOCZY: Your Honor, I apologize. I don't mean to make this difficult. So for Dr. Graham, do you recall I objected to the majority of those exhibits as nondisclosed, and Your Honor accepted them and indicated we should fight about that in posttrial briefing?

THE COURT: Yes.

MR. RAKOCZY: I would like to provisionally move to admit several exhibits conditioned on Your Honor's ruling, meaning if you end up not accepting those exhibits, then I wouldn't want these admitted either, if that makes sense.

THE COURT: It does make sense.

Any position on that, Mr. Berl?

MR. BERL: I don't know what they are.

THE COURT: There is that. There is that. In its conceptual framework, it sounds like an eminently reasonable proposal, Mr. Rakoczy. But let's put some guts to the framing, if you will.

MR. RAKOCZY: So we would move to provisionally admit from Dr. Graham PTX 2034, PTX 3312, PTX 3313, PTX 3314, and PTX 3266.

And I believe they're all studies -- stability study documents from -- or covering those.

MR. BERL: Honestly, I don't have a clue what those are. This is the first time --

THE COURT: It's a contingent question. What I would anticipate doing, in all candor, is we receive those exhibits proffered by Regeneron. If the Court does rely upon any of those contested exhibits, then we would admit that list as well.

But as Mr. Rakoczy pointed out, if the Court does not rely upon those exhibits for any number of reasons, including whether or not they were disclosed, then those would not be considered part of the record nor addressed in the Court's final order.

(PTX 2034, PTX 3312, PTX 3313, PTX 3314, and PTX 3266 were admitted.)

MR. RAKOCZY: Thank you, Judge.

THE COURT: Thank you.

Yes, Mr. Berl? I think the floor's still yours.

MR. BERL: A few logistical questions. We've closed our case. That's our last witness.

THE COURT: Understood.

MR. BERL: So I just wanted -- there were three minor logistical issues I may want to raise.

THE COURT: You've rested that portion of your case.

Anything further from Mylan, then, Mr. Rakoczy?

MR. McLAUGHLIN: A few last exhibits. We looked at the transcripts just trying to clean things up and trying to coordinate and make sure we've got everything in that we intended to move in.

So we would like to move to admit just a few more exhibits that we've been relying on the last couple weeks if that's okay.

THE COURT: Go right ahead slowly, sir.

MR. McLAUGHLIN: DTX 9038, DTX 9023, DTX 913, DTX 902, DTX 5082, DTX 6444.

THE COURT: Thank you. Is that the universe?

MR. McLAUGHLIN: That's it.

THE COURT: All right.

Regeneron?

MS. OBERWETTER: Your Honor, I don't know what those are. So we may need a moment to try to figure out what those are and whether they were used with a witness pursuant to the pretrial order.

THE COURT: Please do.

Counsel, if you wouldn't mind conferring with Ms. Oberwetter and identifying what those are, if anyone knows.

MR. RAKOCZY: I was about to speak, but can I check with my team before I misspeak?

THE COURT: Yes. Sorry. You may.

MR. RAKOCZY: While we're waiting, Your Honor, should we put more witnesses in the box?

MR. BERL: Or there are a couple of logistical questions that I had.

THE COURT: Yeah, we'll take those up. I would ask, as the gaggle works through those loose-end exhibits, if anyone can identify which witness those exhibits were used with, that would certainly be of benefit to Madam Clerk. But I'll add that to their to-do list.

THE CLERK: I found mine, except one.

THE COURT: With that, Mr. Berl, your list of logistical issues.

MR. BERL: Yes, three issues, I think in descending order of complexity.

First, Your Honor, as you're aware, has directed the parties to address various evidentiary issues posttrial, in posttrial briefing. We just wanted clarification whether it's Your Honor's intention that those issues should be raised in the initial brief -- the initial posttrial brief. And our thinking was that, if so, the other side responding to those evidentiary points could respond to them in the proposed findings of fact and conclusions of law.

THE COURT: Yes, Mr. Rakoczy?

MR. RAKOCZY: Your Honor, because we have -- we have a lot of issues to brief in that opening 30-page, we would

request that we address the evidentiary issues in the proposed findings of fact, conclusions of law. And that way, the parties can focus on the merits in their actual briefing.

MR. BERL: I'm fine with that, Your Honor, subject to one concern, which is that, as I understood Your Honor's rulings about when various submissions are due, there's only one round of proposed findings of fact, conclusions of law.

THE COURT: That's correct.

MR. BERL: So if we raise an evidentiary issue, they wouldn't really have an opportunity to respond to it if it were only in the proposed findings of fact and conclusions of law, and vice versa. And so that's why I thought there should be some opportunity for a response.

THE COURT: I've got quite a chart up here of looming decisions on that front to make. Let's reserve those two, proposed findings of fact and conclusions of law, which, against the request of everyone up here, I've not put page limits on. Let's leave it there so that you're using your real estate in the argumentative briefs more wisely.

I've got a good handle on what we still need to sort through, but I would certainly encourage everyone to address each of those in your proposed findings and conclusions.

MR. BERL: So when would Mylan then respond to our evidentiary issues raised?

THE COURT: You would not.

MR. BERL: We would not. Okay.

THE COURT: No. No, because we treat those truly as proposed findings of fact and conclusions of law we've argued here. You're free to augment the argument with research and the rest in those, but we don't need a volley in the papers.

MR. BERL: Excellent. So the second issue relates to closings. It's been my perception that trial has gone very smoothly in person. And I would suggest that, given the complexity of the issues, we would at least prefer, if possible, for closings to occur in person. Obviously, we understand the issues with respect to the courtroom and the projects to clean up the asbestos, but wherever it would be convenient for the Court, whether it's in Wheeling or Elkins or my cocounsel Mr. Ruby suggested even maybe at the law school in Morgantown, anywhere. We're willing to go anywhere, but we'd like to be in person.

THE COURT: Why, Mr. Ruby, do you hate law students?

Any opposition to that suggestion?

MR. RAKOCZY: We have no objection to in person, Your Honor.

THE COURT: No. I would tend to agree, Mr. Berl, that in person is better. I was so tired of getting Court of Zoom during the early portion of the pandemic. We said Zoom just to get that on everyone's calendars. We don't know what our deal will be here.

Our Elkins facility, which is not the easiest to get to for folks traveling from afar, is expansive compared to this, as is Wheeling, although Wheeling is not as big as Elkins. But in all candor, the law school would be easier for me because that's just across town.

Let us work on logistics on one of those venues, and we'll let the parties know what we might be able to pull off.

Like I said -- and if I didn't say that out loud when we set sort of the schedule for posttrial proceedings and briefing, I was more concerned with getting a date for that because we don't know -- like I've told every witness, we're a court without a country for a little while. And that is largely in the hands of the GSA. And for any former government employees, you understand what that means.

MR. RAKOCZY: May I raise one issue about the law school, Your Honor?

THE COURT: Yes.

MR. RAKOCZY: If it was held at the law school, would we have the benefit of courtroom security if we needed to seal the courtroom?

THE COURT: Yes, we would. But those are logistical issues that we will deal with on that front. The main courtroom at the law school would certainly be large enough to accommodate everyone who's been here. They have sufficient AV equipment available to us. I'm just thinking through it. But

that is one of the logistical things we would have to work on, Mr. Rakoczy, but we will work through those.

Elkins is always available to us. And Judge Stamp in Wheeling has been quite gracious to let us use his courtroom at the Wheeling point of holding court, which is now named for him, for a couple criminal trials we have in July. So we have some options. We'll work through that.

MR. BERL: Thank you, Your Honor.

And, lastly, I'd just like to close by saying we understand that this case and the schedule that we have gone through and executed has imposed a substantial burden on the Court and its staff. And we thank the Court and its staff for dealing with us and for your hospitality over the last few weeks. It's been a pleasure to try the case before Your Honor.

And a special thank-you to Ms. Knecht for her daily transcripts, which have been invaluable and surprisingly accurate.

THE COURT: I'll let her address if she takes that as a criticism. Mr. Berl, that will be reflected as a premium in your invoice with the Court's blessing.

MR. RAKOCZY: For Mylan and Biocon, we thank the Court and staff as well. I can't say we appreciate the expedited schedule as much as Mr. Berl.

THE COURT: That objection is noted, Mr. Rakoczy.

Okay. Any other issues from Mylan? I know we do

have the remaining exhibits.

Yes, Counsel -- yes, Ms. Oberwetter?

MS. OBERWETTER: We've gone through the list. We do not have an objection to DTX 9038, DTX 913, DTX 902, or DTX 5082.

DTX 903 [sic], insofar as it was used for impeachment only, as -- it was a disclosed exhibit; so we would ask that it be taken only for that purpose.

THE COURT: Any objection to that, Mr. McLaughlin?

MR. McLAUGHLIN: You're talking about DTX 9023?

MS. OBERWETTER: Correct.

THE COURT: 9023?

MS. OBERWETTER: Correct.

MR. McLAUGHLIN: And what's the proposal?

THE COURT: That it be received as impeachment material.

MR. McLAUGHLIN: That's fine.

MS. OBERWETTER: And then DTX 6444 was the summary judgment stipulation, which does not seem appropriate from our standpoint to be put into evidence. There's a stipulation on the docket. It was used with a witness.

THE COURT: It's part of the record, right? Understood.

MR. McLAUGHLIN: As long as it's on the record, that's fine.

THE COURT: Is that -- that's all of them, then?

MS. OBERWETTER: That is all of them.

THE COURT: Those will be admitted. 9023, for the purpose identified, the stipulation with respect to summary judgment, it's part of the record. I recognize its use and purpose here at trial.

9038, does anyone know which witness that exhibit was used with?

MR. McLAUGHLIN: That came in with Dr. Albini.

THE COURT: And then 9023.

MR. McLAUGHLIN: That came in during Dr. Csaky's first cross-examination.

THE COURT: Okay.

Any others, Madam Clerk?

THE CLERK: That's it.

THE COURT: All right. Those will all be deemed admitted, then. Thank you.

(DTX 9038, DTX 9023, DTX 913, DTX 902, DTX 5082, and DTX 6444 were admitted.)

MR. McLAUGHLIN: Thank you, Your Honor.

THE COURT: Let me say this before everyone scatters to the ends of the earth. Please check with Madam Clerk to make sure she has copies of all the exhibits. I can't imagine that we don't, but we always do need to track one or two down. Please make sure that all those are checked off the list.

Mr. Rakoczy, anything else from Mylan?

MR. RAKOCZY: Nothing from Mylan or Biocon, Your Honor.

THE COURT: Thank you.

Mr. Berl, anything else from Regeneron?

MR. BERL: Nothing from Regeneron. Thank you, Your Honor.

THE COURT: The Court's prior order with the briefing schedule and the rest we'll leave unchanged, with the caveat we added with respect to the proposed findings. Any of the evidentiary issues at trial that may have been held in abeyance or conditionally addressed, please feel free to address those therein.

Thank you all very much. We appreciate all of your hard work. And I know how difficult it is to try a lengthy and complicated case and even more so how difficult it is to be far from office and home to do so. So we appreciate everyone's hard work and preparation. And I really do mean that.

Thank you. Please thank all of your witnesses, in particular, your experts. I've learned a great deal over the last two weeks. I don't know what the heck I'll use it for in my day-to-day life going forward, but as I've regaled my bride and others with tales from this trial, they just looked at me quizzically.

The Fourth Circuit judicial conference is next week.

I look forward to talking about hydrophilic and hydrophobic molecules and the rest with my judicial colleagues. And I'll be sure to thank you all for the reception topics.

With that, at 10 after 1:00, I'll consider this matter adjourned for trial purposes. Thank you all very, very much.

MR. BERL: Thank you, Your Honor.

MR. TRASK: Thank you, Your Honor.

(Proceedings concluded at 1:15 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 23, 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 23rd 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